Part 2

Evidence and judgements

2

Introduction to Part 2

The brief of the Panel, and of the systematic literature review teams that provided the basis for the Panel's work, has included the task of presenting a clear, strong, and reliable foundation for the final recommendations. These in turn form the basis of sound policies and effective programmes to reduce the rates of cancer in populations, and the risk of cancer in people, whether as members of communities, or as families, or as individuals.

In this central part of the Report, seven chapters display the findings of the independently assembled systematic literature reviews, and the judgements of the Panel derived from these reviews and other evidence as needed. The Panel's judgements are displayed in the form of matrices that introduce five of these chapters. Judgements of 'convincing' and 'probable' causal relationships, shown in the top part of these matrices, are the basis for recommendations made in Part 3 of the Report.

Chapter 4, the first and longest chapter that follows, is concerned with types of food and drink. The judgements of the Panel are generally food- and drink-based, reflecting the evidence. Findings on dietary constituents and micronutrients are identified as, for example, on 'foods containing dietary fibre' or 'foods containing folate'. For consistency, findings on methods of food processing are, where possible, shown as part of the whole evidence on the associated foods so that, for example, the processing and preparation of meat is integrated with the evidence on meat. Evidence specifically on dietary supplements and on patterns of diet is included in the two final sections of this chapter.

Chapters 5 and 6 are concerned with physical activity, and with body composition, growth, and development. Evidence in these areas is more impressive than was the case up to the mid-1990s; the evidence on growth and development indicates the importance of a whole life-course approach to the prevention of cancer. As with the chapter on foods and drinks, these chapters include detailed summaries of the evidence collected in the systematic literature reviews together with graphic representations of the most significant evidence.

Chapter 7 summarises and judges the evidence as applied to 17 cancer sites, with briefer summaries based on narrative reviews on cancers of five other body systems and sites. The judgements as shown in the matrices in this chapter correspond with the judgements shown in the matrices in the previous chapters.

Chapter 8, in which judgements are also based on the evidence from the systematic literature reviews amplified by knowledge of physiological processes, concerns the biological and associated determinants of weight gain, overweight, and obesity. Before work on this chapter began, the Panel agreed that a comprehensive review of the evidence would be likely to show that

obesity is or may be a cause of a number of cancers. It was therefore important to identify what aspects of food, nutrition, and physical activity themselves affect the risk of obesity and associated factors.

Improved screening, diagnosis, and medical services, including therapy and surgery, are in many countries improving the rates of survival for people with cancer. The number of cancer survivors — people living after diagnosis of cancer — is therefore increasing. The relevance of food, nutrition, physical activity, and body composition to people living with cancer, and to the prevention of recurrent cancer, is summarised in Chapter 9.

The Panel agreed that its final recommendations should be principally based on the evidence concerning cancer, and also should take into account findings on food, nutrition, physical activity, and the prevention of other chronic diseases, and of nutritional deficiencies and nutrition-related infectious diseases, especially of childhood. Chapter 10, which is also based on a systematic literature review, is a summary of the findings of expert reports in these areas.

The proposals for further research contained in Chapter 11 are, in the view of the Panel, the most promising avenues to explore in order to refine understanding of the links between food, nutrition, physical activity, and cancer, and so improve the prevention of cancer, worldwide.

As expected, a comprehensive assessment of all relevant types of evidence relating to food, nutrition, physical activity, body composition, and the risk of cancer has proved to be a massive task. The Panel was impressed not only by the quantity but also the quality of much of the evidence, and the degree to which a great deal of the evidence was consistent. As a result, recommendations designed to prevent cancer in general can be made with confidence. These are contained in Part 3.

CHAPTER 4

Foods and drinks

This chapter, with the following chapters in Part Two, forms the basis for the population goals and personal recommendations in Part Three.

The Panel decided that the evidence on food, nutrition, and cancer is generally most persuasive for foods rather than for specific nutrients or other food constituents; and that the evidence from epidemiological and experimental studies in this field, usually undertaken to address questions about cancers of specific or related sites, is most usefully synthesised in terms of foods and drinks.

The detailed evidence on foods and drinks is presented in this chapter, and that on physical activity and on body composition in the following two chapters. These three chapters include summaries of the evidence, including meta-analyses presented in graphic form, as well as the Panel's judgements. Chapter 7 presents the evidence on cancer sites in more summarised form.

In this chapter, whenever possible and appropriate, the evidence on dietary constituents, and on food production, preservation, processing, and preparation (including cooking), is integrated with the evidence on foods and drinks. So here, for example, the evidence on carotenoids is considered together with the evidence on vegetables and fruits; the evidence on methods of cooking meats is considered with the evidence on red meat and on processed meats; and the evidence on ethanol is considered with alcoholic drinks.

The result is not perfect. There is no single, ideal way of categorising the evidence on food and nutrition. But an approach emphasising foods and drinks is consistent with the generally accepted view that food-based dietary guidelines and recommendations are particularly valuable as a foundation for policies designed to improve public health.

The first two sections of this chapter summarise and judge the evidence on plant foods; the next two sections that on animal foods; and the following two sections that on fats and oils, and sugars and salt. The next two sections concern drinks, the second of which covers alcoholic drinks. These are followed by sections concerned with those aspects of dietary constituents, and with food production, preservation, processing, and preparation (including cooking), that have not been incorporated in previous sections. The final section summarises evidence on dietary patterns, including being breastfed.

The pattern that emerges, though different in some important respects, is largely similar to that based on the evidence gathered in the mid-1990s, although the confidence with which various exposures are judged to cause or protect from cancer has sometimes changed.

4.1 Cereals (grains), roots, tubers, and plantains

CEREALS (GRAINS), STARCHY ROOTS AND TUBERS, PLANTAINS, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	**Cancer site**	**Exposure**	**Cancer site**
Convincing			Aflatoxins[1]	Liver
Probable	**Foods containing dietary fibre[2]**	**Colorectum**		
Limited — suggestive	Foods containing dietary fibre[2]	Oesophagus		
Substantial effect on risk unlikely	None identified			

1   Foods that may be contaminated with aflatoxins include cereals (grains), and also pulses (legumes), seeds, nuts, and some vegetables and fruits (see chapter 4.2).
2   Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3). Dietary fibre is contained in plant foods (see chapter 4.2 and box 4.1.2).

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

These starchy plant foods have been the staple sources of dietary energy and bulk for humans since the development of settled communities and agriculture. They have to be prepared in some way to make them edible. In whole or relatively unprocessed forms, they are also sources of dietary fibre and various micronutrients. Cereals in whole form contain essential fats. When the outer layers of these foods are removed and they are refined, most of what remains is starch and protein.

In general, with industrialisation and urbanisation, consumption of these foods decreases, and more is consumed in the form of cereal products, which are typically more energy-dense and which may contain substantial amounts of fat, sugar, or salt. Pure starch from these foods is also used as an ingredient in many processed foods. Wheat, rice, maize (corn), and potatoes and their products are now the main cereals and roots/tubers produced and consumed globally.

Overall, *the Panel judges* that evidence indicating that cereals (grains), roots, tubers, or plantains affect the risk of any cancer, remains insubstantial.

The Panel judges as follows:
Foods containing dietary fibre probably protect against colorectal cancer; and there is limited evidence suggesting that such foods protect against oesophageal cancer. Dietary fibre is found in plant foods: vegetables, fruits, and pulses (legumes) (see chapter 4.2), as well as in cereals, roots, tubers, and plantains. All these foods are highest in dietary fibre when in whole or minimally processed form.

Foods high in dietary fibre may have a protective effect because of being bulky and relatively low in energy density. See chapters 6.1, 7.3, 7.9, and Chapter 8 for discussion of the role of energy density in weight gain, overweight, and obesity, and of weight gain, overweight, and obesity in the risk of some cancers, including those of the oesophagus and colorectum.

The Panel also judges that the evidence that foods contaminated with aflatoxins are a cause of liver cancer is convincing. Cereals (grains) and peanuts (see chapter 4.2) are the foods most commonly infested by these fungal toxins. Contamination is most widespread in

countries with hot, damp climates and poor storage facilities.

Within the remit of this Report, the strongest evidence, corresponding to judgements of 'convincing' and 'probable', shows that foods containing dietary fibre probably protect against colorectal cancer; and that foods contaminated with aflatoxins are a convincing cause of liver cancer. Also see chapter 4.2 for judgements of probable protective effects of foods containing various micronutrients also found in cereals, roots, and tubers, particularly when relatively unprocessed.

Cereals (grains) are the staple foods in large parts of the world, supplying most of the energy and bulk in diets. In some regions, roots, tubers, or plantains are staple foods as well as or instead of cereals (grains). These generalisations apply to practically all settled rural and most urban populations. Monotonous 'poverty diets' containing very high levels of these foods, particularly if refined, are low and sometimes inadequate in protein and other nutrients. Gatherer–hunter and pastoral communities usually consume less of these starchy foods. Their nutrient content is variable, largely depending on the degree to which they are refined.

Consumption of cereals, roots, and tubers in general gradually drops with industrialisation and urbanisation, and an increasing amount of wheat in particular is grown for animal feed. These foods are increasingly used as a basis for or ingredients in processed products that are often energy-dense, high in fats or sugars, and sometimes salt. In lower-income countries, total population consumption of these foods may amount to 60–80 per cent of total energy, and in high-income countries, usually to less than 30 per cent. Also see Chapter 1.

Early reports concerned with nutritional deficiencies generally did not pay much attention to these foods and instead gave priority to energy- and nutrient-dense foods of animal origin, such as milk, eggs, and meat. Beginning in the 1970s, interest in dietary fibre increased, following informal epidemiological findings that diets high in dietary fibre were associated with a lower risk of a number of chronic diseases.[1][2] By the 1990s, it was generally agreed that diets relatively high in cereals (grains) and other starchy staple foods, preferably relatively unrefined, protect against obesity, type 2 diabetes, coronary heart disease, and perhaps also digestive disorders.[3][4] Evidence that such diets protect against cancer of any site has been less impressive, but epidemiological studies tend not to distinguish between degrees of refinement of cereals, roots, and tubers.

This section (4.1) includes cereal products and dietary fibre. It also includes contamination by aflatoxins, though this may also affect other plant foods (also see chapter 4.2). Non-starchy root vegetables such as carrots are included in chapter 4.2. Micronutrients found in plant foods are included in chapter 4.2, though most of these are also found in cereals (grains), roots, tubers, and plantains.

4.1.1 Definitions, sources

Cereals (grains)
Cereals (grains) are the seeds and energy stores of cultivated grasses. The main types are wheat, rice, maize (corn), millet, sorghum, barley, oats, and rye. In some countries, 'cereal' is also a term for dry foods made from grains and other ingredients, often eaten with milk for breakfast.

Roots, tubers, plantains
Roots and tubers are energy stores of plants. Names and definitions can vary around the world — potatoes are tubers, which are the tips of underground stems that swell with starch (a polysaccharide) and water. While potatoes are often classed as vegetables (in the USA, for instance), they are grouped separately from non-starchy vegetables in this Report. Sweet potatoes, sometimes called 'yams' in North America, are a type of storage root rather than a tuber, but true yams are starchy tubers. Cassava (manioc) and yucca are elongated roots, and sago is a starchy food made from the pith of some types of palm tree. Taro is cultivated for its edible leaves, as well as its starchy corm, which is similar to a tuber. Plantains are one of several fruits used as vegetables: they grow on trees and look like bananas, but only a small proportion of the starch is converted to sugar during the ripening process, which makes them similar to potatoes to cook with.

Box 4.1.1	Wholegrain and refined cereals and their products

Many of the cereals (grains) that we consume are refined. Grains are first broken into pieces and then refined, sifting away the bran, germ and, usually, the aleurone layer. This removes most of the fibre, oil, and B vitamins, as well as approximately 25 per cent of the protein. Polishing, as often performed on rice, removes additional nutrients. Many high-income countries therefore fortify refined cereals, including flour, with B vitamins and iron. Wholegrain products generally contain the constituents of the grain but, given the absence of an internationally accepted definition, intact grains are present to a variable extent. The extent to which the grain remains intact influences physiological processes in the bowel and hence health.

Cereal foods may be eaten in wholegrain form, although consumption in refined forms, such as white rice, bread, or pasta, is generally much more common, particularly in high-income countries. Refined grains are considered easier than wholegrains to cook and to chew; are light in colour — which is attractive to many consumers; and also have a longer shelf-life than wholegrain products, as the oil in bran goes rancid relatively quickly.

Breakfast cereals, particularly in the United States and parts of Europe, also account for a significant proportion of grain eaten. Many breakfast cereals, although based on grains (whole or refined), may contain substantial amounts of added sugars. Grains are further processed to provide ingredients such as corn syrup, starch, or alcohol. They also form the basis of many animal feeds.

Processed grains have a higher glycaemic index than unprocessed grains and, generally, the greater the degree of processing, the greater the glycaemic index (box 4.1.3).

The concept of dietary fibre arose from observations of the low prevalence of colon cancer, diabetes, and coronary heart disease in parts of Africa amongst people whose diets were high in unrefined carbohydrates and whose stools were typically bulky, and often or sometimes semisolid. Considerable efforts have been dedicated to characterising the dietary components of what has come to be called dietary fibre that might confer health benefit. Naturally occurring dietary fibre is only derived from plant foods. Pulses (legumes) and minimally processed cereals are particularly concentrated sources, but vegetables and fruits also contain significant amounts. Dietary fibre isolated from plant cell walls and in synthetic forms are increasingly entering the food supply.

High intakes of dietary fibre, variously defined, have been associated with reduced risk of cardiovascular disease as well as of some cancers. Definitions of dietary fibre vary. Some are based on chemical analyses of the components of plant cell walls, such as non-starch polysaccharide, others on physiological effects — the carbohydrates that enter the large bowel having escaped digestion in the small intestine being defined as dietary fibre. The latter definition includes oligosaccharides and resistant starch. The World Health Organization and Food and Agriculture Organization have recently proposed that only polysaccharides which form part of plant cell walls should be regarded as dietary fibre and that the health benefits of resistant starch and oligosaccharides are more appropriately considered separately.

This section refers to starchy roots, tubers, and plantains. Carrots, beets, parsnips, turnips, and swedes are non-starchy roots, and are classified as non-starchy vegetables in this Report. Also see chapter 4.2.

Box 4.1.3	Glycaemic index and load

The degree to which different foods and meals raise blood glucose depends not only on the nature of the carbohydrate, but also on the characteristics of the foods consumed. Glycaemic index (GI) is a measure of the degree to which a food raises blood glucose compared with a standard food (usually glucose or white bread) under standard conditions. The test food must contain the same amount of available carbohydrate (usually 50 grams) as the standard. GI was originally used as an aid to food choice in diabetes and has more recently been applied to people without diabetes. The rise in blood glucose after consuming a food depends not only on the GI but also on the amount of food eaten. A related measure, glycaemic load (GL), takes into account both the GI of a food as well as the actual amount of carbohydrate consumed. The GL of a food may be measured directly or calculated by multiplying the GI of a food by the number of carbohydrate grams in a serving of the food.

Factors that influence the GI of a food include the type of carbohydrate, how the food is processed or cooked, and the other components present in the food (for example, fat, protein, fibre). There is some relationship (inverse) between GI and fibre content, although some foods high in fibre have a high GI and vice versa. Factors can affect GI by influencing speed of absorption, for instance higher fat foods tend to have a low GI. The calculated GI of a mixed meal or whole diet has been shown in some studies to correlate with the actual GI obtained by feeding a mixed meal. Although the concept of GI has been controversial, the GI and GL of diets have predicted risks of type 2 diabetes and coronary heart disease and related biomarkers, independent of dietary fibre, in prospective epidemiological studies, suggesting that GI and GL may be useful markers.

The relevance to cancer might lie in the fact that the rise in blood glucose after a meal is closely linked to that of insulin, which apart from its crucial role in carbohydrate and lipid metabolism, is also one of a family of important growth factors (also see Chapter 2).

4.1.2 Composition

Cereals (grains)
The relative amounts of dietary constituents in cereals and cereal foods depend largely on the degree of refinement and other forms of processing (box 4.1.1). Starch makes up about 70 per cent of the raw weight of the storage tissues (endosperm) of unprocessed cereal grains. The outer parts of the grain (the bran and the aleurone layer) contain non-starch polysaccharide, a type of carbohydrate that characterises dietary fibre (box 4.1.2).

Cereals also contain variable amounts of protein, oils, B vitamins, vitamin E and tocotrienols, iron, and various trace elements, as well as phytochemicals, some of which, such as the antioxidants, are bioactive (box 4.1.2). The germ is the embryonic part of cereal plants and contains oils, proteins, and fibre. Various cereals contain other specific components. Wheat contains gluten (a mixture of proteins). Rye has high levels of pentosans and oats contain beta-glucans, both of which are non-starch polysaccharides, a characterising feature of dietary fibre.

Cereals (grains) and pulses (legumes) may be contaminated with aflatoxins. See box 4.1.4.

Roots, tubers, and plantains
Roots and tubers are less concentrated stores of starch, although this accounts for almost all of their raw weight apart from water. Starch content varies from around 15–20 per cent in sweet potatoes to 25–30 per cent in cassava and yams, which translates into around 80–95 per cent of the dietary energy of these roots and tubers. Cooking sweet potatoes makes them taste sweet because an enzyme converts as much as 75 per cent of the starch into maltose (a disaccharide). Roots and tubers eaten with the skin on are high in dietary fibre. These foods are generally poor sources of protein, so although protein deficiency is uncommon, populations that subsist on these foods, and do not eat protein-rich pulses (legumes), are at risk of deficiency, especially children weaned on thin gruels made with these low-protein foods. They contain variable amounts of other nutrients. Potatoes contain vitamin C, for example, and the orange varieties of sweet potatoes contain carotenoids. Yams contain many bioactive compounds and taro corms are high in vitamin B6, fibre, and manganese.

Box 4.1.4	Aflatoxins

Mycotoxins are toxins produced by certain moulds or fungi. Although moulds that contaminate foods are usually destroyed by cooking temperatures, the toxins they produce may remain. Aflatoxins are one type of mycotoxin. All naturally occurring aflatoxins are classified as human carcinogens (group 1) by the International Agency for Research on Cancer; other mycotoxins, such as fumonisins, are suspected carcinogens.[5] It is common to find co-contamination by more than one species of mycotoxin-producing fungus. In Europe, the Joint FAO/WHO Expert Committee on Food Additives and Contaminants recommends that aflatoxin concentrations in foods be kept as low as possible.[6]

The main foods that may be contaminated by aflatoxins are all types of cereal (grain), including wheat, rice, maize (corn), barley, and oats; and pulses (legumes) — notably peanuts. Nuts and seeds may also be contaminated. Feedstuffs for farm animals may also be contaminated with aflatoxins, which can then be secreted in milk or accumulated in tissues.

Aflatoxins, which are produced by *Aspergillus flavus* and *A. parasiticus*, are most problematic in countries with hot, damp climates and poor storage facilities. Under these conditions, foods may become contaminated with fungi and then accumulate such toxins. Such foods are marketed and consumed in the countries in which they are produced; they are also exported to neighbouring countries and intercontinentally. Aflatoxin contamination is therefore a international issue.

Levels of aflatoxin contamination tend to be highest in countries where rates of liver cancer are high, such as some African countries and South-East Asia, including China. In general, rates are low in Europe, but relatively high rates of contamination have on occasion been found in the USA.

Aflatoxin exposure levels are low in Europe and Australia, higher in the USA, and high in many low-income countries. This is particularly the case in tropical and subtropical regions where grains and nuts are stored for long periods under non-ideal conditions.

Rates are reduced by inspection, use of fungicides, and screening of imported foods. However, monitoring of levels of aflatoxin contamination in low-income countries is generally lacking.

4.1.3 Consumption patterns

Cereals and grains

As societies moved to more settled, agricultural ways of life 10–15 000 years ago, cereals became the main staple foods; the types of cereal crops grown depended largely on climate and terrain. Wheat, barley, oats, and rye are traditionally staple foods for people living in the Middle East and Europe; and with rice in Asia; maize (corn) in the Americas; and sorghum and millet in Africa. But the market for cereals and their products is now global, although some, such as sorghum, remain largely regional.

The importance of starchy staples in food systems and diets is broadly connected to economic and industrial development. Both in higher-income countries and across the world, there has been a long-term decline in their consumption. With increasing urbanisation in lower-income countries, wheat and maize are replacing traditional staple foods. An important exception is Asia, where rice remains the staple grain. Cereal cultivation and consumption tends to be highest in most of Asia and lowest in Oceania, parts of Europe, and North America.

Globally, cereal foods provide more than 45 per cent of dietary energy; diets based on these foods tend to be bulky with a low energy density (see chapter 8.8.4). Cereals provide more than 50 per cent of dietary energy in low-income countries, but only around 30 per cent in high-income countries. While grains contribute roughly 20 per cent of dietary energy in Australia, North America, and central Europe, they can provide as much as 70 per cent in parts of Asia (mainly from rice). Although more wheat is grown than rice on a global basis, much of it is used for animal feed. Rice is the principal food for half of the world's population.

Cereals are very versatile once they have been processed from the raw grain. Wheat is mainly milled to make flour for bread, pastries, cakes, and pasta. Maize (corn) is a staple food in Latin America and parts of Asia and Africa, where it is used to make grits, cornmeal (used for polenta as well as corn breads), corn flour, tortillas, tamales, and corn chips. It is also the basis of corn starch (a thickener), corn syrup (a sweetner), and corn oils. Sweetcorn is also eaten as a vegetable, either on or off the cob. Rice is usually processed to remove the bran and aleurone layers, turning 'brown rice' into 'white'. It is also used to make flour (the basis for gluten-free breads), rice powder, noodles, rice paper, rice milk, Japanese mochi, and lao-chao (Chinese fermented rice). Barley is used primarily in Asia (tsampa and miso soya paste) and in North Africa (soups, porridges, and flat breads). Whole rye grains are milled and used to make bread in some north and east European countries. Whole oats are made into porridges and used in muesli and baked goods, such as biscuits. Fonio, millet, sorghum, teff, and triticale are traditional crops and staples in parts of Africa and Asia. Many grains are also fermented to make alcoholic drinks (see chapter 4.8.1).

Roots, tubers, and plantains

Roots, tubers, and plantains are staple foods in some parts of the world. For instance, populations in some regions of sub-Saharan Africa, Latin America, and Oceania base their diets on these foods. Globally, starchy roots provide around 5 per cent of dietary energy. Consumption is highest in the Pacific islands and parts of Africa, with cassava and yams providing more than 40 per cent of dietary energy in Ghana. Potatoes can provide as much as 10 per cent of dietary energy in North America and Europe. Globally, plantains provide less than 0.5 per cent of dietary energy, but they are locally important in some African, Latin American, and Caribbean countries, where they can provide more than 15 per cent of dietary energy. Some populations do not rely on any of these foods — for instance, pastoralist societies such as the Maasai hunters in East Africa, and the Inuit and other Arctic populations, maintain their traditional ways of life and diets.

Dietary fibre

Dietary fibre intake, measured as non-starch polysaccharides, varies from 10–13 grams (g)/day in Japan and the UK to 15–20 g/day or more in Africa and India. Intake among individuals in a population may vary between 7 and 25 g/day.[7]

4.1.4 Interpretation of the evidence

Interpretation of the evidence on any and all foods and drinks, their constituents, their methods of production, preservation, processing and preparation, and other factors, with the risk of cancer, is never simple, for general and specific reasons.

4.1.4.1 General

For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6, and 3.7.

'Relative risk' (RR) is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.1.4.2 Specific

Some considerations specific to cereals (grains), roots, tubers, and plantains are as follows.

Classification. 'Cereals' is a broad classification. Different cereals have different nutritional composition and biological effects, as do different types of dietary fibre. Any effects of specific cereals or their constituents may not become apparent.

Patterns and ranges of intake. Little evidence relates to roots, or tubers other than potatoes, or plantains, some of which, such as cassava (manioc) or yams, are staple foods in some parts of the world.

Terminology. Potatoes are usually (as here) defined as tubers, but are sometimes (in the USA especially) included with vegetables. Bananas, a significant item in many diets, may be (as here) defined as a fruit, or else with plantains as a starchy food. There is no internationally agreed definition for dietary fibre (box 4.1.1).

Measurement. Non-starch polysaccharides are measured precisely by the Englyst method,[8] but there are fewer epidemiological data on non-starch polysaccharides specifically than for dietary fibre. The various analytical techniques used to assess the fibre content of foods give widely different results.

Confounding. In high-income countries, high intakes of wholegrain cereal products tend to go together with other health-conscious dietary and other habits. Also there is possible confounding between dietary fibre and other dietary constituents and in general with 'healthier' dietary patterns and ways of life. Data on dietary fibre come predominantly from dietary sources, that is, plant-based foods (also see box 4.1.1 and chapter 4.2); therefore, no effect can be attributed to different types and sources of dietary fibre.

Production, preservation, processing, preparation. Few studies distinguish between unrefined and refined cereals and their products. Many processed foods grouped as cereal products, such as ready-to-eat breakfast cereals, are high in added sugars and sometimes salt. The ways in which cereals are processed, prepared, and consumed varies greatly in different cultures.

4.1.5 Evidence and judgements

The full systematic literature review (SLR) is contained on the CD included with this Report.

4.1.5.1 Cereals (grains)

The evidence was too limited in amount, consistency, or quality to draw any conclusions.

4.1.5.2 Roots, tubers, and plantains

The evidence was too limited in amount, consistency, or quality to draw any conclusions.

4.1.5.3 Foods containing dietary fibre

Colorectum

Sixteen cohort studies[9-37] and 91 case-control studies investigated dietary fibre and colorectal cancer. The Harvard pooling project also analysed original data from 13 separate cohort studies.[38]

An association was apparent from many, though not all, cohort studies. Ten studies showed decreased risk when comparing high with low intake groups,[14 19 21 25-29 33 34] which was statistically significant in one (figure 4.1.1).[28] Two reported non-significant increased risk,[36 39] one showed no effect on risk,[30] and one reported no association.[18] One study reported non-significant decreased risk in women and non-significant increased risk in men[23]; one study reported non-significant increased risk in women and non-significant decreased risk in men.[37] Meta-analysis was possible on eight studies, giving a summary effect estimate of 0.90 (95% confidence interval (CI) 0.84–0.97) per 10 g/day increment, with moderate heterogeneity (figure 4.1.2). A dose-response relationship was apparent from cohort data.

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

The Harvard pooled analysis from 13 prospective cohort studies (725 628 participants, followed up for 6 to 20 years, 8081 colorectal cancer cases) gave a significant inverse association in the age-adjusted model (0.84, 95% CI 0.77–0.92).[38] However, the association was attenuated and no longer statistically significant after adjusting for other risk factors (0.94, 95% CI 0.86–1.03). One comparison group was statistically significant when maximally adjusted, others were not. Compared with dietary fibre intake of 10 to < 15 g/day, the pooled effect estimate was 1.18 (95% CI 1.05–1.31) for less than 10 g/day (low compared with moderate intake). All other measures were not associated with risk of colorectal cancer. The pooled analysis therefore found that, after accounting for other dietary risk factors, high dietary fibre intake was not associated

Figure 4.1.1 | **Dietary fibre and colorectal cancer; cohort studies**

Relative risk (95% CI)

Wu 1987 Men	1.19 (0.60–2.11)
Wu 1987 Women	0.64 (0.37–1.11)
Heilbrun 1989 Men	0.71 (0.45–1.13)
Giovannucci 1994 Men	1.08 (0.68–1.71)
Steinmetz 1994 Women	0.80 (0.40–1.91)
Gaard 1996 Men	0.82 (0.46–1.46)
Kato 1997 Women	0.95 (0.79–1.24)
Pietinen 1999 Men	1.00 (0.68–1.58)
Soneham 2000 Women	0.96 (0.70–1.32)
Bingham 2003	0.75 (0.50–0.95)
COL00535 Women	0.94 (0.70–1.26)
IARCIM 1977 Men	0.92 (0.64–1.32)
IARCIM 1977 Women	0.86 (0.52–1.42)
Baron 1997 Women	0.79 (0.45–1.38)

Relative risk, highest vs lowest exposure category

Figure 4.1.2 | **Dietary fibre and colorectal cancer; cohort studies**

Relative risk (95% CI)

Heilbrun 1989 Men	0.77 (0.48–1.24)
Bostick 1993 Women	0.88 (0.77–1.01)
Fuchs 1999 Women	0.99 (0.83–1.18)
Terry 2001 Women	1.08 (0.84–1.39)
Colbert 2001 Men	1.02 (0.88–1.18)
Konings 2002 Men	0.95 (0.84–1.07)
Konings 2002 Women	0.85 (0.73–1.00)
Higginbotham 2004 Women	0.83 (0.61–1.13)
Norat 2005 Men	0.77 (0.71–0.83)
Norat 2005 Women	0.89 (0.82–0.97)
Summary estimate	0.90 (0.84–0.97)

Relative risk, per 10 g/day
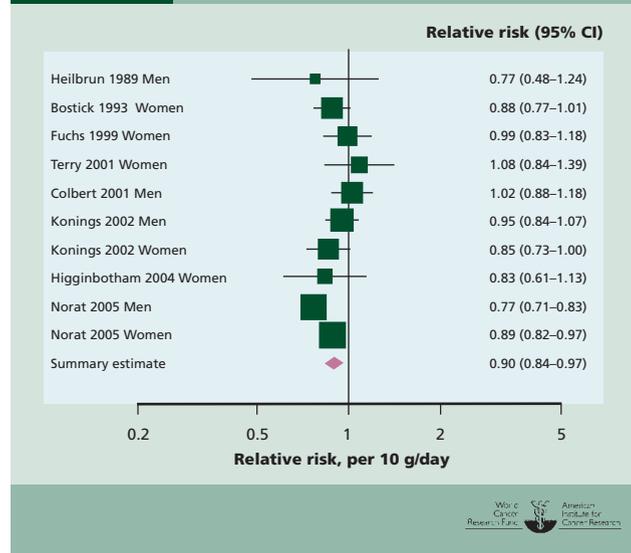
with a reduced risk of colorectal cancer.

Fibre exerts several effects in the gastrointestinal tract but the precise mechanisms for its probable protective role are not clearly understood. Fibre dilutes faecal contents, decreases transit time, and increases stool weight.[40] Fermentation products, especially short-chain fatty acids, are produced by the gut flora from a wide range of dietary carbohydrates that reach the colon. Short-chain fatty acids, particularly butyrate, can induce apoptosis and cell cycle arrest, and promote differentiation. Fibre intake is also strongly correlated with intake of folate.

> **A clear dose-response relationship is apparent from generally consistent cohort studies, supported by evidence for plausible mechanisms, but residual confounding could not be excluded. Foods containing dietary fibre probably protect against colorectal cancer.**

The Panel is aware that since the conclusion of the SLR, six cohort studies[41-46] and one case-control study[47] have been published. This new information does not change the Panel judgement (see box 3.8).

Oesophagus

One cohort study,[48] nine case-control studies,[49-58] and two ecological studies[59 60] investigated dietary fibre and cancer of the oesophagus.

There was some evidence of an association between dietary fibre and reduced oesophageal cancer risk. The single cohort study reported decreased risk when comparing high with low intakes, with an effect estimate of 0.50, though no assessment of statistical significance was included.[48]

The nine case-control studies produced 13 independent effect estimates. Of these, 11 estimates were of decreased risk,[50-53 55 56 58 61] which were statistically significant in eight. One estimate indicated no effect on risk[54] and one other gave non-significant increased risk.[62] The data were most consistent when stratified for adenocarcinomas; of six studies, five reported significant decreased risk; results were less consistent for squamous cell carcinoma. All studies were adjusted for alcohol and smoking except one, which was adjusted for alcohol but not smoking.[50]

The ecological studies were inconclusive. Neither was statistically significant, with one in the direction of increased and the other of decreased risk.

There is no evidence of a plausible biological mechanism through which dietary fibre reduces the risk of oesophageal cancer. It is not possible to conclude whether an as yet unknown mechanism is responsible for an apparent reduction in risk, or whether it is due to other components found in the vegetables and fruits that contain dietary fibre.

> **There is limited evidence from sparse and inconsistent case-control studies only, suggesting that foods containing dietary fibre protect against oesophageal cancer.**

4.1.5.4 Aflatoxins

(Also see box 4.1.4; chapter 4.9; and chapter 7.8). There are two approaches to measuring aflatoxin intake. The first uses local food tables to estimate exposure to aflatoxins from diet. The second approach uses biomarkers of exposure. These are derived from knowledge of aflatoxin metabolism. In humans, metabolised products of aflatoxins can be detected in blood,

urine, or breastmilk. Biomarkers of exposure are more accurate and precise.

Liver

Five cohort studies[63-70] and seven case-control studies[71-79] assessed associations between biomarkers of exposure to aflatoxin and hepatocellular carcinoma.

The cohort studies used a variety of different biomarkers for exposure to aflatoxin, some in blood and some in urine. Despite this variety, all five studies reported increased risk for the highest levels when compared to the lowest, and all of these reported at least one measure that resulted in a statistically significant increased risk (figure 4.1.3). Studies that adjusted for hepatitis virus infection tended to show the greater effects.[65 66] There is some evidence of an interaction whereby the risk is increased by a multiplicative effect if aflatoxin exposure is combined with hepatitis infection. One study showed that people with hepatitis virus antibodies and biomarkers of aflatoxin exposure had a higher risk than those with hepatitis virus antibodies alone, with an effect estimate of 10.0 (95% CI 1.6–60.9).[65]

There is evidence from some of the cohort studies for interaction with glutathione-*S*-transferase (GST) genotype.[63 64] GST is an enzyme involved in the metabolic pathway that 'detoxifies' aflatoxins. Different genotypes show varying efficiencies at this task. Two genes (GSTT1 and GSTM1) were assessed separately. For each, it is possible to have a positive or negative genotype. In each case, a negative genotype increases risk of hepatocellular carcinoma when exposed to aflatoxins. There is clear, consistent evidence that GSTM1/GSTT1 positive genotypes protect against the increased risk of liver cancer from hepatitis infection combined with aflatoxin exposure, which supports a causal role for aflatoxins in hepatocellular carcinoma.

Four case-control studies showed statistically significant increased risk for the highest levels of biomarkers when compared to the lowest.[71 74 78 79] Two studies showed no effect on risk.[73 77] One study showed a non-significant decreased risk.[72] Heterogeneity may be explained by the diversity in methods of exposure assessment.

A dose-response relationship is apparent from most cohort

studies and some of the case-control studies.

The areas in the world where there is considerable aflatoxin contamination of foods coincide with the areas where primary liver cancer rates are high. The epoxide product of aflatoxin AFB_1 is known to be genotoxic and is formed in the liver.[80] It damages DNA, causing G:C base pairs to become T:A. GST enzymes can repair this damage with varying efficiency between genotypes. Recent studies have shown that aflatoxins can damage the p53 gene, which is an important regulator of normal growth.[67] Damage to p53 DNA can lead to increased proliferation of abnormal cells and formation of cancers.

The synergistic effect of hepatitis virus infection and aflatoxin exposure might be explained by hepatitis virus increasing the production of the enzyme (CYP1A2) that produces the genotoxic metabolite of aflatoxin.[81] It is also possible that the hepatitis virus increases the number of G:C to T:A transversions, or that it inhibits nucleotide repair, or that it acts as a tumour promoter.

The evidence is ample and consistent and is supported by strong evidence for mechanisms operating in humans. A dose response is apparent from both cohort and case-control studies. The evidence that aflatoxins and aflatoxin-contaminated foods are a cause of liver cancer is convincing.

4.1.6 Comparison with previous report

The previous report concluded that dietary fibre/non-starch polysaccharides possibly protect against cancers of the pancreas, colorectum, and breast. The previous report also concluded that wholegrain cereals possibly decrease the risk of stomach cancer and that refined cereals possibly increase the risk of oesophageal cancer.

Since the mid-1990s, evidence for a protective effect of dietary fibre against colorectal and oesophageal cancer risk has become somewhat stronger. The finding of the previous report, suggesting that the degree of refinement (other than relative amounts of dietary fibre) may be a factor in modification of the risk of some cancers, was not found.

The previous report classified bananas as plantains. Here they are classified as fruits. The previous report considered dietary fibre separately from cereals (grains) and other plant foods. Here, dietary fibre is considered in the context of cereals (grains) and other plant foods.

4.1.7 Conclusions

The Panel concludes:
The direct evidence that cereals (grains), roots, tubers, or plantains affect the risk of any cancer remains unimpressive.

However, foods containing dietary fibre probably protect against colorectal cancer; and there is limited evidence suggesting that such foods protect against oesophageal cancer. Dietary fibre is mostly found in cereals, roots and tubers, and also in vegetables, fruits, and pulses (legumes) (see chapter

Figure 4.1.3 **Aflatoxins and liver cancer; cohort studies**

Relative risk (95% CI)

	Relative risk (95% CI)
Qian 1994 Men	5.00 (2.11–11.85)
Wang 1996	3.80 (1.11–12.96)
Yu 1997 Men	6.00 (1.22–29.49)
Sun 1999 Men	4.52 (1.57–13.01)

Relative risk, highest vs lowest exposure category
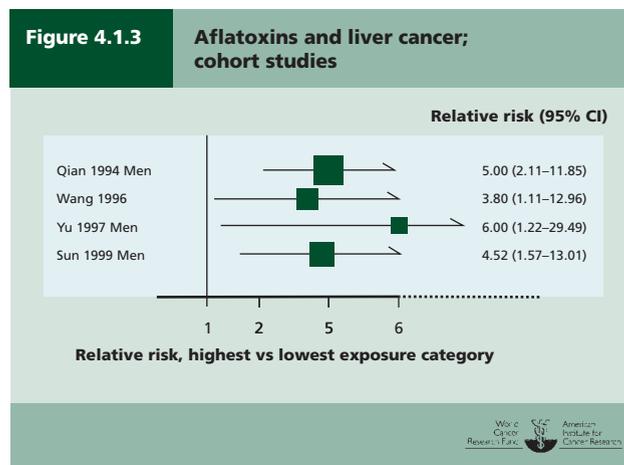
4.2). All of these are highest in dietary fibre when in whole or minimally processed forms.

Foods high in dietary fibre may also have a protective effect indirectly because they are relatively low in energy density. See chapters 6.1, 7.3, 7.9, and 8 for discussion of the role of energy density in weight gain, overweight, and obesity, and of weight gain, overweight, and obesity in the risk of some cancers, including those of the oesophagus and colorectum.

The evidence that foods contaminated with aflatoxins are a cause of liver cancer is convincing. Cereals (grains) and peanuts (see chapter 4.2) are the foods most commonly infested by these fungal toxins. Contamination is most widespread in countries with hot, damp climates and poor storage facilities.

4.2 Vegetables, fruits, pulses (legumes), nuts, seeds, herbs, spices

Vegetables and fruits are generally low in energy density (with a few exceptions) and, when consumed in variety, are sources of many vitamins, minerals, and other bioactive compounds (phytochemicals). Many non-starchy vegetables, including salad vegetables and fruits, may be eaten raw and may also be cooked. Pulses (legumes) are high in protein. Traditional diets all over the world combine cereals (grains) with pulses (legumes) and, in this way, ensure sufficient protein of adequate quality, usually with small amounts of animal foods. Nuts and seeds are concentrated sources of numerous micronutrients and of essential fatty acids. All these foods are sources of dietary fibre. Many herbs and spices have potent pharmacological as well as culinary properties.

Consumption of vegetables and fruits is very variable: high around the Mediterranean littoral and some tropical countries; low in many low-income countries, including some in which fruits are abundant. Consumption of pulses (legumes) is also very variable: beans and chickpeas and their products are basic foods in a number of Latin American, Middle Eastern, and Asian countries, but pulses are insignificant in typical North American and most European diets. Consumption of nuts, seeds, herbs, and spices also varies. Traditional Middle Eastern and Indian cuisines use a great variety of herbs and spices; garlic, usually classified as a herb, is consumed in remarkable quantities in some countries.

In general, *the Panel judges* that findings from cohort studies conducted since the mid-1990s have made the overall evidence, that vegetables or fruits protect against cancers, somewhat less impressive. In no case now is the evidence of protection judged to be convincing. However, in a substantial number of cases, a judgement of probable is justified. Evidence on legumes (pulses), nuts, seeds, and (with two exceptions) herbs and spices remains insubstantial.

The Panel judges as follows:
Non-starchy vegetables probably protect against cancers of the mouth, pharynx, and larynx, and those of the oesophagus and stomach. There is limited evidence suggesting that they also protect against cancers of the nasopharynx, lung, colorectum, ovary, and endometrium. Allium vegetables probably protect against stomach cancer. Garlic (an allium vegetable, commonly classed as a herb) probably protects against colorectal cancer. There is limited evidence suggesting that carrots protect against cervical cancer; and that pulses (legumes), including soya and soya products, protect against stomach and prostate cancers. Fruits in general probably protect against cancers of the mouth, pharynx, and larynx, and those of the

oesophagus, lung, and stomach. There is limited evidence suggesting that fruits also protect against cancers of the nasopharynx, pancreas, liver, and colorectum. There is limited evidence suggesting that chilli is a cause of stomach cancer.

Fruits and non-starchy vegetables are generally low energy-dense foods. For a discussion of the effect of such foods and drinks on weight gain, overweight, and obesity, and the role of weight gain, overweight, and obesity in the risk of some cancers, see Chapters 6, 7, and 8.

Evidence that vegetables and fruits protect against some cancers is supported by evidence on foods containing various micronutrients, found especially in vegetables, fruits, and pulses (legumes), and nuts and seeds, as well as in cereals, roots, tubers, and other plant foods. Foods containing folate probably protect against pancreatic cancer, and there is limited evidence suggesting that these foods also protect against oesophageal and colorectal cancers. Foods containing carotenoids probably protect against cancers of the mouth, pharynx, and larynx, and also lung cancer. Foods containing the carotenoid beta-carotene probably protect against oesophageal cancer; and foods containing lycopene probably protect against prostate cancer. Foods containing vitamin C probably protect against oesophageal cancer. There is limited evidence suggesting that foods containing quercetin protect against lung cancer.

Evidence also relevant to chapter 4.1 is grouped here. Foods containing selenium (also found in animal foods) probably protect against prostate cancer; and there is limited evidence suggesting that they protect against stomach and colorectal cancers. There is limited evidence suggesting that foods containing pyridoxine protect against oesophageal and prostate cancers; and that foods containing vitamin E protect against oesophageal and prostate cancers.

The strongest evidence, here corresponding to judgements of 'probable', shows that non-starchy vegetables and also fruits probably protect against cancers of the mouth, larynx, pharynx, oesophagus, and stomach, and that fruits also probably protect against lung cancer; and that allium vegetables, and garlic specifically, probably protect against stomach cancer. The case that vegetables, fruits, and pulses (legumes) may be protective against cancers of some sites is supported by evidence on foods containing micronutrients found in these and other plant foods. Thus, foods containing carotenoids probably protect against cancers of the mouth, pharynx, larynx, and lung; foods containing beta-carotene and also vitamin C probably protect against oesophageal cancer; foods containing selenium and also lycopene probably protect

VEGETABLES,[1] FRUITS,[1] PULSES (LEGUMES), NUTS, SEEDS, HERBS, SPICES, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	**Cancer site**	**Exposure**	**Cancer site**
Convincing				
Probable	**Non-starchy vegetables[1]**	**Mouth, pharynx, larynx** **Oesophagus** **Stomach**		
	Allium vegetables[1]	**Stomach**		
	Garlic[1]	**Colorectum**		
	Fruits[1]	**Mouth, pharynx, larynx** **Oesophagus** **Lung** **Stomach**		
	Foods containing folate[2]	**Pancreas**		
	Foods containing carotenoids[2]	**Mouth, pharynx, larynx** **Lung**		
	Foods containing beta-carotene[2]	**Oesophagus**		
	Foods containing lycopene[2,3]	**Prostate**		
	Foods containing vitamin C[2,4]	**Oesophagus**		
	Foods containing selenium[2,5]	**Prostate**		
Limited — suggestive	Non-starchy vegetables[1]	Nasopharynx Lung Colorectum Ovary Endometrium	Chilli[1]	Stomach
	Carrots[1]	Cervix		
	Fruits[1]	Nasopharynx Pancreas Liver Colorectum		
	Pulses (legumes)[7]	Stomach Prostate		
	Foods containing folate[2]	Oesophagus Colorectum		
	Foods containing pyridoxine[2,8]	Oesophagus		
	Foods containing vitamin E[2,6]	Oesophagus Prostate		
	Foods containing selenium[2,5]	Lung Stomach Colorectum		
	Foods containing quercetin[2]	Lung		
Substantial effect on risk unlikely	Foods containing beta-carotene[9]: prostate; skin (non-melanoma)			

1 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
2 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).
3 Mostly contained in tomatoes and tomato products. Also fruits such as grapefruit, watermelon, guava, and apricot.
4 Also found in some roots and tubers — notably potatoes. See chapter 4.1.
5 Also found in cereals (grains) and in some animal foods. See chapters 4.1 and 4.3.
6 Also found in plant seed oils. See chapter 4.5.
7 Including soya and soya products.
8 Vitamin B6. Also found in cereals. See chapter 4.1.
9 The evidence is derived from studies using supplements and foods containing beta-carotene: see chapter 4.10.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

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against prostate cancer; and foods containing folate probably protect against pancreatic cancer. Also see chapter 4.1 for the evidence that foods containing dietary fibre, found in plant foods (particularly when in whole or relatively unprocessed forms), probably protect against colorectal cancer.

Vegetables and fruits (including berries), nuts and seeds, and herbs and spices, where they grow and can be cultivated, have always been part of human diets. Gatherer–hunters and pastoral peoples probably consumed more than relatively impoverished urban dwellers: for them, vegetables were the main sources of many vitamins, and fruits were a main source of energy, from sugar (also found in wild honey). They are consumed abundantly as part of many long-established traditional cuisines, around the Mediterranean littoral, the Middle East, in many Asian countries, and the Pacific islands, where substantial amounts of meat, dairy products, and other animal foods are traditionally consumed only occasionally. In contrast, monotonous 'poverty' diets include few of these foods.

Globally, consumption of these foods is lower than now generally recommended. Vegetables and fruits are sometimes seen as relatively expensive. Well stocked supermarkets usually now display a variety of local and imported fresh vegetables and fruits, although supplies in smaller stores are more variable. Consumption of fresh vegetables and fruits in many tropical countries in Africa and Latin America is low: on average people in Brazil, for example, consume roughly the same as people in Britain. The explanation may be that in Africa, many rural communities are obliged to grow cash crops that displace gardens, and that in Latin America knowledge of the value — and pleasure — of many indigenous vegetables and fruits has been lost. Many programmes in tropical countries are now dedicated to regaining this knowledge.[1]

Even before the discovery of vitamins as essential nutrients beginning in the early 20th century, vegetables and fruits have been recommended as 'protective foods'. Early reports concerned with nutritional deficiencies paid less attention to pulses (legumes), nuts, and seeds, even though these plant foods contain protein, and nuts and seeds are nutrient- and also energy-dense, perhaps because they are not much consumed in the countries where most such reports were compiled. Instead, as already mentioned, priority was given to energy- and nutrient-dense foods of animal origin. By the 1980s, most reports concerned with prevention of chronic diseases recommended relatively high intakes of vegetables and fruits and sometimes also pulses (legumes), either because these foods were seen as nourishing substitutes for energy-dense fatty or sugary foods, or else because they were identified as positively protective against cardiovascular disease.[2] Evidence that vegetables and fruits might be protective against some cancers emerged in the 1990s.[3] A common recommendation has been for at least five portions (or at least 400 g) of vegetables and fruits a day.[4]

Non-starchy root vegetables such as carrots are included

here. Chapter 4.1 includes dietary fibre, only found naturally in plant foods. Chapter 4.1 also includes aflatoxins, which also contaminate pulses (legumes), notably peanuts, nuts and seeds, and other plant foods. The micronutrients included here, as contained in vegetables, fruits, pulses (legumes), nuts and seeds, are also found in other plant foods, and some also in animal foods.

4.2.1 Definitions, sources

Vegetables and fruits are defined in this Report by their culinary use, and are grouped for discussion below as vegetables and fruits, pulses (legumes), nuts and seeds, and herbs, spices, and condiments.

Vegetables and fruits
Vegetables are the edible parts of plants, usually including fungi. Typical examples include cultivated or gathered leaves, roots, stalks, bulbs, and flowers. Some foods are culinary vegetables but are classified botanically as fruits; these include cucumbers, peppers, squash, and tomatoes. Non-starchy vegetables are included here, while starchy root vegetables are considered in chapter 4.1. Non-starchy vegetables can be further divided into green, leafy vegetables, such as spinach and lettuce; cruciferous vegetables (the cabbage family), for example, bok choy, broccoli, cabbage, and watercress; and allium vegetables, such as onions, garlic, and leeks.

A fruit is the seed-containing part of the plant; but only those that are eaten as fruits are included in the culinary definition, for example, apples, bananas, berries, figs, grapes, mangoes, and melons. This also includes citrus fruits such as oranges, grapefruits, lemons, and limes; and also dried fruits, such as apricots, figs, and raisins.

Pulses (legumes)
Leguminous plants produce their fruits as pods and are considered here separately. The dried, edible seeds of this family are often called pulses, although this term is used interchangeably with legumes. They include beans, lentils, peas, and peanuts (groundnuts). The dried forms, which have matured and dried on the plant, are eaten most widely. But some varieties are eaten as a green vegetable, such as peas; the pods are sometimes eaten like this too, for example, green beans and runner beans. Some legumes can also be sprouted (germinated) and eaten, such as beansprouts.

Nuts and seeds
Nuts are edible seeds surrounded by a tough, dry shell. This definition includes true nuts (such as hazelnuts and chestnuts), as well as seeds that most people think of as nuts (including Brazil nuts, macadamia nuts, and cashews). Other seeds commonly eaten include sunflower, sesame, pumpkin, and poppy seeds. Nuts and seeds are processed for their oil, ground into pastes, used as ingredients, or eaten raw or roasted as snack foods. Cereals (grains) are also the seeds of plants, but these are discussed separately in this Report (see chapter 4.1). Seeds, like nuts, have a relatively high oil

Box 4.2.1   Micronutrients and other bioactive compounds and cancer risk

Vegetables, fruits, pulses (legumes), nuts, and seeds are sources of a wide variety of micronutrients and other bioactive compounds. Foods containing several of these constituents have been identified in the systematic literature reviews, on which this chapter is based, as being associated with cancer risk. These are carotenoids (including beta-carotene and lycopene), folate, vitamin C, vitamin D, vitamin E, quercetin, pyridoxine, and selenium. Mechanisms by which they might affect cancer risk are discussed in chapter 4.2.5. However, it is not possible to ascribe the association between these foods and lower cancer risk to a causal effect of specific compounds with confidence, as each food contains a complex mixture of different constituents, all of which might also contribute to any effect.

Carotenoids are found in varying concentrations in all vegetables, particularly those that are red or orange. They are a family of more than 600 fat-soluble red/orange pigments that comprise xanthophylls (such as lutein) and carotenes (such as alpha- and beta-carotene, and lycopene). Some carotenoids, most importantly beta-carotene, can be converted by the body to retinol and are sometimes called pro-vitamin A carotenoids. These compounds tend to be the main dietary source of vitamin A in low-income countries.

Only about half of the 50 or so carotenoids in human diets can be absorbed. They have antioxidant and other bioactivities that are discussed in chapter 4.10. Sources of carotenoids include spinach, kale, butternut squash, pumpkin, red (bell) peppers, carrots, tomatoes, cantaloupe melon, and sweet potatoes.

Beta-carotene is found in yellow, orange, and green fruits and green, leafy vegetables including carrots, spinach, lettuce, tomatoes, sweet potatoes, broccoli, cantaloupe melon, oranges, and winter squash (pumpkin).

As a rule of thumb, the greater the intensity of the colour of the fruit or vegetable, the more beta-carotene it contains.

The most concentrated source of lycopene is tomatoes, but it is also present in watermelon, red (bell) peppers, pink or red grapefruit, pink-fleshed guava, and persimmons.

The B-vitamin folate is a family of compounds essential for human health. Folic acid, the synthetic form, is used to fortify manufactured cereal products, spreads, and, in some countries, flour or grains. Folates are involved in a number of metabolic pathways, especially in the synthesis of purines and pyrimidines, which are important for DNA synthesis and cell replication (also see chapter 4.2.5.4). Sources of dietary folate include liver, beans, spinach, broccoli, romaine lettuce, chicory, oranges, and papaya.

Vitamin C (ascorbic acid) is a water-soluble vitamin. Humans, like a small number of other animals, cannot synthesise vitamin C, so it is an essential part of diets. Vitamin C is essential for collagen synthesis and also has antioxidant activity. Severe deficiency causes scurvy. It is added to many foods, including bread and soft drinks, in small amounts as an antioxidant preservative. Natural dietary sources are vegetables, tubers, and fruits, including red/yellow (bell) peppers, kiwi fruits, broccoli, papaya, citrus fruits, strawberries, and potatoes, but it is destroyed by heat or contact with the air (for instance, when vegetables are chopped), or lost into cooking water.

Vitamin E is a fat-soluble vitamin and a potent antioxidant that occurs as eight different forms: alpha- and gamma-tocopherol are the most common. The most important dietary sources of vitamin E are vegetable oils such as palm, sunflower, corn, soya bean, and olive oils. Nuts, sunflower seeds, and wheatgerm are also sources. Wholegrains, fish, peanut butter, green, leafy vegetables, and fortified

breakfast cereals also contain this vitamin.

Pyridoxine is one of a group of water-soluble compounds collectively known as vitamin B6. This vitamin is involved in neurotransmitter synthesis, red blood cell formation and function, niacin (vitamin B3) formation, steroid hormone function, and nucleic acid synthesis (also see chapter 4.2.5.5).[15] Food sources include bananas, fish, poultry, liver, potatoes eaten with the skin, green, leafy vegetables, beans, pulses (legumes), nuts, wholegrains, and fortified breakfast cereals.

Selenium is a mineral element that occurs in different chemical forms. It is toxic in large amounts, but is essential in the diet at trace levels. It is present at varying concentrations in different soils; and since plants take up selenium from the soil, these levels determine the amount present in vegetables. Thus selenium deficiency is more prevalent in regions where the soil selenium content is low. Selenium is a component of the amino acids selenocysteine and selenomethionine, which are integrated into proteins to form selenoproteins. Selenoproteins include antioxidant enzymes such as glutathione peroxidases, thioredoxin reductase, which is important for DNA synthesis, and iodothyronine deiodinase, which is important for the synthesis of thyroid hormones.[16] Dietary sources of selenium include brazil nuts, fish, wholegrains, wheatgerm, and sunflower seeds.

Quercetin is a flavonoid, which is a type of polyphenol; it is not an essential dietary component. Many studies in cultured cells and animals suggest that quercetin has antioxidant activity, which could give rise to a range of biological activities, including reducing inflammation (also see chapter 4.2.5.9). Quercetin is found in apples, green and black tea, onions, raspberries, red wine, red grapes, citrus fruits, leafy, green vegetables, cherries, elderberries, broccoli, blueberries, cranberries, and bilberries.

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content, and the oils produced from them are considered in chapter 4.4.

Herbs, spices, and condiments

Herbs and spices, which are generally used to flavour or preserve foods, are of plant origin, although a very small number of animal products are classed as spices (such as ambergris). Definitions of herbs and spices vary, but herbs are usually the fresh or dry leaves or whole plant, while spices are produced from other parts of the plant, such as the seeds, and are usually dried.[5] Many different parts of

plants are used as herbs or spices, such as the leaves (sage, bay, or basil), stems (ginger, lemongrass), bark (cinnamon), rhizomes (ginger), roots (horseradish), flower buds (cloves), stamens (saffron), seeds (mustard, cumin), kernels (nutmeg), and fruits (peppers).

A condiment is a substance that adds taste to other foods; the term is often used for sauces added at the table, which are usually of plant origin. Examples include vinegars, ketchups, chutneys, harissa, mustard, and soy sauce. Salt is neither a herb nor a spice, although it is used as a condiment (see chapter 4.5).

4.2.2   Composition

Vegetables and fruits

The composition of fruits and vegetables depends both on species and on subtype, as well as on the environmental, farming, production, and storage conditions. These include factors such as sun exposure, soil quality, agricultural practices, harvesting time, ripeness, length of time between harvest and consumption, and preservation and preparation methods. For instance, the outer leaves of lettuces can have higher levels of some micronutrients than the inner leaves; and harvested, unripe fruit that ripens in transit may have lower levels of nutrients than fruits ripened on the plant (box 4.2.1).[6]

Vegetables and fruits contain vitamins, minerals, dietary fibre, and other bioactive compounds, such as phytochemicals (box 4.2.2). This is a collective term for a variety of plant components that often perform important functions in the plant, such as providing colour, flavour, or protection, but are not essential in the human diet. They include salicylates, flavonoids, glucosinolates, terpenes, lignans, and isoflavones. All of these groups of compounds have been shown either in humans or in laboratory experiments to have potentially beneficial health effects when they are included in diets. However, the bioavailability of these compounds is variable (box 4.2.3) and their ultimate heath effects uncertain.

Plant cell walls are the main source of dietary fibre, and all whole fruits and vegetables (but not their juices) contain varying amounts of fibre (box 4.2.4). Most vegetables and fruits are low energy-dense foods, although there are exceptions, for example, avocados, nuts, and seeds.

Some families of fruits and vegetables have characteristic components that may confer a particular health benefit (or risk) to the whole family. For instance, cruciferous vegetables are sources of glucosinolates and their products isothiocyanates and indoles. Allium vegetables and others, such as chicory and Jerusalem artichokes, store energy as inulin (chains of fructose sugars) rather than starch (chains of glucose sugars). The body cannot digest inulin, which is called a prebiotic — a substance that is claimed to have health benefits by promoting the growth of certain types of gut bacteria. Allyl sulphides and allicin in garlic are distinctive flavour molecules that give vegetables of the onion family their 'sting' (box 4.2.3). Green, leafy vegetables are sources of folate, and tomatoes have high levels of lycopene. All of these components, as well as other phytochemicals (box

Foods containing dietary fibre

The concept of dietary fibre arose from observations of the low prevalence of colon cancer, diabetes, and coronary heart disease in parts of Africa amongst people whose diets were high in unrefined carbohydrates and whose stools were typically bulky, and often or sometimes semisolid. Considerable efforts have been dedicated to characterising the dietary components of what has come to be called dietary fibre that might confer health benefit. Naturally occurring dietary fibre is only derived from plant foods. Pulses (legumes) and minimally processed cereals are particularly concentrated sources, but vegetables and fruits also contain significant amounts. Dietary fibre isolated from plant cell walls and synthetic forms are increasingly entering the food supply.

High intakes of dietary fibre, variously defined, have been associated with reduced risk of cardiovascular disease as well as of some cancers. Definitions of dietary fibre vary. Some are based on chemical analyses of the components of plant cell walls, such as non-starch polysaccharide, others on physiological effects — the carbohydrates that enter the large bowel having escaped digestion in the small intestine being defined as dietary fibre. The latter definition includes oligosaccharides and resistant starch. The World Health Organization and Food and Agriculture Organization have recently proposed that only polysaccharides which form part of plant cell walls should be regarded as dietary fibre and that the health benefits of resistant starch and oligosaccharides are more appropriately considered separately.

This box also appears as box 4.1.2 in the previous section

4.2.2), have been shown to have potentially beneficial effects in laboratory experiments, as detailed in the evidence in chapter 4.2.5 (also see Chapter 2).[7-9]

Pulses (legumes)

Dry pulses are seeds and are higher in protein than most other plant foods. Soya beans and peanuts contain 37 g per 100 g and 26 g per 100 g protein dry weight respectively, although, on average, pulses contain around 20 g per 100 g protein dry weight.[10] These foods are typically high in carbohydrates and non-starch polysaccharides (dietary fibre), and are generally low in fat. Soya beans and peanuts are exceptions, being relatively high in fat with 8 g per 100 g and 47 g per 100 g fat, respectively (mostly mono- and polyunsaturated fatty acids). They also contain oligosaccharides that are not digested in the gut but are fermented by bacteria in the colon. Soya beans are distinct from other legumes in that they have a high content of bioactive isoflavones, or phytoestrogens, which have hormone-like effects in the body. They are also good sources of saponins and phytosterols, which decrease cholesterol absorption. Many legumes contain deguelin, which has been shown to have anti-tumour effects in laboratory experiments.[11] Most pulses are virtually indigestible and inedible before cooking; immature legumes that are eaten green have higher levels of sugar and lower levels of non-digestible polysaccharides than dried pulses.

Nuts and seeds

Other seeds and nuts are also relatively high in protein and fat; some contain as much as 60 g fat per 100 g. They are therefore energy-dense foods (see Chapter 8), as well as being nutrient-dense. Weight-for-weight, nuts provide more calories than either meat or cereals (grains), although chestnuts are the exception as they are relatively low in fat. Most nuts contain mainly monounsaturated fatty acids, although the exceptions are coconuts, which contain a high proportion of saturated fatty acids, and walnuts and pecans, which contain mostly polyunsaturated fatty acids (see chapter 4.5.2). Nuts and seeds are high in dietary fibre (box 4.2.4), especially when they are eaten with their skins or hulls; the fibre content is typically 5–11 g per 100 g. Nuts and seeds are also high in vitamins and minerals, particularly the B vitamins, vitamin E, and folate; and the seed coats contain phenolic compounds.

Herbs and spices

Nearly all herbs and spices contain aromatic compounds, which are volatile molecules that are usually fat- rather than water-soluble. The flavour compounds may make up as much as 15 g per 100 g of a spice by weight, although herbs contain much lower levels — typically around 1 g per 100 g. Many plants have evolved to contain these compounds because they act as deterrents to herbivores. Some of these aromatic compounds may be bioactive, although possibly not at the levels found in most diets. Isothiocyanates are responsible for the spicy/hot flavour of mustard and horseradish, produced from glucosinolates in cruciferous plants. Chives and garlic (allium vegetables) contain the distinctive sulphides discussed above. Terpenoids are common components in herbs and spices, providing distinctive flavours. Examples include monoterpenes, such as geranial in lemon grass, and linalool in bergamot; sesquiterpenes, such as bisabolene in ginger; triterpenoids, such as the saponin glycrrhizic acid, found in liquorice root; and tetraterpenoids, such as the carotenoid, lycopene.

4.2.3 Consumption patterns

Fruits and vegetables

The global average for vegetable consumption (based on availability and not including vegetable oils) is 2.6 per cent of total daily energy intake.[17] It is generally highest in North Africa, the Middle East, parts of Asia, the USA and Cuba, and in southern Europe. Although consumption levels are similar in countries of high and low economic status, vegetables represent a greater proportion of daily energy intake in the low-income countries. Intakes range from 5.3 per cent in parts of Asia to as little as 0.2 per cent in sub-Saharan Africa. On average, the availability of vegetables is increasing globally.

The global average for fruit consumption (based on availability) is 2.7 per cent of total daily energy intake. Fruit consumption is generally higher than vegetable consumption, but it shows a greater degree of variability. Fruit consumption is higher in high-income countries, although it represents a similar percentage of total available dietary energy

to that seen in low-income countries. Intakes are highest in some parts of Africa, the Middle East, southern Europe, and Oceania, and lowest in other parts of Africa and Asia. Fruit consumption also tends to be low in north-eastern Europe. Intakes range from as much as 20 per cent of daily energy in parts of Africa to as little as 0.5 per cent in parts of Asia. The availability of fruit has increased globally in recent decades, although there was a slight decrease in the 1990s.

Most countries have national recommendations for the daily amount of vegetables and fruits that need to be eaten to maintain optimal health (Chapter 10). These vary, but they tend to recommend three or more servings per day of vegetables and two or more servings per day of fruits; a serving is about 80 g (or half a US cup). In most high-income countries for which data were available, daily consumption of vegetables fell short of this target, although this is not due to lack of availability; indeed, availability is high due to the wide use of refrigeration. Fruit consumption tended to be closer to national targets. Seasonal availability influences overall availability, although less so in high-income countries where vegetables and fruits are more likely to be imported.

Pulses (legumes)

Globally, pulses supply 2 per cent of total energy intake (based on availability) and 3.5 per cent of daily protein intake.[17] The highest availability is in parts of Africa, South America, Asia, and the Middle East. In these areas, pulses are a dietary staple, and can account for as much as 20 per cent of daily energy intake and 50 per cent of protein intake. In societies with high intakes of meat and other foods of animal origin, pulses are less important in diets, and are usually consumed infrequently or in small amounts. Peanuts and soya beans account for most of the legume products eaten around the world.

Soya bean availability per person represents 0.5 per cent of daily energy intake globally, but it is notably high in parts of Asia, and higher than average in parts of Africa and Central America. In parts of Asia, soya beans account for up to 4.9 per cent of daily energy availability and 15 per cent of protein.

Pulses are eaten in a variety of ways around the world; for instance, Japanese and Chinese bean curd (tofu), Chinese mung bean sprouts, Mexican chilli and refried beans, Indian dahl, Middle Eastern falafel and hummus, Indonesian cultured soya bean cakes (tempeh), Cuban black beans and rice, Boston baked beans, French cassoulet, Brazilian feijoada, Swedish pea soup, and US peanut butter. Soya beans are particularly versatile and their products are a common feature in manufactured foods, although they are not commonly eaten whole. Soya foods include soya drinks and flour, tofu, tempeh, textured vegetable protein, and the many products that can be prepared from these foods. Fermented soya beans produce soy sauce and miso. Soya bean oil is also used widely (see chapter 4.5.3).

Nuts and seeds

Nuts and seeds were an important part of human diets before the advent of agriculture and they remain locally important in a few areas. Globally, tree nuts supply 0.4 per cent of daily

energy availability. The highest availability is in the Middle East and parts of Europe, and the lowest is in South America and parts of Africa; intakes range from 3 per cent of total energy in parts of the Middle East to virtually zero in many low-income countries.

Coconuts represent 0.5 per cent of daily energy availability globally, although coconuts can be locally important in tropical islands, for instance in parts of Oceania, Asia (Sri Lanka and Indonesia), the Caribbean, and in the African islands. In parts of Oceania, for example, coconuts provide as much as 20 per cent of energy in the diet.

Sunflower, rape, mustard, and sesame seeds together supply 0.2 per cent of daily energy intake globally. There are fewer data available for seeds than for many other foods, although sesame seed intake is relatively high in parts of Africa and Asia, providing a maximum of 3.9 per cent of energy in parts of central Africa. Oils from seed crops are widely used (see chapter 4.5.3).

Herbs, spices, and condiments

Although spices are consumed in small amounts to flavour food, they are such a regular feature of some diets that they account for a measurable quantity of daily energy intake. Worldwide, spices provide 0.3 per cent of available dietary energy and in parts of Asia they constitute as much as 1.8 per cent. Herbs and spices tend to be part of the traditional diet in the areas from which they originate, and many traditional cuisines are characterised by the use of herbs, spices, and condiments. Most are now available worldwide, although their use still varies greatly in different parts of the world. Many herbs and spices are believed to have medicinal or tonic value and have been used in this way at least since the times of the earliest medical records. Many modern pharmaceuticals are derived from herbs and other plants.

Many herbs and some spices are biologically very potent: the modern pharmacopoeia lists drugs, many of which have been isolated from herbs, sometimes known as 'plants with healing powers'. There are some in vivo experimental data for potentially beneficial effects in the cases of turmeric, saffron, ginger, pepper, garam masala (a herb and spice mix), and also eugenol and myristin, constituents of a number of herbs and spices.

Conversely, it is at least theoretically possible that some condiments have adverse effects. Two examples are hot chilli juices and harissa, a fiery condiment; both are consumed in substantial quantities in Mexico and the Mahgreb countries of North Africa, respectively, and both irritate the mouth and throat.

4.2.4 Interpretation of the evidence

4.2.4.1 General

For general considerations that may affect interpretation of the evidence, see chapter 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7.

'Relative risk' (RR) is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.2.4.2 Specific

Considerations specific to vegetables, fruits, pulses (legumes), nuts, seeds, herbs, and spices include:

Patterns and ranges of intake. Most studies of consumption of vegetables, fruits, and pulses (legumes) have been conducted in populations that have relatively homogeneous diets. The limited data on nuts, seeds, herbs, spices, and condiments come mainly from a few human case-control studies and some experimental animal studies.

Classification. There is no general agreement on classification. Some studies have included cereals such as corn, and tubers such as potatoes, as vegetables, and plantains as fruit. Broccoli and green peppers are included as 'green vegetables' in some studies, while only leafy greens are included in this category in others; tomatoes are considered 'yellow-orange vegetables' in some but not in others. Some studies report results only for broad categories (for example, 'all vegetables' or 'all fruits'), whereas others have reported results for more narrowly defined categories (for example, 'raw vegetables', 'green vegetables', 'citrus fruits') or for individual food items (for example, 'spinach', 'carrots', 'tomatoes'). In some studies, vegetables and fruits have been categorised according to botanical classification; in others, categorisation has been according to culinary usage. In this report, the terms 'vegetables' and 'fruits' are used according to their culinary definition. Some studies have included pulses as vegetables whereas others have classified these as a separate entity or not at all. Many older studies have not differentiated between retinol and carotenoids. Vitamin E intakes are difficult to quantify since much comes from the vegetable oils used in food preparation, and intakes within populations are usually homogenous because of the widespread occurrence of vitamin E in commonly consumed foods.

Measurement. Assessment of selenium intake is problematic because the content of selenium in foods depends to a large extent on the soil selenium content of the area in which the foods were grown. Blood and toenail levels of selenium are thought to be fairly accurate indicators of intake and have been used in several studies.

Confounding. Smokers consume fewer vegetables and fruits than non-smokers.[18] [19] Fat intake inversely correlates with vegetable and, particularly, fruit intake in the USA.[20] Recent studies of the effects of fruits and vegetables in cancers thought to be caused by smoking have controlled for the effect of smoking. Folate intake is correlated with intake of non-starchy polysaccharide (dietary fibre).

Reporting bias. Studies using self-reporting tend to over-report vegetable and fruit consumption. Where an effect exists, results from such studies are liable to underestimate the extent to which vegetables and fruits modify the risk of cancer.

4.2.5 Evidence and judgements

The full systematic literature review (SLR) is contained on the CD included with this Report.

4.2.5.1 Non-starchy vegetables
Mouth, pharynx, and larynx

Thirty-one case-control studies[21-50] and 3 ecological studies[51-53] investigated non-starchy vegetables and mouth, pharynx, or larynx cancers; 1 cohort study[54] and 6 case-control studies[33 39 45 55-57] investigated non-starchy vegetables and fruits; 23 case-control studies investigated raw vegetables[24 27 28 33 36-43 45 47 50 58-65]; 1 cohort study,[66] 14 case-control studies,[24 26-29 39 41 43 45-47 50 63 67] and 1 ecological study[68] investigated cruciferous vegetables; 1 cohort study[66] and 10 case-control studies[24 26-29 39 47 61 67 69] investigated green, leafy vegetables; 3 cohort studies[66 70 71] and 18 case-control studies[23 24 26-29 39 41-43 46 49 50 63 65 72-75] investigated carrots; and 1 cohort study[66] and 12 case-control studies[26-29 39-43 46 50 58 62 65] investigated tomatoes.

Non-starchy vegetables

Most studies showed decreased risk with increased intake of non-starchy vegetables. Twenty-two studies reported comparisons of high against low intake (figure 4.2.1).[22 23 25 26 29-31 33 35-46 49 50] Of these, 19 showed decreased risk for the highest intake group,[22 25 26 30 31 33 35-44 46 49 50] which was statistically significant in 13.[22 25 30 31 35 37 38 40 42 43 46 49 50] The other 3 studies showed non-significant increased risk.[23 29 45]

Figure 4.2.1 — Non-starchy vegetables and mouth, pharynx, and larynx cancer; case-control studies

Relative risk (95% CI)

Study	Relative risk (95% CI)
Notari 1987	0.42 (0.25–0.71)
Franco 1989	1.70 (0.92–3.16)
Oreggia 1991	0.19 (0.05–0.68)
Franceschi 1991	0.80 (0.55–0.68)
Franceschi 1992	0.40 (0.20–0.80)
Zheng 1993	1.73 (0.79–3.78)
Kune 1993	0.30 (0.11–0.85)
De Stefani 1994	0.40 (0.19–0.85)
Takezaki 1996	0.80 (0.59–1.08)
Esteve 1996	0.61 (0.45–0.81)
Levi 1998	0.14 (0.08–0.23)
De Stefani 1999	0.50 (0.29–0.87)
Franceschi 1999	0.50 (0.33–0.76)
De Stefani 1999	0.57 (0.30–1.08)
Garrote 2001	0.78 (0.40–1.52)
Bosetti 2002	0.17 (0.11–0.27)
Marchioni 2003	0.86 (0.54–1.38)
Lissowska 2003	0.17 (0.07–0.27)
Rajkumar 2003	0.44 (0.28–0.69)
Sanchez 2003	0.54 (0.34–0.86)
Gaud 2004	1.40 (0.71–2.76)
De Stefani 2005	0.60 (0.33–1.10)

Relative risk, highest vs lowest exposure category

Figure 4.2.2

Non-starchy vegetables and mouth, pharynx, and larynx cancer; case-control studies

	Relative risk (95% CI)
De Stefani 1994	0.53 (0.26–1.09)
Levi 1998	0.62 (0.53–0.74)
De Stefani 2000	0.82 (0.64–1.05)
Bosetti 2002	0.75 (0.70–0.81)
Summary estimate	0.72 (0.63–0.82)

Relative risk, per 50 g/day
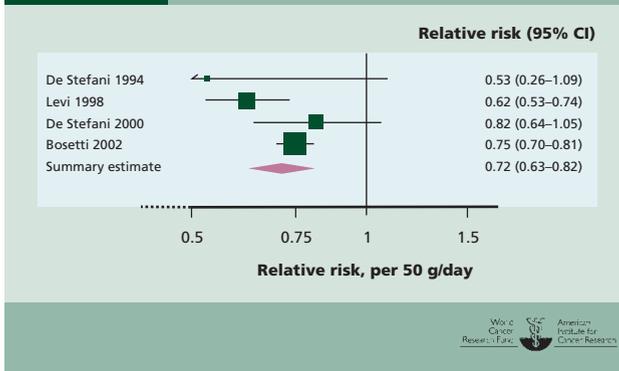
Figure 4.2.3

Non-starchy vegetables and mouth, pharynx, and larynx cancer; case-control studies: dose response

De Stefani 1994

Levi 1998

De Stefani 2000

Bosetti 2002

Non-starchy vegetables (g/day)
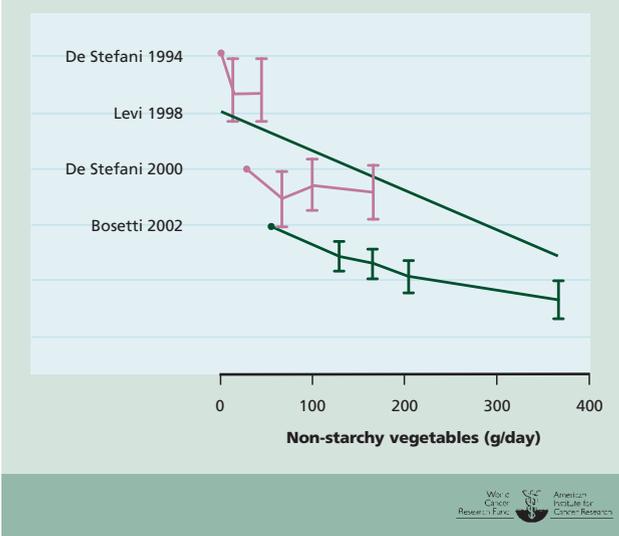
The remaining studies showed no consistent association, probably due to varying exposure definitions and study design.[21 24 27 28 32 34 47 48] Meta-analysis was possible on 4 case-control studies, giving a summary effect estimate of 0.72 (95% confidence interval (CI) 0.63–0.82) per 50 g/day, with moderate heterogeneity (figure 4.2.2). All studies adjusted for sex, smoking, and alcohol consumption.

A dose-response relationship is apparent from the four case-control studies that could be meta-analysed (figure 4.2.3). There is some suggestion that the greatest effect appears to be with the first increment. That is, any increase above the lowest levels of vegetable consumption confers a protective effect. However, it is not clear that the effect continues in a linear fashion with increased dose.

Of the three ecological studies, one (Hong Kong) study found a significant negative association between vegetable consumption and cancer incidence[51]; the other two

(international) found no significant association with cancer mortality.[52 53]

Non-starchy vegetables and fruits
A cohort study that reported results for non-starchy vegetables and fruits in combination reported a statistically significant protective effect in the highest consumers (0.55, 95% CI 0.32–0.95).[54] All six case-control studies looking at the same exposure group reported reduced risk estimates in similar comparisons,[33 39 45 55-57] which were statistically significant in four.[33 39 55 57] All of these studies adjusted for smoking and alcohol consumption.

Raw vegetables
Twenty-three case-control studies reported separate risk estimates for raw vegetable consumption.[24 27 28 33 36-43 45 47 50 58-65] All of these reported comparisons of risk between high and low intake groups, which produced reduced risk estimates in 22[24 27 28 33 36-43 45 47 50 58 60-65]; 16 of these were statistically significant.[24 33 36-40 42 43 47 50 60-63 65] No studies reported statistically significant increased risk estimates. Meta-analysis of 7 case-control studies gave an effect estimate of 0.71 (95% CI 0.59–0.86) per 50 g/day, with moderate heterogeneity.[37 39 42 45 59 62 65] These studies also provided evidence of a dose-response relationship. The heterogeneity could be partially explained by variable exposure definitions. These results are consistent with data for non-starchy vegetables.

Cruciferous vegetables
One cohort study,[66] 14 case-control studies,[24 26-29 39 41 43 45-47 50 63 67] and 1 ecological study[68] reported separate risk estimates for cruciferous vegetable consumption.

The single cohort study showed a non-significant increased risk for increased intake of cauliflower and a non-significant decreased risk for cabbage.[66] Four case-control studies showed statistically significant decreased risk with increased intake, either overall or in specific subgroups.[24 29 43 47] One study showed statistically significant increased risk associated with eating kimchi or pickled cabbage.[67] The other nine studies showed inconsistent and non-significant associations.[26-28 39 41 45 46 50 63] The ecological study showed a statistically significant decreased risk.[68]

Green, leafy vegetables
One cohort study[66] and 10 case-control studies[24 26-29 39 47 61 67 69] reported separate risk estimates for green, leafy vegetable consumption.

The single cohort study showed no effect for the highest intake group of lettuce when compared to the lowest.[66] Nine case-control studies showed decreased risk with increased intake,[24 26 27 29 39 47 61 67 69] which was statistically significant in four.[24 39 61 69] One study showed non-significant increased risk.[28]

Carrots
Three cohort studies[66 70 71] and 18 case-control studies[23 24 26-29 39 41-43 46 50 63 65 72-75] investigated non-starchy root vegetables and mouth, larynx, or pharynx cancers. There was variation in the exposure classification in studies. Most

assessed carrots, but some looked at 'tubers and carrots' or 'non-starchy root vegetables' or 'yellow/orange vegetables'.

One cohort study, looking at 'tubers and carrots', reported a non-significant increased risk when comparing high against low intakes, with a wide confidence interval (1.9, 95% CI 0.6–6.0).[66] Another that reported on 'carotene-rich fruits and vegetables' found a non-significant reduced risk when comparing the highest intake group against the lowest (0.50, p value for linear trend 0.10).[70] The third, which evaluated yellow/orange vegetables in postmenopausal US women, reported a significant reduced risk for the same comparison (0.58, 95% CI 0.39–0.87).[71]

All of the 18 case-control studies reported comparisons of risk between high- and low-intake groups.[23 24 26-29 39 41-43 46 49 50 63 65 72-75] Sixteen reported reduced risk estimates,[23 26-29 39 41-43 50 63 65 72-75] 6 of which were statistically significant.[49 72 75] The other 2 were non-significant in the direction of increased risk.[24 27 28 39 43 46] The majority of studies were hospital-based and analysed carrots as a separate exposure.

Tomatoes

One cohort study[66] and 12 case-control studies[26-29 39-43 46 50 58 62 65] investigated tomatoes and mouth, larynx, or pharynx cancers.

The cohort study reported a non-significant increased risk when comparing the highest intake group against the lowest, with a wide confidence interval (1.7, 95% CI 0.8–3.7).[66]

Of the 12 case-control studies,[26-29 39-43 46 50 58 62 65] 10 reported reduced risk estimates,[26 29 39-43 46 50 58 62 65] 5 of which were statistically significant.[26 29 39 40 62] Only 2 reported an increased risk, which was non-significant.[27 28] These studies were also the only studies not to adjust for both smoking and alcohol intake.

The general mechanisms through which vegetables could plausibly protect against cancers of the mouth, larynx, and pharynx are outlined below.

Although all of the studies mentioned here adjust for smoking behaviour and nearly all adjust for alcohol, the relative risk of smoking is large (particularly when combined with alcoholic drinks). It is therefore difficult to eliminate confidently the possibility of residual confounding with ways of life associated with smoking: for instance, smokers consume fewer vegetables than non-smokers.

A substantial amount of consistent evidence on non-starchy vegetables, including specific subtypes, mostly from case-control studies, shows a dose-response relationship. There is evidence for plausible mechanisms. Non-starchy vegetables probably protect against mouth, pharynx, and larynx cancers.

The Panel is aware that since the conclusion of the SLR, two cohort[76 77] and two case-control studies[78 79] have been published. This new information does not change the Panel judgement (see box 3.8).

Oesophagus

Five cohort studies,[70 80-83] 37 case-control studies[22 40 60 84-115] and 6 ecological studies[51 52 116-119] investigated non-starchy

vegetables and oesophageal cancer. Eight case-control studies investigated vegetable and fruit consumption (combined)[95 104 107 114 120-123]; 16 case-control studies investigated raw vegetables[40 60 85 95-97 103 109 113 114 124-129]; 1 cohort study[66] and 5 case-control studies[86 93 107 124 125] investigated cruciferous vegetables; 1 cohort study[82] and 8 case-control studies[86 101 103 107 109 111 129 130] investigated allium vegetables; 1 cohort study[66] and 11 case-control studies[86 96 98 111 124 127 131-135] investigated green, leafy vegetables; 1 cohort study[66] and 9 case-control studies[58 62 109 111 113 129-132 136] investigated tomatoes.

Non-starchy vegetables

Data suggest an association with reduced risk. Of the five cohort studies, three reported decreased risk when comparing the highest intake group against the lowest, one of which was statistically significant (0.66, 95% CI 0.44–0.99, non-starchy vegetables[82]; 0.5, p value for linear trend 0.1, yel-

Figure 4.2.4   Non-starchy vegetables and oesophageal cancer; cohort and case-control studies

Relative risk (95% CI)

Cohort
Study	RR (95% CI)
Hiryama 1990	1.06 (0.91–1.24)
Yu 1993	0.66 (0.44–0.99)
Guo 1999	0.80 (0.62–1.53)
Tran 2005	1.02 (0.85–1.18)

Case control
Study	RR (95% CI)
Cook-Mozafari 1979 Men	0.85 (0.58–1.25)
Cook-Mozafari 1979 Women	0.81 (0.49–1.33)
Notani 1967	1.06 (5.70–1.64)
Brown 1968	0.70 (0.39–1.20)
Jun-lao 1989	1.50 (0.19–1.89)
De Stefani 1990	0.56 (0.31–1.02)
Ren 1991	2.57 (1.25–5.27)
Negni 1991	0.20 (0.09–0.45)
Sammon 1992	1.44 (0.62–2.10)
Ho 1994	0.60 (0.30–1.35)
Sammon 1998	2.30 (1.06–4.89)
Lauroy 1998	0.24 (0.11–3.54)
De Stefani 1999	0.50 (0.29–0.87)
Takazaki 2000	0.60 (0.45–0.78)
De Stefani 2000	0.64 (0.34–1.20)
Levi 2000	0.19 (0.11–0.33)
Nayor 2000	0.53 (0.36–0.87)
Cheng 2000	0.56 (0.22–1.34)
Bosets 2000	0.79 (0.47–1.32)
Takezaki 2001	0.81 (0.40–1.43)
Terry 2001	0.60 (0.38–5.35)
Zhany 2001	1.94 (1.22–2.85)
Chen 2002	0.62 (0.26–1.35)
Cnuk 2002	10.10 (4.42–23.09)
Xibin 2003	0.44 (0.21–0.34)
Li 2003	0.76 (0.55–1.19)
Hung 2004	0.50 (0.31–0.82)
De Stefani 2005	0.53 (0.27–1.00)
Yang 2005	0.62 (0.32–1.18)

Relative risk, highest vs lowest exposure category

Figure 4.2.5 — Non-starchy vegetables and oesophageal cancer; case-control studies

Relative risk (95% CI)

	Relative risk (95% CI)
Jun-Lao Li 1989	1.08 (1.03–1.14)
De Stefani 2000	0.81 (0.66–0.99)
Levi 2000	0.66 (0.58–0.74)
Cheng 2000	0.90 (0.74–1.11)
De Stefani 2005	0.94 (0.86–1.02)
Summary estimate	0.87 (0.72–1.05)

Relative risk, per 50 g/day
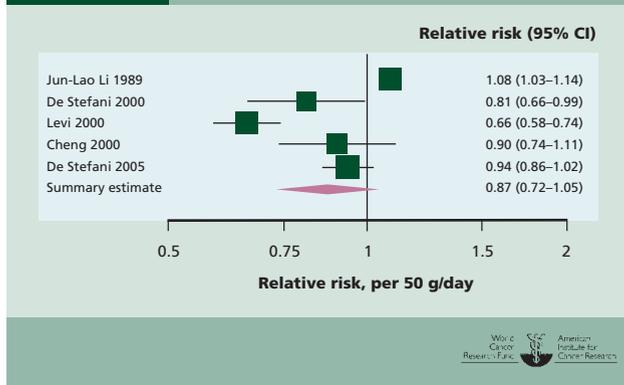
low/orange vegetables[70]; and 0.8, 95% CI 0.60–1.0 and p value for trend 0.08, stated as not statistically significant, non-starchy vegetables[80]). The other two reported a non-significant increased risk (1.06, 95% CI 0.91–1.24, non-starchy vegetables[81]; and 1.02, 95% CI 0.88–1.19, fresh non-starchy vegetables[83]) (figure 4.2.4).

Most (29) of the case-control studies published decreased risk estimates when comparing the highest intake group against the lowest,[40 60 85-90 94-99 101-105 107-109 111-115] which were statistically significant in 14 (figure 4.2.4).[40 88 89 94 97-99 101 102 104 105 109] Five studies reported statistically significant increased risk.[84 91 93 100 106 110] Meta-analysis was possible on 5 of the case-control studies, giving a summary effect estimate of 0.87 (95% CI 0. 72–1.05) per 50 g/day increment, with high heterogeneity (figure 4.2.5). A potential cause of heterogeneity is the disparate nature of the exposure definition in different studies, some of which included pickled and cured vegetables, cooked or uncooked vegetables.

Two of the ecological studies reported a statistically significant, positive association between vegetable consumption and cancer incidence[116 117]; one reported a statistically significant, negative association between vegetable consumption and cancer incidence[51]; and the other three reported no significant association between vegetable consumption and cancer mortality.[52 118 119]

The Panel is aware that data from the European Prospective Investigation into Cancer and Nutrition (EPIC; 521 457 participants from 10 European countries; 65 cases of adenocarcinomas of the oesophagus), published after the conclusion of the SLR,[140] showed a non-significant reduced risk (0.72, 95% CI 0.32–1.64) per 100 g/day increase in vegetable consumption (adjusted for several variables including smoking and alcohol, red meat, and processed meat).

Non-starchy vegetables and fruits
Eight case-control studies investigated vegetable and fruit consumption (combined) and oesophageal cancer. All reported a decreased risk with increased consumption.[95 104 107 114 120-123] Six of these were statistically significant.[95 104 107 114 120 121]

Raw vegetables
Sixteen case-control studies investigated raw vegetables and oesophageal cancer.[40 60 85 95-97 103 109 113 114 124-129]

All of these studies reported associations with decreased risk, which were statistically significant in 10.[40 60 85 95 97 109 113 126 127 129] Dose-response meta-analysis was possible on five studies, giving a summary effect estimate of 0.69 (95% CI 0.58–0.83) per 50 g/day increment (figures 4.2.6 and 4.2.7).

This exposure category could be less disparate than other vegetable groupings, as it is clear that preserved vegetables are not included and variation in cooking methods is removed. This may account for the lack of heterogeneity in direction of effect in this subcategory of vegetables.

Figure 4.2.6 — Raw vegetables and oesophageal cancer; case-control studies

Relative risk (95% CI)

	Relative risk (95% CI)
De Stefani 2000	0.38 (0.21–0.69)
Levi 2000	0.64 (0.57–0.72)
Cheng 2000	0.83 (0.68–1.02)
Sharp 2001	0.84 (0.75–0.95)
De Stefani 2003	0.60 (0.48–0.76)
Summary estimate	0.69 (0.58–0.83)

Relative risk, per 50 g/day
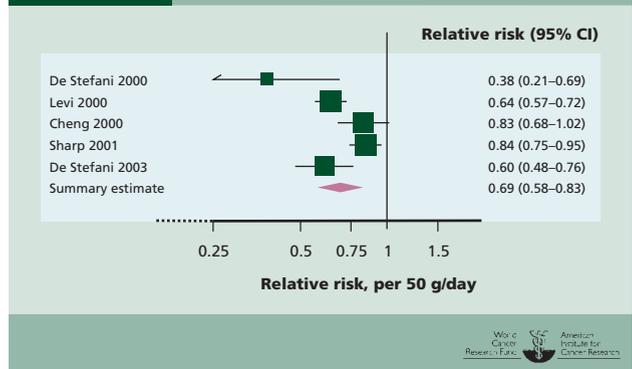
Figure 4.2.7 — Raw vegetables and oesophageal cancer; case-control studies: dose response

Castelletto 1994
Cheng 2000
De Stefani 2000
Levi 2000
Sharp 2001
De Stefani 2003

Non-starchy vegetables (g/day)
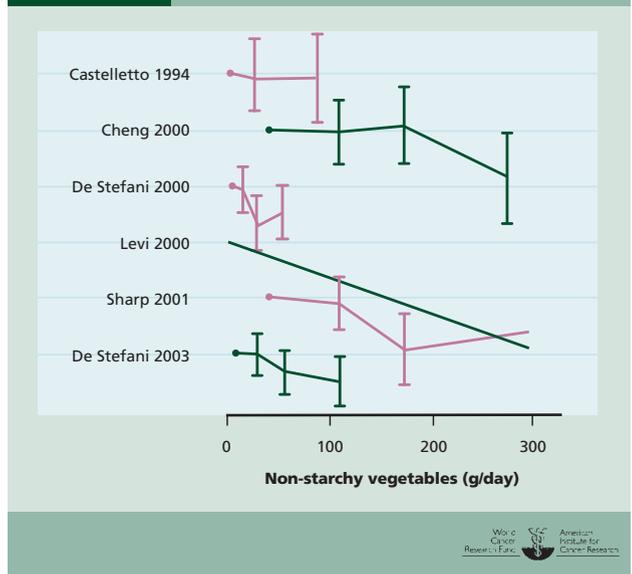
Non-starchy root vegetables and tubers

One cohort study[66] and six case-control studies[114 122 128 132 136 141 142] reported separate risk estimates for consumption of non-starchy root vegetables and tubers.

The single cohort study showed a non-significant increased risk for the highest intake group when compared to the lowest, after adjustment.[66] All six case-control studies showed non-significant decreased risk with increased intake.[114 122 128 132 136 141 142]

Cruciferous vegetables

One cohort study[66] and five case-control studies[86 93 107 124 125] reported separate risk estimates for consumption of cruciferous vegetables.

The single cohort study showed a non-significant decreased risk for increased intake of cauliflower or swede and a non-significant increased risk for cabbage, after adjustment.[66] Three case-control studies showed decreased risk with increased intake,[93 107 124] which was statistically significant in two.[93 124] One study showed a non-significant increased risk[125]; and one study showed a non-significant increased risk in women and a non-significant decreased risk in men.[86]

Allium vegetables

One cohort study[82] and eight case-control studies[86 101 103 107 109 111 129 130] reported separate risk estimates for allium vegetable consumption.

The single cohort study showed that garlic intake had no effect on risk.[82] Four case-control studies showed non-significant decreased risk with increased intake.[101 103 107 130] Two studies showed non-significant increased risk.[86 111] One study showed a statistically significant decreased risk for garlic and that onions/leeks had no effect on risk[109]; and one study showed a statistically significant reduced risk for onions and a non-significant increased risk for garlic.[129]

Green, leafy vegetables

One cohort study[66] and 11 case-control studies[86 96 98 111 124 127 131-135] reported separate risk estimates for green, leafy vegetable consumption.

The single cohort study showed no effect for the highest intake group of lettuce when compared to the lowest.[66] Ten case-control studies showed decreased risk with increased intake,[96 98 111 124 127 131-135] which was statistically significant in five.[96 127 132-134] One study showed a non-significant increased risk in women and a non-significant decreased risk in men.[86]

Tomatoes

One cohort study[66] and nine case-control studies[58 62 109 111 113 129-132 136] reported separate risk estimates for consumption of tomatoes.

The single cohort study showed a non-significant increased risk for the highest intake group of lettuce, when compared to the lowest, after adjustment.[66] Eight case-control studies showed decreased risk with increased intake,[58 62 109 111 113 129 131 132 136] which was statistically significant in two.[62 129] One study showed no effect on risk.[130]

The general mechanisms through which vegetables could plausibly protect against oesophageal cancer are outlined below.

There is more evidence, including on vegetable subtypes, from case-control studies than from cohort studies, but both are moderately consistent and there is some evidence for a dose-response relationship. There is evidence for plausible mechanisms. Non-starchy vegetables probably protect against oesophageal cancer.

The Panel is aware that since the conclusion of the SLR, one cohort[140] and two case-control studies[78 143] have been published. This new information does not change the Panel judgement (see box 3.8).

Stomach

Ten cohort studies,[71 80 140 144-150] 45 case-control studies,[109 151-195] and 19 ecological studies[51 52 116-119 196-209] investigated total vegetables. Eleven cohort studies,[71 144 150 210-218] 21 case-control studies,[89 165 169 178 179 188 191 219-232] and 8 ecological studies[233-240] investigated green-yellow vegetables; 6 cohort studies[70 140 144 146 150 241], 13 case-control studies,[162 174 175 179 180 187 223 227 229 230 232 242 243] and 2 ecological studies[202 240] investigated green, leafy vegetables; 3 cohort studies[70 146 241] and 19 case-control studies[58 109 129 152 156 164 171 172 174 232 243-251] investigated tomatoes; 2 cohort studies[150 214] and 6 case-control studies[157 165 169 226 228 243] investigated white or pale vegetables; 6 cohort studies,[146 148 214 252-254] 25 case-control studies,[109 129 161 162 167 172 174 183 184 191 219 225 226 243 247 248 250 255-264] and 3 ecological studies[202 208 238] investigated raw vegetables; 5 cohort studies[144 146 148 253 265] and 6 case-control studies[158 161 162 164 257 266 267] investigated non-starchy vegetables and fruits.

Non-starchy vegetables

Of 12 independent estimates from the 10 cohort studies that investigated non-starchy vegetable consumption, none was statistically significant.[71 80 140 144-150] Seven studies showed non-significant reduced risk[71 140 144-147 150] and 2 reported non-significant increased risk.[80 149] One study showed non-significant increased risk in women and non-significant decreased risk in men.[148] Most effect estimates were close to 1. Meta-analysis was possible on 9 independent estimates from 7 cohort studies, giving a summary effect estimate of 0.98 (95% CI 0.91–1.06) per 100 g/day, with moderate heterogeneity (figure 4.2.8).

Of 45 case-control studies that reported on non-starchy vegetable consumption, 28 reported statistically significant decreased risk.[109 151-153 156-160 163 164 168 169 171 173 176-179 181 182 184 185 187 190 192] The majority of the 17 remaining studies that reported no significant effect on risk were in the direction of decreased risk.[155 162 165-167 170 172 174 183 191 194 195] Four studies showed non-significant increased risk,[180 188 189 193] 1 study showed no effect on risk,[154] and 1 study stated that there was no significant association.[175] One study showed non-significant decreased risk in women and non-significant increased risk in men[186]; and 1 study showed statistically significant

Figure 4.2.8 Non-starchy vegetables and stomach cancer; cohort and case-control studies

Relative risk (95% CI)

Cohort
Study	Relative risk (95% CI)
Chyou 1990 Men	0.76 (0.53–1.10)
Guo 1994	1.05 (0.93–1.18)
Botterweck 1998	0.92 (0.78–1.09)
McCullough 2001 Men	0.98 (0.84–1.02)
McCullough 2001 Women	1.16 (1.00–1.34)
Fujino 2002 Men	1.12 (0.93–1.34)
Fujino 2002 Women	1.03 (0.77–1.36)
Kobayashi 2002	0.86 (0.72–1.02)
Gonzalez 2006	0.91 (0.66–1.28)
Summary estimate	0.98 (0.91–1.06)

Case control
Study	Relative risk (95% CI)
Risch 1985	0.84 (0.73–0.97)
You 1988	0.81 (0.75–0.86)
De Stefani 1990	0.40 (0.27–0.60)
Menik 1992	0.36 (0.16–0.80)
Hansson 1993	0.60 (0.46–0.79)
Cornee 1995	0.85 (0.57–1.28)
De Stefani 1998	0.39 (0.32–0.48)
Ji 1998 Men	0.86 (0.82–0.90)
Ji 1998 Women	0.94 (0.86–1.01)
Ward 1999	0.22 (0.11–0.43)
Mathew 2000	0.52 (0.18–1.46)
De Stefani 2001	0.89 (0.60–1.32)
Takezaki 2001	0.47 (0.26–0.81)
Sriamporn 2002	0.86 (0.56–1.33)
Hara 2003	1.06 (0.84–1.33)
Sipetic 2003	0.07 (0.03–0.15)
Suh 2003	1.04 (0.89–1.22)
Lagiou 2004	0.51 (0.39–0.68)
Lissowska 2004	0.90 (0.74–1.09)
Boccia 2005	1.09 (0.56–2.12)
Nan 2005	0.90 (0.66–1.25)
Summary estimate	0.70 (0.62–0.79)

0.5 0.75 1 1.5 2

Relative risk, per 100 g/day

Figure 4.2.9 Green-yellow vegetables and stomach cancer; cohort and case-control studies

Relative risk (95% CI)

Cohort
Study	Relative risk (95% CI)
Chyou 1990 Men	0.74 (0.52–1.05)
Kasum 2002 Women	0.57 (0.19–1.75)
Kobayashi 2002	0.56 (0.33–0.94)
Ngoan 2002	0.41 (0.18–0.94)
Khan 2004 Men	0.66 (0.11–3.89)
Khan 2004 Women	0.18 (0.02–2.13)
Summary estimate	0.63 (0.48–0.82)

Case control
Study	Relative risk (95% CI)
Lee 1990	0.94 (0.68–1.29)
Cai 1991	0.44 (0.38–0.50)
Negri 1991	0.24 (0.13–0.44)
Hoshiyama and Sasaba 1992	0.49 (0.32–0.74)
Ji 1998 Men	0.77 (0.69–0.86)
Ji 1998 Women	0.89 (0.77–1.04)
Ward 1999	0.33 (0.24–0.46)
Hamada 2002	1.09 (0.41–2.93)
Nishimoto 2002	0.62 (0.33–3.43)
Hara 2003	1.59 (0.73–3.43)
Ito 2003 Women	0.55 (0.38–0.81)
Lissowska 2004	0.28 (0.12–0.66)
Summary estimate	0.59 (0.46–0.75)

0.5 1 2

Relative risk, per 100 g/day

decreased risk in men and non-significant increased risk in women.[161] No studies reported statistically significant increased risk. Meta-analysis was possible on 20 studies, giving a summary effect estimate of 0.70 (95% CI 0.62–0.79) per 100 g/day, with high heterogeneity (figure 4.2.8). This heterogeneity tended to reflect differences in size, rather than direction, of effect.

A dose-response relationship was apparent from case-control but not cohort data.

Results from ecological studies reporting on non-starchy vegetable consumption were mixed, with almost as many studies reporting increased risk as reported decreased risk.[51 52 116-119 196-209]

Green-yellow vegetables
Eight of the 11 cohort studies that reported on green-yellow vegetable consumption showed decreased risk,[71 144 150 210 211 214-217] statistically significant in 4.[150 210 215 216] Two other studies showed non-significant increased risk[212 213] and 1 study reported no statistically significant association.[218]
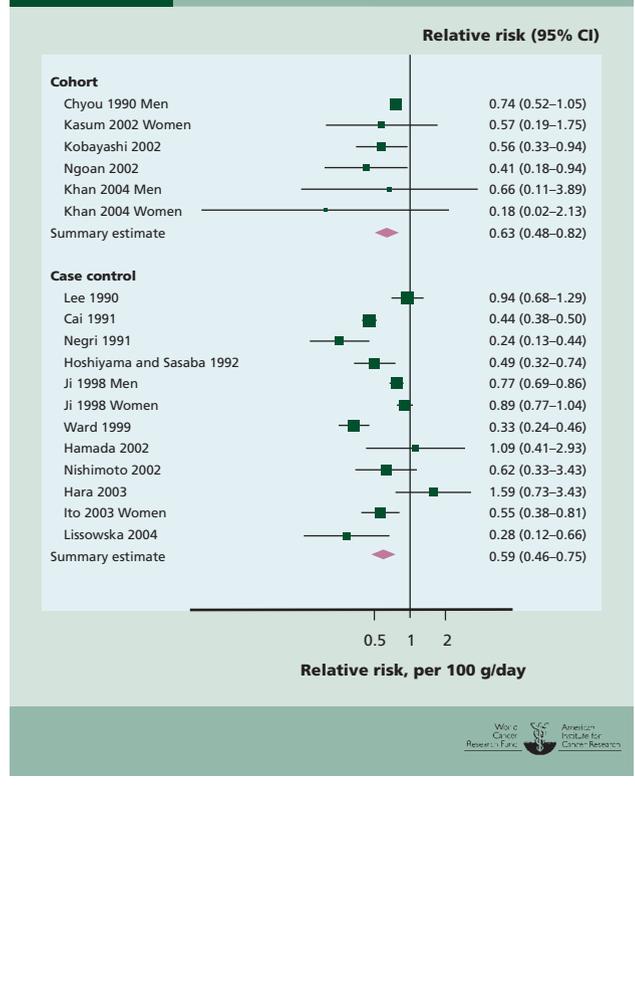
Meta-analysis was possible on 6 independent estimates from 5 studies, giving a summary effect estimate of 0.63 (95% CI 0.48–0.82) per 100 g/day, with no heterogeneity (figure 4.2.9).

Of the 21 case-control studies that reported on green-yellow vegetable consumption, 16 showed decreased risk,[89 165 169 178 179 191 219 220 222-228 230-232] statistically significant in 12.[89 165 169 178 179 191 220 222 223 226 231 232] The remaining 5 studies reported increased risk,[111 188 221 229] 1 of which was statistically significant.[221] Meta-analysis was possible on 12 independent estimates from 11 studies, giving a summary effect estimate of 0.59 (95% CI 0.46–0.75) per 100 g/day, with high heterogeneity (figure 4.2.9).

All of the studies adjusted for age and sex; none was adjusted for infection with *Helicobacter pylori*. Nine studies were maximally adjusted, seven of which reported a significant negative association with higher consumption of green-yellow vegetables, and the other two reported no significant association.

A dose-response relationship was apparent from both

Figure 4.2.10 Green-yellow vegetables and stomach cancer; cohort and case-control studies: dose response

Figure 4.2.11 White or pale vegetables and stomach cancer: cohort and case-control studies
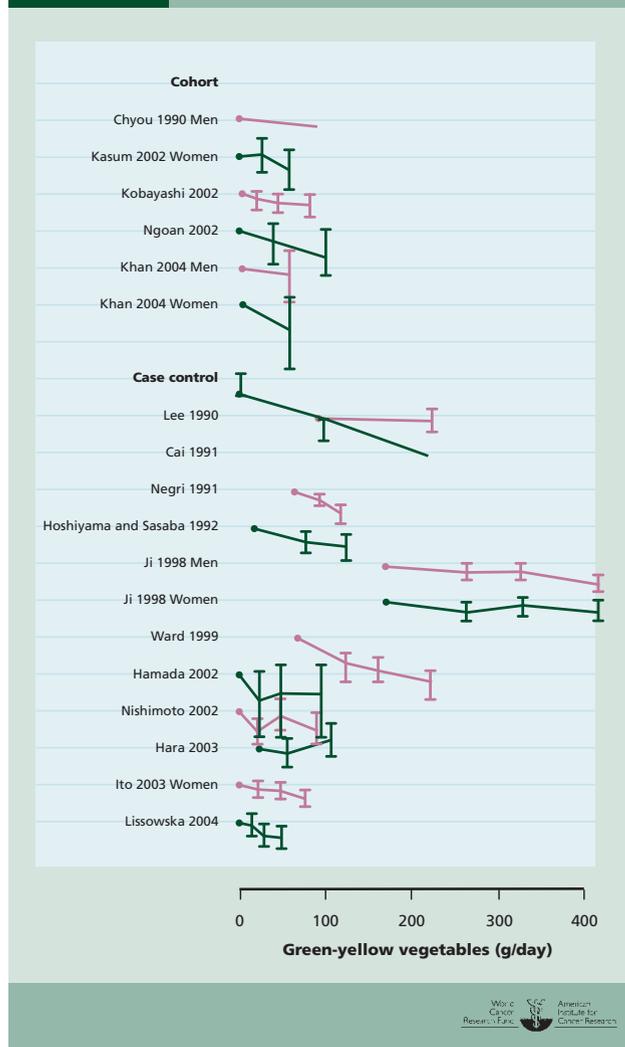
cohort and case-control data on green-yellow vegetable consumption (figure 4.2.10).

Five out of the eight ecological studies that reported on green-yellow vegetable consumption showed decreased risk with increased consumption,[236-240] two showed no association,[233 234] and one study showed increased risk.[235]

This exposure included green-yellow vegetables, green vegetables, yellow vegetables, yellow-orange vegetables, carrots and pumpkins, and high-carotenoid vegetables.

Green, leafy vegetables
Four cohort studies showed non-significant decreased risk with increased intake[70 144 146 150]; two studies showed non-significant increased risk.[140 241] Meta-analysis was possible on four cohort studies, giving a summary effect estimate of 0.85 (95% CI 0.58–1.25) per 100 g/day, with no heterogeneity.[140 144 146 150]

Nine case-control studies showed decreased risk with increased intake,[179 187 223 227 229 230 232 242 243] which was statistically significant in three,[223 232 243] and in men, but not women, in a fourth study.[227] Two further studies showed non-significant increased risk[174 180]; one study showed no effect on risk[162]; and one study stated that there was no significant association.[175] Meta-analysis was possible on six case-control studies, giving a summary effect estimate of 0.90 (95% CI 0.70–1.16) per 100 g/day, with no heterogeneity.[162 179 180 187 229 230]

One ecological study showed statistically significant decreased risk[240] with high intake, the other showed non-significant increased risk.[202]

One cohort study[146] and 15 case-control studies[152 156 164 167 172 231 243-246 261 268-271] also reported separately on lettuce and salad leaves. The single cohort study showed a non-significant decreased risk with increased intake. The effect estimate was 0.88 (95% CI 0.38–2.60) per 50 g/day.[146] Twelve case-control studies showed decreased risk with increased intake of lettuce or salad leaves,[152 156 164 167 231 243 246 261 268-271] which was statistically significant in 7.[156 243 246 261 268-270] Two studies showed non-significant increased risk.[172 245] One study showed no effect on risk.[244] Meta-analysis was possible on 5 case-control studies that investigated lettuce or salad leaves, giving a summary effect estimate of 0.43 (95% CI 0.24–0.77) per 50 g/day, with high heterogeneity.[152 231 268-270] Heterogeneity was related primarily to the size, and not the direction, of the effect.

Tomatoes
Two cohort studies showed a non-significant increased risk with increased intake.[146 241] One study stated that there was a non-significant decreased risk (unquantified).[70] The effect estimates were 1.81 (95% CI 0.85–3.85) per 100 g/day,[146] and 1.1 (95% CI 0.76–1.60) for women and 1.19 (95% CI 0.88–1.61) for men (both for the highest

Figure 4.2.12 Raw vegetables and stomach cancer; cohort and case-control studies
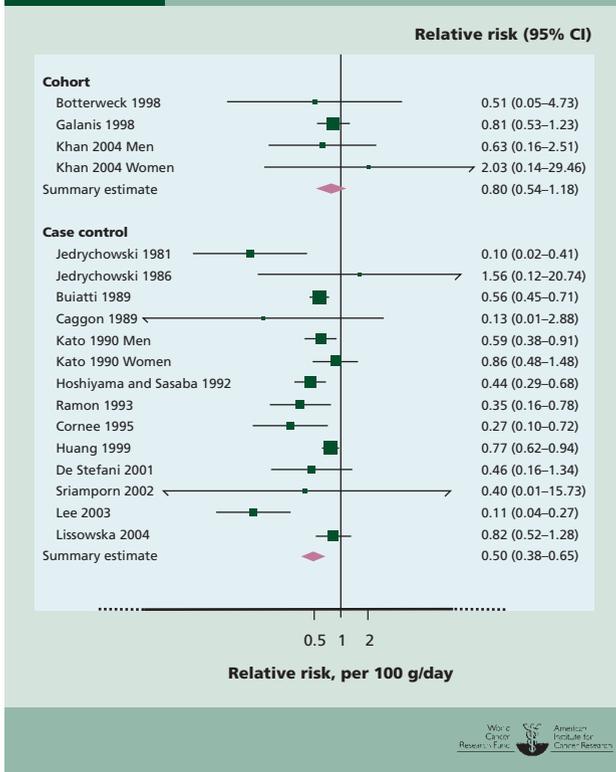
Figure 4.2.13 Raw vegetables and stomach cancer; case-control studies: dose response
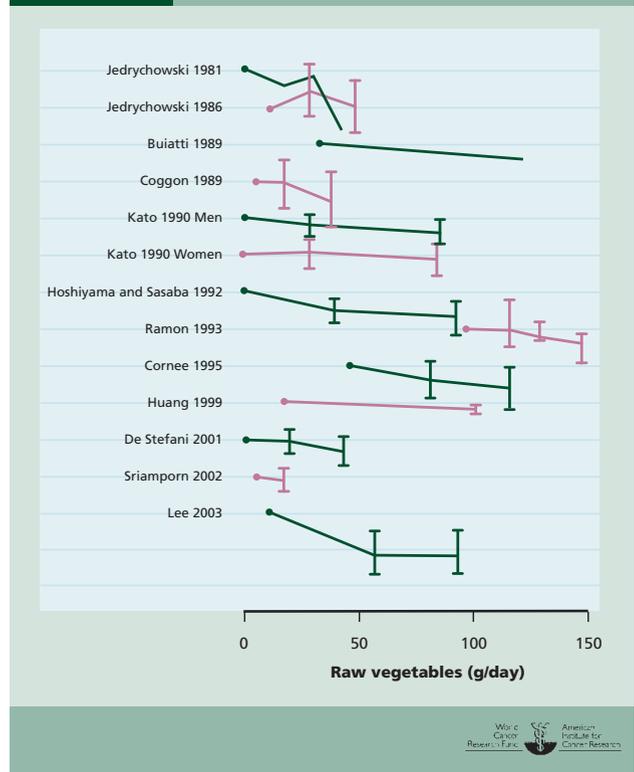
intake group when compared to the lowest).[241]

Most case-control studies showed decreased risk with increased intake, which was statistically significant in 10.[58 109 152 156 164 171 232 246-248] No studies showed statistically significant increased risk. Meta-analysis was possible on 6 case-control studies, giving a summary effect estimate of 0.40 (95% CI 0.19–0.82) per 100 g/day, with high heterogeneity.[109 152 171 232 244 250]

White or pale vegetables

This incorporates a wide range of vegetables. For example, in Japan white vegetables such as daikon (radish) are commonly consumed. Descriptions used for this exposure were white vegetables, pale green or light green vegetables, and raw chicory.

Both cohort studies showed non-significant decreased risk with increased intake.[150 214] Meta-analysis was possible on both studies, giving a summary effect estimate of 0.49 (95% CI 0.24–1.01) per 100 g/day, with no heterogeneity (figure 4.2.11).

All six case-control studies showed decreased risk with increased intake,[157 165 169 226 228 243] which was statistically significant in three.[165 169 243] Meta-analysis was possible on three studies, giving a summary effect estimate of 0.57 (95% CI 0.32–1.02) per 100 g/day, with high heterogeneity, which was caused by varying size, not direction of the effect (figure 4.2.11).

Raw vegetables

Of seven independent estimates from six cohort studies that reported on raw vegetables, four reported non-significant reduced risk,[146 214 253 254] two reported non-significant increased risk,[214 252] and the other reported a significant increased risk.[148] Two of the increased risk estimates, including the one that reached statistical significance, were stratified for women only. Meta-analysis was possible on four estimates from three studies (not including the one that was statistically significant), giving a summary effect estimate of 0.80 (95% CI 0.54–1.18) per 100 g/day, with no heterogeneity (figure 4.2.12).

Of the 25 case-control studies that reported on raw vegetables, 21 reported decreased risk,[109 129 161 162 167 172 174 183 184 191 219 225 226 243 247 248 250 255 256 258 260 261 264] which was statistically significant in 13.[129 161 172 174 225 226 243 247 248 256 260 261 264] None of the remaining 4 studies that reported increased risk reached statistical significance.[257 259 262 263] Meta-analysis was possible on 14 independent estimates from 13 case-control studies, giving a summary effect estimate of 0.50 (95% CI 0.38–0.65) per 100 g/day, with moderate heterogeneity (figure 4.2.12).

A dose-response relationship was apparent from case-control but not cohort data (figure 4.2.13).

Of the three ecological studies, two reported statistically significant reduced risk[208 238] and one reported a non-significant increased risk with increased raw vegetable consumption.[202]

Non-starchy vegetables and fruits

All five cohort studies showed decreased risk for the highest intake group when compared to the lowest,[144 146 148 253 265] which was statistically significant in two,[253 265] and in men, but not women, in a third study.[148] Meta-analysis was possible on two cohort studies, giving a summary effect estimate of 0.81 (95% CI 0.58–1.14) per 100 g/day.[146 253] All six case-control studies showed decreased risk with increased intake,[158 161 162 164 257 266 267] which was statistically significant in four.[158 162 164 257] Meta-analysis was possible on two case-control studies, giving a summary effect estimate of 0.79 (95% CI 0.63–0.99) per 100 g/day.[162 267]

The stomach is a particularly unusual chemical environment and it is possible that, in addition to the general mechanisms described below, specific mechanisms apply, for instance, in relation to nitrosamine formation.

A substantial amount of evidence is available, including on specific subtypes, particularly green-yellow vegetables, with a dose-response relationship in case-control, but not cohort data. There is evidence for plausible mechanisms. Vegetables probably protect against stomach cancer.

Nasopharynx

Five case-control studies[272-276] and two ecological studies[51 277] investigated non-starchy vegetables and nasopharyngeal cancer; a further four case-control studies investigated green vegetables.[278-281] Preserved vegetables were excluded from all categories.

Eight of the case-control studies reported reduced risk when comparing high against low intake groups,[272 273 275 276 278-281] which was statistically significant in three of the non-starchy vegetable studies[272 275 276] and in two of the green vegetable studies.[279 280] One other study stated that there was no significant association.[274] All studies were based in China.

The ecological studies produced mixed results. One showed significant correlations between the consumption of fresh vegetables and reduced risk of nasopharyngeal carcinoma after adjusting for age (r^2 = -0.77, p = 0.009 among men and r^2 = -0.75, p = 0.013 among women).[51] The second study showed an increasing risk with increases in local consumption of non-starchy vegetables (r^2 = 2.36).[277] This study did not report any adjustments for potential confounding variables or whether the finding was significant.

The general mechanisms through which vegetables could plausibly protect against nasopharyngeal cancer are outlined below.

The evidence for non-starchy vegetables is sparse but generally consistent. There is limited evidence suggesting that non-starchy vegetables protect against nasopharyngeal cancer.

Lung

Seventeen cohort studies,[282-300] 27 case-control studies,[301-331] and 6 ecological studies[52 116 332-335] investigated total vegetables and lung cancer (some studies did not separate non-starchy vegetables from this grouping); in addition, there was 1 relevant pooling project publication.[336] Three cohort studies[337-339] and 1 case-control study[321] investigated non-starchy vegetables specifically; 5 cohort studies[285 292 299 340 341] and 17 case-control studies[65 301 307 312 320-322 326 330 342-350] investigated green, leafy vegetables (excluding cruciferous); 2 cohort studies investigated non-starchy root vegetables and tubers[289 291]; and 6 cohort studies,[285 289 293 299 339 341] 21 case-control studies,[65 261 304 307 313 320-322 325-327 342 344 346-348 351-358] and 1 ecological study[333] investigated carrots specifically.

Total vegetables

Out of 19 effect estimates from 17 cohort studies, 14 showed reduced risk with higher levels of vegetable consumption,[282 283 286-289 291-297 299 300] which was statistically significant in 3[286 297 299 300] and in women only in another[285]; 1 reported no effect on risk,[298] 2 showed increased risk,[284 290] none of which was statistically significant, and 2 showed non-significant increased risk in men but not women.[285 296] Meta-analysis was possible on 10 studies, all of which adjusted for smoking, giving a summary effect estimate of 0.95 (95% CI 0.92–0.98) per 80 g serving/day, with no heterogeneity.[282 283 285-287 292 296 297 300] Two studies did not adjust for smoking, 1 of which showed a non-significant lower vegetable intake in cases than in controls,[295] and the other reported no effect on risk.[298]

Pooled analysis from 8 cohort studies (over 430 000 participants, followed up for 6 to 16 years, more than 3200 lung cancer cases) showed a non-significant reduced risk when comparing high against low intake groups (0.88, 95% CI 0.78–1.00), with a p value for trend of 0.12.[336]

Out of 27 case-control studies, 17 showed reduced risk with higher levels of vegetable consumption,[301-304 306-312 314 316 317 319 322 325-331] which was statistically significant in 8[303 304 306 308-310 314 316 319 325-328]; 7 studies showed non-significant increased risk[305 313 315 318 320 323 324] and 1 study showed no effect on risk.[321] Meta-analysis was possible on 10 studies, all of which adjusted for smoking, giving a summary effect estimate of 0.67 (95% CI 0.53–0.86) per serving/day, with high heterogeneity.[303 308 309 313 316 317 323 325 326 328 329] Three studies did not adjust for smoking, all of which showed statistically significant decreased risk.[306 316 319]

A dose-response relationship was apparent from both cohort and case-control data.

Most of the ecological studies are suggestive of an association between increased vegetable consumption and decreased risk.

Non-starchy vegetables

All three cohort studies reported non-significant reduced risk when comparing highest and lowest vegetable intakes, with effect estimates of 0.9 (lung cancer mortality, 95% CI 0.61–1.33),[337] 0.75 (95% CI 0.41–1.37),[338] and 0.54 (p value for trend 0.2, squamous and small-cell carcinomas only) when comparing the highest with the lowest intake groups.[339] The single case-control study reported a non-significant increased risk when comparing high and low vegetable intakes.[321]

Green, leafy vegetables

All five cohort studies reported reduced risk when comparing high to low intake groups,[285 292 299 340 341] which was statistically significant in one.[299] Dose-response meta-analysis was possible on three cohort studies, giving a summary effect estimate of 0.91 (95% CI 0.89–0.93) per serving/day, with no heterogeneity.[285 340] The two non-included studies reported high-versus-low effect estimates of 0.89 (95% CI 0.66–1.19)[292] and 0.45 (95% CI 0.26–0.78).[299] All five cohort studies adjusted for smoking.

Of the 17 case-control studies, 12 reported decreased risk[65 301 307 320 321 326 330 342 343 345-348] (reaching statistical significance in 2[343 345 348] and 5 reported non-significant increased risk.[312 322 344 349 350] Dose-response meta-analysis was possible on 8 case-control studies, giving a summary effect estimate of 0.96 (95% CI 0.91–1.02) per serving/day, with moderate-to-high heterogeneity.[65 322 326 343 346-349] Some of this heterogeneity may be due to variation in exposure classification, with some studies listing 'green vegetables' being included in this category.

Total non-starchy root vegetables and tubers

Both cohort studies reported reduced risk with increased consumption,[289 291] with effect estimates of 0.56 (95% CI 0.36–0.88)[289] when comparing the highest with the lowest intake groups, and 0.70 (95% CI 0.53–0.93) when comparing the third highest quartile with the lowest (the highest intake group had a non-significant decreased risk).[291] Both studies adjusted for smoking.

Carrots

All six cohort studies reported reduced risk,[285 289 293 299 339 341] which was statistically significant in one (0.4, p value for trend 0.003).[341] The other, non-significant, risk estimates ranged from 0.61 to 0.82.[285 289 293 299 339]

Twenty of the 21 case-control studies showed decreased risk when comparing high against low intake groups,[65 261 304 307 313 321 322 325-327 342 344 346-348 351-358] which was statistically significant in 8.[261 304 321 325 327 346 347 351 353 356-358] One study reported no effect.[320] Meta-analysis on studies that adjusted for smoking was possible on 11 studies, giving a summary effect estimate of 0.81 (95% CI 0.73–0.89), per serving/day increment, with high heterogeneity.[65 307 313 322 325-327 347 348 351 352 354-357]

There was some evidence of publication bias for both cohort and case-control studies.

The single ecological study reported lower mean intake of carrots in an area of high lung cancer risk.[333]

The general mechanisms through which vegetables could plausibly protect against lung cancer are outlined below.

> **A substantial amount of evidence is available but some studies were not adjusted for smoking. A dose-response relationship is apparent from both cohort and case-control studies. There is limited evidence suggesting that non-starchy vegetables protect against lung cancer.**

Colorectum

Seventeen cohort studies[81 359-379] and 71 case-control studies investigated non-starchy vegetables and colorectal cancer.

Of 20 effect estimates from 17 cohort studies that reported comparisons of the highest and lowest intake groups, 11 were in the direction of reduced risk,[81 362 364 366 371-374 376-378] 3 of which were statistically significant.[81 366 371 377] One study showed non-significant decreased risk in women and non-significant increased risk in men.[360] The other 8 reported non-significant increased risk.[359 361 363 365 367-370 375] One study stated that there was no significant association.[379] Meta-analysis was possible on 9 independent estimates from 6 studies, giving a summary effect estimate of 1.00 (95% CI 0.90–1.11) per 2 servings/day increment, with moderate to high heterogeneity.[360 362-364 366 370]

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

The general mechanisms through which vegetables could plausibly protect against colorectal cancer are outlined below.

> **A substantial amount of evidence is available but it is inconsistent. There is limited evidence suggesting that non-starchy vegetables protect against colorectal cancer.**

The Panel is aware that since the conclusion of the SLR, three case-control studies[78 261 380] have been published. This new information does not change the Panel judgement (see box 3.8).

Ovary

Five cohort studies,[381-385] eight case-control studies,[89 386-392] and two ecological studies[393 394] investigated non-starchy vegetables, and three cohort studies[381-383] and two case-control studies[395 396] investigated green, leafy vegetables.

Non-starchy vegetables

All of the cohort studies reported decreased risk with increased vegetable consumption.[381-385] Meta-analysis was possible on four cohort studies, giving a summary effect estimate of 0.64 (95% CI 0.33–0.97) for an increase of one serving/day, with no heterogeneity.[381 383-385] The study that could not be included reported an effect estimate of 0.76 (95% CI 0.42–1.37) for the highest intake group when compared with the lowest.[382]

Pooled analysis from 12 cohort studies (over 560 000 participants, followed up for 7 to 22 years, more than 2100 lung cancer cases) showed a non-significant reduced risk when comparing high against low intake groups (0.90, 95% CI 0.78–1.04), with a p value for trend of 0.06.[397]

All of the case-control studies reported reduced risk,[89 386-392] which was statistically significant in five.[89 386 387 391 392]

One ecological study reported a non-significant positive regression/correlation between continents[393] and the other reported a negative regression/correlation between countries.[394]

Green, leafy vegetables

All three cohort studies reported decreased risk with increased green, leafy vegetable consumption.[381-383] Meta-analysis was possible on two cohort studies, giving a summary effect estimate of 0.96 (95% CI 0.88–1.03) per two servings/day, with no heterogeneity.[381 383] The third cohort study reported a statistically significant reduced risk (0.44, 95% CI 0.25–0.79) when comparing the highest and lowest intake groups.[382]

Both case-control studies reported reduced risk from increased consumption of green, leafy vegetables,[395 396] one of which was statistically significant.[396]

The general mechanisms through which vegetables could plausibly protect against ovarian cancer are outlined below.

Evidence from cohort and case-control studies is sparse. There is limited evidence suggesting that non-starchy vegetables protect against ovarian cancer.

The Panel is aware that since the conclusion of the SLR one case-control study[78] has been published. This new information does not change the Panel judgement (see box 3.8).

Endometrium

Ten case-control studies investigated non-starchy vegetable consumption.[398-407] Seven case-control studies investigated cruciferous vegetables and endometrial cancer.[398-400 405 407-410]

Of the 10 studies that reported on non-starchy vegetables, 7 showed decreased risk when comparing the highest with the lowest intake groups,[400-405 407] which was statistically significant in 5.[400 402-404 407] Two reported a non-significant increased risk[398 406] and the other showed no effect on risk.[399] Meta-analysis was possible on 8 studies, giving a summary estimate of 0.90 (95% CI 0.86–0.95) per 100 g of vegetable intake/day, with low heterogeneity.[399 401-407] A dose-response relationship was apparent from these data.

Five out of the seven case-control studies that investigated cruciferous vegetables reported reduced risk when comparing high to low intake groups,[399 405 407-410] which was statistically significant in one.[405] The other two studies reported non-significant increased risk.[398 400] Meta-analysis was possible on five studies, giving a summary effect estimate of 0.79 (95% CI 0.69–0.90) per 100 g/day, with no heterogeneity.[399 405 407 409 410] The two studies that could not be included suggested increased risk, though not statistically significant.[398 400]

A dose-response relationship is apparent from case-control data.

The general mechanisms through which vegetables could plausibly protect against endometrial cancer are outlined below. Cruciferous vegetables contain glucosinolates. Certain hydrolysis products of glucosinolates, including indoles and isothiocyanates, have shown anti-carcinogenic properties in laboratory experiments and in diets in live experiments in animals.[411] The human genotype of glutathione *S*-transferase has been shown to have a significant role in the metabolism of these phytochemicals and may therefore influence potential anti-cancer properties.[412]

Evidence comes from case-control studies only. There is limited evidence suggesting that non-starchy vegetables protect against endometrial cancer.

General mechanisms — non-starchy vegetables

Also see Chapter 2. Non-starchy vegetables provide a plethora of potentially cancer-preventive substances, including several antioxidant nutrients (such as carotenoids and vitamin C), dietary fibre, as well as phytochemicals (such as glucosinolates, dithiolthiones, indoles, chlorophyll, flavonoids, allylsulphides, and phytoestrogens). Phytochemicals might influence cancer risk through their antioxidant activities, modulation of detoxification enzymes, stimulation of the immune system, antiproliferative activities, and/or modulation of steroid hormone concentration and hormone metabolism, to name a few possible mechanisms. Non-starchy vegetables are also a source of folate, which plays an important role in synthesis and methylation of DNA. Abnormal DNA methylation has been linked to aberrant gene expression and also to cancers at several sites, and may be particularly important in rapidly dividing tissues. It is difficult to unravel the relative importance of each constituent and likely that a protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

Carrots are a source of carotenoids, particularly alpha-carotene and beta-carotene, as well as other vitamins and phytochemicals with potentially protective effects. Tomatoes are a source of vitamin C and carotenoids, particularly lycopene. Potential mechanisms of inhibition include the antioxidant properties of carotenoids and ligand-dependent signalling through retinoid receptors (see chapter 4.2.5.3).

There is a complex mixture of phytochemicals present in whole vegetables and these may have additive and synergistic effects responsible for anti-cancer activities.

4.2.5.1.1 Allium vegetables
Stomach

Two cohort studies,[413 414] 27 case-control studies,[109 129 152 162 164 171 178 182 185 187 191 194 195 232 243-245 247 248 251 266 270 415-419] and 2 ecological studies[202 208] investigated allium vegetables and stomach cancer; 1 cohort study,[413] 16 case-control studies,[109 129 182 184 195 232 246 247 251 262 418 420-422] and 2 ecological studies[203 208] investigated garlic and stomach cancer. There was also 1 relevant intervention study that combined allitridium and selenium supplements.[423 424]

Allium vegetables

Both cohort studies reported decreased risk,[413 414] which was statistically significant in one.[413] Meta-analysis was possible on both, giving a summary effect estimate of 0.55 (95% CI 0.35–0.87) per 100 g/day, with no heterogeneity (figure 4.2.14).[413 414]

Twenty of the case-control studies showed reduced risk when comparing high with low intake groups,[129 152 162 164 171 178 182 185 187 191 194 195 232 243 247 248 270 416 418 419] which was statistically significant in 12.[129 152 162 164 182 187 194 243 248 270 416 418] Four studies showed increased risk,[109 245 266 415] which was statistically significant in 2,[245] and the remaining 3 reported no significant effect on risk.[244 251 417] Meta-analysis was possible

Figure 4.2.14	Allium vegetables and stomach cancer; cohort and case-control studies

Relative risk (95% CI)

Cohort
Dorant 1996 — 0.55 (0.35–0.88)
Gonzalez 2006 — 0.31 (0.01–11.69)
Summary estimate — 0.55 (0.35–0.87)

Case control
Haenszel 1972 — 0.49 (0.33–0.72)
Trichopoulos 1985 — 0.23 (0.16–0.35)
You 1988 — 0.32 (0.17–0.59)
Buiatti 1989 — 0.85 (0.72–1.00)
Hansson 1993 — 0.79 (0.47–1.34)
Ji 1998 Men — 0.66 (0.43–1.02)
Ji 1998 Women — 0.69 (0.38–1.24)
Gao 1999 — 0.00 (0.00–0.02)
De Stefani 2001 — 0.29 (0.11–0.81)
Munoz 2001 — 0.70 (0.61–0.80)
Takezaki 2001 — 1.45 (0.74–2.82)
Sipetic 2003 — 0.40 (0.20–0.80)
Lissowka 2004 — 0.86 (0.67–1.10)
Nan 2005 — 0.49 (0.28–0.84)
Zickute 2005 — 0.91 (0.71–1.16)
Summary estimate — 0.59 (0.47–0.74)

0.5 1 2

Relative risk, per 100 g/day

on 14 studies, giving a summary effect estimate of 0.59 (95% CI 0.47–0.74) per 100 g/day, with high heterogeneity (figure 4.2.14).[109 129 152 162 171 178 182 187 191 194 232 247 270 416]

Both ecological studies reported statistically significant decreased risk with increased consumption.[202 208]

A statistically significant dose-response relationship is apparent from cohort and case-control data.

Garlic
The single cohort study, which was specific to supplementary garlic, showed a non-significant increased risk when comparing garlic supplement use versus no supplement use (1.29, 95% CI 0.62–2.67).[413]

Fifteen of the case-control studies showed decreased risk when comparing highest to lowest intake groups,[109 129 182 184 195 232 246 247 251 418 420-422] which was statistically significant in seven.[129 182 232 246 247 418 420 422] One study showed a non-significant increased risk.[262] Meta-analysis was possible on five studies, giving a summary effect estimate of 0.41 (95% CI 0.23–0.73) per serving/day.[109 129 182 232 421]

One ecological study showed statistically significant decreased risk with increased intake[208]; the other showed no significant association.[203]

Intervention study
The double-blind, randomised trial had an intervention duration of 3 years, and a 5- and 10-year follow-up, and more than 5000 participants, all of whom had been identified as being at increased risk of stomach cancer. The intervention

was a combined selenium/allitridium supplement.[423 424] The 5-year follow-up suggested that the intervention was effective in reducing stomach cancer incidence in men (0.36, 95% CI 0.14–0.92) but not in women (1.14, 95% CI 0.22–5.76).[423] The statistically significant protective effect for men had dissipated at the 10-year follow-up.[424] (Also see chapter 4.2.5.8.)

Allium vegetables are high in flavonols and organosulphur compounds. They also, particularly garlic, have antibiotic properties. Although this may act directly against *H pylori* (a known cause of stomach cancers), a study in humans has not shown this effect.[425] It is also possible that antibacterial effects of garlic might inhibit the secondary colonisation of the stomach after *H pylori*-induced atrophy. At present, there is no evidence to support or refute this mechanism. An animal study provides evidence that dietary garlic can reduce the severity of *H pylori*-associated gastritis.[426]

The evidence, though not copious and mostly from case-control studies, is consistent, with a dose-response relationship. There is evidence for plausible mechanisms. Allium vegetables probably protect against stomach cancer.

Colorectum
Garlic
Two cohort studies[361 362] and six case-control studies[427-435] investigated garlic consumption.

Both cohort studies reported non-significant decreased risk when comparing the highest with the lowest intake groups, with effect estimates of 0.77 (95% CI 0.51–1.16)[361] and 0.68 (95% CI 0.46–1.01) (figure 4.2.15).[362]

All six case-control studies showed decreased risk for the highest consumers of garlic,[427-435] which was statistically significant in three (figure 4.2.16).[431 432]

There is considerable preclinical evidence with model carcinogens and transplantable tumours that supports an anticancer effect of garlic and some of its allyl sulphur components. Animal studies demonstrate that allyl sulphides effectively inhibit colon tumour formation and also can inhibit cell growth in the laboratory.[436-439]

Figure 4.2.15	Garlic and colon cancer; cohort studies

Relative risk (95% CI)

Giovannucci 1994 Men — 0.77 (0.51–1.16)
Steinmetz 1994 Women — 0.68 (0.46–1.01)

0.2 0.5 1 2 5

Relative risk, highest vs lowest exposure category
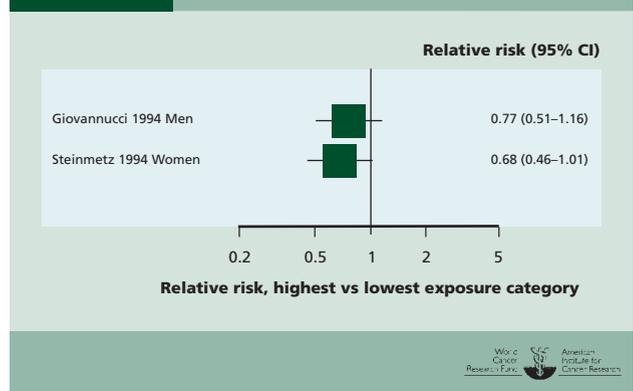
Figure 4.2.16 **Garlic consumption and colorectal cancer; case-control studies**
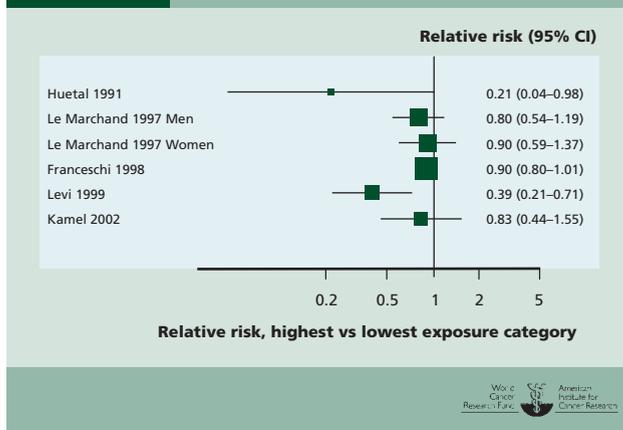
Relative risk (95% CI)

	Relative risk (95% CI)
Huetal 1991	0.21 (0.04–0.98)
Le Marchand 1997 Men	0.80 (0.54–1.19)
Le Marchand 1997 Women	0.90 (0.59–1.37)
Franceschi 1998	0.90 (0.80–1.01)
Levi 1999	0.39 (0.21–0.71)
Kamel 2002	0.83 (0.44–1.55)

0.2   0.5   1   2   5

Relative risk, highest vs lowest exposure category

The evidence, though not copious and mostly from case-control studies, is consistent, with a dose-response relationship. There is evidence for plausible mechanisms. Garlic probably protects against colorectal cancer.

The Panel is aware that since the conclusion of the SLR, one case-control study[78] has been published. This new information does not change the Panel judgement (see box 3.8).

In addition to this judgement, data on garlic have contributed to the evidence base for allium vegetables and stomach cancer (also see chapter 7.5).

4.2.5.1.2 Carrots
Cervix

Five case-control studies[440-444] and one ecological study[445] investigated carrots and cervical cancer.

Case-control studies were consistent in showing reduced risk for the highest levels of consumption, which was statistically significant in three.[440-442] All studies used hospital-based controls and none adjusted for human papilloma virus status. The single ecological study showed non-significant increased risk with high intake of carrots.[445]

Some carotenoids, including beta-carotene and alpha-carotene, which are found at high levels in carrots, are precursors of vitamin A. They also have properties independent of their pro-vitamin A activity. Carotenoids are recognised antioxidants and low blood levels of dietary antioxidants are associated with human papilloma virus persistence.[446]

The evidence, from case-control studies only, is sparse but consistent. There is limited evidence suggesting that carrots protect against cervical cancer.

Data on carrots have contributed to the evidence base for non-starchy vegetables and mouth, pharynx, and larynx cancers (chapter 7.1) and lung cancer (chapter 7.4). Also see chapter 4.2.5.1.

4.2.5.2 Fruits
Mouth, pharynx, and larynx

One cohort study,[447] 35 case-control studies[21 22 24-26 28 30-33 35 36 39-50 59-61 63 64 67 69 72 74 448-450] and 2 ecological studies[52 68] investigated fruits and mouth, pharynx, and larynx cancers; and 1 cohort study,[66] 23 case-control studies[23 26-29 31 33 34 37-39 41-43 45-47 50 63 65 75 451 452] and 1 ecological study[52] investigated citrus fruits. In addition, 1 cohort study[54] and 6 case-control studies[33 39 45 55-57] investigated non-starchy vegetables and fruits in combination (also see evidence on non-starchy vegetables, chapter 4.2.5.1).

General fruits

The single cohort study, which adjusted for smoking, showed a non-significant decreased risk for the highest when compared to the lowest intake groups, with an effect estimate of 0.82 (95% CI 0.64–1.04) (figure 4.2.17).[447]

Most (32) of the case-control studies reported decreased risk associated with higher intake of fruits,[24-26 28 30-33 35 36 39-48 50 59-61 63 64 69 72 74 448 450] which was statistically significant in 17.[26 31 32 35 39-43 46-48 50 63 64 69 72 448] No study reported statistically significant increased risk. Meta-analysis was possible on 7 studies (all of which adjusted for smoking), giving a summary effect estimate of 0.72 (95% CI 0.59–0.87) per 100 g/day, with high heterogeneity (figure 4.2.17).[30 39 42 44 45 69 72] Heterogeneity came from the varying size, not direction, of effect.

One ecological study showed a weak inverse correlation between fruits and oral cancer.[68] The other observed inverse correlations among women for fruit and both oral and laryngeal cancers and positive correlations among men for the same two sites.[52]

Figure 4.2.17 **Fruits and mouth, pharynx, and larynx cancer; cohort and case-control studies**

Relative risk (95% CI)

Cohort

	Relative risk (95% CI)
Chyou 1995	0.82 (0.64–1.04)
Summary estimate	0.82 (0.64–1.04)

Case control

	Relative risk (95% CI)
La Vecchia 1991	0.59 (0.41–0.86)
De Stefani 1994	0.58 (0.30–1.12)
De Stefani 2000	0.66 (0.52–0.85)
Bosetti 2002	0.92 (0.88–0.97)
Marchioni 2003	0.96 (0.86–1.08)
Gaudet 2004	0.90 (0.74–1.10)
Kapil 2005	0.17 (0.10–0.31)
Summary estimate	0.72 (0.59–0.87)

0.1   0.5 0.7 1   1.5

Relative risk, per 100 g/day
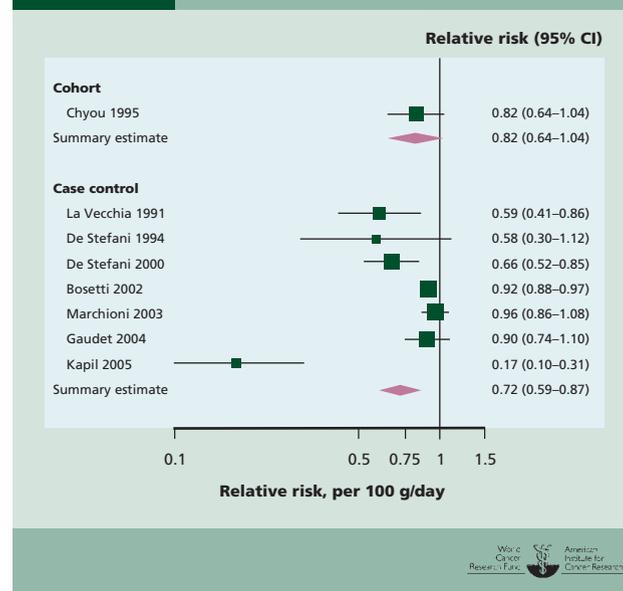
Figure 4.2.18 Citrus fruits and mouth, pharynx, and larynx cancer; case-control studies

	Relative risk (95% CI)
Franco 1989	0.72 (0.56–0.93)
Zheng 1993	0.45 (0.31–0.66)
Levi 1998	0.88 (0.82–0.95)
De Stefani 2000	0.27 (0.14–0.52)
Bosetti 2002	0.91 (0.85–0.97)
Pisa 2002	0.71 (0.51–0.99)
Gaudet 2004	0.89 (0.73–1.10)
Summary estimate	0.76 (0.66–0.87)

Relative risk, per 50 g/day

Figure 4.2.20 Citrus fruits and mouth, pharynx, and larynx cancer; case-control studies: dose response

Franco 1989
Zheng 1993
Levi 1998
De Stefani 2000
Bosetti 2002
Pisa 2002
Gaudet 2004
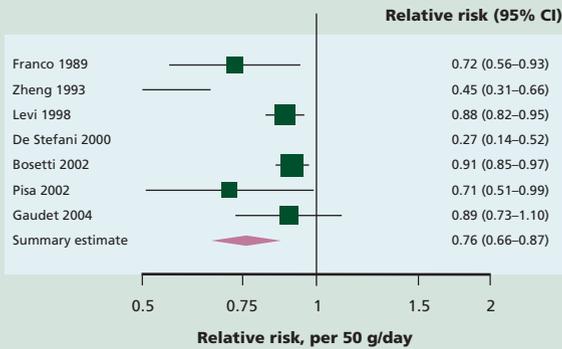
Citrus fruits (g/day)

Figure 4.2.19 Fruits and mouth, pharynx, and larynx cancer; case-control studies: dose response
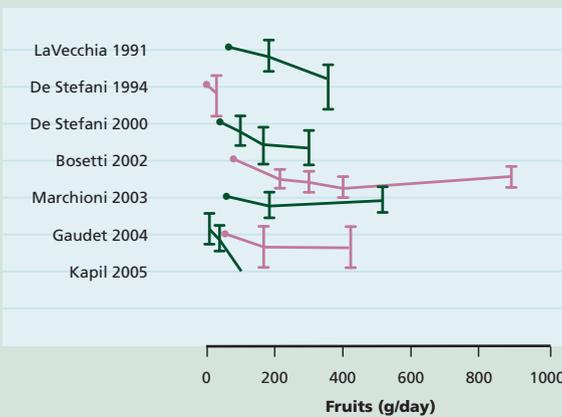
LaVecchia 1991
De Stefani 1994
De Stefani 2000
Bosetti 2002
Marchioni 2003
Gaudet 2004
Kapil 2005

Fruits (g/day)

Citrus fruits

The single cohort study, which was specific to oranges and was adjusted for smoking, showed a non-significant decreased risk for the highest when compared to the lowest intake groups, with an effect estimate of 0.50 (95% CI 0.30–1.00), with a p value for trend of 0.03.[66] This risk estimate was for cancers of the upper aerodigestive tract.

Twenty-two of the case-control studies showed decreased risk associated with higher intake of fruits,[23 27-29 31 33 34 37-39 41-43 45-47 50 63 65 75 451 452] which was statistically significant in 13.[23 27-29 31 33 37 39 42 43 47 50 75] The 23rd study showed no effect on risk.[26] Meta-analysis was possible on 7 studies (all of which adjusted for smoking), giving a summary effect estimate of 0.76 (95% CI 0.66–0.87) per 50 g/day, with high heterogeneity (figure 4.2.18).[23 29 37 39 42 45 65] Heterogeneity

came from the varying size, not direction, of effect.

A dose-response relationship was apparent from case-control but not cohort data for both general and citrus fruits (figures 4.2.19 and 4.2.20). There is some suggestion that the greatest effect appears to be with the first increment. That is, some fruit consumption confers a protective effect compared to none. However, it is not clear that the effect continues in a linear fashion with increased doses.

One ecological study found no significant association between citrus fruit consumption and cancer mortality in men or women.[52]

Studies that reported on combined intake of non-starchy vegetables and fruits showed evidence of an association with decreased risk (see chapter 4.2.5.1).

The general mechanisms through which fruits could plausibly protect against mouth, pharynx, and larynx cancer are outlined below.

The evidence, including on fruit subtypes, though mostly from case-control studies, is consistent, with a dose-response relationship. There is evidence for plausible mechanisms. Fruits probably protect against mouth, pharynx, and larynx cancers.

The Panel is aware that since the conclusion of the SLR, two cohort studies[76 77] and one case-control study[79] have been published. This new information does not change the Panel judgement (see box 3.8).

Oesophagus

Four cohort studies,[80 82 83 447] 36 case-control studies[22 40 60 84 86 87 89 94-96 98-100 102 104 108-110 112-115 125-129 134-136 138 453-456] and 7 ecological studies[52 68 116 118 119 234 457 458] investigated fruits and oesophageal cancer; 1 cohort study,[66] 16 case-control

Figure 4.2.21 | **Fruits and oesophageal cancer; cohort and case-control studies**

Relative risk (95% CI)

Cohort
Yu 1993	0.99 (0.85–1.15)
Chyou 1995	0.65 (0.39–1.08)
Guo 1999	0.90 (0.77–1.06)
Tran 2005	0.80 (0.70–0.91)

Case control
Notani 1987	0.99 (0.63–1.57)
Victoria 1987	0.66 (0.50–0.88)
Nakachi 1988 Women	0.23 (0.12–0.45)
Nakachi 1988 Men	0.31 (0.22–0.44)
Brown 1988	0.50 (0.29–0.87)
Jun-lao 1989	1.00 (0.82–1.22)
De Stefani 1990	0.33 (0.21–0.52)
Negri 1991	0.30 (0.21–0.42)
Tavani 1993	0.40 (0.19–0.85)
Tavani 1994	0.30 (0.11–0.85)
Castelletto 1994	0.70 (0.31–1.57)
Hanaoka 1994	0.50 (0.18–1.39)
Srivastava 1995	3.15 (1.29–7.72)
Gimeno 1995	0.55 (0.33–0.94)
Zhang 1997	0.40 (0.16–0.98)
De Stefani 1999	0.30 (0.17–0.52)
Wang 1999	0.51 (0.27–0.98)
Gao 1999	0.75 (0.36–1.56)
Cheng 2000	0.08 (0.01–0.56)
Nayar 2000	0.96 (0.45–2.05)
De Stefani 2000	0.18 (0.09–0.37)
Takezaki 2000	0.70 (0.52–0.94)
Phukan 2001	0.30 (0.04–2.17)
Terry 2001	0.60 (0.36–0.99)
Wolfgarten 2001	0.32 (0.12–0.89)
Takezaki 2001	0.91 (0.48–1.73)
Sharp 2001	0.64 (0.25–1.65)
Zhang 2001	0.64 (0.42–0.97)
Onuk 2002	7.10 (3.21–15.73)
Lik 2003	0.08 (0.06–0.11)
Hung 2004	0.60 (0.40–0.90)
Yang 2005	0.42 (0.19–0.91)
De Stefani	0.21 (0.10–0.44)

Relative risk, highest vs lowest exposure category
(scale: 0.2 0.5 1 2 5)

Figure 4.2.22 | **Fruits and oesophageal cancer; case-control studies**

Relative risk (95% CI)

Jun-lao 1989	1.52 (0.47–4.91)
Hanaoke 1994	0.30 (0.13–0.67)
Castelletto 1994	0.33 (0.13–0.80)
Gao 1999	0.38 (0.01–20.03)
De Stefani 2000	0.53 (0.42–0.67)
Wolfgarten 2001	0.40 (0.27–0.59)
Sharp 2001	0.84 (0.74–0.96)
De Stefani 2005	0.59 (0.49–0.71)
Summary estimate	0.56 (0.42–0.74)

Relative risk, per 100 g/day
(scale: 0.2 0.5 0.75 1 1.5)
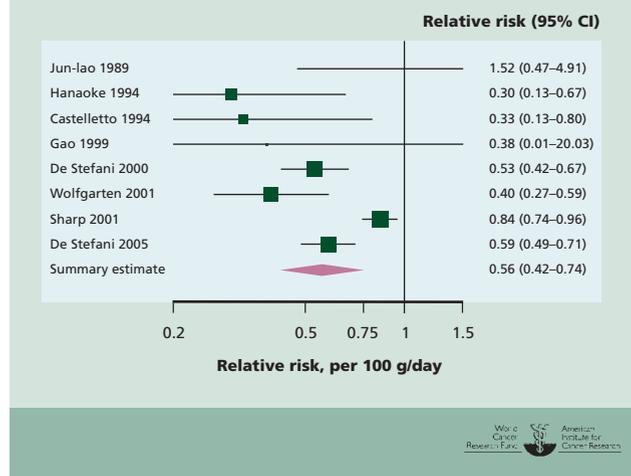
Figure 4.2.23 | **Citrus fruits and oesophageal cancer; cohort and case-control studies**

Relative risk (95% CI)

Cohort
| Kjaerheim 1998 | 0.50 (0.27–0.91) |

Case control
Brown 1988	0.50 (0.29–0.87)
Cheng 1992	0.10 (0.04–0.26)
Castelletto 1994	1.60 (0.81–3.15)
Cheng 1995 Non-smokers	0.39 (0.16–0.97)
Cheng 1995 Never drinkers	0.59 (0.23–1.52)
Zhang 1997	0.70 (0.29–1.71)
Launoy 1998	0.54 (0.33–0.89)
Levi 2000	0.22 (0.09–0.54)
Bosetti 2000	0.42 (0.25–0.71)
Terry 2000	0.90 (0.50–1.61)
Chen 2002	0.48 (0.21–1.10)
De Stefani 2005	0.28 (0.15–0.54)

Relative risk, highest vs lowest exposure category
(scale: 0.2 0.5 1 2 5)

studies,[33 85 86 88 90 97 105 111 113 124 125 128 130 132 133 136 459] and 1 ecological study[52] investigated citrus fruits.

General fruits

All of the cohort studies reported reduced risk with higher intakes of fruit,[80 82 83 447] which was statistically significant in two.[83 447] One study reported a statistically significant dose-response relationship, with a risk estimate of 0.68 (95% CI 0.53–0.88) per 100 g/day after adjustment for smoking.[447] The other three reported risks for the highest intake groups relative to the lowest, with risk estimates of 0.8 (95% CI 0.7–0.9; not adjusted for smoking),[83] 0.9 (95%

CI 0.8–1.1; adjusted for smoking),[80] and 0.99 (95% CI 0.85–1.15; not adjusted for smoking).[82]

Thirty-two of the case-control studies reported reduced risk for the highest intake groups when compared to the lowest (figure 4.2.21),[22 40 60 84 86 87 89 95 96 98 99 102 104 108-110 113-115 125-129 134-136 138 453-456] which was statistically significant in 24.[40 60 84 86 87 89 95 96 102 104 110 113-115 127 134-136 138 454-456] One study reported statistically significant increased risk,[100] one reported no effect on risk,[112] and one reported no statistically significant association.[94] Meta-analysis was possible on eight studies, giving a summary effect estimate of 0.56 (95% CI 0.42–0.74) per 100 g/day, with high heterogeneity (figure

Figure 4.2.24 Citrus fruits and oesophageal cancer; case-control studies

	Relative risk (95% CI)
Cheng 1992	0.46 (0.39–0.55)
Castelletto 1994	1.22 (0.79–1.89)
Cheng 1995 Never drinkers	0.65 (0.48–0.89)
Cheng 1995 Non-smokers	0.57 (0.43–0.75)
Levi 2000	0.75 (0.67–0.84)
Terry 2000	0.97 (0.84–1.13)
De Stefani 2005	0.62 (0.49–0.78)
Summary estimate	0.70 (0.56–0.88)

Relative risk, per 50 g/day
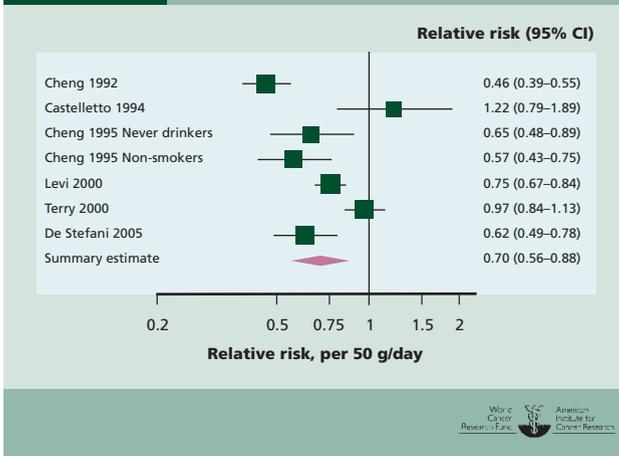
4.2.22). Heterogeneity may be partially explained by differential adjustment for confounders between studies.

All seven ecological studies reported reduced risk with increased intake,[52 68 116 118 119 234 457 458] which was statistically significant in one.[68 458]

Citrus fruits

The single cohort study, which was specific to oranges and was adjusted for smoking, showed a non-significant decreased risk for the highest when compared to the lowest intake groups, with an effect estimate of 0.50 (95% CI 0.30–1.00), with a p value for trend of 0.03.[66] This risk estimate was for cancers of the upper aerodigestive tract; 22 out of 71 cases were oesophageal cancers.

Fifteen of the case-control studies reported decreased risk for the highest intake groups when compared to the lowest,[33 85 86 88 90 97 105 111 113 124 125 130 132 133 136 459] which was statistically significant in 10 (figure 4.2.23).[33 85 86 88 97 105 113 132 133 136 459] The other study reported a non-significant increased risk.[128] Meta-analysis was possible on six studies, giving a summary effect estimate of 0.70 (95% CI 0.56–0.88) per 50 g/day, with high heterogeneity (figure 4.2.24).[33 97 128 130 132 133] Four of these studies adjusted for smoking.[33 97 128 132 133] Heterogeneity may be partially explained by differential adjustment for confounders between studies.

The single ecological study reported a non-significant increased risk.[52]

The general mechanisms through which fruits could plausibly protect against cancer are outlined below.

The evidence, including on fruit subtypes, though mostly from case-control studies, is consistent, with a dose-response relationship. There is evidence for plausible mechanisms. Fruits probably protect against oesophageal cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[140] and two case-control studies[143 460] have been

published. This new information does not change the Panel judgement (see box 3.8).

Lung

Twenty-five cohort studies,[214 216 282-300 337 339 360 461-467] 32 case-control studies,[261 303-306 308-318 320-322 324 326-328 330 331 343 346 349 350 352 355 357 358 468-472] and 7 ecological studies[52 116 332-334 473 474] investigated fruits and lung cancer.

Twenty of the cohort studies showed decreased risk for the highest intake groups when compared to the lowest,[214 216 282-289 291-294 296 297 299 300 337 461-467] which was statistically significant in four.[216 289 292 300 461 464] Four studies showed non-significant increased risk[290 295 339 360] and the other reported no statistically significant association.[298] Meta-analysis was possible on 14 cohort studies, giving a summary effect estimate of 0.94 (95% CI 0.90–0.97) per 80 g serving/day, with low heterogeneity (figure 4.2.25). All but one of these studies adjusted for smoking.[462]

Pooled analysis from 8 cohort studies (over 430 000 participants, followed up for 6 to 16 years, more than 3200 lung

Figure 4.2.25 Fruits and lung cancer; cohort and case-control studies

	Relative risk (95% CI)
Cohort	
Alavanja 2004 (pesticide applicators)	0.89 (0.59–1.35)
Alavanja 2004 (applicator spouses)	0.65 (0.28–1.51)
Breslow 2000	0.92 (0.71–1.18)
Feskanich 2000 (HPFS) Men	1.05 (0.94–1.17)
Feskanich 2000 (NHS) Women	0.94 (0.87–1.02)
Fraser 1991	0.47 (0.32–0.69)
Fu 1997	0.94 (0.67–1.32)
Holick 2002	0.94 (0.89–1.00)
Jansen 2004	0.84 (0.65–1.09)
Miller 2002	0.96 (0.86–1.07)
Olson 2002	0.91 (0.86–0.96)
Shibata 1992	0.99 (0.87–1.14)
Skuladottir 2004	0.95 (0.86–1.05)
Takezaki 2003	0.63 (0.24–1.63)
Vorrips 2000	0.92 (0.86–0.98)
Summary estimate	0.94 (0.90–0.97)
Case control	
Axelsson 1996	0.77 (0.46–1.28)
Brennan 2000	1.08 (0.52–2.28)
De Stefani 2002	0.84 (0.66–1.06)
Gao 1993	0.45 (0.30–0.67)
Hu 2002	1.04 (0.85–1.27)
Ko 1997	1.00 (0.54–1.84)
Kreuzer 2002	0.79 (0.45–1.39)
Lagiou 2004	0.79 (0.60–1.04)
Pawlega 1997	0.01 (0.00–0.24)
Rachtan 2002	0.49 (0.32–0.75)
Raunoi-Ravina 2002	1.19 (0.74–1.91)
De Stefani 1999	0.67 (0.54–0.82)
Suzuki 1994	1.33 (0.56–3.18)
Swanson 1997	0.91 (0.76–1.09)
Summary estimate	0.80 (0.68–0.94)

Relative risk, per serving/day

Figure 4.2.26 | **Fruits and lung cancer; cohort and case-control studies; dose response**

Of the seven ecological studies, four reported non-significant decreased risk in areas of higher fruit consumption,[52 332 473 474] one reported no consistent association,[334] and two reported non-significant increased risk.[116 333]

The general mechanisms through which fruits could plausibly protect against cancer are outlined below. In addition, flavonoids found in fruit directly inhibit expression of CYP1A1 (a cytochrome P450 enzyme that helps to metabolise toxins), resulting in decreased DNA damage.[475] Elevated CYP1A1 activity has been associated with increased risk of lung cancer, primarily in smokers.[476] The protective association of flavonoids is associated with specific CYP1A1 genotypes, which supports the importance of flavonoids and potentially explains heterogeneous results.[476 477]

> **The evidence is ample and consistent. A dose-response relationship is apparent from both cohort and case-control studies and there is evidence for plausible mechanisms operating in humans. The evidence that fruits protect against lung cancer is convincing.**

The Panel is aware that since the conclusion of the SLR, one case-control study[478] has been published. This new information does not change the Panel judgement (see box 3.8).

Stomach

Sixteen cohort studies,[71 80 144-147 149 150 213-217 252-254 414] 51 case-control studies,[89 109 129 151 154 156 158-163 167-169 174-176 178-180 182 184-187 189-191 193 195 219 221 222 224-227 229 230 246 255-258 260 261 264 270 479-482] and 23 ecological studies[52 116 118 119 197 198 200-202 204-209 234 236-240 483-485] investigated fruits.

Ten cohort studies reported decreased risk for the highest intake groups when compared to the lowest,[71 80 144 146 150 214-217 253 254] which was statistically significant in one,[253] and in women only in a second study.[216] Six studies showed increased risk,[145 147 149 213 214 252 414] which was statistically significant in one.[213] Meta-analysis was possible on eight studies, giving a summary effect estimate of 0.95 (95% CI 0.89–1.02) per 100 g/day, with low heterogeneity (figure 4.2.27).

One of the cohort studies considered in the meta-analysis above (EPIC, more than 521 000 participants in over 10 European countries) reported results stratified by *H pylori* status. The effect estimate for the *H pylori*-negative group was 0.72 (95% CI 0.39–1.33) and 0.98 (95% CI 0.81–1.2) for the positive group.[140]

Forty case-control studies showed decreased risk for the highest intake groups when compared to the lowest,[89 109 151 156 158-160 162 163 167-169 174 176 178-180 184 186 187 189-191 195 219 221 222 225 226 229 230 246 256-258 260 261 264 270 479-481] which was statistically significant in 25.[89 109 151 158-160 162 163 167-169 174 176 178 186 187 190 191 221 222 226 229 246 256 261 264 479 481] Seven showed increased risk,[129 161 182 185 193 224 482] which was statistically significant in two.[182 193] One study showed non-significant increased risk in men and non-significant decreased risk in women.[227] Two studies showed no effect on risk[154 255] and the remaining one reported that there was no significant association.[175] Meta-analysis was possible on 26 studies, giving a summary effect estimate of 0.67 (95% CI 0.59–0.76) per 100 g/day, with

cancer cases) showed a statistically significant reduced risk for the highest intake group when compared to the lowest (0.77, 95% CI 0.67–0.87), with a p value for trend of < 0.001.[336]

Twenty-one case-control studies showed decreased risk for the highest intake groups when compared to the lowest,[261 303 305 306 308 309 311 312 315 317 318 320-322 324 327 328 331 343 346 349 350 355 357 358 468 469 472] which was statistically significant in 7.[261 309 311 324 327 343 346 357 358 468 472] Three studies reported no effect on risk[310 316 330 352] and 8 showed increased risk,[304 313 314 326 470 471] which was statistically significant in 3.[304 326 470] Meta-analysis was possible on 14 case-control studies, giving a summary effect estimate of 0.80 (95% CI 0.68–0.94) per serving/day, with moderate heterogeneity (figures 4.2.25 and 4.2.26). All but 2 of these studies adjusted for smoking, and exclusion of these 2 studies did not significantly alter the meta-analysis.[316 352]

Figure 4.2.27 Fruits and stomach cancer; cohort and case-control studies

Relative risk (95% CI)

Cohort

Study	Relative risk (95% CI)
Chyou 1990	0.95 (0.84–1.07)
Botterweck 1998	0.92 (0.83–1.02)
Galanis 1998	0.68 (0.51–0.92)
Fujino 2002 Men	1.01 (0.90–1.13)
Fujino 2002 Women	1.12 (0.85–1.49)
Kobayashi 2002	0.75 (0.55–1.00)
Ngoan 2002	0.94 (0.28–1.19)
Khan 2004 Men	1.14 (0.28–4.70)
Gonzalez 2006	1.04 (0.91–1.19)
Summary estimate	0.95 (0.89–1.02)

Case control

Study	Relative risk (95% CI)
Jedrychowski 1981	0.71 (0.53–0.95)
Jedrychowski 1986	0.98 (0.66–1.47)
You 1988	0.61 (0.48–0.79)
Burr 1989 Men	0.53 (0.32–0.89)
Burr 1989 Women	0.39 (0.15–0.97)
Coggon 1989	0.48 (0.07–3.45)
De Stefani 1990	0.42 (0.30–0.61)
Kato 1990 Men	0.89 (0.65–1.22)
Kato 1990 Women	0.85 (0.49–1.50)
Lee 1990	1.05 (0.79–1.39)
Wu-Williams 1990 Men	0.64 (0.37–1.11)
Hoshiyama 1992	0.54 (0.41–0.70)
Memik 1992	0.57 (0.36–0.90)
Cornee 1995	0.75 (0.67–0.99)
De Stefani 1998	0.49 (0.42–0.58)
Ji 1998 Men	0.49 (0.37–0.80)
Ji 1998 Women	0.55 (0.37–0.80)
Gao 1999	5.46 (0.36–17.98)
Huang 1999	0.93 (0.80–1.08)
Ward 1999	0.90 (0.55–1.47)
Mathew 2000	0.90 (0.55–1.47)
De Stefani 2001	0.65 (0.53–0.79)
Takezaki 2001	0.60 (0.37–0.97)
Nishimoto 2002	0.74 (0.62–1.06)
Lee 2003	0.36 (0.18–0.73)
Sipetic 2003	0.17 (0.07–0.32)
Suh 2003	0.80 (0.69–0.92)
Lissowska 2004	0.65 (0.47–0.91)
Boccia 2995	2.06 (1.10–3.84)
Summary estimate	0.67 (0.59–0.76)

0.5 1 2

Relative risk, per 100 g/day

World Cancer Research Fund / American Institute for Cancer Research

high heterogeneity (figure 4.2.27).

A dose-response relationship is apparent from case-control but not cohort data. There is statistically significant heterogeneity between study types.

Eighteen ecological studies showed decreased risk with increased intake of fruits,[116 118 197 200 201 204-208 234 237-239 484 485] which was statistically significant in eight.[204-208 237] Four studies showed increased risk with increased intake,[52 118 119 202 239 240] which was statistically significant in one.[240] Two studies showed non-significant decreased risk in women and non-significant increased risk in men[209 236]; one study showed non-significant decreased risk in men and non-significant increased risk in women[198]; and one study

showed non-significant increased risk in white men and Japanese men and women, and non-significant decreased risk in white women.[483]

The stomach is a particularly unusual chemical environment and it is possible that, in addition to the general mechanisms described below, specific mechanisms apply, for instance, in relation to nitrosamine formation.[486] It is also plausible that bioactive constituents in fruit would protect against *H pylori*-induced damage, particularly inflammation, which is implicated in the development of stomach cancers.

The evidence is ample and more consistent with a dose-response relationship for case-control studies than for cohorts. There is evidence for plausible mechanisms. Fruits probably protect against stomach cancer.

The Panel is aware that since the conclusion of the SLR, three case-control studies[487-489] have been published. This new information does not change the Panel judgement (see box 3.8).

Nasopharynx

Six case-control studies investigated general fruits and nasopharyngeal cancers[274 275 281 490-492]; a further five case-control studies investigated citrus fruits.[273 278-281] Preserved fruits were excluded from all categories.

Of the six case-control studies that investigated general fruits, four reported decreased risk for the highest intake groups when compared to the lowest,[275 281 491 492] which was statistically significant in two.[275 491] The other two studies reported that there was no significant effect on risk, without further detail.[274 490] All five of the case-control studies that investigated citrus fruits reported decreased risk for the highest intake groups when compared to the lowest,[273 278-281] four of which were statistically significant.[273 278-280]

Preserved fruits were excluded as they introduced substantial heterogeneity.

The general mechanisms through which fruits could plausibly protect against nasopharyngeal cancer are outlined below. In addition, it is possible that active constituents in fruit could act directly on Epstein-Barr virus infection.[493]

The evidence, from case-control studies only, is sparse. There is limited evidence suggesting that fruits protect against nasopharyngeal cancer.

Pancreas

Six cohort studies,[214 216 252 494-496] 16 case-control studies,[219 497-511] and 8 ecological studies[52 197 485 512-515] investigated fruits and pancreatic cancer.

All six cohort studies showed decreased risk for the highest intake groups when compared to the lowest,[214 216 252 494-496] which was statistically significant in one.[496] Meta-analysis was possible on three cohort studies, giving a summary effect estimate of 0.92 (95% CI 0.81–1.04) per 100 g/day, with no heterogeneity.[216 494 495]

Eleven case-control studies showed decreased risk for the highest intake groups when compared to the lowest,[219 497 498 500 501 503-509 511] which was statistically significant in four,[503]

[504] [508] [511] and in men but not women in a fifth study,[506] and in women but not men in a sixth.[501] One study reported a statistically significant increased risk for men and a statistically significant decreased risk for women.[510] No other study reported statistically significant increased risk. Meta-analysis was possible on eight case-control studies, giving a summary effect estimate of 0.89 (95% CI 0.82–0.98) per 100 g/day, with high heterogeneity.[497][498][502][503][505][506][508][510] Heterogeneity could be partly explained by proxy reporting, poor study quality, and varying adjustment for known confounders.

A dose-response relationship is apparent from case-control, but not cohort data.

Ecological studies show no consistent association.[52][197][485][512-515]

The general mechanisms through which fruits could plausibly protect against pancreatic cancer are outlined below.

The evidence is inconsistent. There is limited evidence suggesting that fruits protect against pancreatic cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[516] has been published. This new information does not change the Panel judgement (see box 3.8).

Liver cancer

One cohort study[216][517] and five case-control studies[89][518-521] investigated fruits and liver cancer.

The single cohort study showed non-significant decreased risk for the highest intake groups when compared to the lowest (0.98, 95% CI 0.75–1.21).[216][517]

Four case-control studies showed decreased risk for the highest intake groups when compared to the lowest,[89][518][520][521] which was statistically significant in two.[89][518] One study showed non-significant increased risk.[519] Heterogeneity could be partly explained by poor study quality and varying adjustment for known confounders.

The general mechanisms through which fruits could plausibly protect against liver cancer are outlined below. In addition, grape extracts and auraptene (from citrus fruit) have shown protective effects against the development of hepatocellular carcinoma in rats.[522-525]

The evidence is sparse and inconsistent. There is limited evidence suggesting that fruits protect against liver cancer.

The Panel is aware that since the conclusion of the SLR, one case-control study[526] has been published. This new information does not change the Panel judgement (see box 3.8).

Colorectum

Twenty cohort studies[214][216][359-372][374-376][378][379][527-529] and 57 case-control studies investigated fruits and colorectal cancer.

Thirteen cohort studies showed decreased risk with increased intake,[214][216][360-364][366][371][374-376][378] which was statistically significant in two.[360][364] No studies reported statistically significant increased risk. Meta-analysis was possible on eight cohort studies, giving a summary effect estimate of 0.97 (95% CI 0.92–1.03) per serving/day, with high heterogeneity.[360][362-364][366][370][529] When results were stratified by

sex, a statistically significant decreased risk was apparent in women (0.81, 95% CI 0.85–0.98 per serving/day based on five studies), with low heterogeneity.

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

The mechanism for this sex difference is unknown. There is speculation the mechanism could be related to the (partly understood) explanation for protective effects observed in postmenopausal women provided with hormone replacement therapy. Another possibility is that the result could be artifactual if men are poorer at reporting their diets than women.

The general mechanisms through which fruits could plausibly protect against colorectal cancer are outlined below.

There is a substantial amount of evidence but it is inconsistent. There is limited evidence suggesting that fruits protect against colorectal cancer.

The Panel is aware that since the conclusion of the SLR, one cohort[530] and five case-control studies [261][380][531-533] have been published. This new information does not change the Panel judgement (see box 3.8).

General mechanisms — fruits

Fruits, in particular citrus fruits, are sources of vitamin C and other antioxidants, such as phenols and flavonoids, as well as potentially bioactive phytochemicals. Vitamin C traps free radicals and reactive oxygen molecules, protecting against oxidation damage. It also regenerates other antioxidant vitamins such as vitamin E.[534] Vitamin C also inhibits the formation of carcinogens and protects DNA from mutagenic attack.[535]

Beta-carotene and other carotenoid antioxidants are also found in fruits. Some fruits contain high levels of flavonoids, including apples (quercetin) and grapefruit (naringin). Flavonoids have antioxidant effects and can also inhibit carcinogen-activating enzymes. Flavonoids can also alter the metabolism of other dietary agents. For instance, quercetin directly inhibits expression of CYP1A1 (a cytochrome P450 enzyme that helps to metabolise toxins), resulting in decreased DNA damage.[475] The phytochemical antioxidants contained in fruit could reduce free-radical damage generated by inflammation. A single study reported that apples given in physiological quantities inhibited carcinogen-induced mammary cancer in rodents in a dose-response manner.[536]

There is a complex mixture of phytochemicals present in whole vegetables and these may have additive and synergistic effects responsible for anti-cancer activities.

4.2.5.3 Foods containing carotenoids
Mouth, pharynx, and larynx

Two cohort studies[537][538] investigated total serum carotenoids and two case-control studies[539][540] investigated total dietary carotenoids and mouth, pharynx, and larynx cancers. Ten case-control studies investigated pro-vitamin A carotenoids.[26-29][47][48][450][451][541-544] Three cohort studies investigated serum alpha-carotene[537][538][545]; one cohort study

investigated dietary alpha-carotene[71]; three cohort studies[537 538 545] and two case-control studies[546 547] investigated serum beta-carotene; one cohort study[71] and seven case-control studies[34 35 67 74 540 548 549] investigated dietary beta-carotene. One cohort study[71] and four case-control studies[62 450 540 543 548] investigated dietary lycopene; one cohort study[538] and one case-control study[547] investigated serum lycopene.

Total carotenoids

The two cohort studies both showed decreased risk,[537 538] one was statistically significant for the highest serum levels of total carotenoids when compared to the lowest (0.33, p value for trend 0.05; not adjusted for smoking and alcohol); and 0.22 (95% CI 0.05–0.88; adjusted for smoking and alcohol).[537]

The two case-control studies showed decreased risk for the highest intake group when compared to the lowest,[539 540] which was statistically significant in men but not women in one study[539] and statistically significant for all in the other.[540] Both case-control studies adjusted for smoking.

Pro-vitamin A carotenoids

Nine case-control studies reported decreased risk,[26-29 47 48 450 541-544] which was statistically significant for five studies.[29 48 541-543] One other study reported decreased risk for men and increased risk for women but neither was statistically significant.[451] All studies adjusted for smoking.

Alpha-carotene

All four cohort studies reported decreased risk for the highest intake group or serum level compared to the lowest,[71 537 538 545] which was statistically significant in three,[71 537 545] although one of the latter reported a separate estimate specific to oral cancers, which suggested a non-significant increased risk.[545] Only one study adjusted for smoking.[537] The effect estimates were 0.62 (95% CI 0.41–0.94) for dietary alpha-carotene,[71] and 0.48 (laryngeal cancers, p value for trend 0.18), 1.26 (oral cancers, p value for trend 0.54),[545] 0.20 (95% CI 0.05–0.75; adjusted for smoking),[537] and 0.37 (p value for trend 0.06) for serum levels.[538] These tended to be based on a relatively small number of cases.

Beta-carotene

The single cohort study that investigated dietary beta-carotene intake reported that there was no significant association, but provided no further details.[71] All three cohort studies that investigated serum levels showed decreased risk for the highest group when compared to the lowest,[537 538 545] which was statistically significant in one.[537] The effect estimates were 0.10 (95% CI 0.02–0.46; adjusted for smoking),[537] 0.42 and 0.88 for oral/oropharyngeal and laryngeal cancers, respectively (not adjusted for smoking),[545] and 0.5 (p value for trend 0.17), which was attenuated after adjustment for smoking (0.69).[538]

Five case-control studies reported decreased risk,[34 35 74 540 549] which was significant in two.[35 549] One study reported non-significant increased risk[548] and one study reported a significant increased risk.[67]

Lycopene

One cohort study[71] and four case-control studies[62 450 540 543 548] investigated dietary lycopene and mouth, larynx, and pharynx cancers; one cohort study[538] and one case-control study[547] investigated serum lycopene.

One cohort study reported a non-significant decreased risk for the highest serum lycopene levels when compared to the lowest (0.61; p value for trend 0.37).[538] The other stated that there was no relationship between dietary lycopene and risk.[71]

All four case-controls that investigated dietary lycopene reported decreased risk for the highest intake groups when compared to the lowest,[62 450 540 543 548] which was statistically significant in two.[62 548] The single case-control that investigated serum lycopene reported contrary results, showing that levels were significantly higher in cases than controls.[547]

The general mechanisms through which foods containing carotenoids could plausibly protect against mouth, pharynx, and larynx cancer are outlined below.

There is a considerable amount of evidence, and though it is for different carotenoid types, it is generally consistent, with a dose-response relationship. There is evidence for plausible mechanisms. Foods containing carotenoids probably protect against mouth, pharynx, and larynx cancers.

The Panel is aware that since the conclusion of the SLR, one cohort study[76] has been published. This new information does not change the Panel judgement (see box 3.8).

Lung

Eleven cohort studies,[284 286 288 289 298 299 341 550-555] 16 case-control studies,[306-308 310 311 321 322 327 330 342 344 350 352 556-561] and 1 ecological study[333] investigated total dietary carotenoids and lung cancer; 4 cohort studies[298 562-566] and 5 case-control studies[567-571] investigated total serum or plasma carotenoids; 7 cohort studies,[286 289 293 341 552 566 572 573] 8 case-control studies,[306 308 320 321 327 350 560 574] and 1 ecological study[333] investigated dietary beta-cryptoxanthin; 6 cohort studies[563-566 575-577] and 1 case-control study[578] investigated serum or plasma beta-cryptoxanthin.

**Figure 4.2.28 Carotenoids and lung cancer; cohort studies**

Relative risk (95% CI)

	Relative risk (95% CI)
Shekelle 1981	0.97 (0.95–0.99)
Wright 2004	0.99 (0.97–1.01)
Summary estimate	0.98 (0.96–0.99)

Relative risk, per 1000 µg/day
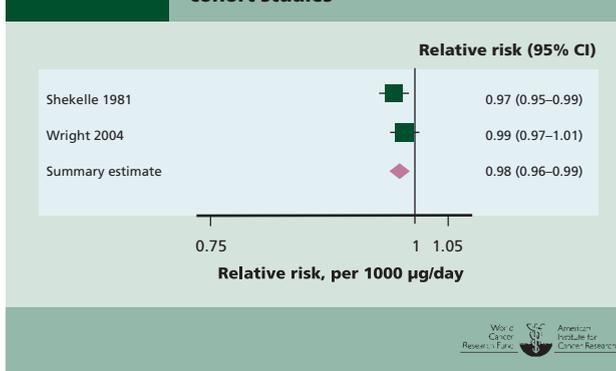
Figure 4.2.29 | **Carotenoids and lung cancer; cohort and case-control studies**

Relative risk, highest vs lowest exposure category

	Relative risk (95% CI)
Cohort	
Bandera 1997	0.75 (0.61–0.93)
Chow 1992	0.80 (0.52–1.24)
Holick 2002	0.84 (0.72–0.98)
Knekt 1999	0.92 (0.60–1.41)
Michaud 2000 (HPFS) Men	0.64 (0.37–1.12)
Michaud 2000 (NHS) Women	0.69 (0.46–1.03)
Neuhouser 2003	0.90 (0.62–1.32)
Yong 1997	0.74 (0.52–1.06)
Case control	
Bond 1987	1.18 (0.73–1.91)
Brennan 2000	0.80 (0.62–1.03)
Candelora 1992	0.30 (0.12–0.73)
Darby 2001	0.74 (0.57–0.97)
Dorgon 1993	0.83 (0.66–3.11)
Fontham 1988	0.88 (0.70–1.11)
Garcia 1995	1.45 (0.68–3.11)
Mohr 1999	0.60 (0.36–1.00)
Nyberg 1998	0.43 (0.20–0.91)
Samet 1985	0.77 (0.54–1.06)
De Stefani 1999	0.43 (0.29–0.64)
Wright 2003	0.61 (0.41–0.91)

Dietary carotenoids

All 11 cohort studies showed decreased risk of lung cancer for the highest intake group when compared to the lowest,[284] [286 288 289 298 299 341 550-555] which was statistically significant in three.[286 550 553] Meta-analysis was possible on two cohort studies, giving a summary effect estimate of 0.98 (95% CI 0.96–0.99) per 1000 μg/day, with no heterogeneity (figure 4.2.28).[553 554] All cohort studies adjusted for smoking.

Twelve of the case-control studies showed decreased risk of lung cancer for the highest intake group when compared to the lowest,[306-308 310 311 321 322 327 330 344 350 352 556 559-561] which was statistically significant in seven (figure 4.2.29).[306-308 321 322 327 344 556 560] Three studies reported increased risk,[342 557 558] which was statistically significant in one,[557] and one reported no effect on risk.[350] Heterogeneity was high, which may be partially explained by varying adjustment for known confounders. Four case-control studies did not adjust for smoking.[306 352 556-558]

The single ecological study showed an association between increased carotenoid intake and decreased lung cancer risk.[333]

Serum or plasma or carotenoids

All four of the cohort studies showed decreased risk of lung cancer for the highest serum or plasma levels when compared to the lowest,[298 562-566] which was statistically significant in three.[298 562 563] Effect estimates were 0.27 (95% CI 0.1–0.7; adjusted for age, sex, smoking habits, alcohol drinking, and cholesterol),[563] 0.57 (95% CI 0.35–0.93; adjusted for age, smoking habits, and the intake of other nutrients, foods, and supplements),[298] 1.84 (low compared to high; p value for trend 0.033; adjusted for age and smoking),[562] and 0.84 (95% CI 0.48–1.47; adjusted for age and smoking).[566]

All five of the case-control studies showed decreased risk of lung cancer for the highest serum or plasma levels when compared to the lowest[567-571]; one was statistically significant.[568]

Dietary beta-cryptoxanthin

All seven cohort studies showed decreased risk with increased intake of beta-cryptoxanthin,[286 289 293 341 552 566 572 573] which was statistically significant in one.[293 566] Meta-analysis was possible on two studies, giving a summary effect estimate of 0.98 (95% CI 0.96–1.00) per 10 μg/day, with no heterogeneity.[286 572]

Pooled analysis from 7 cohort studies (almost 400 000 participants, followed up for 7 to 16 years, more than 3100 lung cancer cases) showed a statistically significant decreased risk when comparing high against low intake groups (0.76, 95% CI 0.67–0.89), p value for trend < 0.001.[579]

Six case-control studies showed increased risk for the highest intake groups when compared to the lowest,[306 308 321 327 560 574] which was statistically significant in four.[306 308 327 560] Two studies showed non-significant increased risk.[320 350]

The single ecological study showed an association between increased intake and increased risk.[333]

Serum or plasma beta-cryptoxanthin

Five cohort studies showed decreased risk with increased intake,[563-566 575 576] which was statistically significant in three.[563 566 575] One study showed statistically significant increased risk.[577] Meta-analysis was possible on two studies (including the latter described study), giving a summary effect estimate of 0.95 (95% CI 0.69–1.29) per 0.05 μmol/l, with high heterogeneity.[563 577]

The single case-control study showed a non-significant decreased risk with increased consumption.[578]

Data on beta-carotene supplements (see chapter 4.10.6.4.2) provide convincing evidence that high-dose supplements have a contrasting effect, at least in smokers, increasing the risk of lung cancer. Data on dietary beta-carotene (15 cohort studies, a pooled analysis, 32 case-control studies, 2 ecological studies) and serum or plasma beta-carotene (13 cohort studies, 16 case-control studies, 1 ecological study) showed no consistent evidence of an association. The full SLR is contained on the CD included with this Report.

The general mechanisms through which foods containing carotenoids could plausibly protect against lung cancer are outlined below.

There is a substantial amount of evidence available from both cohort and case-control studies. A clear dose-response relationship is apparent from cohort studies. Foods containing carotenoids probably protect against lung cancer.

Oesophagus

Three cohort studies[537 545 580] and one case-control study[581] investigated serum beta-carotene; 10 case-control studies investigated dietary beta-carotene and oesophageal cancer[95 107 125 141 548 582-587]; one cohort study[70] and three case-control studies[86 585 587] investigated dietary pro-vitamin A carotenoids.

Serum beta-carotene

One of the cohort studies showed decreased risk for the highest levels when compared to the lowest, which was statistically significant after adjusting for smoking (0.11, 95% CI 0.04–0.34).[537] Another cohort study showed no effect on risk (RR 1.0) and was specific for squamous cell carcinoma.[580] Another study reported a non-significant association but did not provide further details.[545]

The single case-control study showed that serum beta-carotene levels were non-significantly lower in cases than controls.[581]

Dietary beta-carotene

Nine of the case-control studies showed decreased risk for the highest intake group when compared to the lowest,[95 107 125 141 582-587] which was statistically significant in six.[95 141 582-585] One study reported a non-significant increased risk (figure 4.2.30).[548]

Dietary pro-vitamin A carotenoids

The single cohort study showed a non-significant decreased risk for the highest intake group when compared to the lowest, with an effect estimate of 0.70 (95% CI 0.29–1.71) (figure 4.2.30).[70]

Figure 4.2.30 — Beta-carotene and oesophageal cancer; cohort and case-control studies

Relative risk (95% CI)

Cohort
Zheng 1995 — 0.70 (0.29–1.71)

Case control
Decarli 1987 — 0.23 (0.12–0.45)
Brown 1988 — 0.80 (0.45–1.43)
Graham 1990 — 0.66 (0.36–1.22)
Valsecchi 1992 — 2.50 (1.67–3.74)
Tavani 1993 — 0.50 (0.22–1.12)
Tavani 1994 — 0.40 (0.19–0.85)
Hu 1994 — 0.70 (0.37–1.31)
Launoy 1998 — 0.61 (0.31–1.20)
De Stefani 1999 — 0.60 (0.40–0.90)
Franceschi 2000 — 0.30 (0.17–0.52)
Mayne 2001 — 0.43 (0.29–0.63)
Chen 2002 — 0.60 (0.31–1.15)

Relative risk, highest vs lowest exposure category

All case-control studies showed decreased risk for the highest intake group when compared to the lowest,[86 585 587] which was statistically significant in one[585] and in men, but not women, in another (figure 4.2.30).[86]

The general mechanisms through which foods containing carotenoids, including beta-carotene, could plausibly protect against oesophageal cancer are outlined below.

> **There is a substantial amount of consistent evidence available from both cohort and case-control studies. Foods containing beta-carotene probably protect against oesophageal cancer.**

Prostate

Five cohort studies,[588-594] 9 case-control studies,[595-608] and 3 ecological studies[609-611] investigated tomatoes; 3 cohort studies[590 591 612-615] and 14 case-control studies[595 596 598 599 601 602 606 616-625] investigated dietary lycopene; 6 cohort studies[576 594 626-630] and 2 case-control studies[596 608 619] investigated serum or plasma lycopene.

Tomatoes

Three of the cohort studies showed decreased risk for the highest intake groups when compared to the lowest,[588 591 592] which was statistically significant in two.[591 592] One study showed a non-significant increased risk[589] and one study reported that there was no statistically significant association.[594] Meta-analysis was possible on four of the cohort studies, giving a summary effect estimate of 0.69 (95% CI 0.43–1.08) per serving/day, with moderate heterogeneity.[588 589 591 592] One of these studies reported an effect estimate of 0.24 (95% CI 0.13–0.47) per 15 g/day for cumulative intake of tomato sauce.[591] Two of the cohort studies reported on advanced or aggressive prostate cancer.[590 591 594] One reported a risk estimate of 0.11 (95% CI 0.02–0.70) per increase in serving/day for tomato sauce[590] and the other found no statistically significant association.[594]

Seven of the case-control studies showed decreased risk for the highest intake groups when compared to the lowest,[595 598-600 602 603 608] which was statistically significant in one.[602] One study reported non-significant increased risk[597] and the other stated that there was no significant association without further details.[606] Meta-analysis was possible on five relatively high quality studies[595 597-600] and two relatively low quality ones.[602 603] The former gave a summary effect estimate of 0.97 (95% CI 0.91–1.03) per serving/day, with no heterogeneity; the latter gave a summary effect estimate of 0.33 (95% CI 0.04–2.74) per serving/day, with high heterogeneity.

The three ecological studies showed no consistent association.[609-611]

Dietary lycopene

Two cohort studies showed non-significant decreased risk for the highest intake groups when compared to the lowest,[590 614] the other study showed non-significant increased risk.[613] Meta-analysis was possible on all three cohort studies, giving a summary effect estimate of 0.97 (95% CI 0.64–1.45) per 5 mg/day, with low heterogeneity (figures 4.2.31 and
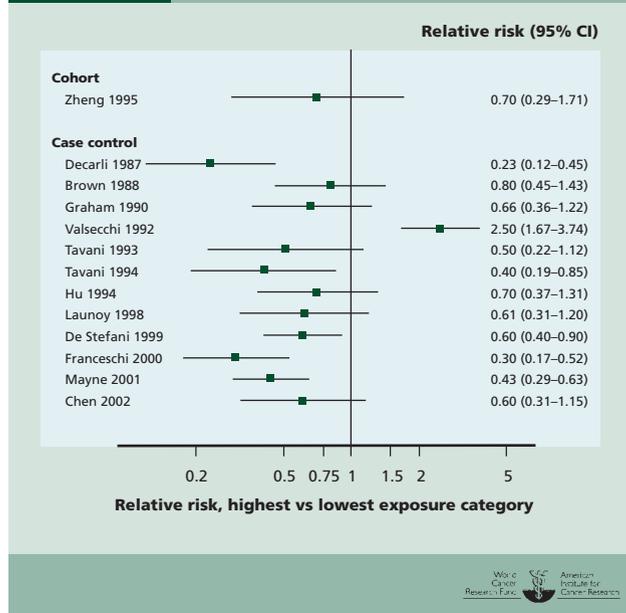
Figure 4.2.31 Lycopene and prostate cancer; cohort and case-control studies

Figure 4.2.32 Dietary lycopene and prostate cancer; cohort and case-control studies: dose response

4.2.32). One of these studies also reported cumulative measures of lycopene consumption, which is a robust measure of long-term consumption.[590] The effect estimate was 0.95 (95% CI 0.92–0.99) per 5 mg/day. All studies were fully adjusted.

Two of the cohort studies reported separately on advanced
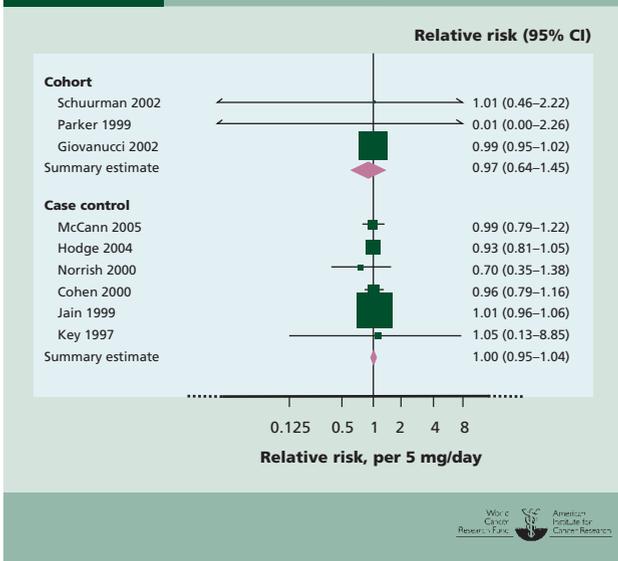
or aggressive cancer, giving estimates of 0.89 (95% CI 0.28–2.84) per 5 mg /day[613] and 0.57 (95% CI 0.37–0.87) for the highest intake groups when compared to the lowest.[591]

Nine case-control studies showed decreased risk for the highest intake groups when compared to the lowest,[595 598 602 606 616 617 619 621 624] which was statistically significant in one.[602] Five studies reported non-significant increased risk.[596 599 601 620 625] Meta-analysis was possible on six relatively high quality case-control studies[595 598 599 601 616 617] and three relatively low quality ones.[602 619 620] The former gave a summary effect estimate of 0.995 (95% CI 0.95–1.04) per 5 mg/day, with no heterogeneity and the latter gave a summary estimate of 0.56 (95% CI 0.23–1.36) per 5 mg/day, with high heterogeneity (figures 4.2.31 and 4.2.32).

Serum or plasma lycopene
Five cohort studies showed a non-significant reduced risk for the highest intake groups when compared to the lowest[576 626-628]; the other study showed a non-significant increased risk.[629] Meta-analysis was possible on four cohort studies, giving a summary estimate of 0.96 (95% CI 0.926–0.999) per 10 μg/l, with no heterogeneity.[576 626 627] All cohort studies were fully adjusted.

Both case-control studies of serum or plasma lycopene showed a statistically significant reduced risk for the highest intake groups when compared to the lowest.[596 619]

Lycopene is most bioavailable from cooked and pureed tomatoes. The best measures of systemic exposure are therefore studies on tomato sauce, particularly of cumulative consumption, or on serum or plasma lycopene. The Panel also gave emphasis to studies on advanced or aggressive cancers, which may be better linked to prognosis than studies that include early stage or latent disease, or screening-detected disease.

The general mechanisms through which foods containing carotenoids, including lycopene, could plausibly protect against prostate cancer are outlined below. In addition, amongst the common carotenoids, lycopene is thought to be the most efficient antioxidant in the body.[631]

> **There is a substantial amount of consistent evidence, in particular on tomato products, from both cohort and case-control studies. There is evidence for plausible mechanisms. Foods containing lycopene probably protect against prostate cancer.**

The Panel is aware that since the conclusion of the SLR, two cohort studies[632 633] and one case-control study[634] have been published. This new information does not change the Panel judgement (see box 3.8).

Prostate
Also see chapter 4.10.6.4.2 for evidence on beta-carotene supplements. Six cohort studies[147 360 591 594 613 635 636] and 21 case-control studies[595 598 599 602 616 617 619-621 624 625 637-648] investigated dietary beta-carotene and prostate cancer.

Ten cohort studies[576 594 626 628-630 635 649-652] and five case-control studies[584 596 608 619 653] investigated serum or plasma beta-carotene.

Dietary beta-carotene

Three cohort studies showed non-significant increased risk with increased intake.[594][635][636] Three studies showed no effect on risk.[360][591][613] Meta-analysis was possible on all six cohort studies, giving a summary effect estimate of 1.00 (95% CI 0.99–1.01) per 700 μg/day, with no heterogeneity.[360][591][594][613][635][636]

Two cohort studies reported results separately for advanced/aggressive prostate cancer.[594][613] Meta-analysis was possible on both studies, giving a summary effect estimate of 0.97 (95% CI 0.88–1.06) per 700 μg/day, with no heterogeneity.

Fourteen case-control studies showed decreased risk with increased intake,[595][599][602][616][617][619-621][625][637][638][642][646][648] which was statistically significant in two relatively low quality studies.[602][646][648] Four studies showed no effect on risk[624][639][644][645] and three studies showed non-significant increased risk.[598][640][641] Meta-analysis was possible on nine relatively high quality[595][598][599][616][617][637-640] and six relatively low quality case-control studies,[602][619][620][624][641][642] giving summary effect estimates of 0.99 (95% CI 0.98–1.00) and 0.98 (95% CI 0.94–1.01) per 700 μg/day, with no and moderate heterogeneity, respectively.

Serum or plasma beta-carotene

Five cohort studies showed decreased risk with increased intake,[576][626][628][649][651][652] which was statistically significant in one.[649] Four studies showed non-significant increased risk.[594][626][629][635] Meta-analysis was possible on seven cohort studies, giving a summary effect estimate of 1.00 (95% CI 0.91–1.09) per 10 μg beta-carotene/100 ml, with moderate heterogeneity.[576][626][629][635][649]

Four case-control studies showed decreased risk with increased intake,[584][608][619][653] which was statistically significant in one relatively low quality study.[653] One study showed non-significant increased risk.[596]

It is unlikely that foods containing beta-carotene have a substantial effect on the risk of prostate cancer.

The Panel is aware that since the conclusion of the SLR, two cohort studies[632][633] have been published. This new information does not change the Panel judgement (see box 3.8).

Skin

Also see chapter 4.10.5.1 for evidence on beta-carotene supplements. Two cohort studies[654][655] and seven case-control studies[656-663] investigated dietary beta-carotene and skin cancer. Three cohort studies[655][664-666] and one case-control study[657] investigated beta-carotene from food and supplements combined; eight cohort studies[545][630][651][655][667-672] and three case-control studies[584][673][674] investigated serum or plasma beta-carotene.

Dietary beta-carotene

Both cohort studies showed non-significant increased risk with increased intake, both for basal cell carcinoma.[654][655] One case-control study showed a non-significant decreased risk of basal cell carcinoma for the highest intake group when compared to the lowest[662]; one showed a non-significant

increased risk of squamous cell carcinoma.[658][659] Three case-control studies showed decreased risk of melanoma for the highest intake group when compared to the lowest,[657][661][663] which was statistically significant in two.[657][663] Two studies showed non-significant increased risk of melanoma.[656][660]

Beta-carotene from foods and supplements

Two cohort studies showed increased risk of basal cell carcinoma for the highest intake group when compared to the lowest.[655][665] One cohort study showed non-significant increased risk of squamous cell carcinoma.[666] One cohort study showed a non-significant increased risk of melanoma.[664] One case-control study showed a statistically significant decreased risk of melanoma for the highest intake group when compared to the lowest.[657]

Serum or plasma beta-carotene

Two studies showed decreased risk for skin cancer of unspecified type with increased serum or plasma beta-carotene,[669][671] which was statistically significant in one.[669] One cohort study showed non-significant decreased risk of non-melanoma skin cancer.[667] One cohort study (fully adjusted) showed a non-significant decreased risk for basal cell carcinoma[672]; two showed a non-significant increased risk[630][655]; and one a non-significant increased risk in women and a non-significant decreased risk in men.[651] Two studies showed non-significant decreased risk on squamous cell carcinoma.[668][672] Two studies showed decreased risk of melanoma, which was statistically significant in one[545][670]; and one study showed non-significant increased risk.[630] Meta-analysis was possible on both cohort studies that investigated squamous cell carcinoma, giving a summary effect estimate of 0.99 (95% CI 0.98–1.00) per μg beta-carotene/100 ml, with no heterogeneity.[668][672] Meta-analysis was possible on two cohort studies that investigated melanoma, giving a summary effect estimate of 0.90 (95% CI 0.78–1.03) per μg beta-carotene/100 ml, with moderate heterogeneity.[545][670]

One case-control study showed a statistically significant decreased risk of non-melanoma skin cancer, which, at 0.999 per μg/100 ml (95% CI 0.999–0.999), was close to no effect.[673] One case-control study showed non-significant increased risk of basal cell carcinoma for the highest intake group when compared to the lowest.[584] The same study showed non-significant increased risk of squamous cell carcinoma and non-significant increased risk of melanoma.[584] One additional study showed non-significant decreased risk of melanoma.[674]

It is unlikely that foods containing beta-carotene have any substantial effect on the risk of non-melanoma skin cancer.

General mechanisms — foods containing carotenoids

Carotenoids are antioxidants, which can prevent lipid oxidation and related oxidative stress. Oxidative stress induced by free radicals causes DNA damage. Base mutation, single- and double-strand breaks, DNA cross-linking, and chromo-

somal breakage and rearrangement can all occur if this initial damage is left unrepaired. This damage could plausibly be prevented or limited by dietary antioxidants found in fruits and vegetables.[675]

Many of the carotenoids, including beta-carotene, are also retinoid (vitamin A) precursors. The pro-vitamin A carotenoids may be converted to retinol where they function in cellular differentiation, immunoenhancement, and activation of carcinogen-metabolising enzymes.[580][676]

Lycopene is the most potent carotenoid antioxidant, has an antiproliferative effect, reduces plasma low-density lipoprotein cholesterol, improves immune function, and reduces inflammation.

4.2.5.4 Foods containing folate

Foods naturally containing folates are vegetables, fruits, and liver, but increasingly foods such as breakfast cereals are fortified with folic acid.

Pancreas

Three cohort studies,[677][678] two case-control studies,[509][679] and one ecological study[515] investigated folate from foods and/or supplements, and pancreatic cancer.

One cohort study reported a statistically significant reduced risk for the highest intake groups (without specifying the source of folate) when compared to the lowest[677]; one reported no effect on risk in men[678] and the other reported a non-significant increased risk in women.[678] Meta-analysis was possible on all three cohort studies, giving a summary effect estimate of 0.94 (95% CI 0.80–1.11) per 100 μg/day, with high heterogeneity.[677][678]

When these results were stratified according to dietary or supplemental folate, this heterogeneity was removed. Two cohort studies reported separately on dietary folate.[678] Both reported non-significant decreased risk; meta-analysis was possible on both, giving a summary effect estimate of 0.86 (95% CI 0.73–1.00) per 100 μg/day, with no heterogeneity (figure 4.2.33). All three cohort studies reported separately on supplemental folate, showing non-significant increased risk, with no heterogeneity.[677][678]

In addition, one of the cohort studies included a nested case-control study investigating blood folate levels. This reported a statistically significant decreased risk for the highest levels when compared to the lowest, with an effect estimate of 0.45 (95% CI 0.24–0.82).[680]

The Panel is aware of an additional cohort study, published after the conclusion of the literature review, which showed a statistically significant decreased risk for the highest intake groups when compared to the lowest.[681] The effect estimate was 0.25 (95% CI 0.11–0.59) for dietary folate and 0.33 (95% CI 0.15–0.72) for total folate (combining dietary and supplemental sources). No association was observed with folate supplements only.

One of the case-control studies reported a statistically significant reduced risk for the highest intake groups when compared to the lowest.[679] The other reported a non-significant decreased risk in women and no effect on risk in men.[509]

The ecological study showed a statistically significant decreased risk in areas of high folate intake.[515]

The possible differential effect between folate from foods and from supplements could be explained by folate serving as a marker for fruit and vegetable intake, by a different metabolic effect of the folic acid in supplements, or by confounders associated with supplement use.

The general mechanisms through which foods containing folate could plausibly protect against pancreatic cancer are outlined below.

The evidence available is sparse but a dose-response relationship was apparent from cohort studies. There is limited evidence suggesting that foods containing folate protect against pancreatic cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[681] has been published. This new information does not change the Panel judgement (see box 3.8).

Oesophagus

Eight case-control studies investigated dietary folate[113][124][125][136][548][583][585][587] and two case-control studies investigated red cell and/or plasma folate.[682-684]

All eight case-control studies that investigated dietary folate reported decreased risk for the highest intake groups when compared to the lowest,[113][124][125][136][548][583][585][587] which was statistically significant in two.[583][587] Most studies adjusted for smoking and alcohol.

Both case-control studies that investigated red cell and/or plasma folate reported that levels were lower (statistically significant) in cases than controls.[682-684] One study was adjusted for smoking and alcohol.[684]

The general mechanisms through which foods containing folate could plausibly protect against oesophageal cancer are outlined below. In addition, folate may reduce human papilloma virus proliferation in cells.[685]

The evidence, from case-control studies only, is sparse. There is limited evidence suggesting that folate protects against oesophageal cancer.

The Panel is aware that since the conclusion of the SLR, one case-control study[78] has been published. This new information does not change the Panel judgement (see box 3.8).

Figure 4.2.33 Folate and pancreatic cancer; cohort studies

Relative risk (95% CI)

	Relative risk (95% CI)
Skinner 2004 Women	0.85 (0.63–1.15)
Skinner 2004 Men	0.86 (0.71–1.04)
Summary estimate	0.86 (0.73–1.00)

Relative risk, per 100 μg/day
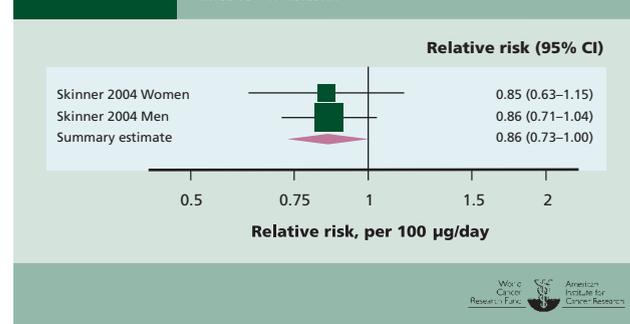
Colorectum

Nine cohort studies investigated dietary folate and colorectal cancer.[686-694] Two cohorts investigated serum folate.[694 695]

Seven cohort studies that investigated dietary folate showed decreased risk for the highest intake groups when compared to the lowest, [686-690 692 693] which was statistically significant in one.[689] Two cohort studies reported non-significant increased risk.[691 694] Meta-analysis was possible on four studies, giving a summary effect estimate of 0.84 (95% CI 0.76–0.93) per 100 μg/day, with low heterogeneity (figure 4.2.34).[686 689 692 696]

One study of serum folate levels showed statistically significant decreased risk for the highest intake groups when compared to the lowest, with an effect estimate of 0.52 (95% CI 0.27–0.97).[695] The other showed a non-significant decreased risk for colon cancer (0.96, 95% CI 0.4–2.3) and a non-significant increased risk for rectal cancer incidence (2.94, 95% CI 0.84–10.33).[694]

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

A published meta-analysis of seven cohort studies and nine case-control studies reported a statistically significant decreased risk of colorectal cancer for the highest dietary folate intake when compared to the lowest (0.75, 95% CI 0.64–0.89).[697]

The general mechanisms through which foods containing folate could plausibly protect against colorectal cancer are outlined below. In addition, folate intake is also strongly correlated with intake of dietary fibre, which probably prevents colorectal cancer (also see chapter 7.1).

The evidence from cohort studies is plentiful, with a dose-response relationship, but there is unexplained inconsistency. Residual confounding from dietary fibre is possible. There is limited evidence suggesting that foods containing folate protect against colorectal cancer.

The Panel is aware that since the conclusion of the SLR, four cohort[698-701] and two case-control studies[380 702] have been

| Figure 4.2.34 | Dietary folate intake and colorectal cancer; cohort studies |

Relative risk (95% CI)

Giovannucci 1998 Women	0.91 (0.76–1.10)
Su 2001 Women	0.93 (0.72–1.19)
Su 2001 Men	0.69 (0.52–0.90)
Konings 2002 Men	0.81 (0.64–1.03)
Konings 2002 Women	0.90 (0.63–1.29)
Larsson 2005 Women	0.77 (0.60–0.98)
Summary estimate	0.84 (0.76–0.93)

0.5   0.75   1   1.5   2

Relative risk, per 100 μg/day

published. This new information does not change the Panel judgement (see box 3.8).

General mechanisms — foods containing folate

Also see Chapter 2. Folate plays an important role in the synthesis and methylation of DNA.[703] Abnormal DNA methylation leading to aberrant gene expression has been demonstrated in several types of cancer. Folate deficiency may produce misincorporation of uracil instead of thymine into DNA. The effects of folate deficiency and supplementation on DNA methylation are gene- and site-specific, and appear to depend on cell type, target organ, stage of transformation, and degree and duration of folate depletion.

Animal studies have shown that dose and timing of folate intervention are critical in determining its effect: exceptionally high folate doses, and intervention after the formation of microscopic neoplastic foci, may promote rather than suppress colorectal carcinogenesis, at least in the animal models studied.[704]

There is a known interaction between folate and alcohol and the risk of some cancers.

4.2.5.5 Foods containing pyridoxine (vitamin B6)
Oesophagus

Six case-control studies investigated foods containing pyridoxine and oesophageal cancer.[88 125 548 583 585 587]

All six studies showed decreased risk for the highest intake groups when compared to the lowest,[88 125 548 583 585 587] which was statistically significant in four.[88 125 583 585] All studies adjusted for alcohol and five adjusted for smoking.

Together with folate and cobalamin (B12), vitamin B6 is involved in one-carbon metabolism and thus is important for DNA synthesis, repair, and methylation.

The evidence, from case-control studies only, was sparse. There is limited evidence suggesting that pyridoxine protects against oesophageal cancer.

The Panel is aware that since the conclusion of the SLR, one case-control study[78] has been published. This new information does not change the Panel judgement (see box 3.8).
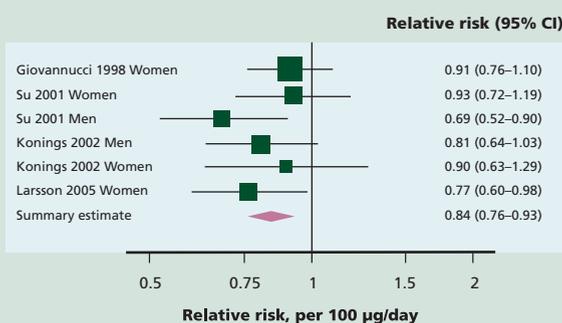
4.2.5.6 Foods containing vitamin C
Oesophagus

One cohort study,[70] 19 case-control studies,[86 88 94 95 104 105 107 113 120 121 124 125 136 548 583 585-587 705-707] and 3 ecological studies[118 203 708] investigated vitamin C and oesophageal cancer.

The single cohort study reported a non-significant reduced risk for the highest intake groups when compared to the lowest after adjustment for smoking, with an effect estimate of 0.70 (95% CI 0.3–1.7).[70]

Eighteen of the case-control studies showed decreased risk for the highest intake groups when compared to the lowest,[86 88 94 95 104 105 107 113 120 121 124 136 548 583 585-587 705-707] which was statistically significant in 13 (figure 4.2.35).[86 88 95 104 105 113 120 121 136 548 583 585 705 707] Three studies showed a non-significant increased risk, all specific to adenocarcinoma.[124 125 706]

None of the ecological studies reported a statistically significant association.[118 203 708]

Figure 4.2.35 — Vitamin C and oesophageal cancer; case-control studies

	Relative risk (95% CI)
Mettlin 1981	0.42 (023–0.77)
Tuyns 1983 Men	0.63 (0.50–0.79)
Tuyns 1983 Women	0.56 (0.20–0.91)
Brown 1988	0.50 (0.27–0.91)
Barone 1992	0.40 (0.10–1.55)
Kabat 1993	0.53 (0.22–1.25)
Hu 1994	0.60 (0.31–1.15)
Launoy 1998	0.40 (0.20–0.79)
De Stefani 1999	0.70 (0.52–0.94)
De Stefani 1999	0.50 (0.31–0.82)
Terry 2000	0.60 (0.38–0.95)
De Stefani 2000	0.14 (0.06–0.35)
Franceschi 2000	0.40 (0.24–0.65)
Mayne 2001	0.53 (0.36–0.79)
Zhang 1997	1.30 (0.48–3.49)
Chen 2002	0.60 (0.30–1.20)

Relative risk, highest vs lowest exposure category

It is biologically plausible that vitamin C should protect against cancer. It traps free radicals and reactive oxygen molecules, protecting against lipid peroxidation, reducing nitrates, and stimulating the immune system.[586 709] Moreover, it can recycle other antioxidant vitamins such as vitamin E.[534] Vitamin C has also been shown to inhibit formation of carcinogens and protect DNA from mutagenic attack.[535] However, evidence supporting a specific mechanism in the oesophagus is limited.[586]

> **A substantial amount of consistent evidence is available, from both cohort and case-control studies. Foods containing vitamin C probably protect against oesophageal cancer.**

The Panel is aware that since the conclusion of the SLR, one case-control study[710] has been published. This new information does not change the Panel judgement (see box 3.8).

4.2.5.7 Foods containing vitamin E
Oesophagus
One cohort study,[70] nine case-control studies,[86 88 95 105 125 548 583 585 587] and one ecological study[708] investigated dietary vitamin E and oesophageal cancer. Three cohort studies[537 545 711] and four case-control studies[581 682 683 712] investigated serum vitamin E.

Dietary vitamin E
The single cohort study showed decreased risk for the highest intake groups when compared to the lowest, with an effect estimate of 0.8 (95% CI 0.3–2.0; adjusted for smoking).[70]

Eight case-control studies reported decreased risk for the highest intake groups when compared to the lowest,[86 88 95 105 125 548 583 585] which was statistically significant in seven[86 88 95 105 548 583 585]; the other study reported no effect on risk.[587] All studies adjusted for alcohol and all but one also adjusted for smoking.

The single ecological study reported no association.[708]

Serum vitamin E
All three cohort studies showed decreased risk for the highest intake groups when compared to the lowest,[537 545 711] which was statistically significant in two. The effect estimates were 0.63 (95% CI 0.44–0.91) for alpha-tocopherol (the same study showed no significant association with serum gamma-tocopherol),[711] and 0.39 (95% CI 0.19–0.80) for gamma-tocopherol.[537] The third cohort study found lower mean values in cases than controls (8.52 vs 10.21 mg/l), which was not statistically significant.[545] The two former studies were maximally adjusted.[537 711]

Two case-control studies reported that cases had higher plasma vitamin E than controls,[682 683] statistically significant in one.[683] One study reported statistically significant lower levels in cases than those in controls[712]; and another reported no significant difference.[581] None of these studies was well adjusted.

The general mechanisms through which foods containing vitamin E could plausibly protect against oesophageal cancer are outlined below.

> **Much of the evidence on vitamin E, mostly from case-control studies, was of poor quality. There is limited evidence suggesting that foods containing vitamin E protect against oesophageal cancer.**

Prostate
Two cohort studies,[147 613 650 713] 13 case-control studies,[595 599 601 604 607 616 619-621 625 637 714-717] and 1 ecological study[708] investigated dietary vitamin E and prostate cancer; 4 cohort studies[629 630 718-722] and 1 case-control study[716] investigated serum vitamin E; 8 cohort studies[576 626 627 629 635 650 652 713 718 723-725] and 2 case-control studies[619 653] investigated serum or plasma alpha-tocopherol; 6 cohort studies[576 626 627 629 650 718 724] and 1 case-control study[619] investigated serum gamma-tocopherol.

Dietary vitamin E
Most studies showed non-significant decreased risk, although there is heterogeneity in the direction of effect reported and effect estimates are usually very close to 1 (no effect). One cohort study reported an effect size of 0.96 (0.75–1.2) per 10 mg/day for advanced/aggressive prostate cancer.[613] Meta-analysis was possible on seven relatively good quality case-control studies, giving a summary effect estimate of 1.04 (95% CI 0.99–1.11) per 10 mg/day, with low heterogeneity.[595 599 601 616 637 714 715] Dietary studies produce no consistent effect.

Serum or plasma alpha-tocopherol
Seven cohort studies showed decreased risk for the highest

intake groups when compared to the lowest,[576 626 629 635 650 652 713 718 723-725] which was statistically significant in one.[576] One cohort study showed no effect on risk.[627] Meta-analysis was possible on seven cohort studies, giving a summary effect estimate of 0.99 (95% CI 0.97–1.00) per mg/l, with no heterogeneity.[576 626 713 723-725]

Both case-control studies showed decreased risk for the highest intake groups when compared to the lowest,[619 653] which was statistically significant in one.[653]

Serum gamma-tocopherol
All six cohort studies showed decreased risk for the highest intake groups when compared to the lowest,[576 626 627 629 650 718 724] which was statistically significant in two.[650 724] Meta-analysis was possible on all six cohort studies, giving a summary effect estimate of 0.90 (95% CI 0.81–0.996) per mg/l, with moderate heterogeneity.

The single case-control study showed non-significant decreased risk for the highest intake groups when compared to the lowest.[619]

The general mechanisms through which foods containing vitamin E could plausibly protect against prostate cancer are outlined below. Vitamin E has also been shown to inhibit the growth of human prostate tumours induced in mice.[726]

The evidence, mostly from case-control studies, was inconsistent. There is limited evidence suggesting that foods containing vitamin E protect against prostate cancer.

The Panel is aware that since the conclusion of the SLR, two cohort studies[632 633] have been published. This new information does not change the Panel judgement (see box 3.8).

General mechanisms — foods containing vitamin E
Vitamin E is an antioxidant that has been reported to prevent DNA damage, enhance DNA repair, prevent lipid peroxidation, and prevent activation of carcinogens such as nitrosamines. Vitamin E protects vitamin A and selenium in the body. In addition to acting as a free-radical scavenger, vitamin E enhances the body's immune response, which may play a role in cancer defences.[727]

4.2.5.8 Foods containing selenium
Data from selenium levels in serum or nails can be interpreted more robustly than dietary data because they are less prone to certain sources of error; serum data are a short-term reflection of intake; levels in nails are cumulative and reflect long-term intake.

It is not possible to rule out residual confounding between selenium levels and healthy lifestyles. Individuals with higher selenium levels may be more likely to be following several strategies to improve their health, including taking supplements.

It is plausible that an effect attributed to selenium could only be apparent in areas of selenium deficiency.

Lung
Two cohort studies,[288 464] two case-control studies,[469 557] and two ecological studies[728 729] investigated dietary selenium and lung cancer.

Ten cohort studies,[463 575 577 730-738] seven case-control studies,[570 571 739-743] and four ecological studies[729 744-746] investigated plasma or serum selenium; three cohort studies[747-749] investigated selenium levels in nails.

Dietary selenium
One cohort study showed non-significant decreased risk for the highest intake group when compared to the lowest.[464] One cohort study showed non-significant increased risk in non-smokers and non-significant decreased risk in smokers.[288] Both case-control studies showed a non-significant increased risk for the highest intake group when compared to the lowest.[469 557] One ecological study showed statistically significant decreased risk in high-intake areas,[728] the other showed no consistent association.[729]

Plasma or serum selenium
Seven cohort studies showed decreased risk for the highest selenium levels when compared to the lowest,[463 575 731-734 736-738] which was statistically significant in two.[733 737] Four studies showed increased risk,[577 730 735 738] which was statistically significant in two.[735 738] Meta-analysis was possible on four cohort studies, giving a summary effect estimate of 0.969 (95% CI 0.940–0.999) per 10 μg/l, with low heterogeneity.[577 731 733 736]

Six case-control studies showed decreased risk for the highest levels when compared to the lowest,[570 739-743] which was statistically significant in four.[739 740 742 743] One study showed non-significant increased risk.[571]

One ecological study showed statistically significant decreased risk in areas of high plasma selenium[729]; the others showed no consistent effect.[729 744-746]

Nails
Two cohort studies showed decreased risk for the highest selenium levels when compared to the lowest,[748 749] which was statistically significant in one.[749] One study showed non-significant increased risk.[747]

The general mechanisms through which selenium could plausibly protect against lung cancer are outlined below.

The evidence available is sparse. There is limited evidence to suggest that foods containing selenium protect against lung cancer.

Prostate
One cohort,[713 750] 7 case-control studies,[599 601 639 715 716 751 752] and 2 ecological studies[729 753 754] investigated dietary selenium; 12 cohort studies[652 730 732 755-765] and 4 case-control studies[716 741 752 754 766 767] investigated serum or plasma selenium; and 3 cohort studies,[615 724 768] 3 case-control studies,[717 769 770] and 1 ecological study[771] investigated levels in nails. Further to this, 1 randomised controlled trial[772 773] and 2 cohorts[612 628 713] investigated selenium supplements (see chapter 4.10.6.4.5).

Dietary selenium

One cohort study showed a statistically significant decreased risk. The effect estimate was 0.66 (95% CI 0.44–0.98) per 50 μg/day.[713] This study did not adjust for confounders.

Two case-control studies showed non-significant decreased risk for the highest intake groups when compared to the lowest[751 752]; five showed increased risk,[599 601 639 715 716] one of which was statistically significant.[715] Meta-analysis was possible on three studies, giving a summary effect estimate of 1.07 (95% CI 0.92–1.25) per increase in 50 μg/day, with no heterogeneity.[599 601 639]

The two ecological studies reported that increasing selenium intake was associated with decreasing prostate cancer levels.[729 753 754]

Serum or plasma selenium

Eight cohort studies that investigated serum or plasma selenium showed decreased risk for the highest intake groups when compared to the lowest,[652 732 755-759 761 763 764] which was statistically significant in two. Four reported non-significant increased risk.[730 760 762 765] Meta-analysis was possible on nine of these studies, giving a summary effect estimate of 0.95 (95% CI 0.89–1.00) per 10 μg/l, with moderate heterogeneity (figure 4.2.36).[732 755 757 758 761 762 764 765]

Two of these 12 cohort studies reported separately on advanced/aggressive cancer.[730 755 758] Both showed decreased risk for the highest intake groups when compared to the lowest, which was statistically significant in one.[758] Meta-analysis was possible on both, giving a summary effect estimate of 0.87 (95% CI 0.79–0.97) per 10 μg/l, with no heterogeneity (figure 4.2.37).[755 758]

A dose-response relationship is apparent from the studies on advanced or aggressive disease (figure 4.2.38).

All four of the case-control studies showed decreased risk for the highest intake groups when compared to the lowest,[716 741 752 766 767] which was statistically significant in three.[741 752 767]

Nails

Two cohort studies investigated selenium levels in nails for all prostate cancer. Both showed non-significant decreased risk for the highest intake groups when compared to the lowest. Meta-analysis was possible on both studies, giving a summary effect estimate of 0.91 (95% 0.81–1.02) per 100 ng/g, with moderate heterogeneity.[724 768]

Two cohort studies investigated selenium levels in nails for advanced or aggressive prostate cancer. Both showed statistically significant decreased risk for the highest intake groups when compared to the lowest. Meta-analysis was possible on both, giving a summary effect estimate of 0.80 (95% 0.69–0.91) per 100 ng/g, with no heterogeneity.[615 768]

One case-control study showed non-significant decreased risk for the highest intake groups when compared to the lowest,[770] one showed no effect on risk[717] and the other showed a non-significant increased risk.[769]

The single ecological study reported a non-significant association.[771]

These data are supported by data on supplements, which have been shown to decrease prostate cancer risk (see chapter 4.10.6.4.5).

There is no significant heterogeneity within the meta-

Figure 4.2.37 — Selenium (in serum or plasma) and advanced or aggressive prostate cancer; cohort studies

Relative risk (95% CI)

	Relative risk (95% CI)
Nomura 2000	0.80 (0.64–1.00)
Li 2004	0.89 (0.80–1.00)
Summary estimate	0.87 (0.79–0.97)

Relative risk, per 10 µg/litre
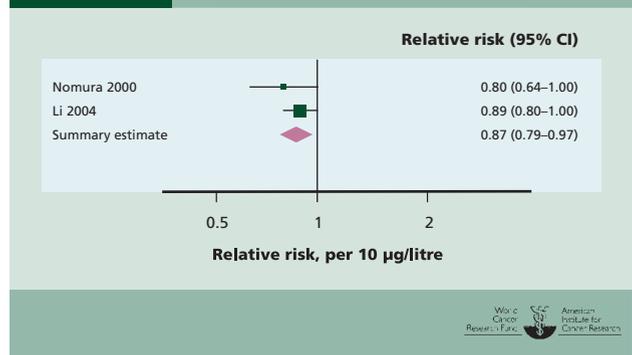
Figure 4.2.36 — Selenium (in plasma or serum) and prostate cancer; cohort studies

Relative risk (95% CI)

	Relative risk (95% CI)
Nomura 2000	0.89 (0.40–0.99)
Li 2004	0.95 (0.89–1.01)
Knekt 1990	0.99 (0.78–1.24)
Goodman 2001	1.01 (0.93–1.11)
Brooks 2001	0.77 (0.65–0.89)
Ringstad 1988	0.99 (0.97–1.01)
Willett 1983	0.64 (0.37–1.12)
Virtamo 1987	1.16 (0.82–1.65)
Salonen 1984	1.03 (0.63–1.70)
Summary estimate	0.95 (0.89–1.00)

Relative risk, per 10 µg/litre
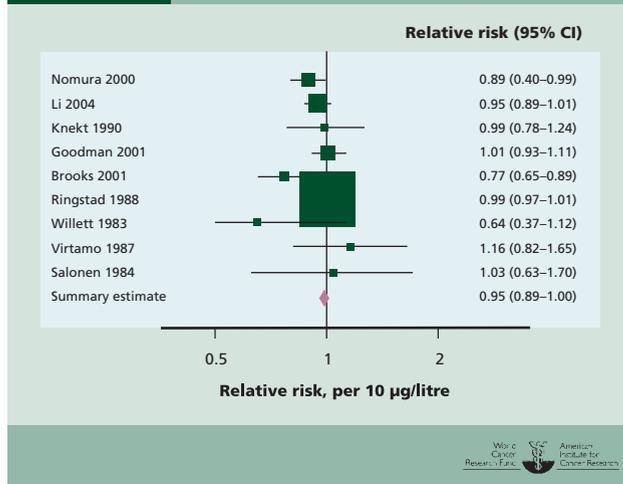
Figure 4.2.38 — Selenium (in serum or plasma) and advanced or aggressive prostate cancer; cohort studies: dose response

Li 2004

Nomura 2000

Selenium (µg/l)
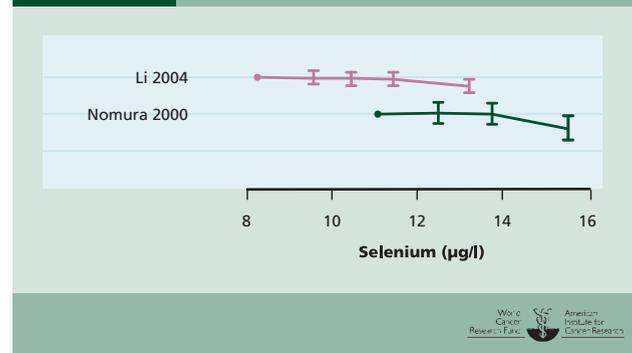
analyses of advanced/aggressive cancer. The low to moderate heterogeneity observed for other outcomes and different study types may be explained by the variable inclusion of latent cancers in the outcome and by variations in study quality.

The general mechanisms through which foods containing selenium could plausibly protect against prostate cancer are outlined below. In addition, selenoproteins are involved in testosterone production, which is an important regulator of both normal and abnormal prostate growth.[774][775]

> **The evidence from cohort and case-control studies is consistent, with a dose-response relationship. There is evidence for plausible mechanisms. Foods containing selenium probably protect against prostate cancer.**

Stomach

One case-control study[776] and five ecological studies[238][729][777-779] investigated dietary selenium and stomach cancer. Three cohort studies,[731][732][736] nine case-control studies,[738][741][754][780-785] and three ecological studies[236][729][786] investigated blood selenium. One cohort study[787] and one case-control study[788] investigated selenium in toenails or hair. In addition, one randomised controlled trial and one combined trial investigated selenium supplements.[423][424]

Dietary selenium
The single case-control study showed that dietary selenium was not significantly associated with risk of stomach cancer.[776]

Most ecological studies showed that low selenium levels were associated with increased stomach cancer risk,[238][777-779] one of which was statistically significant.[779]

Blood selenium
All three cohort studies that investigated blood selenium levels showed decreased risk for the highest levels when compared to the lowest,[731][732][736] which was statistically significant in men in one study.[732] Meta-analysis was possible on all three, giving a summary effect estimate of 0.89 (95% CI 0.78–1.00) per 0.1 μmol/l, with moderate heterogeneity.[731][732][736]

All nine case-control studies showed statistically significant decreased risk for the highest levels when compared to the lowest.[738][741][754][780-785] Meta-analysis was possible on six of these, giving a summary effect estimate of 0.44 (95% CI 0.35–0.55) per 0.1 μmol/l, with high heterogeneity.[741][754][782-785] This heterogeneity was caused by varying size, not direction, of effect.

All three ecological studies reported inverse associations between blood or plasma selenium and stomach cancer mortality,[236][729][786] which were statistically significant in two.[236][786]

A dose-response relationship is apparent from case-control but not cohort data.

Two additional cohort studies, both from China, stratified results according to tumour location.[789][790] The apparent protective effect was strengthened for cardia cancers, but disappeared for proximal.

Nails and hair
The single cohort study that investigated selenium in nails showed statistically significant decreased risk for the highest levels when compared to the lowest in men, but not women. The effect estimates were 0.4 in men (95% CI 0.17–0.96; 72 cases) and 1.68 in women (95% CI 0.43–6.54; 20 cases).[787]

The single case-control study found that mean hair selenium levels were significantly lower in the 15 stomach cancer cases than in controls.[788]

The general mechanisms through which foods containing selenium could plausibly protect against stomach cancer are outlined below. In addition, selenoproteins with powerful antioxidant activity may provide protection against the inflammatory effect of *H pylori*, which can lead to gastric cancer in infected individuals.[791]

> **A substantial amount of evidence was available on selenium, from dietary questionnaires, as well as blood, nails, and hair, mostly from case-control studies. There is limited evidence suggesting that foods containing selenium protect against stomach cancer.**

Colorectum

Fifteen case-control studies investigated dietary selenium and colorectal cancer.[738][785][792-795]

Dietary, serum or plasma, toenail selenium
Meta-analysis was possible on six independent effect estimates from five case-control studies, giving a summary effect estimate of 0.86 (95% CI 0.78–0.95) per 10 μg/dl serum, with high heterogeneity.[785][792-795] All of these studies reported decreased risk, which was statistically significant in four of the five studies.[792-795] The heterogeneity is therefore derived from varying size, but not direction of effect. The remaining 10 studies reported non-significant decreased risk.[738] These data are supported by limited evidence suggesting that there is also a protective effect from selenium supplements (see chapter 4.10.6.4.5).

The general mechanisms through which foods containing selenium could plausibly protect against colorectal cancer are outlined below.

> **A substantial amount of data was available, from case-control studies only. There is limited evidence suggesting that foods containing selenium protect against colorectal cancer.**

General mechanisms — foods containing selenium
Dietary selenium deficiency has been shown to cause a lack of selenoprotein expression. Twenty-five selenoproteins have been identified in animals and a number of these have important anti-inflammatory and antioxidant properties.[796] Four are glutathione peroxidises, which protect against oxidative damage to lipids, lipoproteins, and DNA. These enzymes are rapidly degraded during selenium deprivation. Three are thioredoxin reductases and, amongst other functions, these regenerate oxidised ascorbic acid to its active antioxidant form.

Selenoproteins appear to reach their maximal levels relatively easily at normal dietary selenium intake and not to increase with selenium supplementation. It is, however, plausible that supraphysiological amounts of selenium might affect programmed cell death, DNA repair, carcinogen metabolism, immune system, and anti-angiogenic effects.[797]

4.2.5.9 Foods containing quercetin

Lung

Two cohort studies[147 798] and three case-control studies[327 477 799] investigated foods containing quercetin and lung cancer.

Both cohort studies showed statistically significant decreased risk for the highest intake groups when compared to the lowest.[147 798] The effect estimates were 0.63 (95% CI 0.52–0.78)[147] and 0.42 (95% CI 0.25–0.72).[798] Both studies adjusted for smoking.

Two case-control studies showed decreased risk for the highest intake groups when compared to the lowest,[327 477] which was statistically significant in one.[327] One study reported non-significant increased risk.[799] The effect estimates were 0.58 (95% CI 0.39–0.85),[327] 0.7 (95% CI 0.4–1.1),[477] and 1.89 (95% CI 0.72–4.92).[799] The latter study may have been over-adjusted.

Quercetin is a flavonoid. It is an antioxidant and also directly inhibits expression of CYP1A1 (a cytochrome P450 enzyme that helps to metabolise toxins), resulting in decreased formation of DNA adducts.[475] Elevated CYP1A1 activity has been associated with increased risk of lung cancer, primarily in smokers.[476] The evidence for CYP1A1/flavonoid interactions is supported by the observation that protective associations of flavonoids are associated with specific CYP1A1 genotypes.[476 477]

> **The evidence available is sparse and inconsistent. There is limited evidence suggesting that foods containing quercetin protect against lung cancer.**

4.2.5.10 Pulses (legumes)

Studies conducted in Western countries, as most cohorts have been, are likely to have limited power to detect an association between pulses, and particularly soya intake, and cancer risk because consumption tends to be low.

Stomach

Three cohort studies,[144 146 241] 22 case-control studies,[109 157 161 162 165 175 179 180 185-187 190 219 224 243 244 247 249-251 270 271 482] 2 cross-sectional studies,[196 800] and 16 ecological studies[116-119 197 198 200-203 208 209 236 238 239 801] investigated pulses (legumes) and stomach cancer. Two cohort studies,[802 803] 9 case-control studies,[109 129 159 178 184 194 226 229 262] and 2 ecological studies[208 804] investigated soya and soya products.

Pulses (legumes)

All three cohort studies reported decreased risk with increased intake of pulses (legumes),[144 146 241] which was statistically significant in one.[146] Meta-analysis was possible on two studies, giving a summary effect estimate of 0.93 (95% CI 0.82–1.05) per 20 g/day, with moderate heterogeneity.[144 146]

Twelve case-control studies showed decreased risk for the highest intake groups when compared to the lowest,[109 157 161 165 179 185-187 190 219 247 249 250 271] which was statistically significant in six.[109 161 165 179 190 249] Six studies reported increased risk,[162 224 243 251 270 482] which was statistically significant in two.[224 243 270] The remaining four studies reported no effect on risk,[180 244] or stated that there was no significant effect on risk.[175] Meta-analysis was possible on eight studies, giving a summary effect estimate of 0.93 (95% CI 0.87–0.99) per 20 g/day, with moderate to high heterogeneity.[157 162 179 180 186 187 247 249]

A dose-response relationship is apparent from case-control but not cohort data.

One ecological study reported a statistically significant association, so that higher soya consumption was associated with lower stomach cancer risk.[208] The other 15 reported no significant association.[116-119 197 198 200-203 209 236 238 239 801]

Soya and soya products

Both cohort studies showed decreased risk for the highest intake groups when compared to the lowest,[802 803] which was statistically significant in one.[803] The effect estimates were 0.60 (44 cases, 95% CI 0.40–1.10)[802] and 0.86 (121 cases, 95% CI 0.77–0.96) per 20 g/day.[803] The smaller study was not adjusted for any confounders.

All nine case-control studies showed decreased risk for the highest intake groups when compared to the lowest,[109 129 159 178 184 194 226 229 262] which was statistically significant in five.[129 159 178 184 226] Meta-analysis was possible on seven studies, giving a summary effect estimate of 0.82 (95% CI 0.72–0.94) per 20 g/day, with high heterogeneity.[109 129 159 178 194 226 229] Heterogeneity is derived from the size, and not the direction, of the effect.

A dose-response relationship is apparent from case-control data, as well as from one of the two cohort studies.

Both ecological studies reported statistically significant inverse relationships, with stomach cancer risk decreasing in areas of increased soya consumption.[208 804]

The general mechanisms through which pulses (legumes), soya and soya products could plausibly protect against stomach cancer are outlined below. In addition, laboratory experiments have shown that genistein slows down the development of stomach cancers promoted by sodium chloride by increasing apoptosis, and lowering cell proliferation and blood vessel growth.[805] Additionally, in a rodent model, a diet containing miso inhibited N-nitrosamine-induced stomach tumours.[806]

> **The evidence, mostly from case-control studies, is inconsistent. There is limited evidence suggesting that pulses (legumes), including soya and soya products, protect against stomach cancer.**

Prostate

Three cohort studies,[589 592-594] 11 case-control studies,[595 597 599-601 604 608 617 620 624 715] and 6 ecological studies[116 118 609 807-809] investigated pulses (legumes) and prostate cancer. Four cohort studies,[597 810-813] 4 case-control studies,[603 715 814-816] and 2 ecological studies[804 808] investigated soya and soya products.

Pulses (legumes)

Two cohort studies reported statistically significant decreased risk with increased intake[589] [592]; the third study reported that there was no significant association.[594] The reported effect estimates were 0.93 (95% CI 0.87–0.996)[589] and 0.817 (95% CI 0.714–0.934)[592] per serving/week. The latter was specific to beans and lentils.

Eight of the case-control studies showed decreased risk with increased intake,[595 597 599 608 617 620 624 715] which was statistically significant in two.[597 624] One study showed a non-significant increased risk[604] and the other reported no effect on risk.[600] One study showed a non-significant increased risk for dried beans and lentils and a non-significant decreased risk with fresh beans and lentils.[601] Meta analysis was possible on four relatively good quality case-control studies, giving a summary effect estimate of 0.97 (95% CI 0.95–0.98) per serving/week, with no heterogeneity.[595 597 599 601]

A dose-response relationship is apparent from two of the cohort studies, as well as case-control data.

The five ecological studies generally fail to show a clear relationship between consumption of pulses and prostate cancer risk; correlations range from -0.15 to -0.63.[116 118 609 807-809]

Soya and soya products

The cohort studies reported a wide range of results based on different specific exposures.[810-813] One study, which reported on soya and soya products, showed a non-significant decreased risk for the highest intake groups when compared to the lowest, with an effect estimate of 0.79 (95% CI 0.53–1.18).[810] One study reported a statistically significant decreased risk with increased intake of soya milk (0.93, 95% CI 0.87–0.99) per serving/week and a non-significant decreased risk with increased intake of vegetarian soya products (0.93, 95% CI 0.85–1.01) per serving/week.[813] One reported no association between soya bean paste soup intake and prostate cancer.[811] The final study reported non-significant harmful effects for miso soup and foods cooked in soy sauce, with effect estimates of 1.05 (95% CI 0.94–1.18) and 1.06 (0.474, 2.39) respectively per serving/day.[812]

All four case-control studies showed non-significant decreased risk with increased intake.[597 603 715 814-816] Meta analysis was possible on two case-control studies, giving a summary effect estimate of 0.98 (95% CI 0.95–1.00).[597 715]

The two ecological studies reported no clear relationship between soya consumption and prostate cancer.[804 808]

Heterogeneity is likely to be derived from the wide variety in specific foods being investigated.

The general mechanisms through which pulses (legumes), soya and soya products could plausibly protect against prostate cancer are outlined below. In addition, phytoestrogens in pulses and soya can have an androgenic effect, potentially inhibiting testosterone-induced growth of the prostate.

The evidence, mostly from case-control studies, is inconsistent. There is limited evidence suggesting that pulses (legumes), including soya and soya products, protect against prostate cancer.

General mechanisms — pulses (legumes)

Pulses (legumes), particularly soya foods, contain various compounds that may have anti-cancer effects, including protease inhibitors, saponins, and phytoestrogens, such as genistein and daidzein, which are found in high concentrations in soya.[817] These compounds could plausibly influence oestrogen metabolism. They have also been shown to have antioxidant effects, inhibit the growth of blood vessels to a tumour, and may influence apoptosis and cell growth.[818]

4.2.5.11 Nuts and seeds

The evidence was too limited in amount, consistency, or quality to draw any conclusions

4.2.5.12 Herbs and spices

Garlic can be classified as a herb or as an allium vegetable. Data on garlic have contributed to the evidence base for allium vegetables and stomach cancer (see chapter 4.2.5.1.1) and garlic also probably protects against colorectal cancer (see chapter 4.2.5.1.1).

4.2.5.12.1 Chilli

Stomach

Fourteen case-control studies investigated chilli use and stomach cancer.[171 175 176 180 182 187 189 219 246 247 259 415 819-821]

Nine studies showed increased risk for the highest intake groups when compared to the lowest,[175 176 180 187 189 219 259 415 820 821] which was statistically significant in four,[175 180 259 821] statistically significant in men but not women in a fifth study,[219] and statistically significant in non-drinkers of alcohol, but not alcohol drinkers, in a sixth.[176] Four studies showed decreased risk,[171 182 246 247] which was statistically significant in three.[182 246 247] One study reported no significant effect on risk.[819]

Chilli may be used to disguise 'off' flavours in foods, therefore these data may be confounded by socioeconomic status, the availability of refrigeration, and *H pylori* infection.

Some constituents of chilli are irritants which could therefore plausibly increase inflammation in the stomach.

The evidence, from case-control studies only, is inconsistent. There is limited evidence suggesting that chilli is associated with an increased risk of stomach cancer.

4.2.4 Comparison with previous report

The previous report concluded that the evidence that diets high in vegetables and fruits protect against cancers of the mouth, pharynx, oesophagus, lung, and stomach was convincing; and that the evidence that diets high in vegetables protect against colorectal cancer was also convincing. The previous report also judged that diets high in vegetables and fruits probably protected against cancers of the larynx, pancreas, breast, and bladder. The panel also noted a pattern whereby diets high in vegetables and fruits possibly protected against cancers of the cervix, ovary, endometrium, and thyroid; and that diets high in vegetables possibly pro-

tected against cancers of the liver, prostate, and kidney.

Since the mid-1990s, a number of cohort studies have somewhat weakened the overall evidence for the protective effects of vegetables and fruits. A number of judgements of probable protective effects are made for non-starchy vegetables and for fruits (mouth, pharynx, larynx, oesophagus, stomach, and (fruits only) lung). In general, the reason for this is that the more recent cohort studies failed to show the effect seen in case-control studies.

The previous report also made judgements on types of vegetables and fruits in a footnote, while choosing not to enter these into the matrix. The evidence that green vegetables protected against lung and stomach cancer was judged convincing; and probable for mouth and oesophageal cancer. The evidence that cruciferous vegetables protected against colorectal and thyroid cancer was judged probable. The evidence that allium vegetables protected against stomach cancer was judged probable. The evidence that raw vegetables and citrus fruits protected against stomach cancer was judged convincing. These classifications are somewhat different from those made in this Report, but mostly also generated more confident judgements than are made here.

Vitamins, minerals, and other bioactive constituents of foods and drinks were assessed as such in the previous report, whereas here they are assessed either as contained in foods and drinks or (see chapter 4.10) as supplements. The previous report judged that carotenoids (in food) probably protected against lung cancer; that vitamin C (in food) probably protected against stomach cancer; and that these vitamins and vitamin E possibly protected against cancers of a number of sites.

The previous panel regretted the lack of evidence on pulses (legumes), nuts, seeds, herbs, and spices, and made no significant judgements. Since then, evidence on soya and its products, and on garlic (as well as allium vegetables in general) and chilli, has increased and allowed some judgements.

The previous report judged that aflatoxin contamination was a probable cause of liver cancer. Since then, the overall evidence, particularly on the underlying mechanisms, has strengthened.

The previous report emphasised evidence on vegetables and on fruits as a whole, while noting evidence on categories of vegetables and fruits. This Report has not made any separate judgement on raw vegetables and fruits. The previous report classified bananas as plantains. Here they are classified as fruits. The previous report considered micronutrients and phytochemicals contained in foods of plant origin in separate chapters. Here, the evidence has been characterised in terms of foods containing specified micronutrients, and they are considered together with vegetables and fruits, pulses (legumes), nuts and seeds, and other plant foods. Similarly, the previous report considered dietary fibre separately from cereals (grains) and other plant foods. Here, dietary fibre is considered in the context of cereals (grains) and other plant foods, including those assessed in this section.

4.2.7 Conclusions

The Panel concludes:

Findings from cohort studies conducted since the mid-1990s have made the overall evidence that vegetables, or fruits, protect against cancers, somewhat less impressive. In no case now is evidence of protection judged to be convincing. However, there is evidence that some types of vegetables, and fruits in general, probably protect against a number of cancers. The few judgements on legumes (pulses), nuts, seeds, and (with two exceptions) herbs and spices, reflect the small amount of epidemiological evidence.

Non-starchy vegetables probably protect against cancers of the mouth, pharynx, and larynx, and those of the oesophagus and stomach. There is limited evidence suggesting that they also protect against cancers of the nasopharynx, lung, colorectum, ovary, and endometrium. Allium vegetables probably protect against stomach cancer. Garlic (an allium vegetable, commonly classed as a herb) probably protects against colorectal cancer.

Fruits in general probably protect against cancers of the mouth, pharynx, and larynx, and of the oesophagus, lung, and stomach. There is limited evidence suggesting that fruits also protect against cancers of the nasopharynx, pancreas, liver, and colorectum.

There is limited evidence suggesting that carrots protect against cervical cancer; and that pulses (legumes), including soya and soya products, protect against stomach and prostate cancers. There is limited evidence suggesting that chilli is a cause of stomach cancer.

Fruits and non-starchy vegetables are low energy-dense foods. For a discussion of the effect of such foods and drinks on weight gain, overweight, and obesity, and the role of weight gain, overweight, and obesity in the risk of some cancers, see Chapters 6, 7, and 8.

Evidence that vegetables, fruits, and pulses protect against some cancers is supported by evidence on various micronutrients, which act as markers for consumption of vegetables, fruits, and pulses (legumes), and other plant foods. Foods containing folate probably protect against pancreatic cancer, and there is limited evidence suggesting that these also protect against oesophageal and colorectal cancers. Foods containing carotenoids probably protect against cancers of the mouth, pharynx, and larynx, and also lung cancer. Foods containing the carotenoid beta-carotene probably protect against oesophageal cancer; and foods containing lycopene, found in tomatoes and also fruits such as watermelon, guavas, and apricots, probably protect against prostate cancer. Foods containing vitamin C, found in some vegetables, citrus and other fruits, and potatoes, probably protect against oesophageal cancer. There is limited evidence suggesting that foods containing quercetin, such as apples, tea, and onions, protect against lung cancer.

Evidence on foods containing other micronutrients is grouped here, for ease of reference. Foods containing

selenium probably protect against prostate cancer; there is limited evidence suggesting that they protect against stomach and colorectal cancers. There is limited evidence suggesting that foods containing the B vitamin pyridoxine protect against oesophageal and prostate cancers; and that foods containing vitamin E protect against oesophageal and prostate cancers.

4.3 Meat, poultry, fish, and eggs

MEAT, POULTRY, FISH, EGGS, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	**Cancer site**	**Exposure**	**Cancer site**
Convincing			**Red meat[1]** **Processed meat[2]**	**Colorectum** **Colorectum**
Probable			**Cantonese-style salted fish[3]**	**Nasopharynx**
Limited — suggestive	Fish Foods containing vitamin D[4][7]	Colorectum Colorectum	Red meat[1] Processed meat[2] Foods containing iron[4][5] Smoked foods[6] Grilled (broiled) or barbecued (charbroiled) animal foods[6]	Oesophagus Lung Pancreas Endometrium Oesophagus Lung Stomach Prostate Colorectum Stomach Stomach
Substantial effect on risk unlikely	None identified			

1 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
2 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
3 This style of preparation is characterised by treatment with less salt than typically used, and fermentation during the drying process due to relatively high outdoor temperature and moisture levels. This conclusion does not apply to fish prepared (or salted) by other means.
4 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).
5 Although red and processed meats contain iron, the general category of 'foods containing iron' comprises many other foods, including those of plant origin.
6 The evidence is mostly from meats preserved or cooked in these ways.
7 Found mostly in fortified foods and animal foods.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

These animal foods are sources of protein and micronutrients. The amount and nature of the fat content of meat, poultry, and fish depends on methods of rearing, processing, and preparation, as well as the type of animal.

Production and consumption of red meat and processed meat generally rise with increases in available income. Consumption of beef and products made with beef is still increasing, notably in China and other middle- and low-income countries. In many countries, poultry is now also intensively reared and consumption has increased greatly. Much fish is now farmed.

In general, *the Panel judges* that the evidence on red meat and processed meat is stronger than it was in the mid-1990s. Epidemiological evidence on other methods of preserving and preparing meats and other animal foods is sparse; the overall evidence remains suggestive, at most. The evidence on poultry, fish, and eggs is generally insubstantial.

The Panel judges as follows:
The evidence that red meats and processed meats are a cause of colorectal cancer is convincing. Cantonese-style salted fish is a probable cause of nasopharyngeal cancer. This finding does not apply to any other type of fish product. Cantonese-style salted fish is also subject to fermentation.

There is limited evidence suggesting that fish, and also foods containing vitamin D, protect against colorectal cancer. There is limited evidence suggesting that red meat is a cause of cancers of the oesophagus, lung, pancreas and endometrium; that processed meat is a cause of cancers of the oesophagus, lung, stomach and prostate; and that foods containing iron are a cause of colorectal cancer. There is also limited evidence that animal foods that are grilled (broiled), barbecued (charbroiled), or smoked, are a cause of stomach cancer.

Red meat can be relatively high in animal fats. For a discussion of the role of animal fats on cancer, see chapter 4.4 and Chapter 7. Meat can also be energy dense. For discussion on the role of energy-dense foods on weight gain, overweight, and obesity, and the role of weight gain, overweight, and obesity in the risk of some cancers, see Chapters 6 and 8.

The strongest evidence, corresponding to judgements of 'convincing' and 'probable', shows that red meat and processed meat are causes of colorectal cancer, and that Cantonese-style salted fish is probably a cause of nasopharyngeal cancer. *The Panel also notes* limited evidence suggesting that red meat and processed meat are causes of other cancers.

It is generally, though not universally, agreed that humans evolved as omnivores, and that healthy diets usually include foods of plant and of animal origin — including meat, poultry, fish, and eggs, as well as milk and other dairy products.

Most people who do not eat meat, flesh, or any food of animal origin do so for religious or ethical reasons. Impoverished communities eat little flesh and meat is reserved for feasts. Partly because meat-eating is a sign of prosperity and partly because many people enjoy eating meat, poultry, and fish, production and consumption generally rise as available income increases. Consumption of beef is, for example, now increasing very rapidly in China, and consumption of 'burgers' made from beef is increasing worldwide.

Early reports concerned with nutritional deficiencies identified meat, poultry, and fish as good sources of protein, iron, and other nutrients, and eggs as a 'complete food', especially for children. By contrast, in the second half of the 20th century, reports on meat, poultry, fish, and eggs tended to focus on red meat as a source of fat and saturated fatty acids and on eggs as a source of dietary cholesterol in the causation of coronary heart disease. These reports promoted poultry and fish as better choices than red meat, either because they contain less fat and saturated fatty acids or, in the case of oily fish, they contain unsaturated fats identified as protective. Little attention has been given to flesh from wild animals and birds, despite this being known to have a different nutritional profile — lower in total fat and higher in unsaturated fatty acids. On the other hand, since the mid-1990s more attention has been given in epidemiological studies to processed meat as a cause or possible cause of cancers of some sites.

For discussion of the role of red meat and processed meat in energy-dense foods and drinks, the effect of energy-dense foods and drinks on weight gain, overweight, and obesity, and the role of weight gain, overweight, and obesity in the risk of some cancers, see Chapters 6 and 8.

In this Report, methods of production, preservation, processing, and preparation (including cooking), that are solely or mainly to do with meat and other animal foods, are included here. Processed meat as a category is included here. The mineral iron is also covered here, although it is also found in plant foods.

4.3.1 Definitions and sources

Meat and poultry
In this Report, meat includes all animal flesh apart from fish and seafood. Meat can be further classed as either red meat, which generally refers to flesh from animals that have more red than white muscle fibres (in this Report, beef, goat, lamb, and pork), or poultry, which usually has more white than red muscle fibres (from birds such as chickens, guinea fowl, and turkeys). Meat can also be categorised by dividing it into meats from skeletal muscles or the internal organs (offal, such as the brain, liver, heart, intestines, and tongue). Meat can also be divided according to whether the animal was domesticated or wild. Most meats consumed around the world today are from domesticated animals. 'Wild' meats, that is from non-domesticated or free-ranging species, are a significant source of protein and energy among some populations. Some non-domesticated animals, such as deer or buffalo, are also farmed. However, the evidence presented in this chapter applies only to meat from domesticated animals. Some meats are processed in various ways (box 4.3.1).

Fish
This Report uses the culinary definition of fish, which includes shellfish. There are more than 27 000 species of salt and freshwater fish; many more crustaceans, bivalves, and cephalopods can also be eaten. Fish and shellfish are the only foods that, globally, are still obtained in significant quantities from the wild. But many species are on the verge of commercial extinction and aquaculture is increasing worldwide. For instance, more than a third of the salmon eaten worldwide is farmed. Like meat, fish is also processed, for instance by drying, salting, and smoking.

Eggs
Eggs are the ova of animals and in this Report mean only

Box 4.3.1 | Processed meat

What is 'processed meat'? The question is important because, as shown here, the evidence that processed meat is a cause of colorectal cancer is convincing.

In the broad sense of the word, most meat is processed — cooking is a process. But as commonly used, the term 'processed meat' refers to meats (usually red meats) preserved by smoking, curing, or salting, or by the addition of preservatives. Meats preserved only by refrigeration, however they are cooked, are usually not classified as 'processed meat'.

There is no generally agreed definition of 'processed meat'. The term is used inconsistently in epidemiological studies. Judgements and recommendations are therefore less clear than they could be.

Ham, bacon, pastrami, and salami are processed meats. So are sausages, bratwursts, frankfurters, and 'hot dogs' to which nitrites or nitrates or other preservatives are added (box 4.3.2). Minced meats sometimes fall inside this definition, often if they are preserved chemically, but not always. The same point applies to 'hamburgers'. Given the importance of this issue, transnational burger caterers should specify the methods they use to process their products.

those of birds; because they are generally eaten before they have been fertilised, they do not contain an embryo. Eggs are eaten both on their own and as an ingredient in a variety of baked goods, sauces, and other composite foods. Chicken eggs are most commonly eaten, although people also eat duck, ostrich, and quail eggs. Fish eggs (roe) and turtle eggs are not included here.

4.3.2 Composition

Meat and poultry

Meat contains around 20–35 per cent protein by weight. The fat content by weight ranges from less than 4 per cent in lean poultry to 30–40 per cent in fatty meat from domesticated, farmed animals. About 50 per cent of the fatty acids in lean meat are monounsaturated fatty acids, while saturated fatty acids make up around 40–50 per cent (see chapter 4.4.2). Poultry contains a lower proportion of saturated fatty acids (30–35 per cent) and a higher proportion of polyunsaturated fatty acids (15–30 per cent compared with 4–10 per cent).[1] There are differences between meats from domesticated animals and wild meats. Wild animals are typically more mature, leaner, and contain a greater variety of aromatic compounds than farmed animals. They will have received no medication and their diets will have been uncontrolled. Wild animals are not only lower in fat, but also have a higher proportion of polyunsaturated fatty acids than farmed varieties and a lower proportion of saturated fatty acids.

Two iron-containing components of muscle tissue, myoglobin and cytochromes, give meat its red colour. It also contains relatively high levels of B vitamins, particularly B6 (pyridoxine) and B12, as well as vitamin D, and provides

Box 4.3.2 Nitrates, nitrites, and *N*-nitroso compounds

Nitrate occurs naturally in plants; levels vary between species and with different soil conditions and the amount of fertiliser used. In high-income countries, vegetables account for 70–97 per cent of dietary nitrate intake.[2] Between 5 and 20 per cent of the nitrate in diets is converted by the body into nitrite, a substance that is also found in some vegetables (notably potatoes). Nitrite is used to preserve processed meats (it is extremely toxic to bacteria) and gives cured meats their recognisable colour and flavours. The addition of nitrite and nitrate to food is regulated and monitored in most countries.

Nitrite can react with the degradation products of amino acids to form *N*-nitroso compounds (nitrosamines or nitrosamides). These may be formed in meat during the curing process or in the body (particularly in the stomach) from dietary nitrite (or nitrate).

Several *N*-nitroso compounds are known human or animal carcinogens.[3] There is concern that nitrite, from processed meats for example, nitrates in vegetables, and preformed nitrosamines may be involved in carcinogenesis, particularly in the stomach (see Chapter 2). Dietary nitrates and nitrites are probable human carcinogens because they are converted in the body to *N*-nitroso compounds.[3]

Box 4.3.3 Foods containing iron

Iron deficiency is the most common and widespread nutritional disorder in the world. It is most common among children and premenopausal women, and results in iron deficiency anaemia.

Haem iron is found only in foods of animal origin, such as meat and meat products, fish, and blood products. Non-haem iron is found in plant foods, such as lentils, beans, leafy vegetables, tofu, chickpeas, black-eyed peas, figs, and apricots. The amount of dietary iron needed to meet the body's requirements depends on its bioavailability from the diet. This varies with the diet, as well as factors related to the consumer such as their iron status. Iron from animal sources is better absorbed than iron from plant sources, but non-haem iron absorption is enhanced when the body's iron status is low, or when iron-rich foods are eaten together with vitamin-C rich foods or with meat.

Iron has a central role in metabolism. It is involved in oxidative metabolism within cells and is a component of a number of enzymes. Free iron can also catalyse the generation of free radicals, which cause oxidative damage to specific cell components including DNA, protein, and membrane lipids. Iron metabolism and transport are strictly regulated to reduce the likelihood of cells being exposed to free iron and so to oxidative damage; most iron in living tissues is bound to proteins, such as transferrin and ferritin, which prevent its involvement in free-radical generation. Also see chapter 4.10.

readily absorbable iron, zinc, and selenium. Eating red meat increases levels of *N*-nitroso compounds in the body (box 4.3.2), which may be partially due to its high haem content (box 4.3.3). If meat is cooked over an open flame, at high temperatures, and charred or 'well done', heterocyclic amines or polycyclic aromatic hydrocarbons can be formed (box 4.3.4).

Vitamin D is a fat-soluble vitamin that plays a critical role in calcium and bone metabolism and in controlling cell differentiation. Low levels may lead to osteomalacia or, in children, rickets and possibly osteoporosis, with increased fracture risk. Most vitamin D is derived from the action of sunlight on the skin. Foods such as milk or fat spreads (see chapter 4.9) may be fortified, and then become the major dietary source of vitamin D; natural sources include sardines and other oily fish, meat, and eggs.

Fish

Fish has similar levels of protein to meat. It has a fat by weight content of between 0.5 per cent in low-fat fish such as cod or skate to as much as 20 per cent in oily fish such as Atlantic salmon or eels. Fat from fish contains lower levels of saturated fatty acids (around 20–25 per cent) than meat.

Fish oils from saltwater fish contain long-chain n-3 fatty acids (see chapter 4.4.2). Wild fish have a lower fat content than farmed fish, with a higher proportion of n-3 fatty acids. Only marine algae and phytoplankton produce these fatty acids, so the fish that feed on them are the primary dietary sources. These fatty acids are essential to the development and function of the brain and retina; they also reduce inflammation, blood clotting, and cholesterol production. The body

can convert alpha-linolenic acid (found in plant foods and essential in the diet) to eicosapentaenoic acid and docosohexanoic acid, which are found in fish oils, but the rates of conversion are low.

Fish contain lower levels of B vitamins, iron, and zinc than meat and poultry, but oily fish are a source of retinol and vitamin D. Fish are also a source of calcium if the bones are eaten with the flesh, for example, when canned.

Fish and shellfish have the potential to accumulate pollutants that are washed into rivers and oceans, and these tend to accumulate in their fat. These pollutants can include heavy metals and organic compounds, some of which are known carcinogens. Farmed fish are exposed to veterinary medicines, and some environmental toxins may reach high concentrations in their food. But farmed fish are less likely than wild fish to become contaminated with environmental pollutants. The balance of risks and benefits of eating fish at various stages of the life course needs to be determined. Also see chapter 4.9.

Eggs
Eggs, like meat, poultry, and fish, contain all the essential amino acids needed by humans. A typical large hen's egg has roughly equal weights of protein and fat, with 60 per cent of the energy coming from fat. A typical large shelled egg contains 6 g protein; 1 g carbohydrate; 4.5 g fat (2.0 g monounsaturated, 0.5 g polyunsaturated, and 1.5 g saturated fatty acids); and about 200 mg cholesterol. It also contains retinol, folate, thiamin, riboflavin, vitamin B12, vitamin D, and iron. The yolk's colour comes from carotenoids, and contains all of the fat and cholesterol and most of the iron, thiamin, and retinol. The white is 90 per cent water and is virtually fat free, containing mainly protein, with some vitamins, and traces of glucose.

In Asia, eggs containing 2–3 week old chick fetuses may occasionally be included in diets. There is no nutritional difference between these and unfertilised eggs, except that fertilised eggs contain additional calcium absorbed from the shell.

4.3.3 Consumption patterns

Meat and poultry
Globally, meat accounts for about 8 per cent of total energy availability, 18 per cent of dietary protein, and 23 per cent of dietary fat. Meat consumption is considerably higher in high-income countries (10 per cent of total energy intake compared with 7 per cent in low-income countries), and is particularly high in the USA, parts of South America, some parts of Asia, northern Europe, and most of Oceania. Consumption is particularly low in most of Africa and other parts of Asia where vegetarian ways of life are commonplace. Bangladesh has the lowest level of intake (0.6 per cent) and Mongolia the highest (28 per cent).[7]

As a general rule, meat consumption increases with economic development. Worldwide, between 1961 and 2002, meat consumption per person doubled, with pork and poultry showing the greatest increases; in Japan it increased nearly six-fold. Globally, overall energy availability increased in the same period by just 12 per cent. Consumption of meat and other animal foods from wild and undomesticated animals is low on a global basis, but these foods are important parts of diets within many middle- and low-income countries, as well as being delicacies in high-income countries.

Fish
Worldwide, fish (including shellfish) account for 1 per cent of available dietary energy; these foods are particularly important in island and coastal communities. For instance, in the Maldives, marine fish account for 15 per cent of dietary energy, but in some landlocked, low-income countries, this figure is practically zero. In general, fish consumption is highest in Asia and Oceania. Freshwater fish provide a relatively small proportion of dietary energy (0.3 per cent), but they are a more important source of dietary energy in low-income countries, and are particularly important in regions with large lakes and rivers. Salting is a traditional method of preserving raw fish throughout much of the world (box 4.3.5).

Salting is a traditional method of preserving raw fish throughout much of the world. The freshness of the fish and the salting and drying conditions vary considerably between regions, although fish are usually dried outside, in direct sunlight. This results in varying levels of fermentation and/or insect infestation. Salted fish is a component of diets typical of Asia, Africa, and parts of the Mediterranean.

Depending on the precise conditions, salt-preserved fish may also undergo fermentation. The degree of fermentation that occurs depends on the freshness of the raw fish, the amount of salt used, the outdoor temperature, and the duration of the drying process. In general, excluding the factor of freshness, salted fish is less likely to be fermented in the northern part of China compared with the southern part of China (where nasopharyngeal cancer is more common). Cantonese-style salted fish is characterised by using less salt and a higher degree of fermentation during the drying process, because of the relatively high outdoor temperature and moisture levels.

Cantonese-style salted fish are a traditional part of the diet in southern China, Taiwan, Malaysia, and Singapore.

Eggs
Worldwide, eggs provide 1.2 per cent of available food energy. Egg consumption is highest in the Far East, North America, and Europe, ranging from nearly 3 per cent in these areas to virtually zero in many African countries; it is significantly higher in high-income countries. Preserved eggs (pickled, salted, or cured) are traditional in some cultures.

4.3.4 Interpretation of the evidence

4.3.4.1 General
For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7.

'Relative risk' (RR) is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.3.4.2 Specific
Some considerations specific to meat, poultry, fish, and eggs include:

Classification. 'Fish' is a broad classification. Different fish have different nutritional profiles and biological effects, one obvious example being white fish and oily fish. These are often not distinguished in epidemiological studies.

Terminology. As yet, there is no agreed definition for 'processed meat'. Some studies count minced meat, or ham, bacon, and sausages as processed meats; others do not. See the footnote to the matrix and box 4.3.1.

Confounding. People who consume large amounts of meat and processed meats tend to consume less poultry, fish, and vegetables, and vice versa. So an apparent effect of meat and

processed meat could possibly be due, at least in part, to low intakes of these other foods.

Production, processing, patterns. Practically all the evidence relates to these foods as preserved, processed, or prepared (cooked) in some way. Evidence on meat, poultry, and increasingly on fish, is practically all from these foods as produced industrially. There is very little evidence on wild animals and birds, despite the quantity and nature of their body fat, and other aspects of their nutritional profile, being different. Epidemiological evidence on specific methods of preservation, processing, and preparation/cooking of meat, poultry, and fish is mostly patchy, despite some of these being known to generate carcinogens established as such in experimental studies. Also see chapter 4.9.

4.3.5 Evidence and judgements

The full systematic literature review (SLR) is contained on the CD included with this Report.

4.3.5.1 Meat
4.3.5.1.1 Red meat
Some studies may have included processed meats in their classification of red meat intake.

Colorectum
Sixteen cohort studies[8-24] and 71 case-control studies investigated red meat and colorectal cancer.

All of the cohort studies that reported analyses of risk for the highest intake group when compared to the lowest showed increased risk (figure 4.3.1),[8-24] which was statistically significant in four (one of these was specific to rapid-acetylator genotypes).[9 10 12 18 23] Meta-analysis was possible

Figure 4.3.1 | **Red meat and colorectal cancer; cohort studies**

Relative risk (95% CI)

	Relative risk (95% CI)
Philips 1975	2.70 (1.60–4.55)
Slattery 2001 Women	1.04 (0.62–1.75)
Kato 1997 Women	1.23 (0.68–2.22)
Singh 1998	1.41 (0.90–2.21)
Pietinen 1999 Men	1.20 (0.80–1.80)
Jarvinen 2001	1.50 (0.77–2.93)
Tiemersma 2002 Men	2.70 (1.09–6.66)
Tiemersma 2002 Women	1.20 (0.51–2.84)
Wei 2003 Men	1.35 (0.80–2.27)
Wei 2003 Women	1.31 (0.73–2.36)
Chen 2003	1.48 (0.85–2.59)
English 2004	1.40 (1.02–1.93)
Norat 2004	1.17 (0.92–1.49)

Relative risk, highest vs lowest exposure category

Figure 4.3.2 **Red meat and colorectal cancer; cohort studies**

	Relative risk (95% CI)
Willet 1990 Women	1.81 (1.17–2.80)
Bostick 1994 Women	0.96 (0.80–1.14)
Giovannucci 1994 Men	2.20 (1.24–3.91)
Singh 1998	4.51 (0.38–53.27)
Chen 1998 Men, NAT rapid	2.57 (0.78–8.84)
Chen 1998 Men, NAT slow	0.88 (0.45–1.75)
Tiemersma 2002 Men	3.44 (0.83–14.18)
Tiemersma 2002 Women	1.42 (0.22–9.00)
English 2004	1.23 (0.88–1.73)
Summary estimate	1.43 (1.05–1.94)

Relative risk, per time/week
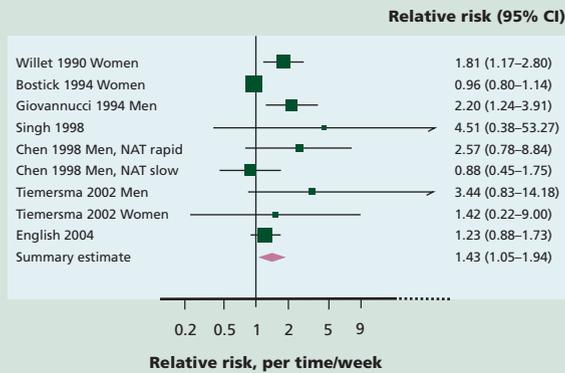
Figure 4.3.3 **Red meat and colorectal cancer; cohort studies**

	Relative risk (95% CI)
Pietinen 1999	1.05 (0.74–1.48)
Norat 2005	1.49 (0.91–2.43)
Larsson 2005 Women	1.43 (1.05–0.95)
Summary estimate	1.29 (1.05–1.59)

Relative risk, per 100 g/day
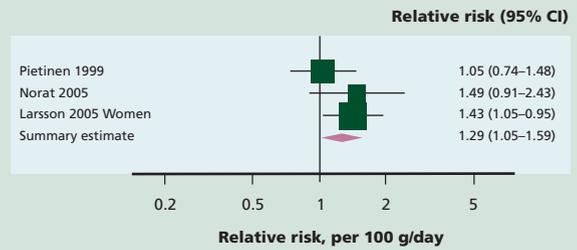
on seven studies that measured red meat intake in 'times per week' and three studies that measured grams per day. The summary effect estimates were 1.43 (95% confidence interval (CI) 1.05–1.94) per times/week and 1.29 (95% CI 1.04–1.60) per 100 g/day, respectively (figures 4.3.2 and 4.3.3). There was moderate heterogeneity in the former analysis and low heterogeneity in the latter.

A dose-response relationship is apparent from cohort data (figure 4.3.4).

These data are supported by a recently published meta-analysis of 15 prospective studies, which reported a summary effect estimate of 1.28 (95% CI 1.18–1.39) per 120 g/day.[25]

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

The general mechanisms through which red meat could plausibly cause cancer are outlined below. In addition, dietary haem iron induces colonic cytotoxicity and hyperproliferation.[26]

A substantial amount of data from cohort and case-control studies showed a dose-response relationship, supported by evidence for plausible mechanisms operating in humans. Red meat is a convincing cause of colorectal cancer.

The Panel is aware that since the conclusion of the SLR, six cohort[27-32] and four case control studies[33-36] have been published. This new information does not change the Panel judgement (see box 3.8).

Oesophagus

Twelve case-control studies[37-50] investigated red meat and oesophageal cancer.

Eight studies reported increased risk for the highest intake group when compared to the lowest,[37-39 41-45 49 50] which was statistically significant in five.[37 41 42 45] Three studies reported

Figure 4.3.4 **Red meat and colorectal cancer; cohort studies: dose response**

Kinlen 1983 Men
Kinlen 1983 Women
Giovannucci 1994 Men
Bostick 1994
English 2004

Red meat (times/week)
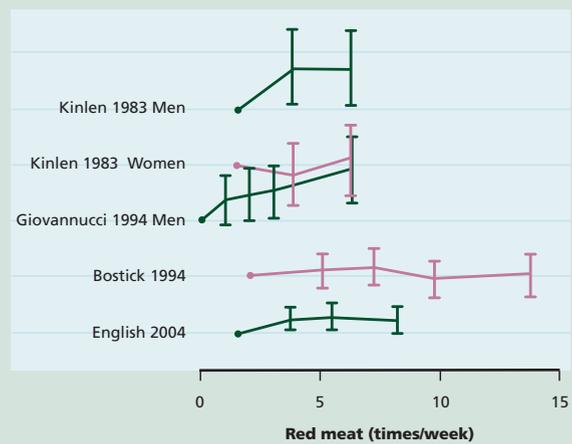
non-significant decreased risk[38 40 46]; one study reported no significant effect on risk,[47 48] but did not provide further details. Most of these studies adjusted for smoking and alcohol.

The general mechanisms through which red meat could plausibly cause cancer are outlined below.

There is limited evidence, from case-control studies, some of which were poor quality, suggesting that red meat is a cause of oesophageal cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[51] has been published. This new information does not change the Panel judgement (see box 3.8).

Lung

One cohort study[52] and nine case-control studies[53-62] investigated red meat and lung cancer.

The single cohort study showed increased risk for the highest intake group when compared to the lowest, with an effect estimate of 1.6 (95% CI 1.0–2.6; p value for trend < 0.014), based on 158 cases.[52]

Seven case-control studies showed increased risk for the highest intake group when compared to the lowest,[53-58 60 61] which was statistically significant in four.[54 55 60 61] One study reported non-significant decreased risk[59] and one study showed no effect on risk.[62] All except the latter study adjusted for smoking.

The general mechanisms through which red meat could plausibly cause cancer are outlined below.

There is limited evidence, mostly from inconsistent case-control studies, suggesting that red meat is a cause of lung cancer.

Pancreas

Seven cohort studies[63-69] and four case-control studies[46 70-72] investigated red meat and pancreatic cancer.

Six cohort studies showed increased risk for the highest intake group when compared to the lowest,[63-65 67-69] which was statistically significant in one,[64] and two of the studies also had statistically significant tests for trend.[65 67] One study reported a non-significant increased risk that was very close to no effect.[66] Meta-analysis was possible on two studies, giving a summary effect estimate of 1.00 (95% CI 0.95–1.05) per 20 g/day, with no heterogeneity.[63 66] However, the two included studies were not typical. The effect estimates for the highest intake group when compared to the lowest in the other five cohort studies were 1.45 (95% CI 1.19–1.76),[64] 1.73 (95% CI 0.99–2.98; with a statistically significant test for trend),[65] 2.4 (95% CI 1–6.1; with a statistically significant test for trend),[67] 1.1 (95% CI 0.9–1.2),[68] and 1.4 (95% CI 0.4–4.8) for men and 2.7 (95% CI 0.8–8.9) for women.[69]

All of the case-control studies showed increased risk for the highest intake group when compared to the lowest,[46 70-72] which was statistically significant in three.[46 71 72] Meta-analysis was possible on three case-control studies, giving a summary effect estimate of 1.11 (95% CI 1.08–1.15) per 20 g/day, with no heterogeneity.[46 71 72]

The general mechanisms through which red meat could plausibly cause cancer are outlined below. In addition, both the secretory function of the pancreas and cell turnover within the pancreas are altered by the types of foods eaten.[73] Amino acids and fatty acids stimulate more pancreatic secretions than do carbohydrates.[74]

Evidence from cohort studies is less consistent than that from case-control studies. There is limited evidence suggesting that red meat is a cause of pancreatic cancer.

Endometrium

One cohort study[75] and seven case-control studies[46 76-81] investigated red meat and endometrial cancer.

The single cohort study showed a non-significant increased risk for the highest intake group when compared to the lowest, with an effect estimate of 1.10 (95% CI 0.70–1.73).[75]

Five case-control studies showed increased risk for the highest intake group when compared to the lowest,[46 76-79] which was statistically significant in two.[77 78] Two studies showed non-significant reduced risk.[80 81] Meta-analysis was possible on six studies, giving a summary effect estimate of 1.20 (95% CI 1.03–1.39) per 50 g red meat/day, with moderate heterogeneity.[46 76-80]

The general mechanisms through which red meat could plausibly cause cancer are outlined below.

The evidence, mostly from case-control studies, is sparse. There is limited evidence suggesting that red meat is a cause of endometrial cancer.

The Panel is aware that since the conclusion of the SLR, one case-control study[82] has been published. This new information does not change the Panel judgement (see box 3.8).

General mechanisms

There are several potential underlying mechanisms for an association between red meat consumption and cancer, including the generation by stomach and gut bacteria of potentially carcinogenic N-nitroso compounds. Some red meats are also cooked at high temperatures, resulting in the production of heterocyclic amines and polycyclic aromatic hydrocarbons (box 4.3.4). Haem promotes the formation of N-nitroso compounds and also contains iron. Free iron can lead to production of free radicals (box 4.3.3). Iron overload also activates oxidative responsive transcription factors, pro-inflammatory cytokines, and iron-induced hypoxia signalling.[83]

Figure 4.3.5 Processed meat and colorectal cancer; cohort studies

	Relative risk (95% CI)
Philips 1975	2.05 (1.50–4.06)
Goldbohm 1994 Men	1.84 (0.85–3.97)
Goldbohm 1994 Women	1.66 (0.82–2.36)
Bostick 1994 Women	1.51 (0.72–3.17)
Gaard 1996 Women	3.50 (1.02–11.95)
Gaard 1996 Men	1.98 (0.70–5.59)
Kato 1997 Women	1.09 (0.59–2.02)
Pietinen 1999 Men	1.20 (0.75–1.92)
Tiemersma 2002 Men	1.00 (0.51–1.95)
Tiemersma 2002 Women	0.80 (0.43–1.50)
Flood 2003 Women	0.97 (0.73–1.28)
Wei 2003 Men	1.27 (0.87–1.85)
Wei 2003 Women	1.32 (0.95–1.83)
English 2004	1.50 (1.11–2.02)
Chao 2005 Men	1.11 (0.80–1.54)
Chao 2005 Women	1.16 (0.85–1.58)
Norat 2005	1.42 (1.09–1.85)

Relative risk, highest vs lowest exposure category

4.3.5.1.2 Processed meat

The variation in definitions for processed meat used by different studies (see chapter 4.3.1) is likely to contribute to the observed heterogeneity.

Colorectum

Fourteen cohort studies[8-10 14-19 21 27 69 84 85] and 44 case-control studies investigated processed meat and colorectal cancer.

Twelve cohort studies showed increased risk for the highest intake group when compared to the lowest (figure 4.3.5),[8-10 14-19 21 27 69 85] which was statistically significant in three.[9 14 15 85] One study reported non-significant decreased risk and one study reported that there was no effect on risk.[84] Meta-analysis was possible on five studies, giving a summary effect estimate of 1.21 (95% CI 1.04–1.42) per 50 g/day, with low heterogeneity (figures 4.3.6 and 4.3.7). What heterogeneity there is could be explained by the disparity in category definitions between studies, as well as by improved adjustment for confounders in recent studies. A dose-response relationship was also apparent from cohort studies that measured in times/day (figure 4.3.8).

The majority of case-control studies showed increased risk with increasing intake of processed meat. Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

These data are supported by a recently published meta-analysis of 14 cohort studies, which reported a summary effect estimate of 1.09 (95% CI 1.05–1.13) per 30 g/day.[25]

The general mechanisms through which processed meat could plausibly cause cancer are outlined below.

> **There is a substantial amount of evidence, with a dose-response relationship apparent from cohort studies. There is strong evidence for plausible mechanisms operating in humans. Processed meat is a convincing cause of colorectal cancer.**

The Panel is aware that since the conclusion of the SLR, five cohort[28 30 32 86 87] and two case-control studies[36 88] have been published. This new information does not change the Panel judgement (see box 3.8).

Oesophagus

Two cohort studies[89 90] and eight case-control studies[40 41 43 44 49 50 91-94] investigated processed meat and oesophageal cancer.

Both cohort studies showed non-significant increased risk for the highest intake groups when compared to the lowest.[89 90] The effect estimates were 1.24 (95% CI 0.73–2.1)[90] and 1.6 (95% CI 0.4–6.9).[89] Both analyses adjusted for age, smoking, and alcohol.

Six case-control studies showed increased risk for the highest intake groups when compared to the lowest,[43 44 49 50 91-93] which was statistically significant in one.[93] Two studies showed non-significant reduced risk.[40 41 94]

The general mechanisms through which processed meat could plausibly cause cancer are outlined below.

Figure 4.3.6 Processed meat and colorectal cancer; cohort studies

Relative risk (95% CI)

Study		Relative risk (95% CI)
Goldbohm 1994		1.69 (1.10–2.58)
Pietinen 1999		0.99 (0.79–1.24)
Chao 2005 Men		1.40 (1.04–1.88)
Chao 2005 Women		1.14 (0.64–2.05)
Norat 2005		1.30 (0.93–1.80)
Larsson 2005 Women		1.13 (0.85–1.51)
Summary estimate		1.21 (1.04–1.42)

Relative risk, per 50 g/day

Figure 4.3.7 Processed meat and colorectal cancer; cohort studies: dose response

Processed meat (g/day)

Figure 4.3.8 Processed meat and colorectal cancer; cohort studies: dose response

Processed meat (times/day)
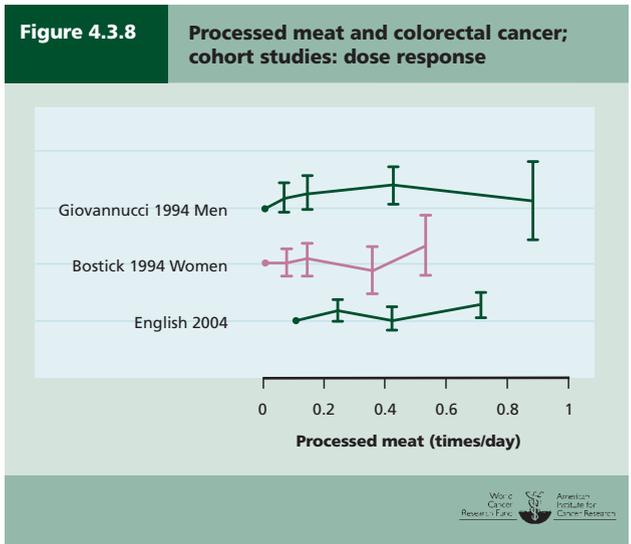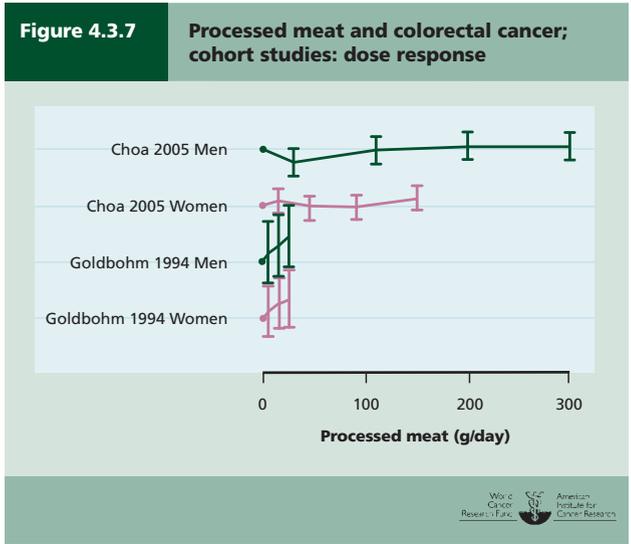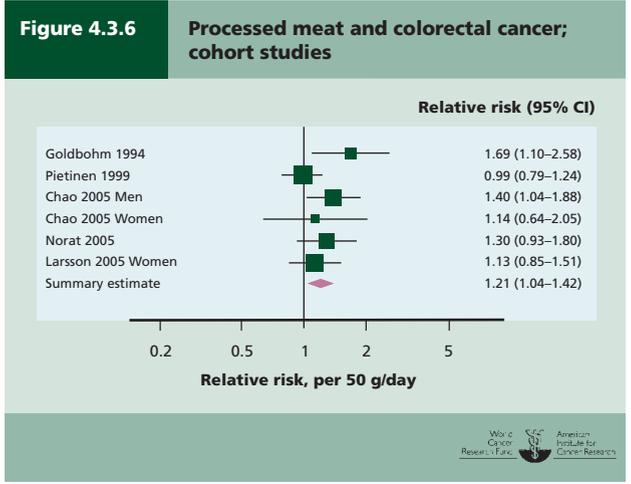
There is limited evidence, mostly from case-control studies, suggesting that processed meat is a cause of oesophageal cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[51] has been published. This new information does not change the Panel judgement (see box 3.8).

Lung

Four cohort studies[52 69 95 96] and 10 case-control studies[33 55-57 59 97-104] investigated processed meat and lung cancer.

Three cohort studies reported non-significant increased risk for the highest intake group when compared to the lowest.[69 95 96] One study reported no effect on risk.[52 95] Meta-analysis was possible on two of the studies, giving a summary effect estimate of 1.03 (95% CI 0.92–1.16) per serving/week, with no heterogeneity.[52] All four cohort studies adjusted for smoking.

Six case-control studies reported increased risk for the highest intake group when compared to the lowest,[33 56 57 59 99 100 102-104] which was statistically significant in two.[100 102] Four studies reported non-significant decreased risk.[55 97 98 101] All of the studies adjusted for smoking.

The general mechanisms through which processed meat could plausibly cause cancer are outlined below.

There is limited, inconsistent evidence suggesting that processed meat is a cause of lung cancer.

Stomach cancer

Eight cohort studies,[51 69 105-110] 21 case-control studies,[49 111-132] 1 cross-sectional study,[133] and 1 ecological study[134] investigated processed meat and stomach cancer.

Five cohort studies showed increased risk for the highest intake group when compared to the lowest,[51 106-108 110] which was statistically significant in one.[51] Two studies reported non-significant decreased risk[105 109]; and one showed no effect on risk in men and non-significant decreased risk in women.[69] Meta-analysis was possible on all eight cohort studies, giving a summary effect estimate of 1.02 (95% CI 1.00–1.05) per 20 g/day, with no heterogeneity.

Thirteen case-control studies showed increased risk for the highest intake group when compared to the lowest,[49 113 117 119-121 124-132] which was statistically significant in seven.[120 125 128-132] Three studies showed decreased risk,[118 122 123] which was statistically significant in one[118]; and one showed no effect on risk.[116] Four other studies reported no significant difference between mean intakes in cases and controls.[111 112 114 115] Meta-analysis was possible on nine studies, giving a summary effect estimate of 1.13 (95% CI 1.01–1.25) per 20 g/day, with high heterogeneity.[49 117-119 121 123 128-130]

A dose-response relationship is apparent from case-control but not cohort data.

The single ecological study reports a statistically significant correlation between increased processed meat and stomach cancer risk.[134]

The general mechanisms through which processed meat could plausibly cause cancer are outlined below.

The evidence is inconsistent. There is limited evidence suggesting that processed meat is a cause of stomach cancer.

The Panel is aware that since the conclusion of the SLR, one cohort[135] and two case-control studies[136 137] have been published. This new information does not change the Panel judgement (see box 3.8).

Prostate

Four cohort studies[138-141] and six case-control studies[142-147] investigated processed meat and prostate cancer.

All four cohort studies showed increased risk for the highest intake group when compared to the lowest,[138-141] which was statistically significant in two.[139 141] Meta-analysis was possible on all four cohort studies, giving a summary effect estimate of 1.11 (95% CI 0.995–1.25) per serving/week, with high heterogeneity. Heterogeneity was caused by varying size, not direction, of effect.

Two of these studies reported separately on advanced or aggressive cancer. Both showed increased risk with increasing intake of processed meat,[138 141] which was statistically significant in one.[141] Meta-analysis was possible on both studies, giving a summary effect estimate of 1.09 (95% CI 0.98–1.22) per serving/week, with moderate heterogeneity.

Four case-control studies showed non-significant decreased risk with increasing intake of processed meat[143-145 147]; two showed non-significant increased risk.[142 146] Meta-analysis was possible on five case-control studies, giving a summary effect estimate of 1.01 (95% CI 0.98–1.04) per serving/week, with low heterogeneity.[143-147] The general mechanisms through which processed meat could plausibly cause cancer are outlined below.

There is limited evidence from sparse and inconsistent studies suggesting that processed meat is a cause of prostate cancer.

The Panel is aware that since the conclusion of the SLR, two cohort studies[148 149] have been published. This new information does not change the Panel judgement (see box 3.8).

General mechanisms

Nitrates are produced endogenously at the low pH in the stomach and are added as preservatives to processed meats, both of which may contribute to *N*-nitroso compound production and exposure. *N*-nitroso compounds are suspected mutagens and carcinogens.[150] Many processed meats also contain high levels of salt and nitrite. Some processed meats are also cooked at high temperatures, resulting in the production of heterocyclic amines and polycyclic aromatic hydrocarbons. Red meat contains haem iron. Haem promotes the formation of *N*-nitroso compounds and also contains iron. Free iron can lead to production of free radicals (box 4.3.3).

4.3.5.2 Poultry

The evidence was too limited in amount, consistency, or quality to draw any conclusions.

4.3.5.3 Fish, shellfish
Colorectum

Nineteen cohort studies[8-10 14-18 21 23 69 85 151-161] and 55 case-control studies investigated fish and colorectal cancer.

Nine cohort studies showed decreased risk for the highest intake group when compared to the lowest,[8 15-17 21 69 85 154 157 158 160] which was statistically significant in two.[15 16] Eight studies showed non-significant increased risk.[9 10 18 23 151-153 155 156 159] One study showed no effect on risk[14] and one study reported that there was no statistically significant association.[161] Meta-analysis was possible on seven cohort studies, giving a summary effect estimate of 0.96 (95% CI 0.92–1.00) per serving/week, with low heterogeneity.[8 9 14 18 21 158 160]

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

Heterogeneity may be partially explained by varying definitions of fish in different studies that included fresh and/or salted or dried fish. It is also possible that high fish intake is associated with low meat intake, which is a potential confounder that has not been adjusted for.

It is biologically plausible that fish n-3 polyunsaturated fatty acids (PUFAs) protect against cancer. Fish oils reduce tumours in animal studies.[162] Likely mechanisms are thought to revolve around their role in reduction of n-6 PUFA-derived eicosanoid biosynthesis (eicosanoids promote inflammation) and direct inhibition of COX-2 (cyclooxygenase-2, an enzyme involved in the production of prostaglandins), which is also implicated in the cancer process (see Chapter 2). This mechanism, though plausible, is not well supported.[163] Alternative suggestions include the relatively high selenium or vitamin D content of fish.

> **A substantial amount of data is available but the results are inconsistent, and residual confounding by meat could not be excluded. There is limited evidence suggesting that eating fish protects against colorectal cancer.**

The Panel is aware that since the conclusion of the SLR, six cohort[28 30 164 165] and two case-control studies[33 166] have been published. This new information does not change the Panel judgement (see box 3.8).

4.3.5.3.1 Cantonese-style salted fish
Nasopharynx

One cohort study[167] and 21 case-control studies[161-188] investigated Cantonese-style salted fish (box 4.3.5) intake in adults and nasopharyngeal cancer. Sixteen case-control studies[168 170-174 177-179 181 188-193] investigated intake in childhood and 10 case-control studies[168 171-174 177 188 189 194 195] investigated intake in infancy (less than 3 years).

Adult intake

The single cohort study showed increased risk for the highest intake group when compared to the lowest. Intake was assessed in the 1960s, 1970s, and 1980s. The p value for trend for the association between each decade's intake and increased risk was < 0.001, 0.014, and 0.21, respectively.

Seventeen of the case-control studies showed increased risk for the highest intake group when compared to the lowest,[169-178 182-188] which was statistically significant in nine.[170 172 173 176 178 182 185-188] One study showed a non-significant decreased risk[168]; three studies reported that there was no association.[179-181] Meta-analysis was possible on nine studies, giving a summary effect estimate of 1.28 (95% CI 1.13–1.44) per serving/ week, with high heterogeneity (figure 4.3.9). Heterogeneity was related to size, and not direction, of effect.

Figure 4.3.9 — Salted fish and nasopharyngeal cancer; case control

Relative risk (95% CI)

Study	Relative risk (95% CI)
Yuan 2000	1.73 (0.66–4.52)
Lee 1994	1.17 (0.85–1.61)
Zheng 1994	2.50 (1.63–3.85)
Sriamporn 1992	1.35 (1.06–1.72)
Yu 1989	1.10 (1.00–1.21)
Yu 1986	1.31 (1.13–1.51)
Weiming 1995	1.71 (1.08–2.70)
Cai 1996	1.06 (1.00–1.02)
Zou 1999	1.32 (1.13–1.54)
Summary estimate	1.28 (1.13–1.44)

Relative risk, per time/week
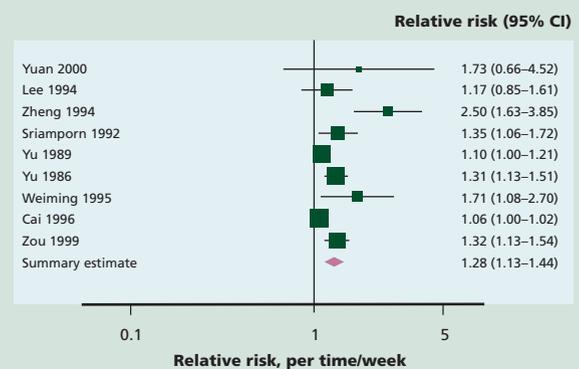
Figure 4.3.10 — Salted fish and nasopharyngeal cancer; case-control studies

Relative risk (95% CI)

Study	Relative risk (95% CI)
Ward 2000	0.80 (0.52–1.24)
Yuan 2000	1.82 (0.86–3.86)
Armstrong 1998	4.22 (2.23–7.99)
Lee 1994	4.40 (0.72–26.76)
Zheng 1994	4.07 (0.36–45.80)
Zheng 1994b	17.20 (2.28–104.79)
West 1993	1.30 (0.67–2.52)
Sriamporn 1992	2.50 (1.20–5.20)
Yu 1989	1.80 (0.90–3.60)
Yu 1986	7.50 (0.88–63.89)
Ning 1990	2.20 (1.30–3.71)
Ye 1995	5.00 (1.27–19.72)
Ye 1995b	2.00 (0.88–4.56)
Cai 1996	1.32 (0.98–1.77)
Chen 1994	5.51 (1.74–17.44)
Wang 1993	8.99 (1.60–50.44)
Zou 1999	3.04 (1.66–5.69)

Relative risk, highest vs lowest exposure category

125
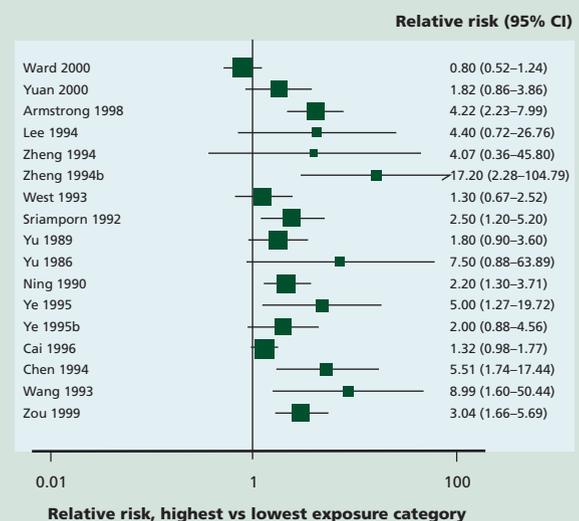
Figure 4.3.11 Salted fish and nasopharyngeal cancer; case-control studies: dose response

pounds with a common carcinogenic mechanism.[150] Salted fish has been shown to contain *N*-nitrosamines, with the highest levels in salted fish from areas with the highest mortality from nasopharyngeal cancer.[196 197] The variation in nitrosamine content of salted fish may contribute to heterogeneity in assigning risk to salted fish consumption in different geographic locations. There is also some evidence that genotype interacts with the risk associated with salted fish intake, particularly the gene for the cytochrome P450 enzyme, CYP2E1.[192 198]

> **Evidence from several case-control studies is consistent and shows a dose-response effect. There is evidence for plausible mechanisms. Cantonese-style salted fish is probably associated with increased risk of nasopharyngeal cancer.**

4.3.5.4 Eggs
The evidence was too limited in amount, consistency, or quality to draw any conclusions.

4.3.5.5 Foods containing vitamin D
Colorectum
Eleven cohort studies[17 24 154 199-210] and 17 case-control studies investigated total vitamin D and/or dietary vitamin D and colorectal cancer. Four cohort studies investigated plasma or serum vitamin D.[22 210-212]

Childhood intake
Fifteen case-control studies that investigated the intake of salted fish at 10 years of age showed increased risk for the highest intake group when compared to the lowest,[168 170 172-174 177-179 181 188-193] which was statistically significant in 8[170 172 173 177-179 188 190] (figure 4.3.10). One study showed a non-significant decreased risk.[171] Meta-analysis was possible on 9 studies,[171 173 174 177 178 181 188-190] giving a summary effect estimate of 1.35 (95% CI 1.14–1.60) per serving/week, with high heterogeneity. Heterogeneity was related to size, and not direction, of effect.

Nine case-control studies that investigated the intake of salted fish at 3 years of age showed increased risk for the highest intake group when compared to the lowest,[171-174 177 188 189 194 195] which was statistically significant in five.[172 173 177 188 195] One study showed no effect on risk.[168] Meta-analysis was possible on five studies,[171 173 174 177 189] giving a summary effect estimate of 1.42 (95% CI 1.11–1.81) per serving/week, with moderate heterogeneity. Heterogeneity was related to size, and not direction, of effect.

A dose-response relationship is apparent from case-control data (figure 4.3.11). Cohort and case-control data suggest a delayed and/or cumulative effect from eating Cantonese-style salted fish.

General mechanisms
Evidence suggests that high intake of nitrate and nitrosamine from salted fish accounts for some of this increased risk of nasopharyngeal cancer development. Nitrosamines are known mutagens and animal carcinogens that induce gene mutation. The *N*-nitrosamines are a large group of com-

Dietary vitamin D
Twelve estimates from 11 cohort studies reported analyses of the highest intake groups compared to the lowest.[17 154 199-206] Six of these showed non-significant decreased risk[154 199-202 205]; 2 studies reported no effect on risk[17 205]; and 4 studies show non-significant increased risk.[203 204 206] Meta-analysis was possible on 9 studies that investigated dietary vitamin D, giving a summary effect estimate of 0.99 (95% CI 0.97–1.00) per 100 IU/day, with moderate heterogeneity.[17 154 199 202 204-206 209 210]

Serum or plasma vitamin D
All four cohort studies showed non-significant decreased risk for the highest intake groups when compared to the lowest.[22 210-212] Effect estimates were 0.73 (stated as non-significant)[211]; 0.4 (95% CI 1–1.4; serum 25-hydroxyvitamin D) and 1.1 (95% CI 0.4–3.2; serum 1,25 hydroxyvitamin D)[212]; 0.6 (95% CI 0.3–1.1; serum 25-hydroxyvitamin D) and 0.9 (95% CI 0.5–1.7; serum 1,25 hydroxyvitamin D)[210]; and 0.53 (95% CI 0.27–1.04).[22]

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

The effects of vitamin D and calcium are strongly interrelated because both are growth restraining, both induce differentiation and apoptosis in intestinal cells, and calcium-mediated effects are strongly dependent on vitamin D levels. Data from observational studies are probably hampered by the fact that total levels of the biologically active form are not only dependent on diet but also on supplements and UV exposure of the skin.

The evidence on vitamin D was inconsistent. There is limited evidence suggesting that foods containing vitamin D, or better vitamin D status, protect against colorectal cancer.

The Panel is aware that since the conclusion of the SLR, two case-control studies[166 213] have been published. This new information does not change the Panel judgement (see box 3.8).

4.3.5.6 Foods containing iron
Colorectum
Four cohort studies[214-217] and 23 case-control studies investigated iron intake and colorectal cancer. One cohort study investigated haem iron intake.[218]

The four cohort studies showed increased risk for the highest intake group when compared to the lowest,[214-216 218] which was statistically significant in two.[214 218] Effect estimates were 1.17 (95% CI 0.6–2.3)[216]; 3.35 (95% CI 1.74–6.46; colon cancer)[214]; and 2.18 (95% CI 1.24–3.86; proximal colon cancer).[218] One study reported a non-significant higher intake in cancer cases (18.4 mg) than in controls (17.4 mg).[215] The other reported that mean iron intakes were similar between male colon cancer cases, rectal cancer cases, and male sub-cohort cases (13.2, 13.3, and 13.2 mg per day, respectively), and between female colon cancer cases, rectal cancer cases, and female sub-cohort cases (11.4, 11.6, and 11.7 mg/day, respectively).[217]

Data suggest that the effect may be limited to proximal cancer cases and attenuated in distal cancer. Two studies reported results separately for proximal and distal colon cancer cases.[214-218] The effect estimates for the former were 1.44 (95% CI 1.23–1.69)[214] and 2.18 (95% CI 1.24–3.86),[218] and 1.03 (95% CI 0.8–1.32)[214] and 0.90 (95% CI 0.45–1.81) for the latter.[218]

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

It is biologically plausible that iron increases colorectal cancer risk due to its catalytic activity on the formation of reactive oxygen species. Haem promotes the formation of *N*-nitroso compounds and also contains iron. Free iron can lead to production of free radicals (box 4.3.3). However, this role has not been confirmed in animal studies. Another hypothesis is that dietary haem induces colonic cytotoxicity and hyperproliferation.[26] Iron overload also activates oxidative responsive transcription factors, proinflammatory cytokines, and iron-induced hypoxia signalling.[83]

The evidence is sparse, of poor quality, and inconsistent. There is limited evidence suggesting that foods containing iron are in general a cause of colorectal cancer. (Also see chapter 4.3.5.1.1 for evidence on red and processed meat, which are classified as convincing causes of colorectal cancer.)

The Panel is aware that since the conclusion of the SLR, two cohort studies[87 219] have been published. This new information does not change the Panel judgement (see box 3.8).

4.3.5.7 Smoked foods
Stomach
Seventeen case-control studies[116 118 220-235] and two ecological studies[236 237] investigated smoked foods and stomach cancer.

Fourteen case-control studies showed increased risk for the highest intake group when compared to the lowest,[118 220 221 224-235] which was statistically significant in 11.[118 224-234] One study reported non-significant decreased risk[222] and 2 studies reported no effect on risk.[116 223] More than half of the effect estimates were greater than 1.5. None of the studies adjusted for infection with *Helicobacter pylori*.

One ecological study reported a statistically significant increased risk with higher intake of smoked foods[236]; the other reported decreased risk, though one constituent of smoked food (3,4-benzopyrene) was associated with increased risk.[237]

Heterogeneity may be partly explained by variation between studies in the definition of smoked foods — some were specific to smoked meats and most included meats.

Smoked foods, particularly meats, may contain polycyclic aromatic hydrocarbons, depending on the fuel burned to produce the smoke.[238] Smoked meats are also often salted or cured, meaning that they are likely to raise endogenous production of *N*-nitroso compounds in the stomach (box 4.3.4).

There is limited evidence from case-control and ecological studies, some of which were of poor quality, that smoked foods are causes of stomach cancer.

The Panel is aware that since the conclusion of the SLR, three case-control studies[136 137 239] have been published. This new information does not change the Panel judgement (see box 3.8).

4.3.5.8 Grilled (broiled) or barbecued (charbroiled) animal foods
Stomach
Three cohort studies[240-242] and 12 case-control studies investigated grilled (broiled) and barbecued (charbroiled) foods and stomach cancer.

Two cohort studies showed increased risk for the highest intake group when compared to the lowest,[240 242] which was statistically significant in one.[242] One study reported a non-significant reduced risk.[241] Effect estimates were 1.67 (p value for trend < 0.05)[242]; 1.77 (95% CI 0.59–5.33) for grilled (broiled) fish and 2.08 (95% CI 0.97–4.46) for grilled (broiled) meat[240]; and 0.84 (95% CI 0.55–1.29).[241] None of the studies adjusted for *H pylori* infection.

Eight case-control studies showed increased risk for the highest intake group when compared to the lowest,[126 129 130 233 243 245-247] which was statistically significant in seven. One study reported a statistically significant decreased risk[121]; two studies reported non-significant decreased risk[220 248]; and one study stated that there was no significant effect on risk.[244]

Charring or cooking meats over open flame generates heterocyclic amines and polycyclic hydrocarbons, which may cause cancer (box 4.3.4).

There is limited, inconsistent evidence, mostly from case-control studies, that grilled (broiled) or barbecued (charbroiled) animal foods are causes of stomach cancer.

4.3.6 Comparison with previous report

The panel responsible for the previous report judged that diets relatively high in red meat were probable causes of colorectal cancer, and noted a pattern whereby red meat was a possible cause of cancers of the pancreas, breast, prostate, and kidney.

The previous report considered methods of production, preservation, processing, and preparation (including cooking). Cured meats were judged to be a possible cause of colorectal cancer; and grilled, barbecued, and fried meats, and other foods to be a possible cause of colorectal cancer; and grilling (broiling) and barbecuing (charbroiling) to be a possible cause of stomach cancer. Processed meat was not identified as such. The evidence on Cantonese-style salted fish was judged to be convincing for nasopharyngeal cancer. The panel noted that the risk was highest when this food is eaten frequently in early childhood. This Report concluded the evidence to be probable, in view of the paucity of prospective data

Since the mid-1990s, the results of cohort studies have strengthened the evidence on red meat and processed meat as causes of colorectal cancer.

4.3.7 Conclusions

The Panel concludes:

The evidence on red meat and processed meat is stronger than in the mid-1990s. Epidemiological evidence on other methods of preserving and preparing meats and other animal foods is sparse, and the overall evidence remains suggestive, at most. The evidence on poultry, fish, and eggs is generally insubstantial.

The evidence that red meats and processed meats are a cause of colorectal cancer is convincing. Cantonese-style salted fish is a probable cause of nasopharyngeal cancer. This finding does not apply to any other type of fish product. Cantonese-style salted fish is also subject to fermentation.

There is limited evidence suggesting that fish, and also foods containing vitamin D, protect against colorectal cancer. There is limited evidence suggesting that red meat is a cause of cancers of the oesophagus, lung, pancreas and endometrium; that processed meat is a cause of cancers of the oesophagus, lung, stomach and prostate; and that foods containing iron are a cause of colorectal cancer. There is also limited evidence that foods that are grilled (broiled), barbecued (charbroiled), and smoked are a cause of stomach cancer. The evidence comes mostly from meat preserved or prepared in these ways.

Meat, as mentioned above, is likely to be relatively high in animal fats. For discussion of the role of animal fats on cancer, see chapter 4.4. Meat may also be energy dense. For discussion on the role of energy-dense foods on weight gain, overweight, and obesity, and the role of weight gain, overweight, and obesity in the risk of some cancers, see Chapters 6 and 8.

4.4 Milk and dairy products

MILK, DAIRY PRODUCTS, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	**Cancer site**	**Exposure**	**Cancer site**
Convincing				
Probable	**Milk**[1][4]	**Colorectum**	**Diets high in calcium**[2][3]	**Prostate**
Limited — suggestive	Milk[1]	Bladder	Milk and dairy products[2] Cheese[4]	Prostate Colorectum
Substantial effect on risk unlikely	None identified			

1 Milk from cows. Most data are from high-income populations, where calcium can be taken to be a marker for milk/dairy consumption. *The Panel judges* that a higher intake of dietary calcium is one way in which milk could have a protective effect.
2 Effect only apparent at high calcium intakes (around 1.5 g/day or more). Evidence for milk and dairy products (but not calcium) was derived only from data for countries with populations that have high calcium and dairy consumption.
3 Includes diets that naturally contain calcium and that contain foods fortified with calcium. See box 4.10.1.
4 Although both milk and cheese are included in the general category of dairy products, their different nutritional composition and consumption patterns may result in different findings.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

Milk and products made from milk, such as cheese, butter, ghee, and yoghurt, have been consumed ever since suitable animals were domesticated. Whole milk and cheese and yoghurt made from whole milk have a high proportion of energy from fat and from protein, although the absolute concentrations in liquid milk are lower than those in cheese due to the higher water content. They also contain a number of vitamins, including retinol and riboflavin, and minerals, particularly calcium. In countries where consumption of milk and dairy products is high, these are the main sources of calcium. Low-fat dairy products retain all of the protein, the water-soluble vitamins, and the mineral content. However, the fat-soluble vitamins are significantly reduced. Low-fat milk or whole milk is sometimes fortified with vitamins A and D.

Until the late 19th century, milk from animals was used as a substitute for human milk for feeding infants. Adults did not usually consume such milks; if they did, it was in low amounts. Populations that kept milk-giving animals consumed other dairy products. From the early 20th century, a number of factors were responsible for cow's milk becoming almost a staple food in the USA and some European countries. These included the industrialisation of cattle farming; the identification of milk as a basic food, especially for children; and the development of refrigeration techniques and ultra-heat treated packaging. Dried milk is now a common ingredient in many processed foods.

Overall, *the Panel judges* that the evidence on milk and dairy products, and on calcium, shows that their impact on the risk of cancer varies in different tissues.

The Panel judges as follows:
Milk probably protects against colorectal cancer. There is limited evidence suggesting that milk protects against bladder cancer. There is limited evidence suggesting that cheese is a cause of colorectal cancer. Diets high in calcium are a probable cause of prostate cancer; and there is limited evidence suggesting that high consumption of milk and dairy products is a cause of prostate cancer.

The strongest evidence, corresponding to judgements of 'convincing' and 'probable', shows that milk probably protects against colorectal cancer, and that diets high in calcium are a probable cause of prostate cancer.

Milk and dairy products are important components of diets in some but not all parts of the world. Until recently in history, milk from several ruminant animals was used as a partial substitute for or in addition to human milk; but these milks were usually consumed infrequently and, if at all, later in childhood or by adults. In countries where milk-giving animals were raised, their products were consumed in the form of cheese, butter, ghee, and in fermented form as yoghurts or in combination with alcoholic drinks.

From the late 19th century, consumption of cow's milk greatly increased in the USA, the UK, and some other European countries. This was a result of a massive increase in dairy farming supported by new techniques such as condensation, drying, and cooling. In the 20th century, consumption was further boosted by pasteurisation and doorstep delivery, the decline of breastfeeding, and the common view that modified cow's milk is a suitable food for infants and an excellent food for young children. Dried milk is a mainstay of programmes of food aid to impoverished countries. However, populations living outside North America and northern Europe have until recently consumed little milk as such, and dairy products consumed are in the form of yoghurt or products derived from it. This may be due to the limited capacity to digest lactose beyond infancy observed in these populations. Yoghurt is fermented, which lowers lactose concentration, and is therefore better tolerated.

Reports in the early part of the 20th century of different forms of malnutrition in young children, which documented a requirement for high amounts of animal protein to cure these conditions, supported the categorisation of milk, eggs, and meat as protective foods. By contrast, reports published since the 1960s have identified whole milk and dairy products, which have a high proportion of energy from fat and saturated fatty acids, as foods that contribute to the pathogenesis of coronary heart disease. More recently, some reports concerned with the prevention of osteoporosis in Western populations have recommended high intakes of calcium.

This chapter is concerned with milk and its products. The evidence on milk is on milk from cows, and the evidence on cheese is from all sources. It does not consider human milk or infant formula. For human milk, see chapter 4.11. Nor does it consider soya drinks or other plant-derived alternatives. For soya drinks, see chapter 4.2. For butter, see chapter 4.5.

Calcium is included here because in countries where milk and dairy products are important in diets, these are the main sources of what is a generally high intake of calcium. Dietary calcium also comes from bones when these are consumed (small or tinned fish, for example, and in stews), egg shells, and from some plant foods. In many countries, plant foods are the main source of calcium. See chapters 4.1, 4.2, and 4.4.

4.4.1 Definitions, sources

Milk is produced by all mammal species to suckle their young. It has evolved to be the ideal nourishment for mammalian infants of each species and, in normal conditions, contains all the nutrients they need at that stage of their lives. Although all mammal species produce milk, only a few are employed widely as milk producers, and they are all ruminants. Milk from other species must be modified before feeding to infants to allow for their limited capacity to metabolise and excrete nitrogenous compounds and salts in early life.

Ruminant animals have a large, multichambered stomach that contains microbes, which allows them to ferment cellulose and extract nutrients from green and dried grasses. Some species or breeds (notably European cows) have been

bred to produce copious amounts of milk. Around the world, other bovine animals used to supply milk include zebu cows in Asia, water buffalo in Asia and some parts of Europe, and yaks, although usually only in the mountainous regions in Asia. Goats and sheep are also important and widespread milk-producing animals, as well as camels, which live in arid climates around the world. In some areas of the world, other animals such as horses, old- and new-world camels, and reindeer are locally important.

Fresh milk can be consumed raw (untreated) or, as is common in many high-income countries, pasteurised (see chapter 4.9.3). Milk is also commonly processed into a wide variety of foods including cream, concentrated milks, cheese, fats such as butter and ghee, and fermented foods such as yoghurt.

4.4.2 Composition

Milk and dairy products in whole form have a high proportion of energy from fat and protein, and contain some vitamins and minerals.[1] The precise composition varies between species and breeds, and with the nature of their feed. Sheep and yak milks are particularly high in protein; buffalo, sheep, and yak milks are high in fat. Typical whole cow's milk contains 3.4 g protein and 3.6 g fat per 100 g.[1] Reduced fat (semi-skimmed) and low-fat (skimmed) milks are produced from whole milk, and the foods made from these milks have a correspondingly lower fat and fat-soluble vitamin content than those made from whole milk.

Around two thirds of the fatty acids in cow's milk are saturated. Polyunsaturated fatty acids make up less than 4 per cent of milk fat (see chapter 4.5.2). Fat accounts for half of the energy in whole milk. Milk contains all the essential amino acids in the appropriate proportions for humans (see chapter 4.10.1).

The only significant carbohydrate found in milk is the disaccharide lactose. Milk products such as cheese and yoghurt contain varying amounts of lactose. Hard cheeses contain only traces, soft cheeses 2–3 per cent, yoghurts 4 per cent, compared to 5 per cent found in whole milk; this is because cheese and yoghurt have been fermented by bacteria used in the production of these foods.

Milk, cheese, and yoghurt contain high levels of calcium (box 4.4.1). They are also sources of riboflavin and vitamin B12, and full-fat dairy products are sources of retinol, and to a lesser extent, other fat-soluble vitamins. Milk also contains several growth factors and hormones, though these are probably digested in the stomach. However, milk consumption has been shown to elevate circulating levels of insulin-like growth factor.

4.4.3 Consumption patterns

Consumption of milk and dairy products throughout the world is highly variable. The overall global average of around 5 per cent of available dietary energy[2] conceals wide variations. The range is from 10–15 per cent of dietary energy in

<table>
<tr><td>Box 4.4.1</td><td>Foods containing calcium</td></tr>
</table>

In countries with high intakes of milk and dairy products, these are the main source of calcium. Most of the epidemiological studies reviewed here are from those countries.

Calcium is found in plant as well as in animal foods, but it is less easily absorbed. Other animal sources include small fish (when eaten with their bones) and meat (when rendered on the bone in stews). Plant sources include green vegetables, nuts, and pulses (legumes).[1 3]

Calcium is the most abundant mineral in the body and is the major mineral constituent of bones. It is central to a variety of functions in the body, such as bone metabolism, nerve and muscle activity, and the control of cell differentiation and proliferation. Calcium metabolism is controlled by various factors, including vitamin D and related hormonal compounds formed by the liver and kidney, necessary for the absorption of calcium from foods, and its regulation in the body.

the USA and some European countries to less than 0.5 per cent in some African and Asian countries.

4.4.4 Interpretation of the evidence

4.4.4.1 General
For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7

'Relative risk' (RR) is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.4.4.2 Specific
Patterns and ranges of intake. Most studies are carried out in high-income countries where consumption of cow's milk and its products is high, and where the main dairy product consumed is milk.

Classification. Studies usually do not make any distinction between dairy products, such as cheeses from different sources and with different compositions.

4.4.5 Evidence and judgements

The full systematic literature review (SLR) is contained on the CD included with this Report.

4.4.5.1 Milk and dairy products
Prostate
Ten cohort studies,[4-15] 13 case-control studies,[16-29] and 2 ecological studies[30 31] investigated milk and dairy products and prostate cancer; 16 cohort studies,[5-8 10 12 14 32-40] 11 case-control studies,[21 26 27 41-51] and 11 ecological studies[30 31 52-61] investigated milk.

Milk and dairy products
Seven cohort studies showed increased risk with increased intake of milk and dairy products,[4 6 8-11 13 15] which was statistically significant in two.[6 10] Two studies showed non-significant decreased risk[5 12 14]; and one study showed no effect on risk.[7] Meta-analysis was possible on eight studies, giving a summary effect estimate of 1.06 (95% confidence interval (CI) 1.01–1.11) per serving/day, with moderate heterogeneity.[4-12]

Five of these cohort studies reported separately on advanced/aggressive prostate cancer.[5 7 9 10 12] Two studies showed increased risk with increased intake of milk and dairy products,[9 10] which was statistically significant in one.[9] Three studies showed non-significant decreased risk.[5 7 12] Meta-analysis was possible on four studies, giving a summary effect estimate of 1.00 (95% CI 0.94–1.06) per serving/day, with low heterogeneity.[5 7 10 12] The study that could not be included in the meta-analysis was inconsistent with this result, reporting an effect estimate of 2.35 (95% CI 1.29–4.26) per serving/day increase (dry weight).[9]

Eight case-control studies showed increased risk with increased intake of milk and dairy products,[16 19-21 23 24 26 28] which was statistically significant in one. [28] Four studies showed non-significant decreased risk[17 18 22 25 27]; and one study reported that there was no statistically significant effect on risk.[29] Meta-analysis was possible on five relatively high-quality studies, giving a summary effect estimate of 1.03 (95% CI 0.99–1.07) per serving/day, with low heterogeneity.[16-20]

One ecological study showed no significant association, with an age-adjusted correlation coefficient of -0.49.[30] One other ecological study reported no statistically significant effect.[31]

There are many separate exposures being measured within this broad category, which may explain the observed heterogeneity.

A dose-response relationship is apparent from cohort data on all prostate cancer, but not from cohort data on advanced/aggressive prostate cancer or case-control data.

Milk
Six cohort studies showed increased risk with increased intake of milk,[6 8 33 36 37 39] which was statistically significant in one.[6] Three studies showed no effect on risk[32 34 35] and one study showed non-significant decreased risk.[14] The remaining six studies did not report quantified results, but stated results were not statistically significant.[5 7 10 12 38 40] Meta-analysis was possible on eight studies, giving a summary effect estimate of 1.05 (95% CI 0.98–1.14) per serving/day, with low heterogeneity.[6 8 14 32-36]

Six studies reported separately on advanced/aggressive prostate cancer.[7 12 33 36 39 40] Three studies showed increased risk with increased intake of milk, with effect estimates of 1.30 (95% CI 1.04–1.61) per serving/day[36]; 2.8 (in men aged 72.5 years or less, for the highest intake groups compared to the lowest, with no CI reported)[33]; and an increased risk with a p value for trend of 0.005.[39] Three studies did not report quantified results but stated that there was no significant association.[7 12 40]

Seven case-control studies showed increased risk with increased intake of milk,[27 41-44 47-51] which was statistically significant in three (including the single relatively high quality study).[41 43 44 47] Two studies showed non-significant decreased risk[21 45]; one study reported no effect on risk[46] and one study stated that there was no significant association but did not present results.[26] Meta-analysis was possible on six relatively low quality studies, giving a summary effect estimate of 1.08 (95% CI 0.98–1.19) per serving/day, with moderate heterogeneity.[21 27 42-45]

Ten ecological studies reported correlations in the direction of increased risk.[31 52 54-61] One study did not provide a quantified result, but stated there was no statistically significant association.[53] One study showed a non-significant decreased risk in areas of increased intake.[30]

Milk could plausibly cause prostate cancer through the actions of calcium (see chapter 4.4.5.1.1). Also, consumption of milk increases blood levels of insulin-like growth factor-1, which has been associated with increased prostate cancer risk in some studies.[62 63]

The evidence is inconsistent from both cohort and case-control studies. There is limited evidence suggesting that milk and dairy products are a cause of prostate cancer.

The Panel is aware that since the conclusion of the SLR, two cohort studies[64 65] and one case-control study[66] have been published. This new information does not change the Panel judgement (see box 3.8).

4.4.5.1.1 Milk
Colorectum
Thirteen cohort studies[67-82] and 36 case-control studies investigated milk and colorectal cancer. Fifteen cohort studies[72-77 79 80 82-101] and 58 case-control studies investigated dietary calcium.

Milk
Nine cohort studies showed decreased risk with increased intake of milk,[67 69 70 72 74 75 77 80-82] which was statistically sig-

Figure 4.4.1 — Milk and colorectal cancer; cohort studies

Relative risk (95% CI)

Keamey 1996 Men — 0.80 (0.57–1.11)
Gaard 1996 Women — 1.05 (0.74–1.49)
Gaard 1996 Men — 0.98 (0.86–1.11)
Ma 2001 Men — 0.64 (0.35–1.19)
McCullough 2003 Women — 1.08 (0.86–1.36)
McCullough 2003 Men — 0.86 (0.72–1.01)
Summary estimate — 0.94 (0.85–1.03)

Relative risk, per serving/day

Figure 4.4.2 — Milk and colorectal cancer: cohort studies: dose response

Ma 2001 Men
McCullough 2003 Women
McCullough 2003 Men
Keamey 1996 Men

Milk (servings/day)
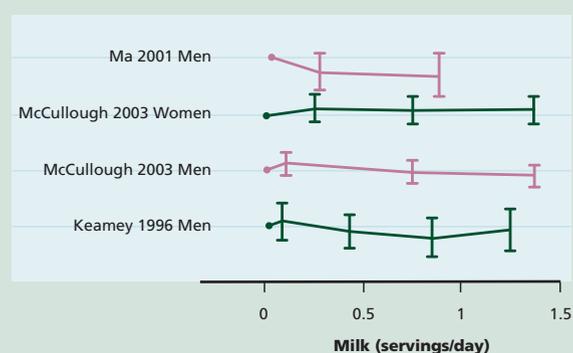
nificant in two.[67 80] Two studies showed non-significant increased risk[69 71 78 79] and two studies showed non-significant increased risk in women and non-significant decreased risk in men.[68 73 76] Meta-analysis was possible on four studies, giving a summary effect estimate of 0.94 (95% CI 0.85–1.03) per serving/day, with low heterogeneity (figures 4.4.1 and 4.4.2).[72 73 76 81]

In addition, there was a pooled analysis from 10 cohort studies which included 534 536 participants with 4992 cases of colorectal cancer. Milk intake was related to a statistically significant reduced risk of colorectal cancer (relative risk (RR) 0.78; 95% CI 0.69–0.88) for the highest intake group when compared to the lowest.[102]

Dietary calcium
Eleven studies showed decreased risk with increased intake of calcium,[76 79 82 84 85 90-93 99] which was statistically significant in three.[84 85 90] One study showed non-significant increased risk[74]; one study showed non-significant increased risk in women and non-significant decreased risk in men[73]; and two studies showed non-significant decreased risk of colon cancer and non-significant increased risk of rectal cancer.[88 89] Meta-analysis was possible on 10 cohort studies giving a summary effect estimate of 0.98 (95% CI 0.95–1.00) per 200 mg/day, with low heterogeneity (figure 4.4.3).[72 73 76 77 79 83 87 90 98 99] When meta-analysis was restricted to eight studies that reported results separately for colon cancer, a summary effect estimate of 0.95 (95% CI 0.92–0.98) per 200 mg/day was produced, with no heterogeneity.[72 73 76 77 83 87 89 90]

Dose-response plot
Figure 4.4.4 shows the dose-response curve for dietary calcium intake and colorectal cancer incidence.

In addition, there was a pooled analysis from 10 cohort studies which included 534 536 participants with 4992 cases of colorectal cancer. Dietary calcium intake was related to a statistically significant reduced risk of colorectal cancer (RR 0.86; 95% CI 0.78–0.95) for the highest
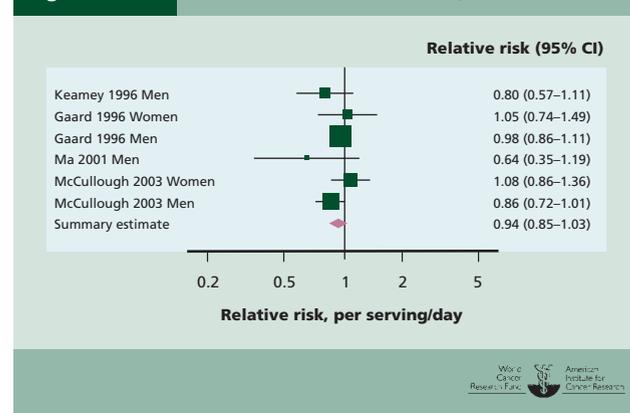
Figure 4.4.3 Dietary calcium and colorectal cancer: cohort studies

Relative risk (95% CI)

	Relative risk (95% CI)
Stemmermann, 1990 Men	0.98 (0.91-1.06)
Bostick 1993 Women	0.95 (0.87-1.02)
Martinez 1996 Women	0.95 (0.89-1.01)
Kearney 1996 Men	0.95 (0.85-1.05)
Gaard 1996 Men	0.86 (0.68-1.09)
Gaard 1996	0.98 (0.71-1.36)
Tangrea 1997 Men	1.00 (0.92-1.08)
Terry 2002 Women >=55 years	0.85 (0.75-0.96)
Terry 2002 Women <55 years	0.97 (0.80-1.19)
McCullough 2003 Men	0.95 (0.88-1.02)
McCullough 2003 Women	1.02 (0.93-1.11)
Koh 2004	1.00 (1.00-1.00)
Lin 2005 Women	0.99 (0.90-1.10)
Summary estimate	0.98 (0.95-1.00)

Relative risk, per 200 mg/day

intake group when compared to the lowest.[102]

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

Dietary calcium intake can be interpreted as a marker of dairy intake only in those populations (usually European, Australian, or from the Americas) that consume relatively regular and large amounts of milk and dairy products. Other dietary sources of calcium include vegetables, nuts, pulses, and fish or meat cooked on the bone (box 4.4.1).

The general mechanisms through which milk could plausibly protect against cancer are outlined below.

Figure 4.4.4 Dietary calcium and colorectal cancer; cohort studies: dose response

Lin 2005 Women
Bostick 1993 Women
Terry 2002 Women ≥55 years
Terry 2002 Women <55 years
McCullough 2003 Women
McCullough 2003 Men
Pietinen 1999 Men
Kearney 1996 Men
Martinez 1996 Women

Dietary calcium (mg/day)
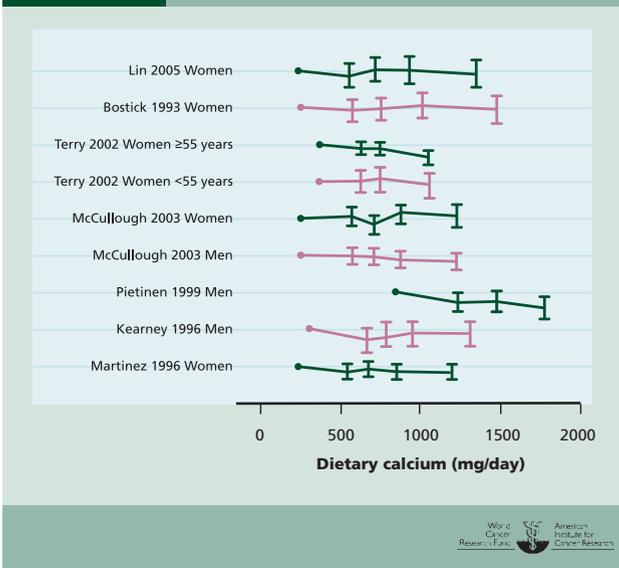
The evidence on milk from cohort studies is reasonably consistent, supported by stronger evidence from dietary calcium as a dietary marker. There is evidence for plausible mechanisms. Milk probably protects against colorectal cancer.

The Panel is aware that since the conclusion of the SLR, three cohort[80 103 104] and three case-control studies[66 105 106] have been published. This new information does not change the Panel judgement (see box 3.8).

Bladder cancer

Five cohort studies,[34 107-111] 14 case-control studies,[48 112-124] and 1 ecological study[56] investigated milk and bladder cancer.

All five cohort studies showed decreased risk with increased intake of milk,[34 107-111] which was statistically significant in one.[108] Meta-analysis was possible on four studies, giving a summary effect estimate of 0.82 (95% CI 0.67–0.99) per serving/day, with moderate heterogeneity.[34 108-110]

Seven case-control studies showed decreased risk with increased intake of milk,[48 112 115-117 121 122] which was statistically significant in four.[115 117 121 122] Four studies showed non-significant increased risk,[113 114 120 123] and three studies stated that there was no significant association.[118 119 124] Meta-analysis was possible on three relatively high-quality case-control studies, giving a summary effect estimate of 1.00 (95% CI 0.87–1.14) per serving/day, with high heterogeneity.[113-115]

A dose-response relationship is apparent from cohort, but not case-control data.

The single ecological study reported a correlation of 0.45 between milk consumption and death from bladder cancer.[56]

The general mechanisms through which milk could plausibly protect against cancer are outlined below.

The evidence is inconsistent and comes mainly from evidence on dietary calcium. There is limited evidence suggesting that milk protects against bladder cancer.

General mechanisms — milk
The probable effect of milk in reducing cancer risk is likely to be mediated at least in part by calcium. Calcium from diet is an import micronutrient, and intracellular calcium directly influences cell growth and apoptosis. Calcium may also bind to bile and fatty acids, preventing them from damaging the intestinal lining.[125] Milk includes many bioactive constituents, however, which may also play a role.

4.4.5.1.2 Cheese
Colorectum
Eleven cohort studies[67 68 70 72 74 78-80 82 126-128] and 25 case-control studies investigated cheese and colorectal cancer.

Eight cohort studies showed increased risk with increased intake of cheese, none of which was statistically significant.[67 68 70 72 74 79 80 126 127] Two studies reported non-significant decreased risk[78 82] and one study reported that there was no significant association.[128] Two meta-analyses were possible

on three and two cohort studies, respectively, giving summary effect estimates of 1.14 (95% CI 0.82–1.58) per serving/day[72 79 126] and 1.11 (95% CI 0.88–1.39) per 50 g/day,[80 82] both with low heterogeneity.

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

No specific mechanism has been identified but cheese could plausibly cause colorectal cancer through the indirect mechanisms connected to saturated fats. Saturated fats intake increases insulin production and expression of insulin receptors on colonic cells.[129] Saturated fats can also induce expression of certain inflammatory mediators associated with carcinogenesis.[130]

Epidemiological evidence for cheese intake is consistently in contrast to the probable protective effect from milk.

The evidence is inconsistent. There is limited evidence suggesting that cheese is a cause of colorectal cancer.

The Panel is aware that since the conclusion of the SLR, two cohort studies[66 103 104] and one case-control study[66] have been published. This new information does not change the Panel judgement (see box 3.8).

4.4.5.2 Diets high in calcium

For evidence on calcium supplements, see chapter 4.10.6.4.4.

Calcium is a good marker for dairy intake in Western diets. In areas outside the USA, Europe, and Oceania, dairy products are not as widely consumed and the range of calcium intake is smaller (see also box 4.4.1).

Prostate

Nine cohort studies,[4-8 10 11 131-133] 12 case-control studies,[18 19 23 24 134-144] and 2 ecological studies[145 146] investigated dietary calcium and prostate cancer.

Seven cohort studies showed increased risk with increased intake of dietary calcium,[4-7 10 11 131 133] which was statistically significant in three.[6 10 133] Two studies showed non-significant decreased risk, including the only unadjusted study.[8 132] Meta-analysis was possible on eight cohort studies, giving a summary effect estimate of 1.27 (95% CI 1.09–1.48) per g/day, with moderate heterogeneity.[5-8 10 11 131-133]

Four of these cohort studies reported separately on advanced/aggressive prostate cancer.[5 7 10 133] Three studies showed increased risk with increased intake of milk and dairy products,[7 10 133] which was statistically significant in one.[133] One study showed non-significant decreased risk.[5] Meta-analysis was possible on all four studies, giving a summary effect estimate of 1.32 (95% CI 1.05–1.64) per g/day, with moderate heterogeneity.[5 7 10 133]

Six case-control studies showed non-significant decreased risk with increased intake of dietary calcium.[18 134 136 138-140 143 144] Five studies showed increased risk,[19 23 24 135 137 141] which was statistically significant in one[19 138]; and one other study showed no effect on risk.[142] Meta-analysis was possible on three relatively high-quality studies, giving a summary effect estimate of 1.16 (95% CI 0.64–2.14) per gram of calcium/day, with high heterogeneity.[18 19 134]

A dose-response relationship was apparent from cohort but not case-control data.

One ecological study from Germany showed a significant increased risk of prostate cancer with higher calcium intakes.[146] Another study from Taiwan reported a non-significant decreased risk with higher calcium intakes.[145]

High calcium intake downregulates the formation of 1,25 dihydroxy vitamin D(3) from vitamin D, thereby increasing cell proliferation in the prostate.[7] Prostate cancer tumours in rats treated with 1,25 dihydroxy vitamin D(3) were significantly smaller and presented smaller numbers of lung metastases.[147]

The evidence, from both cohort and case-control studies, is substantial and consistent with a dose-response relationship. There is evidence for plausible mechanisms. Diets high in calcium are a probable cause of prostate cancer.

The Panel is aware that since the conclusion of the SLR, two cohort studies[64 65] have been published. This new information does not change the Panel judgement (see box 3.8).

4.4.6 Comparison with previous report

The previous report judged that milk and dairy products possibly increase the risk of prostate and kidney cancer. Calcium was judged possibly not to affect the risk of colorectal cancer. Since the mid-1990s, more evidence has emerged on prostate cancer, and that for kidney cancer is now inconclusive.

4.4.7 Conclusions

The Panel concludes:
The evidence on the relationship between milk and dairy products, and also diets high in calcium, and the risk of cancer, points in different directions.

Milk probably protects against colorectal cancer; there is limited evidence suggesting that milk protects against bladder cancer. But there is limited evidence suggesting that cheese is a cause of colorectal cancer.

Diets high in calcium are a probable cause of prostate cancer; there is limited evidence suggesting that high consumption of milk and dairy products is a cause of prostate cancer.

4.5 Fats and oils

Fats and oils are the most energy-dense constituents of food supplies and diets. Their contribution to total dietary energy increases with industrialisation and urbanisation. Meat from most industrially bred animals is higher in fat than that from wild animals, and such meat fats, together with fat from milk and dairy products, are a major source of fat in most high-income countries. Many processed foods contain substantial amounts of oils from plant sources. Production and consumption of animal fats and oil from plant sources have greatly increased in recent decades, most of all in China and elsewhere in Asia.

In general, *the Panel judges* that there is only limited evidence suggesting that diets relatively high in fats and oils (in total, or any type) are in themselves a cause of any cancer. This judgement contrasts with those of some earlier reports, which concluded from evidence then available that diets high in fats and oils might be a substantial cause of some cancers. Overall, the evidence does not suggest that diets relatively high in fats and oils might protect against the risk of any cancer.

The Panel judges as follows:
There is limited evidence suggesting that total fat is a cause of lung cancer, and of postmenopausal breast cancer; that animal fat is a cause of colorectal cancer; and that consumption of butter is a cause of lung cancer. *The Panel stresses* that the principal cause of lung cancer is tobacco smoking.

The evidence on fats and oils does not justify any judgement of 'convincing' or 'probable'. For discussion of the role of fats and oils in energy-dense foods and drinks, the effect of energy-dense foods and drinks on weight gain, overweight, and obesity, and the role of weight gain, overweight, and obesity in the risk of some cancers, see Chapters 6 and 8.

Fats or oils may be an intrinsic part of the plant or animal, as contained in the germ of cereals (grains) and the tissues of animals, or extracted and added to food in manufacture, cooking, or at the table.

Production and consumption of fats and oils in general rises with industrialisation and urbanisation, and in particular with the extent to which animal production is intensified, milk and dairy products are consumed, and processed foods include extracted oils. Availability and price are also key factors. In lower-income countries, average population consumption of fat may amount to less than 15 per cent, though usually to 20–30 per cent of total energy; in high-income countries, usually to 30–40 per cent. On a global basis, and most notably in China and elsewhere in Asia, production and consumption of animal fats and plant oils are increasing.

Early reports issued in the context of food insecurity in industrialised countries, including Europe and North America, recommended maintenance and even an increase in consumption of fats and oils. In the second half of the 20th century, reports on fats, oils, and chronic diseases tended to focus on the possible role of diets relatively high in fats and oils in the causation of obesity, type 2 diabetes, coronary

heart disease, and cancers of some sites. In recent decades, more attention has been given to issues of the nutritional quality of fats and oils. Distinctions are made between relatively saturated (including hydrogenated) fats, such as from meat, milk, and their products, or from hydrogenated oils in baked goods and many other processed foods; relatively monounsaturated oils, notably olive oil; and relatively polyunsaturated oils, from seeds, nuts, fish, and other sources, some of which — like vitamins — are essential to human health and life. These distinctions are to some extent reflected in the studies reviewed here.

For discussion of the role of fats and oils in energy-dense foods and drinks, the effect of energy-dense foods and drinks on weight gain, overweight, and obesity, and the role of weight gain, overweight, and obesity in the risk of some cancers, see Chapters 6 and 8.

In this Report, fats and oils are classified as foods. This section also covers dietary cholesterol, as well as total fat and individual fatty acids as dietary constituents. Food processes affecting the composition of fats and oils, such as hydrogenation, are also covered here.

4.5.1 Definitions and sources

Dietary fat is mostly made up of triglycerides (three fatty acid molecules attached to a glycerol backbone). Triglycerides are lipids, a class of hydrocarbon-containing organic compounds, which also includes cholesterol. Lipids are used by plants, animals, and humans as a means of storing energy, as structural components of cell membranes, and as precursors of important hormones.

Fatty acids are classified as either 'saturated' or 'unsaturated', depending on their chemical structure (see chapter 4.5.2), and these differences determine their shape and physical properties. Fats high in saturated fatty acids are generally solid at room temperature, whereas those rich in unsaturated fatty acids are liquid. *Trans*-fatty acids, formed in a process called hydrogenation (box 4.5.1), are physically more like saturated fats (harder at lower temperatures), and have similar effects on the body.

The term 'fats' is often used for fats and for oils. Fats can be classified according to their source, use, or chemical composition. Those that are solid or semisolid at ambient temperature are generally high in saturated fatty acids and are often of animal origin; and oils, which are from plant and marine sources, are liquid at ambient temperature in their places of origin. Palm oil and coconut oil, which are relatively high in saturated fatty acids, are semisolid in temperate climates but liquid in the tropics, where coconut and other palm trees grow (also see chapter 4.5.2).

Fats and oils are eaten as part of animal and plant foods, are contained in manufactured foods, used for cooking, and may be added at the table. Animal fats include tallow, lard, and suet, produced as part of the slaughtering process, and butter. Margarine and other fat spreads are made from fish and plant oils. Plant oils are extracted from oily fruits (such as olives), seeds (such as rape and sunflower), nuts (such as walnuts), and other sources.

A small amount of dietary fat is essential to allow absorption of fat-soluble vitamins (A, D, E, and K) and to provide the essential fatty acids that cannot be made by the body. Fat also helps food to taste more interesting and be more palatable, for instance in terms of its texture. Linoleic acid and alpha-linolenic acid are the two essential fatty acids, and are found in vegetables, nuts, and seed oils; lower levels are also found in meat, eggs, and dairy products. Oily fish also contain long-chain unsaturated fatty acids, which influence inflammatory processes in the body.[1] For instance, eicosapentaenoic and docosahexaenoic acids, and related fatty acids, are precursors to prostaglandins, which are hormone-like compounds with diverse effects, including roles in blood vessel dilation and constriction, blood clotting, and inflammation.

Cholesterol is found only in foods of animal origin, such as cheese, butter, meat, seafood, and egg yolks. Most of the cholesterol in the body is manufactured in the liver, rather than coming from these dietary sources.[1] The proportion and types of saturated and unsaturated fatty acids eaten in the diet are more important influences on cholesterol metabolism than the amount of dietary cholesterol.

4.5.2 Composition

The properties of fats and oils are determined by the length and structure of the fatty acids they contain. Liquid oils tend to be higher in unsaturated fatty acids, whereas more solid fats have more saturated fatty acids.

Whether or not a fatty acid is saturated depends on the chemical bonds that join together the chain of carbon atoms that forms the backbone of the molecule. Saturated fatty acids have only single bonds, whereas unsaturated fatty acids have at least one double bond between two adjacent carbon atoms. Monounsaturated fatty acids have only one double bond; polyunsaturated fatty acids have two or more double bonds. The position of the first double bond along the carbon chain is denoted by an 'n'. Thus linoleic acid is 'n-6' and alpha-linolenic acid is 'n-3'. These were previously known as 'omega-6' and 'omega-3' fatty acids.

Saturated fatty acids are long and straight, forming well ordered, relatively solid structures. But each of the double bonds in an unsaturated fatty acid causes the carbon chain to kink; and the more kinks, the less well they pack together, which means they form less solid structures. So, saturated fats are usually solid at room temperature and unsaturated fats are liquid (oils). *Trans*-fatty acids are unsaturated fatty acids formed by a process called hydrogenation, which removes and reconfigures the double bonds, making the carbon chain less kinked. Plant oils can be turned into saturated fats by this process, which, when only partially complete, also leads to production of *trans*-fatty acids (box 4.5.1).

Fats from ruminants (cattle and sheep) contain more saturated fatty acids than pork or poultry fats. Fats from under the skin have a smaller proportion of saturated fatty acids than fats stored around the organs. Beef suet is the hardest culinary fat, while chicken, duck, and

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Box 4.5.1   Hydrogenation and *trans*-fatty acids

The main single factor that has increased production and consumption of total fat and saturated fatty acids throughout the world, and therefore the energy density of food supplies, is the industrial process of hydrogenation, invented at the beginning of the 20th century.[2] The hydrogenation process was at first used mostly for the manufacture of margarine, but it is now used in the manufacture of many processed foods supplied and consumed throughout the world.

Complete hydrogenation converts the unsaturated fatty acids in oils of plant and marine origin into saturated fatty acids. This process has two commercial benefits.

First, it greatly extends 'shelf-life': oils high in unsaturated fatty acids become rancid, whereas fats high in saturated fatty acids 'keep' for very much longer. Second, it enables conversion of whatever plant and marine oils are cheapest at the time into a uniform, reliable ingredient and product.

Partial hydrogenation produces *trans*-fatty acids, which, although chemically unsaturated, physiologically behave more like saturated fatty acids. For instance, high levels in the diet increase the risk of coronary heart disease. Biscuits and other baked goods may contain as much as 25 per cent or more of their fats in *trans* form. Small amounts of *trans*-fats are also naturally found in milk and butter.

Because of the evidence on coronary heart disease, regulatory authorities in many countries now require food manufacturers to list *trans*-fatty acid content on nutrition labels of processed foods. Hydrogenated fats found in foods, and labelled as such, are hydrogenated to a variable extent and may therefore contain unspecified amounts of *trans*-fatty acids. This may not be clear on labels where a declaration of *trans*-fatty acid content is not required.

The Panel notes that any effect of *trans*-fatty acids specifically on the risk of any cancer is not known.

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goose fats are semiliquid at room temperature.

In general, the amount and type of body fat carried by animals and poultry depend on how they live, and this determines the fat content of their meat, unless some of it has been removed during processing. Wild and free-living land animals and birds are lean, and much of their fat is unsaturated; domesticated animals and birds carry more fat, which is higher in saturated fatty acids. Indeed, they are often bred to be more fatty, so that their meat is more succulent.

4.5.3 Consumption patterns

Consumption of total fats and oils varies greatly throughout the world. Average intake of total fat is highest (30–40 per cent of total energy) in most urbanised and industrialised regions such as Europe, North America, Australia, and New Zealand, where people consume relatively more meat and milk and their products. By contrast, fat usually accounts for only 20–30 per cent of total energy in lower-income parts of the world, for instance in Africa, Asia, and Latin America; this may be even lower in rural areas, where people consume low levels of added fats or oils (for instance, from processed foods). However, in general, consumption of fats — and in particular plant oils — is increasing in middle- and low-income countries. (Also see Chapter 1.)

Higher amounts of separated animal fats (as distinct from the fats that are naturally components of foods of animal origin) are consumed in high-income countries. Availability is typically highest in North America, northern Europe, Australia, and New Zealand — as much as 10 per cent in parts of northern Europe, compared with less than 0.5 per cent in much of Africa and Asia.[3]

More plant oils are also consumed in high-income countries; availability is highest in North America, southern Europe and some parts of the Middle East, and lowest in parts of Asia and Africa. Greece has the highest level of consumption — almost 20 per cent of dietary energy — compared with 1.4 per cent in Laos.

Soya bean oil is the most widely consumed oil in the world, particularly in North America, as well as in some Asian and African countries. Sunflower seed oil is the second most widely consumed vegetable oil (particularly in Europe, South Africa, Argentina, Chile, and New Zealand) and palm oil the third (particularly in some African, Asian, and Latin American countries, as well as in Australia). Olive oil is the most widely consumed oil in southern Europe (particularly in Greece, Italy, and Spain). Rapeseed oils are most common in northern Europe and Canada, while groundnut oil is common in some African countries.

The industrial revolution brought significant changes to food supplies, methods of food production, and hence people's diets (see chapter 1.1.3). Before then, it is thought that the amounts of n-6 and n-3 oils in diets had been roughly equal. But with the move to urban–industrial ways of life, vegetable oils (which are predominantly n-6) became cheap and widely available. The ratio of n-6 to n-3 fatty acids is now thought to be between 10 and 20 to 1 in many high-income countries.[4]

The World Health Organization recommends limiting average fat intake for populations to between 15 and 30 per cent of total daily energy intake, and saturated fatty acids to less than 10 per cent.[5] In higher-income countries, fat consumption as a percentage of total energy has been decreasing for some time. However, this is no longer the case in some countries such as the USA, where the percentage of energy from fat has started to increase again.

4.5.4 Interpretation of the evidence

4.5.4.1 General

For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7.

'Relative risk' (RR) is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.5.4.2 Specific

Some considerations specific to fats and oils are as follows.

Patterns and ranges of intake. In high-income countries where most studies are undertaken, average consumption of fats and oils is relatively high and variation in consumption is not great.

Classification. Studies tend to use classifications relevant to coronary heart disease, some of which may not be relevant to cancer. Thus, they examine not only animal and vegetable fats; meat, fish, and dairy fats; but also saturated and unsaturated fatty acids; monounsaturated and polyunsaturated fatty acids; n-3 and *trans*-fatty acids; and oleic, linoleic, and other individual fatty acids. This makes aggregation and analysis of intakes of fats and oils as a whole, problematic.

Study design. Practically all studies have analysed consumption of fats and oils as an issue of quantity (percentage of total energy intake) rather than nutritional quality (effect of different types of fats and oils). But oils are complex mixtures of nutrients and other bioactive compounds, some of which may have harmful effects on cancer risk and others beneficial effects.

Reporting bias. The use of questionnaires to record consumption of fats and oils may change behaviour. As people become more conscious of what they consume, they tend to under-report true consumption of foods and drinks they regard as unhealthy, including fats and oils. So studies using questionnaires may disproportionately underestimate consumption of fats and oils.

4.5.5 Evidence and judgements

The relationship between the risk of cancer and fat and oil intake may be assessed as weight of fat consumed or adjusted for total energy intake, so that fat is assessed as a proportion of total dietary energy.[6] Where this is the case, this has been stated below.

The full systematic literature review (SLR) is contained on the CD included with this Report.

4.5.5.1 Total fats

Lung

Nine cohort studies,[7-15] 17 case-control studies,[16-32] and 4 ecological studies[33-36] investigated total fat and lung cancer. (Also see chapter 7.4.)

Six cohort studies showed non-significant increased risk for the highest intake group when compared to the lowest.[7 8 10 11 13 14] Three studies showed decreased risk,[9 12 15] which was statistically significant in one.[15] Meta-analysis was possible on two cohort studies, with a summary effect estimate of 1.01 (95% confidence interval (CI) 0.94–1.09) per 10 g fat/day, with high heterogeneity.[11 12] Six of the studies adjusted for smoking, including the two studies in the meta-analysis and not including the statistically significant reduced risk.[7-12]

Pooled analysis from 8 cohort studies (over 430 000 partici-

pants, followed up for 6 to 16 years, more than 3100 lung cancer cases) showed a non-significant increased risk of 1.01 (95% CI 0.98–1.05) per 5 per cent daily energy intake from fat.[37]

Twelve of the case-control studies showed increased risk for the highest intake group when compared to the lowest,[16 17 19-21 23 25 27-29 31 32] which was statistically significant in five.[16 17 19-21 25 31] No studies reported statistically significant reduced risk. Most (12) of these studies adjusted for smoking.[16 19-22 24 25 27 30-32]

The ecological studies reported mixed results, most of which were not statistically significant.[33-35] One study reported a statistically significant decreased risk with increased fat intake.[36]

Although no evidence for plausible mechanisms was found, based on the epidemiological evidence, there is limited evidence suggesting that total fat is a cause of lung cancer.

The mixed results from cohort studies contrast with the more consistent results from other studies. Overall, there is limited evidence suggesting that consumption of total fat is a cause of lung cancer. *The Panel emphasises* **that the principal cause of lung cancer is smoking tobacco.**

Breast (all ages)

Nineteen cohort studies,[38-60] 49 case-control studies,[61-118] and 10 ecological studies[119-128] investigated total fat intake and breast cancer.

Breast (premenopause)

Total fat intake for all ages, and also for premenopausal breast cancer, did not give any overall indication of effect.

Breast (postmenopause)

Nine cohort studies[38 40 43 45 50-52 57-59] and 16 case-control studies[62-65 75 79 85 86 96-98 101 102 109 110 112 116] reported results specifically for postmenopausal breast cancer.

Six cohort studies showed increased risk with increasing fat intake,[38 40 45 50-52 59] which was statistically significant in three.[38 51 52] Three studies reported non-significant reduced risk.[40 43 57 58] Meta-analysis was possible on five cohort studies, giving a summary estimate of 1.06 (95% CI 0.99–1.14) per 20 g/day, with moderate heterogeneity.[38 43 45 50 51]

Pooling project data (7329 invasive postmenopausal breast cancer cases among 351 821 women) showed a reduced risk, with an estimate of 0.96 (95% CI 0.86–1.08) per 25 g increase in energy-adjusted total fat. Menopausal status was not an effect modifier on these data.[129 130]

Eleven case-control studies showed increased risk with increasing fat intake,[62 64 65 75 85 86 96-98 102 109 110 112] which was statistically significant in three.[97 109 112] Five studies showed decreased risk,[63 64 79 101 116] which was statistically significant in one.[64] Meta-analysis was possible on seven control studies, giving a summary estimate of 1.11 (95% CI 1.06–1.16), with no heterogeneity.[62 63 65 75 97 102 109]

There is also evidence on percentage energy from fat. There are four cohort studies[131-134]; three reported decreased risk.[131 133 134] The other study reported non-significant increased risk.[132] There were two case-control studies; both reported a non-significant decreased risk.[135 136]

There is interest in the varying role that different types of individual fatty acids might have on breast cancer risk but there are insufficient data to draw any conclusions. There are mechanistic data connecting polyunsaturated fatty acids and peroxidation.

Higher endogenous oestrogen levels after menopause are a known cause of breast cancer.[137] [138] Dietary fat is relatively well established as a cause of increased endogenous oestrogen production.[139] Low-fat diets are usually associated with high fibre consumption, which may reduce oestrogen concentration by decreasing intestinal reabsorption. In premenopausal women, there is little evidence that serum oestrogen levels are associated either with fat consumption or with breast cancer risk.

An alternative mechanism by which dietary fat could influence steroid hormone levels is that increased serum-free fatty acids could displace oestradiol from serum albumin, thus increasing free oestradiol concentration.[140] However, the serum concentration of sex hormone-binding globulin is a more important determinant of the proportion of oestradiol that can enter the breast epithelial cells. Sex hormone-binding globulin decreases with increasing body mass index and insulin resistance.

Energy-dense diets (among other factors) lower the age of menarche. Early menarche is an established risk factor for breast cancer.

Evidence from prospective epidemiological studies of different types shows inconsistent effects on the whole, while case-control studies show a significant positive association. Mechanistic evidence is speculative. Overall, there is limited evidence suggesting that consumption of total fat is a cause of postmenopausal breast cancer.

4.5.5.1.1 Butter
Lung
Two cohort studies[8] [141] and eight case-control studies[142-149] investigated butter and lung cancer. (Also see chapter 7.4.)

One cohort study showed statistically significant increased risk, with a summary estimate of 1.8 (95% CI 1.0–3.0) for the highest intake group when compared to the lowest.[8] The other cohort study showed non-significant decreased risk in three independent estimates: 0.92 (95% CI 0.65–1.30) for men; 0.90 (95% CI 0.46–1.77) for women; and 0.94 (95% CI 0.62–1.42) for non-smokers.[141] Both studies adjusted for smoking.

Seven case-control studies showed increased risk for the highest intake group when compared to the lowest,[143-149] which was statistically significant in three.[143] [145] [149] One study showed a non-significant decreased risk.[142] Most studies adjusted for smoking.[142] [143] [145-149]

Although no evidence for plausible mechanisms was found, based on the epidemiological evidence, there is limited evidence suggesting that butter is a cause of lung cancer.

There is a limited amount of inconsistent evidence suggesting that consumption of butter is a cause of lung cancer.

4.5.5.2 Foods containing animal fat
The evidence here refers to animal fats as foods, for instance, lard, suet, or dripping, and not to estimated amounts contained within other foods (such as meat and milk and their products, or baked goods).

Colorectum
Five cohort studies investigated animal fats and colorectal cancer.[150-154] (Also see chapter 7.9.)

Three studies showed increased risk with increasing intake of animal fats,[150] [151] [153] which was statistically significant in one,[150] and statistically significant when comparing the second highest intake to the lowest intake group, but not when comparing the highest to lowest, in another study.[151] One study reported no effect on risk[152] and another showed non-significant increased risk in men and non-significant decreased risk in women.[154] Meta-analysis was possible on three studies, giving a summary effect estimate of 1.13 (95% CI 0.92–1.38) per 20 g/day, with moderate heterogeneity.[150] [152] [154]

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

There is a limited amount of fairly consistent evidence suggesting that consumption of foods containing animal fat is a cause of colorectal cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[155] has been published. This new information does not change the Panel judgement (see box 3.8).

4.5.6 Comparison with previous report

The panel responsible for the previous report judged it possible that diets relatively high in total fat, and/or in saturated/animal fat, were causes of cancers of the lung, colorectum, breast, endometrium, and prostate. That panel noted a pattern whereby diets relatively high in fat could increase the risk of some cancers, and pointed out that fats and oils are energy-dense, and agreed that energy-dense diets increase the risk of obesity, itself a risk factor for some cancers.

The previous report judged that diets high in dietary cholesterol were a possible cause of cancers of the lung and pancreas. The overall evidence now does not support an association.

Since the mid-1990s, the results of cohort studies have overall tended to weaken the evidence on fats and oils as direct causes of cancer.

4.5.7 Conclusions

The Panel concludes:
Findings from cohort studies conducted since the mid-1990s have made the overall evidence associating fats and oils with the risk of any cancer somewhat less impressive.

There is limited evidence suggesting that total fat is a

cause of lung cancer or postmenopausal breast cancer; that foods containing animal fat are a cause of colorectal cancer; and that butter is a cause of lung cancer. *The Panel stresses* that the main cause of lung cancer is smoking tobacco.

Fats and oils are the most energy-dense constituents of foods. For discussion of the effect of energy-dense foods on weight gain, overweight, and obesity, and the role of weight gain, overweight, and obesity in the risk of some cancers, see Chapters 6, 7, and 8.

4.6 Sugars and salt

SUGARS AND SALT, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	**Cancer site**	**Exposure**	**Cancer site**
Convincing				
Probable			**Salt**[1] **Salted and salty foods**	**Stomach** **Stomach**
Limited — suggestive			Foods containing sugars[2]	Colorectum
Substantial effect on risk unlikely	None identified			

1 'Salt' here means total salt consumption, from processed foods, including salty and salted foods, and also salt added in cooking and at the table.
2 'Sugars' here means all 'non-milk extrinsic' sugars, including refined and other added sugars, honey, and as contained in fruit juices and syrups. It does not include sugars naturally present in whole foods such as fruits. It also does not include lactose as contained in animal or human milk.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

Sugars are sweeteners and, in some forms, also a preservative and a bulking agent. Free sugars in the solid state or as syrups are ingredients in many processed foods and drinks. Nutritionally, sugars supply energy and nothing else. Sugars added to food were a luxury until sugar from cane became a major international cash crop, beginning in the 16th century. Consumption of added sugars, from beet as well as cane, and syrups increased rapidly in industrialised countries in the 19th and 20th centuries. High-fructose corn syrups are now also used extensively. Overall consumption of sugars is increasing worldwide, particularly in lower-income countries. In recent decades, and in many countries, consumption of added sugars, notably in the form of sugary drinks, accounts for a substantial proportion of energy intake.

Salt (sodium chloride) is also a preservative. The sodium and chloride in salt are essential nutrients in small amounts. In nature, foods are generally low or very low in sodium. Like sugar, salt historically was scarce and a precious commodity; the Romans paid their labourers in salt, thus the word 'salary' (from 'sal' for salt). Consumption of salt, in the form of many processed, salted, and salty foods, or of salt added in cooking and at table, remains variable. Consumption of salt, and salty and salt-preserved foods, is high in some maritime nations such as Japan, Portugal, and other Portuguese-speaking countries. In inland regions, such as landlocked African countries, consumption has been very low.

Overall, *the Panel judges* that the evidence on salt

is confined to stomach cancer, and that on sugars is limited.

The Panel judges as follows:
Salt is a probable cause of stomach cancer. Salt-preserved foods are also a probable cause of stomach cancer. There is limited evidence suggesting that sugars are a cause of colorectal cancer. Within the remit of this Report, the strongest evidence, corresponding to judgements of 'convincing' and 'probable', shows that salt, and also salt-preserved foods, are probably causes of stomach cancer.

'Extrinsic', mainly refined, sugars amount to a substantial part of most industrialised food supplies. Sugars and syrups manufactured from cane, beet, and corn are profitable cash crops and are ingredients in many processed foods and drinks.

There is reason to believe that humans have evolved with a built-in desire for sweet foods. It has also been proposed that humans have a specific appetite for salt that might have evolved because sodium is scarce in nature. In any case, as sugars and salt become readily available and increasingly cheap, consumption tends to rise. In industrialised settings, sugars and salt are mostly consumed, not in food preparation or at the table, but as ingredients of processed foods.

Reports concerned with undernutrition have often, and still do, recommend substantial consumption of sugars and fats; their energy density enables quick weight gain, and the

taste preference promotes energy consumption. By contrast, reports concerned with prevention of chronic diseases frequently recommend restraint in consumption of sugars. One reason for this is that sugars are the dietary cause of dental caries. Sugars in the amounts typically consumed in many industrialised countries have also been identified as a cause of obesity, and therefore also indirectly of obesity-related disease. Reports concerned with nutritional deficiencies often recommend the iodisation of salt supplies, to prevent goitre. Reports concerned with the prevention of chronic diseases frequently highlight that salt intakes are usually greatly in excess of requirements, and recommend substantial decreases in salt consumption to prevent hypertension and cardiovascular disease, especially stroke.

For sugared drinks, see chapter 4.7. For the contribution of sugar to weight gain, overweight, and obesity in drinks or through energy density of foods, see Chapter 8. For salted animal products, including Cantonese-style salted fish, see chapter 4.3.

Non-caloric chemical sweeteners are included here.

4.6.1 Definitions, sources

4.6.1.1 Sugars

Sugars here means all sugars in the diet. These are mainly but not only 'extrinsic sugars', which include sucrose (commonly called sugar), maltose, lactose, glucose, and fructose; in foods and drinks, including juices and milk, and in honey and syrups, including high-fructose corn syrup; refined sugars added to food in processing, preparation (cooking), and at the table. 'Intrinsic' sugars are those naturally present in whole foods such as fruits.

Sugars are now cheap and are used widely as sweeteners, preservatives, and bulking agents. They also often have the function of making processed starches, fats, and other ingredients more palatable. Also see box 4.6.1

Sucrose is refined from sugar beet and sugar cane. Maltose and glucose are refined predominantly from corn. High-fructose corn syrup comprises a mixture of glucose with fructose, commonly in close to equal amounts, and is now used in great quantity in food and drink manufacture, particularly in the USA.

The amount of sugars in manufactured foods and drinks varies. Sugared drinks are about 10 per cent by weight added sugars, and up to 100 per cent of their energy comes from sugars. Sugars are often added to fruit juices. Jams and other preserves are about 60 per cent sugars. Cakes, biscuits (cookies), and other baked goods contain starches, fats, and sugars in varying proportions. Most chocolate and much confectionery are high in sugars. It is often supposed that almost all added sugars are contained in obviously sweet foods: this is not so. Breakfast cereals may contain anything from negligible amounts to 50 per cent sugars. Yoghurts may contain anything between 0 to 20 per cent sugars; and ready-to-eat desserts even more. Many canned products include added sugars. Savoury processed foods, such as soups, pickles, bread, and buns, often contain significant amounts of sugars.

| Box 4.6.1 | Sugar, sugars, sugary foods, and drinks |

As indicated in chapter 4.6.4, it is particularly difficult to measure and assess the overall effect of sugars as possible modifiers of the risk of any disease, including cancer. This is partly because of inconsistency in the classification of sugars. Sometimes 'sugar' is equated with sucrose, which has been the chief sugar in human diets, but now is less so. Some studies investigate only 'packet' sugar purchased for use in the home; this is in general a relatively small and diminishing proportion of total sugars consumed. Other studies include sugars as found naturally in fruits and milk.

4.6.1.2 Salt

The term 'salt', in common usage, refers to sodium chloride. It is now a cheap commodity. Like sugar, salt is a preservative and a flavour enhancer. Both salt and sugar trap free water from foods, thus preventing microbial proliferation and spoilage. Salt is found in some rocks and dissolved in seawater, and can be extracted from seawater by evaporation. Both sodium and chloride are essential components of the diet in small amounts.

Usually most salt in diets is contained in processed foods, with only a relatively small amount added in cooking or at the table (box 4.6.2). Some traditional diets include substantial amounts of salt-preserved foods, including salted meat, fish, vegetables, and sometimes also fruits; and also salted foods such as bacon, sausages, and ham, which contain from 3 to 5 g of salt per 100 g. Industrialised diets include many processed foods that are not salt-preserved but contribute substantial amounts of salt to the diet, even if they do not seem salty, as well as more obviously salty foods such as potato crisps (chips), salted nuts, and other salty snack foods. Most of the sodium consumed in urban environments comes from salt added to processed foods, and thus is beyond the control of typical consumers. Many foods such as bread, soups, breakfast cereals, and biscuits may contain substantial amounts of salt; anything from 1 to 4 g per 100 g.

4.6.2 Composition

4.6.2.1 Sugars

Sugars are simple carbohydrates, and provide 3.75 kilocalories per gram (see chapter 4.10.1). Sugars are single molecules such as glucose, fructose, and galactose (monosaccharides), or two molecules bound together (disaccharides) such as sucrose (fructose and glucose), lactose (glucose and galactose), or maltose (two glucose molecules).

The body metabolises different sugars at different rates; for instance, fructose is absorbed and metabolised more slowly than either glucose or sucrose. It is also slightly sweeter than glucose or sucrose, and thus is able to replace them in lower total amounts. Non-caloric chemical sweeteners produce a sweet taste, but are not sugars (box 4.6.3).

There is no dietary requirement for sugars. The World

Health Organization recommends that average consumption of sugars by populations should be less than 10 per cent of total energy.[1]

4.6.2.2 Salt

Pure salt, as sodium chloride, contains no metabolisable energy. Formulated, granulated table salts often include additives, such as anti-caking agents, which prevent salt crystals from sticking together; potassium iodide, included to prevent iodine deficiency; traces of other sodium compounds (carbonate or thiosulphate); and also sugar, to stabilise the potassium iodide. Sea salt may be refined to almost pure sodium chloride, or unrefined, in which case they may include traces of other minerals, algae, and a few salt-tolerant bacteria. Salt may also be flavoured, for example with celery or garlic.

Sodium is essential for the body to function normally. It is a major electrolyte in extracellular fluid. The body's sodium content and its concentration in body fluids are controlled homeostatically to very precise limits; excess sodium is excreted in the urine. Sodium is also involved in regulation of osmolarity, acid-base balance, and the membrane potential of cells. The daily requirement for sodium has been estimated at around 500 mg for adults. On a pragmatic basis, WHO recommends restricting average salt consumption for populations to less than 5 g per day.[1]

4.6.3 Consumption patterns

4.6.3.1 Sugars

Sugars supply on average around 8 per cent of dietary energy worldwide. This figure disguises a wide range of intakes in different parts of the world. Diets in high-income countries contain roughly twice the amount of sugars as those in lower-income countries. In North America and some European countries, average consumption is around 15–17 per cent of dietary energy, with a fairly wide range around this average. In the USA, in the last decades of the 20th century, many processed foods were reformulated to contain less fat but more sugars. In some parts of Asia, consumption is negligible, although globally sugar supplies are increasing rapidly. Children in high-income countries usually obtain a higher proportion of their daily energy from sugar than adults.[11]

Consumption of sugars has generally increased over the last century, particularly in high-income countries, and also more recently in many countries undergoing economic transition in Asia, Africa, the Middle East, and Latin America.

4.6.3.2 Salt

The use of salt as a preservative has generally decreased as industrial and domestic use of refrigeration has increased (box 4.6.4). But diets containing few salt-preserved foods may nevertheless be high in salt.

The average adult daily intake of salt worldwide varies from less than 6 g to 18 g. Very high levels of intake are found in Japan, some parts of China, Korea, Portugal, Brazil, and other Portuguese-speaking countries, where diets contain substantial amounts of salt-preserved, salt-pickled, salted, or salty foods. The average adult intake is around 9–12 g per day in high-income countries, including Europe and North America.

4.6.4 Interpretation of the evidence

4.6.4.1 General

For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7.

'Relative risk' (RR) is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.6.4.2 Specific

Classification. Studies of sugars may be of total sugars; of

Box 4.6.4	Refrigeration

Freezing and cooling by use of natural ice and snow is a method of food preservation traditionally available only in cold climates or in winter in temperate climates. Natural ice refrigeration on an industrial scale first developed in the late 19th century, when refrigerated containers used in trains, ships, and then later trucks, greatly increased the production and consumption of red meat. Domestic freezing, chilling, and refrigeration on a mass scale is a phenomenon mostly of the second half of the 20th century.

Today, much perishable food is sold frozen or chilled. Together with the growth of industrial refrigeration, domestic refrigerators began to be used in the USA, Australia, and New Zealand on any scale in the 1920s, and in Europe and Japan mostly since the 1950s. In Japan, for example, households possessing refrigerators increased from 9 per cent in 1960 to 91 per cent in 1970, and 99 per cent in 2004. Supermarkets with freezers, chill cabinets, and domestic refrigerators are now commonplace in the cities and towns of tropical countries; poorer rural communities still rely on drying, fermenting, salting, bottling, tinning, and other methods of food preservation, as well as their own gardens and farms. It is unlikely that refrigeration itself has any direct effect on the risk of cancer. Its effects are indirect.

Refrigeration:
- Enables consumption of fresh perishable foods including seasonal vegetables and fruits all year round, as well as of fresh meat.
- Reduces microbial and fungal contamination of perishable foods, notably cereals (grains) and pulses (legumes).
- Reduces the need for and use of salting, smoking, curing, and pickling as methods of preserving vegetables, fruits, and meat.

It can therefore be said that refrigeration (including freezing and chilling) indirectly influences risk of those cancers, the risk of which is affected by the above factors.

Evidence amounting to a judgement of 'convincing' or 'probable' for such factors is summarised in earlier sections of this chapter, and in Chapter 7, and relates to cancers of the mouth, pharynx, larynx, nasopharynx, oesophagus, lung, stomach, pancreas, liver, and colorectum.

In particular, many studies have noted a reciprocal relationship between use of refrigeration and consumption of salt and foods preserved with salt. Meta-analysis of eight case-control studies[2-9] has shown a significant association between the use of refrigeration (usually as gauged by possession of a domestic refrigerator) and reduced risk of stomach cancer.

The one cohort study[10] identified measured effects in the Netherlands over a 25-year period, in which almost the entire population had access to commercial and domestic refrigeration, and did not find any association.

sugars added at the table; of sugary foods and/or drinks; of sucrose; or of added sugars generally; and may or may not include those sugars naturally present in foods. Studies using such varying classifications are difficult to compare. Similarly, studies of salt may be of salt added in cooking and/or at the table; of salty or salted foods; or of salt consumption as a whole. These studies are also difficult to compare. See box 4.6.1 and box 4.6.2.

Measurement. Measurement of salt intake is notoriously difficult, and is best done by measuring the excretion of sodium in urine over a 24-hour period. But this method has only rarely been used.

Study design. See Classification. Also studies may underestimate the amounts of sugars and of salt in foods and drinks consumed outside the home.

Reporting bias. Added sugars are generally regarded as unhealthy, and studies that depend on self-reporting may disproportionately underestimate the consumption of sugars.

4.6.5 Evidence and judgements

The full systematic literature review (SLR) is contained on the CD included with this Report.

The relationship between the intake of sugars and the risk of cancer is often adjusted for total energy intake, meaning that sugars are assessed as a proportion of total dietary energy.[12] Where this is the case, this has been stated.

4.6.5.1 Sugars
Colorectum
One cohort study[13] and 7 case-control studies[14-20] investigated sugars as foods and colorectal cancer. Seven cohort studies[21-27] and 16 case-control studies investigated sugars as nutrients, defined as sucrose or fructose.

Sugars as foods
The single cohort study stated that there was no association between usually adding sugar to cereals and colorectal cancer.[13]

All seven case-control studies showed increased risk with increased sugar intake,[14-20] which was statistically significant in two.[17 18] The classification of 'sugars as foods' varied considerably between studies.

Sugars as nutrients
Four cohort studies reported on total sugar intake.[21 22 25 26] One study reported a non-significant increased risk for the highest intake group when compared to the lowest, with an effect estimate of 1.03 (95% confidence interval (CI) 0.73–1.44).[22] One study reported a non-significant lower sugar intake in cases than controls.[21] Two cohort studies stated that there was no association between sugar intake and risk.[25 26]

Three cohort studies reported on sucrose intake.[23 24 27] Two cohort studies showed non-significant increased risk when comparing the highest intake group against the lowest.[23 27] Effect estimates were 1.45 (95% CI 0.88–2.39)[23] and 1.30 (95% CI 0.99–1.69) in men.[27] One study reported a non-statistically significant decreased risk (0.89 (95% CI 0.72–1.11) in women).[27]

Three cohort studies reported separate results for fructose[23 24 27]; one reported a significant increased risk in men of 1.37 (95% CI 1.05–1.78).[27] Two other studies reported non-significant decreased risk.[23 27]

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

In most, though not all, animal experiments, sucrose and fructose are associated with increased colonic proliferation and aberrant crypt foci. These sugars may interfere with levels of blood glucose and/or triglycerides, either directly or through hormones like insulin and others (also see Chapter 2).[28]

The evidence is hard to interpret. There is limited evidence suggesting that sugar is a cause of colorectal cancer.

4.6.5.2 Salt
Stomach
Three cohort studies,[10 29 30] 21 case-control studies,[2 4 31-48] and 12 ecological studies[49-60] investigated total salt use and stomach cancer. Two cohort studies[10 61] and 13 case-control studies[4 9 39 43 62-71] investigated salt added at the table; 1 cohort study[72] and 8 case-control studies[4 39 73-78] investigated sodium intake.

Total salt use
Two cohort studies showed increased risk with increased salt intake,[10 30] which was statistically significant in one study in men but not women.[30] One study showed statistically significant decreased risk.[29] Meta-analysis was possible on two cohort studies, giving a summary effect estimate of 1.08 (95% CI 1.00–1.17) per 1 g/day, with moderate heterogeneity (figure 4.6.1). The study that could not be included

Figure 4.6.1	Total salt use and stomach cancer; cohort and case-control studies

Relative risk (95% CI)

Cohort
Van de brandt 2003 — 1.07 (0.97–1.18)
Tsugane 2004 Men — 1.14 (1.08–1.21)
Tsugane 2004 Women — 1.01 (0.92–1.11)
Summary estimate — 1.08 (1.00–1.17)

Case control
You 1988 — 1.00 (0.99–1.01)
Nazario 1993 — 1.17 (1.08–1.27)
Ramon 1993 — 1.36 (1.01–1.82)
Ye 1998 — 1.03 (0.99–1.07)
Setiawan 2000 — 1.02 (0.99–1.04)
Munoz 2001 — 0.96 (0.93–1.00)
Tsukino 2004 — 0.98 (0.88–1.10)
Setiawan 2005 — 1.00 (0.86–1.16)
Setiawan 2005 — 0.96 (0.99–1.04)
Summary estimate — 1.01 (0.99–1.04)

0.5   0.75   1   1.5   2

Relative risk, per g/day

was inconsistent with this summary, with an effect estimate of 0.53 (95% CI 0.31–0.91) for the highest intake group when compared to the lowest; however, this study did not adjust for other factors.[29] The two cohort studies that reported increased risk used much more detailed questionnaires to assess salt intake (150 compared to 27 items). They also adjusted for a greater number of confounders than the study that reported decreased risk.

Twelve of the case-control studies showed increased risk with increased salt intake,[2 32 34 35 39 40 42-46] which was statistically significant in six.[32 40 42-45] None of the studies showed statistically significant decreased risk. Most other studies reported either risk estimates close to 1.0 or reported that there was no statistical association. Meta-analysis was possible on eight case-control studies, giving a summary effect estimate of 1.01 (95% CI 0.99–1.04) per 1 g/day, with high heterogeneity (figure 4.6.1).

A dose-response relationship was apparent from cohort but not case-control data.

Seven ecological studies reported increased risk with increased salt intake,[49 52-55 57 58] which was statistically significant in four.[53 54 57 58] The remaining five studies reported either a decreased risk with increased salt intake[50 56 59 60] or no association,[51] none of which was statistically significant. Stomach cancer rates are highest in those areas of the world, such as parts of Asia and Latin America, where diets are traditionally salty due to the regular consumption of meat, fish, vegetables, and other foods preserved by salting, as well as of salty foods.

Salt added at the table
Both cohort studies reported that there was no significant effect, and estimates were close to one (1.0) (95% CI 0.6–1.6)[61] and 0.9 (95% CI 0.56–1.44).[10]

Twelve case-control studies showed increased risk for the highest intake group when compared to the lowest,[4 9 39 43 62-64 66-71] which was statistically significant in eight.[4 9 43 62-64 67] One other study reported similar intakes in cases and control.[65]

Sodium
The single cohort study showed a non-significant decreased risk.[72]

Six case-control studies showed increased risk for the highest intake group when compared to the lowest,[39 73-77] which was statistically significant in three.[39 74 77] Two studies showed decreased risk, which was statistically significant in both.[4 78] Meta-analysis was possible on five studies, giving a summary effect estimate of 1.18 (95% CI 1.02–1.38) per 1 g/day, with high heterogeneity.[39 74-76 78]

Interaction with Helicobacter pylori *infection*
Two case-control studies that investigated total salt use also investigated the potential for interaction with *H pylori* infection (also see box 7.5.1).[79 80] One study was suggestive of a multiplicative effect on risk for high salt use and *H pylori* positive status[79]; the other stated that there was no association.[80]

Salt intake may be inversely related to the availability of refrigeration both within and between populations. Salt-

preserved foods may be eaten more by those to whom refrigeration is not available.
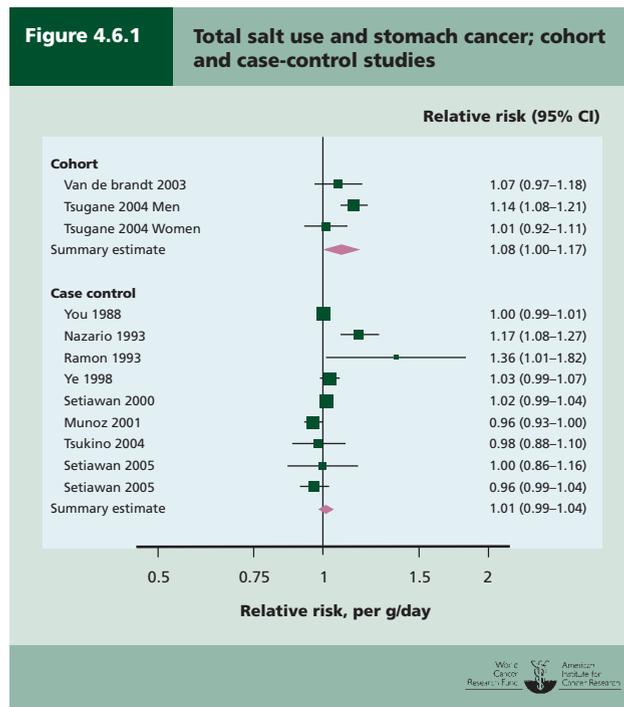
There is evidence from laboratory experiments that high salt intake damages the lining of the stomach.[81] It has also been shown to increase endogenous *N*-nitroso compound formation.[82] In addition, a high salt diet has been shown to have a synergistic interaction with gastric carcinogens.[82] It may only contribute to gastric cancer in subjects who have *H pylori* infections and are also exposed to a chemical carcinogen.

There is a substantial amount of evidence from studies on total salt use, salt added at the table, and sodium intake. For total salt use, a dose-response relationship was apparent from cohort but not case-control studies. For sodium intake, a dose-response was also apparent from case-control studies. The mechanistic evidence is strong. Salt is a probable cause of stomach cancer.

The Panel is aware that since the conclusion of the SLR, one cohort[83] and two case-control studies[84][85] have been published. This new information does not change the Panel judgement (see box 3.8).

4.6.5.2.1 Salted and salty foods
Stomach

Four cohort studies[86-89], 17 case-control studies[4][6-8][33][41][45][90-99] and 1 ecological study[100] investigated salted or salty foods and stomach cancer.

Three cohort studies showed non-significant increased risk with increased salt intake.[86][88][89] One study reported that there was no association.[87] Meta-analysis was possible on three cohort studies, giving a summary effect estimate of 1.32 (95% CI 0.90–1.95) per one serving/day with no heterogeneity (figure 4.6.2).

Eleven case-control studies showed increased risk for the highest intake groups when compared to the lowest,[6-8][41][45][91][94-98] which was statistically significant in seven.[6-8][45][94-96] Two studies showed non-significant decreased risk.[4][99] Four studies reported either the same intakes in cases and controls or no statistical association.[33][90][92][93] Meta-analysis was possible on four case-control studies, giving a summary effect estimate of 5.2 (95% CI 2.49–10.83) per one serving/day, with high heterogeneity (figure 4.6.2).

A dose-response relationship is apparent from case-control, but not cohort data (figure 4.6.3).

Heterogeneity may be partly explained by variation between studies in the precise foods being assessed.

The single ecological study showed non-significant decreased risk in areas of increased salt consumption.[100]

The mechanisms through which salt could plausibly cause stomach cancer are given above.

The evidence from both case-control and cohort studies is consistent. A dose-response relationship is apparent from case-control but not cohort studies. There is robust evidence for mechanisms operating in humans. Salted and salty foods are a probable cause of stomach cancer.

Figure 4.6.3 Salted/salty foods and stomach cancer; cohort and case-control studies: dose response
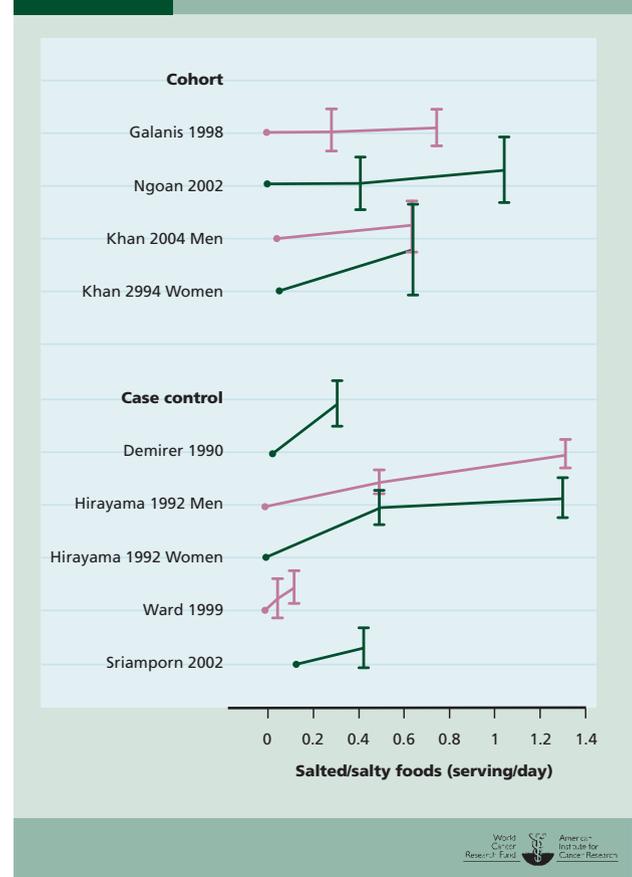
Figure 4.6.2 Salty/salted foods and stomach cancer; cohort and case-control studies

The Panel is aware that since the conclusion of the SLR, two case-control studies[84] [85] have been published. This new information does not change the Panel judgement (see box 3.8).

4.6.6 Comparison with previous report

The judgement of the previous report on sugars and colorectal cancer was in effect similar to that in this Report.

The previous report judged that salt and also salting are probable causes of stomach cancer. This judgement is also much the same as that in this Report.

4.6.7 Conclusions

The Panel concludes:
Salt is a probable cause of stomach cancer. Salted and salty foods are also a probable cause of stomach cancer. There is limited evidence suggesting that sugars are a cause of colorectal cancer.

4.7 Water, fruit juices and other soft drinks, and hot drinks

WATER, FRUIT JUICES, SOFT DRINKS, HOT DRINKS, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	Cancer site	Exposure	Cancer site
Convincing			**Arsenic in drinking water[1]**	**Lung**
Probable			**Arsenic in drinking water[1]** **Maté[2]**	**Skin** **Oesophagus**
Limited — suggestive			Arsenic in drinking water[1] Maté[2] High-temperature drinks	Kidney Bladder Mouth, pharynx, larynx Oesophagus
Substantial effect on risk unlikely	Coffee: pancreas; kidney			

1   The International Agency for Research on Cancer has graded arsenic and arsenic compounds as class 1 carcinogens. The grading for this entry applies specifically to inorganic arsenic in drinking water.
2   As drunk traditionally in parts of South America, scalding hot through a metal straw. Any increased risk of cancer is judged to be caused by epithelial damage resulting from the heat, and not by the herb itself.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

Water is essential. Without water, people die in a matter of days. As well as adequate supplies of water, a major public health issue throughout the world is the safety of domestic and other water. Water quality may be compromised by chemical or microbiological contamination.

Fruit juices made from fruits or fruit pulps are often concentrated for storage and transport, then diluted with water to produce the final product. Sugar and other ingredients are frequently added in this final reconstitution process. Soft drinks are usually made from water, sugar, colourings, flavourings, and mixtures of herbs and other ingredients, to give a distinctive taste and character. Consumption of branded, carbonated soft drinks, and cola drinks in particular, has increased greatly in the 20th century, and continues to increase throughout the world. The rise is most marked in lower income groups.

Tea and coffee are now the main hot drinks consumed worldwide. Both contain stimulants and other bioactive constituents, and many people add milk and sugar. A great variety of herbal infusions are also drunk, including maté, the traditional hot drink in parts of South America.

Overall, *the Panel judges* that the direct evidence relating non-alcoholic drinks to cancer is contamination of water supplies with inorganic arsenic and irritation of the oral cavity by maté, and possibly by other very high-temperature drinks. For evidence relating sugared soft drinks to body fatness, see Chapter 8.

The Panel judges as follows:
The evidence that inorganic arsenic in drinking water is a cause of lung cancer is convincing. Water contaminated in this way is probably a cause of skin cancer. Arsenic and arsenic compounds are recognised carcinogens. There is limited evidence suggesting that water contaminated in this way is a cause of cancers of the kidney and bladder.

Maté, a herbal infusion, as drunk traditionally in parts of Latin America, is probably a cause of oesophageal cancer. Damage caused by the very high temperature of the drink, rather than by the herb itself, is judged to be responsible. There is limited evidence suggesting that maté is a cause of cancers of the mouth, pharynx, and larynx, for the same reason. There is also limited evidence suggesting that high-temperature drinks are a cause of oesophageal cancer.

It is unlikely that coffee has any substantial effect on the risk of cancer either of the pancreas or of the kidney.

Within the remit of this Report, the strongest evidence, corresponding to judgements of 'convincing' or 'probable', shows that inorganic arsenic in drinking water is a cause

of lung cancer and probably a cause of skin cancer. Maté is probably a cause of oesophageal cancer. It is unlikely that coffee has any substantial effect on the risk of either cancer of the pancreas or of the kidney.

Chapter 4.7 concerns all non-alcoholic drinks.

Water, including that contained in drinks and foods, is an invariable part of all diets. Bottled spring and mineral waters are consumed by people who can afford them. Juices made from fruits and water, often sweetened (at first with honey and then sugar), have been drunk throughout history. Cordials, squashes, and other drinks made mainly from colourings and flavourings, with some fruit juices, herbs, or other ingredients added, started to become popular from the beginning of the 19th century. Carbonated sweet drinks (sometimes known as sodas) such as cola were first mass-manufactured in the USA and are now commonly consumed throughout the world.

Tea was cultivated and drunk in China for over a thousand years. Then, from the 18th century, it became commonly drunk in Britain, and was cultivated in India and other countries, and drunk in other parts of the world. The original teas were green and drunk without adding milk or sugar. Manufacture of black teas came later; from the 19th century, teas became the main hot stimulant drink in Britain, almost always drunk with milk and often with sugar added. Coffee was cultivated in and exported to many parts of the world from the 19th century; it remains the main cash crop in a number of tropical countries such as Ethiopia and Brazil. Coffee is the main hot stimulant drink in the Americas, many European countries, and also in the Arab world. In some parts of the world, coffee is usually drunk black, with or without sugar; in other countries, milk or cream is often added. Chocolate is also consumed as a beverage.

Reports concerned with infectious diseases, especially of childhood, usually emphasise the importance of safe water supplies. Reports concerned with the prevention of chronic diseases sometimes specify sugared soft drinks as contributors to overweight and obesity. They occasionally recommend substantial consumption of water as healthy in itself and preferable to soft or alcoholic drinks.

Contaminants of water, and also of foods and other drinks, are grouped here with water. High-temperature foods are grouped here with high-temperature drinks.

For the relationship between sugared drinks and body fatness, see Chapter 8.

4.7.1 Definitions, sources

4.7.1.1 Water

Water comes from rain, underground aquifers accessed by wells, springs, and freshwater lakes and rivers.

People cannot live without water, which is vital for the normal functioning of the body. Even mild dehydration (water loss of 1–2 per cent of the body weight) can produce symptoms such as dry mouth and headaches. Stopping all fluid intake may cause death in days, the number depending on

the health of the individual and external conditions such as temperature and humidity.

Water can be used as a vehicle to provide fluoride and can contribute to intakes of essential elements, calcium, iron, and copper, depending on its origin and the piping materials used.

The water content of the body is around 70 per cent: men's bodies contain a higher proportion of water than those of women because women have more body fat, which has minimal amounts of water. Adults produce an average of around 1.5 litres of urine each day and lose an additional litre of water through breathing, from the skin by evaporation or sweating, and in the faeces. Approximately 80 per cent of water intake comes from drinks; food provides the other 20 per cent.

Tap water quality is regulated in most countries based on World Health Organization guidelines for drinking water that includes tap water and bottled water.[1]

Around the world, ground, rain, and river waters are also drunk, often without first being treated to secure safety. More than 1 billion people (around 15 per cent of the world's population) lack access to safe, clean water[2] and are at risk of exposure to water-borne contaminants and infectious diseases. Arsenic, the bacterium *Helicobacter pylori,* and parasitic schistosomes are among the many contaminants that may be found in water supplies. In many low-income countries, access to clean water is limited for the low-income segments of the populations and those living in rural areas.

4.7.1.2 Fruit juices

Fruit juices include liquids extracted from whole or pulped fruits. Commercially prepared fruit juices may be pasteurised to extend shelf-life, and concentrated at source to be reconstituted before packaging, closer to the point of sale.

4.7.1.3 Soft drinks

The term 'soft drinks' is used for a wide range of coloured and flavoured non-alcoholic drinks, usually sold in cans, cartons, or bottles. They may be carbonated (such as cola drinks or lemonade) or still (such as fruit squashes). Some soft drinks are milk-based (milkshakes and yoghurt drinks). Depending on the ingredients, some soft drinks may be marketed with health claims, and are sometimes known as 'functional drinks' (also see box 4.10.2).

4.7.1.4 Hot drinks

The most common hot drinks currently consumed are tea and coffee. These are infusions (brewed using boiling water) usually drunk hot, sometimes very hot (box 4.7.1). Coffee is made from ground, roasted coffee beans — the dried seeds of coffee plant berries. The beans naturally contain caffeine. Decaffeinated coffees are produced by various processes, using water, organic solvents, steam, or by interfering with the expression of the gene coding for caffeine. Instant coffee comprises the soluble solids derived from dried, double-brewed coffee. Coffee is a large bush native to Ethiopia, cultivated in many hot and humid climates. The main coffee-exporting countries are Brazil, Vietnam, and Colombia.

Although many herbal infusions are known as teas, tea is

specifically the infusion of the dried leaves of the plant *Camellia sinensis*. Green tea is made from leaves that have first been cooked, pressed, and dried. To produce black tea, the fresh leaves are withered, rolled repeatedly, allowed to turn deep brown, and then air-dried until they are dark in colour. Tea leaves contain caffeine and theophylline. Decaffeinated teas are produced using similar processes to those used for coffee. Most tea is grown in Asia.

Maté is a type of herbal tea prepared from the dried leaves of the plant *Ilex paraguariensis* that has stimulant properties similar to the other methylxanthine-containing drinks (coffee and tea).

Herbal and other teas are also consumed cold. Iced teas are popular in the USA and some other countries: these are sugared and considered here as soft drinks.

4.7.2 Composition

4.7.2.1 Water

Water is a molecule comprising hydrogen and oxygen: chemically, H_2O. Rainwater may contain traces of air pollutants; water from underground aquifers may contain traces of minerals from surrounding rocks and other surfaces. Ground water may also be contaminated with natural minerals as well as with various industrial and agricultural chemicals, some of which are carcinogenic in laboratory conditions (box 4.7.2). Mineral water from springs and other sources con-

tains higher trace amounts of various minerals and other substances, often detectable to taste. Some spring water is naturally carbonated. Bottled water is either still or carbonated, sometimes artificially. The safety of water in terms of chemical and microbial contamination is well regulated by the WHO programme on chemical safety, but unfortunately, monitoring and surveillance in most countries are limited.

Arsenic residues can arise from agricultural, mining, and industrial practices, or may occur naturally from volcanic activity. WHO guidelines recommend that levels of arsenic in drinking water should not exceed 10 μg/l.[4] Levels of arsenic in affected areas may range from tens to hundreds, or even thousands, of micrograms per litre. In unaffected areas, levels are typically less than 10 μg/l. Inorganic arsenic (arsenate or arsenite) is the form that predominantly contaminates drinking water.

Arsenic is classified as a human carcinogen by the International Agency for Research on Cancer. Drinking water contaminated with arsenic is also classed separately as a human carcinogen.[5]

The bacterium *H pylori* is found in water supplies contaminated with faeces. It is an established necessary cause of distal stomach cancer (see box 7.5.1).

Chronic schistosomiasis (infestation with schistosomes) is a known cause of bladder and liver cancer (see chapters 7.16 and 7.8).[6] It is caused by contact with water contaminated by parasite eggs.

Box 4.7.1	High-temperature, and irritant drinks and foods

Constant mechanical irritation of epithelial surfaces causes inflammation, which predisposes to the development of cancer (see Chapter 2). It has also been suggested that foods and drinks with chemically irritant components may be a cause of cancers of those sites with which they come into direct contact. Again, there is not much evidence for this theory, with the possible exception of chilli and stomach cancer (see chapter 4.2).

There is, however, some evidence that some thermally hot (and therefore irritant) drinks are a cause of cancers of those sites with which they come into direct contact. As shown in this section, maté, the herbal infusion, is probably a cause of cancer of the oesophagus, and there is limited evidence suggesting that it is also a cause of other cancers of the oral cavity. This is probably not because of any carcinogen in the herb itself, but because of the way the infusion is traditionally drunk in the pampas region within the southern cone of Latin America, in northern Argentina, Paraguay, and southern Brazil. It is drunk extremely hot from a gourd through a metal straw, which is often kept rested in the mouth, rather like the stem of a tobacco pipe.[3] There is no substantive evidence that maté prepared in the style of tea, loose or in sachets (bags), affects the risk of cancer.

There is also limited evidence suggesting that various other very hot drinks and foods are a cause of cancer of the oesophagus when they are consumed regularly. The implications of this evidence, while so far not strong, suggest that more research may be warranted (see chapter 4.7.5.6).

Box 4.7.2	Contamination of water, and of foods and other drinks

Water contaminants that are causes of cancer are inorganic arsenic (reviewed here) and *Helicobacter pylori* and schistosomes (see Chapter 7).

Many other contaminants of water are identified as or have been thought to be carcinogenic, usually as a result of animal and other experiments, or else as a result of industrial accidents or gross overuse. These include herbicides and pesticides, fertilisers that contain and release nitrates, and disinfectants that also produce potentially toxic contaminants such as chlorinated and brominated organic compounds. They also include chemicals deliberately added to drinking water as public health measures, notably chlorine and fluoride.

These and other industrial, agricultural, and other chemicals are the subject of tests and regulations for toxicity and safety in use. Nevertheless, they are often popularly believed to be significant causes of cancer. This subject is controversial and is likely to remain so.

Currently there is no substantial epidemiological evidence that any of these substances, singly or in combination, as currently regulated and usually consumed in water, or in foods and other drinks, has any significant effect on the risk of any cancer. *The Panel considers* that the evidence is insufficient to conclude that usual intakes of industrial, agricultural, and other chemicals have an effect on the risk of human cancer. Toxicity and carcinogenicity of pollutants as a result of industrial accidents or overuse are outside the scope of this Report.

4.7.2.2 Fruit juices

Bottled or canned or otherwise packaged fruit juices are made from the fruits they contain or from fruit pulp. As well as added water, they usually also contain some added sugars, preservatives, and other additives. They often contain trivial amounts of dietary fibre. Fruit and vegetable juices have different nutritional properties from whole fruits and vegetables. For these reasons, the international 'at least five a day' campaign to encourage people to eat more fruits and vegetables (at least five portions per day) recommends that juices only count as one portion per day, irrespective of the amount consumed.

4.7.2.3 Soft drinks

Soft drinks are made from water, colourings, flavourings, and herbal or other ingredients. They may or may not contain fruit juice. They also contain either sugars or, in 'diet' form, chemical sweeteners (see chapter 4.6 and box 4.6.3). They may or may not be carbonated. The original formulations of cola drinks contained stimulants from the coca and cola plants. Soft drinks may also include yoghurt and other milk derivatives, as yoghurt drinks or fruit 'smoothies', and also added vitamins and minerals. 'Sports' drinks contain sugars, electrolytes, and other additives.

4.7.2.4 Hot drinks

The main hot drinks are tea (usually black tea but also green tea, which is often preferred in China) and coffee. Both contain various antioxidants and phenolic compounds, some of which have been shown to have anti-cancer properties in laboratory conditions.[7] They both also contain caffeine (and the related compound theophylline in tea). There is more caffeine in tea leaves than in coffee beans, but brewed coffee contains more caffeine than brewed tea. Caffeine and theophylline are bioactive, quickening reaction times, relieving fatigue, and stimulating the cardiovascular and central nervous systems.

Tea and coffee, when drunk without adding milk, cream, sugar, lemon, or honey, contain no energy and trivial amounts of some micronutrients; the bioactive chemicals they contain are mentioned above. When these drinks are consumed frequently, both may be substantial dietary sources of some of these bioactive constituents. Thus, coffee is a major source of some antioxidants in the US diet.[8]

4.7.3 Consumption patterns

4.7.3.1 Water

Environmental conditions, health, activity levels, and other factors determine the amount of water needed, but there is no international recommendation for daily consumption. The Institute of Medicine in the USA recommends 2.7 litres per day total water for women and 3.7 litres for men. The UK's Food Standards Agency estimates that most people need to drink at least 1.2 litres of fluids per day. More than half of the world's population has access to drinking water through taps in their homes or outside. Tap water should be regulated to meet international quality guidelines, such as those prepared by WHO.[9]

Most people who do not have access to clean drinking water live in Asia, sub-Saharan Africa, and some parts of Latin America. High concentrations of arsenic in drinking water have been found in areas of Bangladesh, China, and West Bengal (India), and also in more localised areas of Argentina, Australia, Chile, Mexico, Taiwan, China, the USA, and Vietnam. In many of these regions, the drinking water source is groundwater naturally contaminated by arsenic-rich geological formations.[10]

4.7.3.2 Fruit juices

There is little information on the general or local consumption of fruit juices.

4.7.3.3 Soft drinks

In 2004, global consumption of soft drinks was estimated at 480 000 million litres (including bottled water),[11] of which cola and other carbonated drinks accounted for 40 per cent. In terms of sales, carbonated drinks are the largest single category. World sales of cola drinks continue to rise, as do more recently, sales of bottled waters, fruit juices, and 'functional drinks'. The USA is the biggest per capita consumer of soft drinks, followed by Mexico and Chile. The USA alone accounts for more than a 20 per cent share of the global total. Asia is the fastest growing market for soft drinks: sales are increasing at around 3.5 per cent each year.

Average consumption of soft drinks in the USA is around a 12-ounce can (about 350 ml) per person/day. Older children consume about this amount, and sometimes more. Most of these drinks are sugared. At this level, soft drinks contribute a substantial proportion of total sugars intake.

4.7.3.4 Hot drinks

After water, tea and coffee are the most commonly consumed drinks in the world. There are various different methods of preparing these hot drinks depending on culture and personal preference. Coffee consumption is high in northern Europe and North America. Low-income countries export most of the world's coffee; high-income countries consume approximately seven times as much (per capita) as low-income countries.

Average worldwide consumption of tea is around 0.5 kg per person/year; this is exceeded significantly in several Asian countries (notably, China, India, and Japan), and in the UK and Ireland. Worldwide, black tea is the most popular type, although green tea is more commonly drunk in Asia. Maté, as traditionally prepared, is drunk almost exclusively in parts of South America.

4.7.4 Interpretation of the evidence

4.7.4.1 General

For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7.

'Relative risk' (RR) is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.7.4.2 Specific

Classification. Different types of tea, coffee, and soft drinks are consumed in different cultures. The ways in which tea and coffee are prepared and drunk also vary. For coffee, this includes the degree of roasting, the methods of brewing (which determine the strength and composition), and the different substances added. Similarly, tea may be consumed with or without milk and in different strengths. Associations seen in one population but not another may reflect some aspect of the drink as consumed in that population rather than the drinks themselves. In some studies, fruit juices and bottled waters are included in the definition of soft drinks.

Measurement. Fluid intake is best estimated from urine collection, but this is rarely done. Instead, estimates are usually made from food frequency questionnaires.

Confounding. In interpreting the results of epidemiological studies of all types of drink, confounding by other habits should be considered. For example, heavy consumers of soft drinks, tea, or coffee may also be smokers and drinkers of alcohol.

People who are physically active often consume more liquid than those who are not. Physical activity is therefore a confounder of the relationship between the volume of fluid drunk and cancer risk, but may not be adequately adjusted for.

Reporting bias. Soft and cola drinks are often identified as unhealthy, and studies that depend on self-reporting may disproportionately underestimate consumption.

4.7.5 Evidence and judgements

The full systematic literature review (SLR) is contained on the CD included with this Report.

4.7.5.1 Water

The evidence was too sparse or inconsistent to draw any conclusion about the relationship between water quantity and cancer risk.

4.7.5.1.1 Water-borne contaminants: arsenic

Ecological studies based on known arsenic concentrations in water may be interpreted more robustly than for many other dietary exposures.

Lung

Two cohort studies,[12-17] 2 case-control studies[18 19] and 12 ecological studies[20-30] investigated arsenic in drinking water and lung cancer.

Both cohort studies showed statistically significant increased risk of lung cancer for the highest intake group compared to the lowest.[12-17] Although meta-analysis was not possible, both studies reported that a dose-response relationship was apparent. One study (in Taiwan) based in a population with endemic black foot disease, a manifestation of arsenicosis, reported an effect estimate of 3.29 (95% confidence interval (CI) 1.60–6.78) for average arsenic level in

well water.[13] The other study reported a quantified effect estimate, which was 3.66 (95% CI 1.81–7.03), but this study (based in Japan) did not adjust for smoking.[17]

Both case-control studies showed increased risk of lung cancer for the highest intake group compared to the lowest,[18][19] which was statistically significant in one.[19] The other study did not report confidence intervals. Effect estimates were 3.01[18] and 8.9 (95% CI 4.0–19.6).[19]

Ecological studies were made in populations from Argentina,[27] Belgium,[21] Chile,[29] China,[23] Switzerland,[20] and Taiwan,[22-26 30] as well as worldwide.[28] Eight studies showed increased risk of lung cancer with increasing levels of arsenic in drinking water,[21-25 27 29 30] which was statistically significant in four.[24 27 29 30] Two studies showed decreased risk,[20 26] which was statistically significant in one.[26] One study reported different inconsistent results for men and women (correlation coefficients of -0.51 for men and 0.07 for women).[28] One study showed that measures to lower arsenic levels in drinking water by using tap water rather than well water were associated with a fall in lung cancer rates in a region of Taiwan with endemic black foot disease.[25]

The general mechanisms through which arsenic could plausibly cause cancer are outlined below. In addition, soluble arsenic in drinking water induces lung cancers in animal models and causes chronic lung disease.[5]

> **The evidence is ample and consistent, both from cohort and case-control as well as ecological studies. There is a dose-response relationship and the effect size is relatively large. There is robust evidence for mechanisms. The evidence that arsenic is a cause of lung cancer is convincing.**

Skin

Two cohort studies,[31 32] 5 case-control studies,[33-37] 1 cross-sectional study,[38] and 11 ecological studies[20 22 24 27 29 30 39-43] investigated arsenic in drinking water and skin cancer.

Both cohort studies showed non-significant increased risk with increasing levels of arsenic in the water[31 32]; however, for one study the increased risk was apparent in women but not in men.[32] Effect estimates were 1.82 (95% CI 0.5–4.66) for women and 0.83 (95% CI 0.17–2.43) for men in Utah,[32] and 1.21 (95% CI 1.00–1.47) per 100 μg/l.[31]

Two case-control studies measured arsenic levels in toe- and fingernails.[36 37] Such measures are less subject to error and bias than some other methods to assess actual exposure to a carcinogen. One study reported a significant increased risk for melanoma with a risk estimate of 1.65 (95% CI 1.27–2.14) per 100 ng/g[36]; the other study reported non-significant increased risk 1.02 (95% CI 0.90–1.17) per 100 ng/g for basal cell carcinoma and 1.12 (95% CI 0.95–1.32) for squamous cell carcinoma.[37]

Two case-control studies that reported on dietary arsenic showed increased risk with increased intake,[33 35] which was statistically significant in one.[33] One study reported a non-significant decreased risk.[34]

The cross-sectional study showed a statistically significant increased risk, with a partially adjusted effect estimate of 5.04 (95% CI 1.07–23.8) for > 0.71 versus 0 parts per mil-

lion average arsenic content in water.[38]

All 11 ecological studies reported increased risk for skin cancer with increased arsenic exposure,[20 22 24 27 29 30 39-43] which was statistically significant in 4,[24 29 30 40 41] and statistically significant in women but not in men in 1[27]; and significant in men but not women in another study.[20] The effect increased with age (cumulative exposure), where that was measured, and the reported effect estimates were usually large, more than half being greater than 2.5.

The general mechanisms through which arsenic could plausibly cause cancer are outlined below.

The evidence is consistent, from cohort, case-control and ecological studies. There is robust mechanistic evidence. Arsenic is a probable cause of skin cancer.

Kidney

Three cohort studies,[32 44 45] one time-series study,[46] and nine ecological studies[20 22 24 27 29 30 40 47 48] investigated arsenic in drinking water and kidney cancer.

All three cohort studies showed increased risk for the highest intake levels compared to the lowest,[32 44 45] which was statistically significant in one.[45] Effect estimates were 1.49 (95% CI 0.67–3.31; adjusted for smoking),[44] 2.82 (95% CI 1.29–5.36),[45] and 1.13 (women; confidence intervals not reported) and 1.43 (men; confidence intervals not reported).[32]

The single time-series study reported a statistically significant decreased risk in kidney cancer following the installation of a tap water supply system in an arsenic-endemic area of Taiwan.[46]

All nine ecological studies showed increased risk with higher levels of arsenic in drinking water,[20 22 24 27 29 30 40 47 48] which was statistically significant in six.[24 27 30 40 48]

The general mechanisms through which arsenic could plausibly cause cancer are outlined below. In addition, arsenic in drinking water is well absorbed in the gastrointestinal tract, and both inorganic arsenic and its methylated metabolites are excreted in urine.[49] Arsenic can modify the urinary excretion of porphyrins in animals and humans.[50]

The evidence is sparse. There is limited evidence suggesting that arsenic is a cause of kidney cancer.

Bladder

Six cohort studies,[14 17 32 44 45 51] 1 time-series study,[52] 7 case-control studies,[18 53-60] and 11 ecological studies[20 22 24 29 30 40 47 48 61-64] investigated arsenic in drinking water and bladder cancer.

Four cohort studies showed increased risk for the highest intake levels compared to the lowest,[14 17 44 45] which was statistically significant in two.[17 45] One study showed non-significant decreased risk.[32] The single cohort study that measured arsenic levels in finger- or toenails reported an effect estimate of 1.05 (95% CI 0.85–1.29) per 100 ng/g.[51]

Three case-control studies showed increased risk for the highest intake levels compared to the lowest,[18 56-59] which was statistically significant in one.[18] Two studies showed non-significant decreased risk,[53 55] two studies showed no

effect on risk,[54 60] including the single case-control study that measured arsenic levels in finger- or toenails.[60]

Six ecological studies showed increased risk with higher levels of arsenic in drinking water; all were statistically significant.[22 24 29 30 40 62 64] Two studies reported decreased risk,[47 61] which was statistically significant in one.[47] One study showed a non-significant decreased risk in men and a non-significant increased risk in women.[20] Two studies did not provide quantified results.[48 63]

The general mechanisms through which arsenic could plausibly cause cancer are outlined below. In addition, arsenic in drinking water is well absorbed in the gastrointestinal tract, and both inorganic arsenic and its methylated metabolites are excreted in urine.[49] Arsenic can modify the urinary excretion of porphyrins in animals and humans.[50]

The evidence is inconsistent. There is limited evidence suggesting that arsenic is a cause of bladder cancer.

General mechanisms — arsenic

Arsenic is carcinogenic to humans and causes chromosomal abnormalities.[10] It can result in changes in the methylation of oncogenes or tumour-suppressor genes. It also interferes with the activities of several enzymes of the haem biosynthetic pathway. Exposure to arsenite or arsenate results in generation of reduced oxygen species (free radicals) in laboratory animals and human cells. Arsenic biotransformation is thought to deplete cells of reduced glutathione, leading to a state of oxidative stress, characterised by decreased scavenging of free radicals, which can directly damage DNA and induce cell proliferation.[65]

There are several compounds suspected to modulate the chronic environmental toxicity of arsenic –- variables that may either enhance or suppress its genotoxicity and carcinogenicity. Among them are nutritional factors like selenium and zinc, as well as drinking water co-contaminants like antimony.[66]

4.7.5.2 Soft drinks

The evidence was too limited in amount, consistency, or quality to draw any conclusions

4.7.5.3 Fruit juices

The evidence was too limited in amount, consistency, or quality to draw any conclusions.

4.7.5.4 Coffee

Pancreas

Eighteen cohort studies,[67-83] 37 case-control studies,[77 84-119] and 11 ecological studies[120-130] investigated coffee and pancreatic cancer.

Seven cohort studies showed increased risk for the highest intake groups when compared to the lowest,[67 68 71 72 78 80] which was statistically significant in two.[72 80] Seven studies showed non-significant decreased risk.[69 70 73 75 79 81 83] Two studies stated that there was no significant effect on risk.[77 82] One study reported a non-significant increased risk in men and decreased risk in women[76]; and one study reported a non-significant increased risk in women and a non-signifi-

cant decreased risk in men.[74] Meta-analysis was possible on eight cohort studies, giving a summary effect estimate of 1.00 (95% CI 0.94–1.07) per cup/day, with low heterogeneity (figure 4.7.1).

Some, though not all, of the cohort studies suggest a J-shaped dose-response relationship. An effect at high levels of coffee consumption cannot be excluded.

Case-control studies reported inconsistent results.[77 84-119] Eighteen studies reported increased risk,[84-87 89-91 94 97 99 102-106 112 114 116 119] of which nine were statistically significant.[85 87 94 102 112 114] Eleven studies reported decreased risk,[77 92 93 95]

[96 101 107 109 111 113 118] which was statistically significant in one.[118] Three studies showed no effect on risk[88 98] and one study stated there was no significant effect on risk.[110] Four other studies reported different effects in men and women; however none was statistically significant.[100 108 115 117] Meta-analysis was possible on 26 studies, giving a summary effect estimate of 1.04 (95% CI 1.01–1.07) per cup/day, with moderate heterogeneity (figures 4.7.1 and 4.7.2). Studies that did not adjust for smoking behaviour were more likely to report increased risk. Confounding with smoking could not be excluded.

The ecological studies overall showed an increased mortality between coffee consumption and pancreatic cancer.[120-130] Correlation coefficients ranged from +0.15[122] to +0.59.[124 125]

There is ample evidence, including prospective data, which is consistent and with low heterogeneity, and which fails to show an association. It is unlikely that coffee has any substantial effect on the risk of pancreatic cancer.

Figure 4.7.1	Coffee and pancreatic cancer; cohort and case-control studies

Relative risk (95% CI)

Cohort
Snowdon 1984	0.98 (0.69–1.40)
Zheng 1993 Men	0.93 (0.81–1.08)
Shibata 1994	1.13 (0.79–1.62)
Stensvold 1994 Men	0.97 (0.83–1.14)
Stensvold 1994 Women	1.08 (0.85–1.37)
Harnack 1997 Women	1.24 (1.02–1.49)
Michaud 2001 Men	0.86 (0.74–1.00)
Michaud 2001 Women	0.96 (0.87–1.07)
Lin 2002 Men	1.14 (0.92–1.41)
Lin 2002 Women	0.86 (0.58–1.26)
Stolzenberg-Solomon 2002 Men	1.05 (0.94–1.17)
Summary estimate	1.00 (0.94–1.07)

Case control
Elinder 1981	0.85 (0.66–1.09)
MacMahon 1981	1.13 (1.05–1.23)
Wynder 1983 Men	1.01 (0.93–1.10)
Wynder 1983 Women	1.00 (0.90–1.10)
Gold 1985	1.06 (0.89–1.26)
Mack 1986	1.20 (1.07–1.34)
La Vechhia 1987	1.06 (0.89–1.27)
Gorham 1988	1.15 (0.98–1.35)
Falk 1988 Men	1.09 (1.03–1.16)
Falk 1988 Women	1.06 (0.97–1.15)
Clavel 1989 Women	2.00 (1.22–3.28)
Olsen 1989 All respondents	0.97 (0.87–1.08)
Clavel 1989 Men	1.32 (0.91–1.92)
Cuzick 1989	0.93 (0.83–1.05)
Farrow 1990 Men	1.03 (0.94–1.13)
Jain 1991	1.00 (1.00–1.00)
Ghadirian 1991	0.99 (0.93–1.05)
Bueno de Mesquita 1992	0.78 (0.61–1.00)
Stefanati 1992	1.14 (0.80–1.62)
Lyon 1992	1.15 (1.02–1.30)
Zatonski 1993	0.53 (0.27–1.02)
Kalapothaki 1993	0.85 (0.68–1.06)
Sciallero 1993	1.02 (0.84–1.24)
Partanen 1995	0.97 (0.92–1.03)
Gullo 1995	1.25 (1.12–1.40)
Silverman 1998 Men	1.05 (0.98–1.13)
Silverman 1998 Women	1.03 (0.94–1.13)
Villeneuve 2000 Men	1.05 (0.94–1.17)
Villeneuve 2000 Women	0.99 (0.88–1.12)
Kreiger 2001 Women	1.00 (0.77–1.32)
Summary estimate	1.04 (1.01–1.07)

0.5   0.8 1 1.2   2

Relative risk, per cup/day

Figure 4.7.2	Coffee and pancreatic cancer; cohort studies: dose response

Snowdon 1984
Zheng 1993
Shibata 1994
Stensvold 1994 Men
Stensvold 1994 Women
Honack 1997 Women
Michaud 2001 Men
Michaud 2001 Women
Lin 2002 Men
Lin 2002 Women
Stolzenberg-Solomon 2002 Men

0   2   4   6   8   10

Coffee (cups/day)

Kidney

Five cohort studies,[73 74 131-134] 18 case-control studies,[135-152] and 1 ecological study[153] investigated coffee and kidney cancer.

Two cohort studies showed non-significant decreased risk for the highest intake groups when compared to the lowest.[73 131] One study showed non-significant increased risk[133]; one study stated that there was no association[132 134]; and another study showed non-significant increased risk in women and non-significant decreased risk in men.[74] Effect estimates were 0.15 (95% CI 0.02–1.16),[73] 0.87 (95% CI 0.66–1.16) per cup/day,[131] 2.69 (95% CI 0.89–8.1),[133] and 0.7 (no CI; men) and 1.2 (no CI; women) for highest versus lowest categories of exposure.[74]

The case-control studies reported inconsistent results, only one of which was statistically significant (in women but not in men).[146] Seven studies showed non-significant decreased risk for the highest intake groups when compared to the lowest.[135-138 140 142 143 145] Four studies showed non-significant increased risk[141 144 149 152]; one study reported no effect on risk; four studies stated that there was no association[147 148 150 151]; and two studies showed increased risk in women, which was statistically significant in one,[146] and non-significant decreased risk in men.[139 146] Only four of the best quality case-control studies were able to be meta-analysed, giving a summary estimate of 0.99 (95% CI 0.96–1.01) (figure 4.7.3).

The ecological study reported correlation of incidence of 0.62 for men and 0.4 for women.[153]

> There is substantial evidence both from cohort and case-control studies, which is consistent and of low heterogeneity, and which fails to show an association. It is unlikely that coffee has a substantial effect on the risk of kidney cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[154] has been published. This new information does not change the Panel judgement (see box 3.8).

4.7.5.5 Tea

The evidence was too limited in amount, consistency, or quality to draw any conclusions.

| Figure 4.7.3 | Coffee and kidney cancer; case-control studies |

Relative risk (95% CI)

Mattioli 2002	0.89 (0.63–1.26)
Yuan 1998	0.98 (0.95–1.01)
McLaughlin 1984	1.00 (0.95–1.04)
Kreiger 1993	0.99 (0.94–1.04)
Summary estimate	0.99 (0.96–1.01)

Coffee (cups/day)

4.7.5.6 Herbal teas, infusions
4.7.5.6.1 Maté
Oesophagus

Eight case-control studies[155-163] and one ecological study[164] investigated maté and oesophageal cancer.

Seven case-control studies showed increased risk for the highest intake groups when compared to the lowest (figure 4.7.4)[155-159 161-163] which was statistically significant in four.[155 157 159 161] One study showed non-significant decreased risk.[160] Meta-analysis was possible on five studies, all adjusting for smoking, giving a summary effect estimate of 1.16 (95% CI 1.07–1.25) per cup/day, with moderate heterogeneity relating to size but not direction of effect (figure 4.7.5). The two studies not included in the meta-analysis did not adjust for smoking; both reported non-significant increased risk.[156 159]

The single ecological study showed a non-significant relationship between increased maté consumption and oesophageal cancer mortality.[164]

The general mechanisms through which maté could plausibly cause cancer are outlined below.

> The evidence, from case-control studies, is consistent and a dose-response relationship is apparent. There is robust evidence for plausible mechanisms. Regular consumption of maté, as drunk in the traditional style in South America, is a probable cause of oesophageal cancer.

Mouth, pharynx, and larynx

Six case-control studies investigated maté and mouth, pharynx, and larynx cancers.[165-170]

All six case-control studies showed increased risk for the highest intake groups when compared to the lowest,[165-170] which was statistically significant in four.[165 167-169]

The general mechanisms through which maté could plausibly cause cancer are outlined below.

> The evidence is sparse. There is limited evidence suggesting that maté is a cause of mouth, pharynx, and larynx cancers.

General mechanisms — maté

Maté is typically drunk scalding hot through a metal straw. This produces heat damage in the mouth, pharynx, larynx, and oesophagus. Repeated damage of this nature can lead to cancer (also see Chapter 2). Chemical carcinogenesis from constituents of maté has also been postulated.[171 172]

4.7.5.7 High-temperature foods and drinks
Oesophagus

Three cohort studies[173-176] and 15 case-control studies[162 177-196] investigated hot foods or drinks and oesophageal cancer.

Two cohort studies showed increased risk for consuming high-temperature foods or drinks,[173 174] which was statistically significant in one.[174] The other study stated that there was no association for hot drinks.[175 176] Effect estimates were 1.44 (95% CI 0.91–2.26; hot food),[173] and 1.5 (95% CI 1.1–2.0; men; hot tea) and 1.8 (95% CI 1.1–2.9; women;
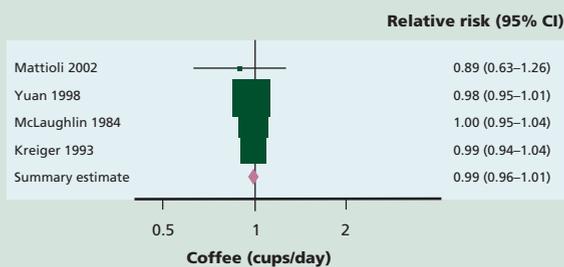
Figure 4.7.4 **Maté and oesophageal cancer; case-control studies**

Relative risk (95% CI)

	Relative risk (95% CI)
Victora 1987	1.47 (0.67–3.25)
Sewram 2003	1.62 (1.01–2.61)
Castelletto 1994	1.70 (1.00–2.89)
De Stefani 2003	3.50 (1.39–8.82)
De Stefani 1990	12.21 (3.78–39.42)
Dietz 1998	5.48 (0.96–31.44)
Rolon 1995	0.90 (0.44–1.86)
Vassallo 1985 Men	4.80 (1.90–12.11)
Vassallo 1985 Women	34.60 (4.88–245.40)

0.2 0.5 1 2 5 10 35

Relative risk, highest vs lowest exposure category
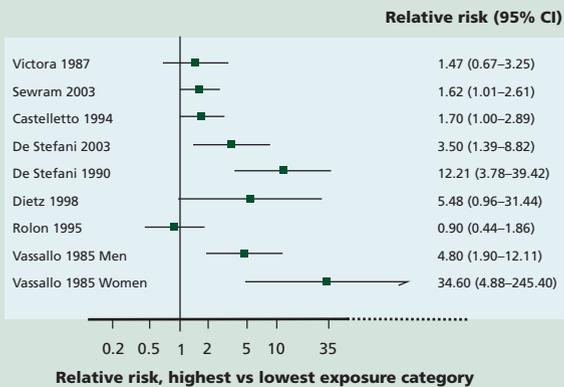
World Cancer Research Fund / American Institute for Cancer Research

Figure 4.7.5 **Maté and oesophageal cancer; case-control studies**

Relative risk (95% CI)

	Relative risk (95% CI)
Vassallo 1995 Men	1.26 (1.18–1.35)
Vassallo 1995 Women	1.43 (1.20–1.69)
De Stefani 1990	1.17 (1.12–1.22)
Rolon 1995	1.04 (0.95–1.13)
Sewram 2003	1.17 (1.09–1.25)
De Stefani 2003	1.04 (1.00–1.08)
Summary estimate	1.16 (1.07–1.25)

0.95 1 1.4 1.75

Relative risk, per cup/day
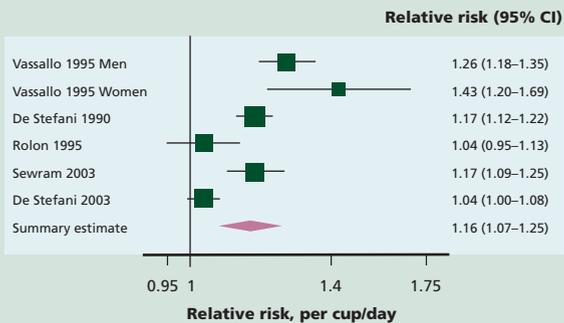
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hot tea).[174] Both these studies adjusted for smoking.

Seven case-control studies investigated food temperature[162 178-183 189-191]; seven investigated hot drinks[177 182 184-186 188 192 193]; and four investigated high-temperature hot drinks and soups combined.[191 194-196] For high-temperature food, six studies showed increased risk,[162 178-183 187 189 191] which was statistically significant in three[162 179 180 187 189]; one study showed non-significant decreased risk.[190] For hot drinks, five studies showed increased risk,[177 182 185 186 188] which was statistically significant in four[177 185 186]; two studies showed no significant association[192 193]; one study showed non-significant decreased risk.[184] For hot drinks and soups combined, all four studies showed increased risk,[191 194-196] which was statistically significant in two.[194 195] Several studies did not adjust for smoking or alcohol.[177 180 182 186 194 195]

High-temperature foods and/or drinks produce heat damage in the mouth, pharynx, larynx, and oesophagus.

Repeated damage of this nature can lead to cancer (also see chapter 2.4.1.3).

> **The evidence is inconsistent. There is limited evidence suggesting that high-temperature drinks are a cause of oesophageal cancer.**

4.7.6 Comparison with previous report

Water was not reviewed in the previous report, which had little to say about contaminants in water and did not review arsenic contamination. The previous report did not review soft drinks as such.

The previous report judged that green tea possibly protects against stomach cancer, but this was not supported by the current review. The previous report judged that black tea probably has no relationship with cancers of the stomach, pancreas, and kidney. This time the evidence was judged too limited to draw a clear conclusion. The judgements of the previous report on coffee were practically the same as in this Report, except that the previous report judged that drinking more than five cups per day was a possible cause of bladder cancer. The evidence now indicates that coffee is unlikely to have a substantial effect on risk of this cancer. The previous report judged it possible that maté and other very hot drinks increase the risk of oesophageal cancer. Since the mid-1990s, a greater body of consistent data has been published on maté.

Skin cancer was not reviewed in the previous report.

4.7.7 Conclusions

The Panel concludes:

The evidence that inorganic arsenic in drinking water is a cause of lung cancer is convincing. Water contaminated in this way is probably a cause of skin cancer. There is limited evidence suggesting that water contaminated in this way is a cause of cancers of the kidney and bladder.

Maté is probably a cause of oesophageal cancer when drunk scalding hot through a metal straw, as traditional in parts of South America. The temperature is judged to be responsible for any increased risk of cancer. There is limited evidence suggesting that maté as drunk traditionally is a cause of cancers of the mouth, pharynx, and larynx. There is limited evidence suggesting that high-temperature drinks are a cause of oesophageal cancer.

It is unlikely that coffee has a substantial effect on the risk of cancer either of the pancreas or of the kidney.

4.8 Alcoholic drinks

ALCOHOLIC DRINKS, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	Cancer site	Exposure	Cancer site
Convincing			Alcoholic drinks	Mouth, pharynx and larynx Oesophagus Colorectum (men)[1] Breast (pre- and postmenopause)
Probable			Alcoholic drinks	Liver[2] Colorectum (women)[1]
Limited — suggestive				
Substantial effect on risk unlikely	Alcoholic drinks (adverse effect): kidney[3]			

1 The judgements for men and women are different because there are fewer data for women. Increased risk is only apparent above a threshold of 30 g/day of ethanol for both sexes.
2 Cirrhosis is an essential precursor of liver cancer caused by alcohol. The International Agency for Research on Cancer has graded alcohol as a class 1 carcinogen for liver cancer. Alcohol alone only causes cirrhosis in the presence of other factors.
3 The evidence was sufficient to judge that alcoholic drinks were unlikely to have an *adverse* effect on the risk of kidney cancer; it was inadequate to draw a conclusion regarding a protective effect.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

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Many plant and some animal foods can be fermented to produce alcoholic drinks; alcohol has been made this way for thousands of years.

The main alcoholic drinks consumed, in ascending order of alcohol (ethanol) content, are beers and ciders; wines; wines 'fortified' with spirits; and spirits (liquors) and liqueurs. The alcohol content of the many different drinks within each of these categories varies.

Alcoholic drinks induce changes in mood; they also produce physical effects such as loss of coordination. In most countries they are the legal 'intoxicant' of choice, used as a social and professional lubricant; however, certain cultures forbid the drinking of alcohol.

With industrialisation and urbanisation, and the ready availability of alcoholic drinks (which may or may not be taxed), consumption tends to rise.

Alcohol relaxes people's social inhibitions, but it is addictive; dependency on alcohol can seriously affect people's personal and professional lives.

It has been known for a long time that prolonged high consumption of alcohol is a cause of cirrhosis of the liver, though not all people are equally susceptible. Knowledge of its other ill-effects is more recent.

Overall, *the Panel judges* that alcoholic drinks are a cause of cancers of a number of sites and that, in general, the evidence is stronger than it was in the mid-1990s. The evidence does not show any 'safe limit' of intake. The effect is from ethanol, irrespective of the type of drink. Ethanol is classified by the International Agency for Cancer Research as a human carcinogen.

The Panel judges as follows:
The evidence that alcoholic drinks are a cause of cancers of the mouth, pharynx, and larynx, oesophagus, colorectum (men), and breast is convincing. They are probably a cause of liver cancer, and of colorectal cancer in women. It is unlikely that alcoholic drinks have a substantial adverse effect on the risk of kidney cancer.

In final summary, the evidence is that alcoholic drinks are a cause of cancers of the mouth, pharynx, and larynx; the oesophagus; the colorectum in men, and the breast; and probably of liver cancer and colorectal cancer in women. It is unlikely that alcoholic drinks have a substantial adverse effect on the risk of kidney cancer.

Chapter 4.8 concerns all alcoholic drinks.
Alcoholic drinks have been popular in most societies ever

since the effects on mood of the fermented products of plant foods and some animal foods were discovered, probably in Palaeolithic or even earlier times.

Ethanol is the active ingredient in alcoholic drinks; the concentration varies, depending on the type of drink. In the past, beers were made from grains, ciders from fruits, mead from honey, and brews from milk; these were followed by wines, generally made from grapes and with higher concentrations of ethanol. The process of distillation was a later invention, which produced more highly concentrated alcoholic drinks made from grains, fruits, sugar, and other substrates.

Alcohol is liable to be addictive. Its specific effects are to induce a mood of euphoria and disinhibition, which may be dangerous. Much domestic and other violence, and many reckless and violent incidents, and crimes such as arson, wounding, homicide, and car crashes, are alcohol-related.

Reports concerned with food, nutrition, and the prevention of disease have often excluded alcohol. This is because alcohol is also a drug, the impact of which is behavioural and social, as well as biological. More recently, alcoholic drinks have been included in such reports because of the evidence that low to moderate consumption protects against coronary heart disease (but not cerebrovascular disease), and also because of the evidence on cancer, given that ethanol is a human carcinogen.

4.8.1 Definitions and sources

Alcohol is the common term for ethanol, one of a family of alcohols, produced in nature when sugar molecules are broken down to release energy by yeasts. This process of fermentation is used to produce alcoholic drinks. Alcohol is a source of dietary energy (see chapter 4.10.1). It also acts as a drug, affecting both mental and physical responses (alcohol intoxication). Alcoholic drinks include beers, wines, and spirits. Other alcoholic drinks that may be locally important include fermented milks, fermented honey-water (mead), and fermented apples (cider).

Most alcoholic drinks are manufactured industrially. Some are made domestically or illegally, as 'moonshine' or 'hooch'.

4.8.1.1 Beers
Beer, ale, and lager are traditionally produced from barley; today other cereal grains are used. Beer contains between 3 and 7 per cent alcohol. The grain starches are converted to sugars and then fermented by yeasts. The term 'beer' in this Report includes ales and lagers.

4.8.1.2 Wines
Wines are usually produced from grapes and contain between around 9 to 15 per cent alcohol; they are crushed to produce juice and must, which is then fermented. The colour of the grapes and the length of fermentation determine the colour and strength of the final product. Grape vines grow best in temperate regions. Wines can also be produced from other fruits and from rice (sake). Here, wine is taken to mean grape wines. Wines may be fortified with spirits (see chapter 4.8.2.2) to produce drinks of alcohol con-

tent between about 16 and 20 per cent.

4.8.1.3 Spirits/liquors
Spirits are usually produced from cereal grains and sometimes from other plant foods. They are distilled, to give a drink with a higher concentration of ethanol than either beers or wines — around 35–50 per cent or higher. Some of the most globally familiar spirits are brandy (distilled wine), whisky and gin (distilled from grains), rum (from molasses), aguardente also known as cachaça (from sugar), vodka (sometimes from grain, sometimes potatoes), and tequila and mescal (from agave and cactus plants). Spirits and liqueurs are also made from fruits.

4.8.2 Composition

Alcohol has an energy content of 7 kilocalories per gram, and is metabolised in the liver. On average, blood alcohol levels reach a maximum between 30 and 60 minutes after drinking an alcoholic drink, and the body can metabolise 10–15 g alcohol per hour.

Alcohol alters the way the central nervous system functions. Very high alcohol consumption (where blood alcohol reaches 0.4 per cent) can be fatal, as can long-term, regular, high intakes.

4.8.2.1 Beers
There are many varieties of beer, with different compositions. Their alcohol content ranges from around 3 to 7 per cent by volume; beers generally contain a variety of bioavailable phenolic and polyphenolic compounds, which contribute to the taste and colour, many of which have antioxidant properties. Beer is also a source of magnesium, potassium, riboflavin, folate, and other B vitamins.

4.8.2.2 Wines
The composition of wine depends on the grape varieties used, as well as the growing conditions and the wine-making methods, which may vary between vineyards. The alcohol content ranges from around 9 to 15 per cent by volume. Red wines contain high levels of phenolic and polyphenolic compounds (up to a total of around 800–4000 mg/l), particularly resveratrol, derived from the grape skins. Like those in beer, these phenolic compounds add taste and colour. White wines contain fewer phenolics. Red wine has been shown to have antioxidant activity in laboratory experiments. Wine also contains sugars (mainly glucose and fructose), volatile acids (mainly acetic acid), carboxylic acids, and varying levels of calcium, copper, iron, magnesium, potassium, and vitamins B1, B2, B6, and C. Wines may be flavoured with herbs and fortified with spirits (see chapter 4.8.2.3) to produce drinks of alcohol content between about 16 and 20 per cent.

4.8.2.3 Spirits/liquors
The alcohol content of spirits/liquors and liqueurs is usually between 35 and 50 per cent by volume, but can be even higher. Distilled drinks may have herbs and other ingredients added to give them their distinctive character.

4.8.3 Consumption patterns

Much of the information on average consumption of alcoholic drinks, internationally and nationally, is not informative. Within almost all populations, consumption varies widely, usually as a function of availability, price, culture or religion, and dependency. In general, men consume substantially more alcoholic drinks than women. In countries where considerable amounts of alcoholic drinks are produced domestically and by artisanal methods, overall consumption will (if only for this reason) be underestimated. In many countries, alcohol is a public health problem. This is not so much because of the average level of intake, but because a minority of the population, which in high-income countries includes an increasing number of young people, drink alcohol excessively ('binge' drinking).

Worldwide, alcoholic drinks supply an average of 2.3 per cent of total dietary energy. This ranges from around 10 per cent in some northern European countries, to (as recorded) practically zero in Islamic countries. Average consumption is nearly four times higher in high-income compared with low-income countries, and tends to be highest in Europe, North America, and Oceania. Consumption varies within countries: many people do not consume alcoholic drinks, some drink occasionally and others consume 15–25 per cent or more of their dietary energy as alcohol.

Alcoholic drinks are illegal in Islamic countries. In countries where these drinks are legal, there are often restrictions on price and availability to adults, and in particular to young people.

Many countries recommend restriction of alcohol intake for health reasons. In the USA, men are advised not to exceed two drinks per day and women one drink per day. In the UK, the government advises men not to exceed 3–4 units per day and women 2–3 units per day. One US 'drink' is equivalent to about 15 g ethanol, almost two UK units; a unit is 10 ml or 8 g of pure ethanol.

Box 4.8.1	Types of alcoholic drink

The Panel judges that alcoholic drinks are or may be a cause of various cancers, irrespective of the type of alcoholic drink. The causal factor is evidently alcohol (ethanol) itself. There is no significant evidence that alcohol protects against any cancer. The extent to which alcoholic drinks are a cause of various cancers depends on the amount of alcohol drunk.

Epidemiological studies commonly identify the type of alcoholic drink consumed. Some of the evidence reviewed in chapter 4.8.5 does appear to show that some types of drink seem to have different effects. For example, for cancers of the mouth, pharynx, and larynx, the evidence is stronger for consumption of beer and spirits than for wine. Here is the possibility of residual confounding: wine drinkers in many countries tend to have healthier ways of life than beer or spirit drinkers.

Apparent discrepancies in the strength of evidence may also be due partly to variation in the amounts of different types of alcoholic drinks consumed. In general, the evidence suggests similar effects for different types of alcoholic drink.

4.8.3.1 Beers
Beers are the most widely consumed alcoholic drinks worldwide. They provide an average of 1 per cent of dietary energy, with a peak of more than 6 per cent in parts of northern Europe. People living in Europe, North America, and Oceania tend to drink the most beer.

4.8.3.2 Wines
Wines provide an average of 0.2 per cent of dietary energy worldwide. They are drunk mainly in Europe, Australasia, and the Americas, with highest levels of consumption in western and southern Europe.

4.8.3.3 Spirits/liquors
There are few data on average consumption of spirits/liquors.

4.8.4 Interpretation of the evidence

4.8.4.1 General
For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7.

'Relative risk' (RR) is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.8.4.2 Specific
Confounding. At high levels of consumption, the effects of alcohol are heavily confounded by other behaviours, such as smoking tobacco.

Reporting bias. Self-reporting of consumption of alcoholic drinks is liable to underestimate consumption, sometimes grossly, because alcohol is known to be unhealthy and undesirable, and is sometimes drunk secretly. Heavy drinkers usually underestimate their consumption, as do drinkers of illegal or unregulated alcoholic drinks.

Measurement. In recent years, the strength and serving size of some alcoholic drinks have increased. For example, in the UK, wine is commonly served in 250 ml glasses as opposed to the standard 125 or 175 ml glass. In addition, alcohol content of drinks varies widely. Studies that measure consumption in terms of number of drinks may be referring to very different amounts of alcohol (also see box 4.8.1).

4.8.5 Evidence and judgements

The full systematic literature review (SLR) is contained on the CD included with this Report.

4.8.5.1 Alcoholic drinks
There are two different measures of exposure: the number of alcoholic drinks per time period and/or ethanol intake in grams or millilitres per time period. The former measure is likely to be less precise because the size and strength of each drink are unknown.

Figure 4.8.1	Alcoholic drinks and mouth, pharynx, and larynx cancer; cohort and case-control studies

Relative risk (95% CI)

Cohort
Gronbaek 1998 — 11.70 (4.91–27.87)
Kjaerheim 1998 — 3.20 (1.64–6.25)
Boeing 2002 — 9.22 (2.75–30.25)

Case control
Maier 1992 — 9.00 (5.21–15.54)
Wynder 1976 — 22.10 (7.83–62.36)
Herity 1982 — 5.60 (2.99–12.48)
Elwood 1984 — 7.70 (3.16–18.76)
Zagraniski 1986 — 4.00 (1.80–8.89)
De Stefani 1987 — 9.30 (3.49–24.81)
Brownson 1987 — 4.55 (2.81–8.37)
Blot 1988 Men — 8.50 (5.41–14.32)
Blot 1988 Women — 9.10 (3.92–21.12)
Tuyns 1988 — 2.56 (1.81–3.62)
Franco 1989 — 8.50 (2.48–29.15)
Falk 1989 — 2.12 (0.89–5.04)
Sankaranarayanan 1989 a — 6.25 (0.76–51.16)
Sankaranarayanan 1989 b — 3.15 (0.74–13.12)
Merletti 1989 Men — 2.10 (0.62–7.07)
Merletti 1989 Women — 3.40 (0.90–12.87)
Zheng 1990 — 1.59 (1.05–2.41)
Sankaranarayanan 1990 a — 7.69 (3.56–16.62)
Sankaranarayanan 1990 b — 8.18 (2.79–23.97)
La Vecchia 1991 — 3.50 (2.03–7.11)
Choi 1991 Men — 3.42 (1.77–6.60)
Choi 1991 Women — 1.48 (0.12–18.14)
Zheng 1990 Men — 0.80 (0.52–1.22)
Franceschi 1992 — 3.00 (1.38–6.51)
Zheng 1992 Men — 1.56 (0.97–2.50)
Gonzalo 1992 — 4.64 (0.41–52.39)
Mashberg 1993 — 7.10 (4.12–12.25)
Day 1993 White — 5.50 (5.72–13.54)
Day 1993 Black — 16.60 (6.28–44.95)
Ng 1993 Men — 4.36 (1.39–13.68)
Ng 1993 Women — 2.62 (0.51–13.40)
Hedberg 1994 — 3.10 (1.21–7.95)
Rao 1994 — 1.51 (1.12–2.04)
Guo 1995 — 2.25 (1.23–4.13)
Takezaki 1996 Men — 3.40 (1.18–9.77)
Takezaki 1996 Women — 2.30 (1.58–3.58)
Zheng 1997 — 1.17 (0.58–2.35)
Sandersson 1997 — 20.80 (11.42–37.87)
Dosemeci 1997 — 1.60 (0.72–3.58)
Pintos 1998 — 4.10 (2.80–6.00)
Rao 1998 — 1.38 (1.00–1.91)
Wasnik 1998 — 1.84 (1.02–3.32)
Su 1998 Men — 5.14 (0.95–27.81)
Smith 1998 — 2.57 (1.22–5.42)
Franceschi 1999 — 11.90 (6.22–22.77)
Rao 1999 — 1.53 (1.10–2.14)
Hayes 1999 Men — 7.70 (3.31–17.93)
Zavras 2001 — 4.90 (1.20–19.95)
Brown 2001 — 60.40 (20.98–173.86)
Schlecht 2001 — 2.70 (0.90–8.11)
Garrote 2001 — 5.73 (1.77–18.53)
Zang 2001 — 4.80 (3.47–6.64)
Dal Maso 2002 — 4.30 (1.92–9.61)
Pisa 2002 — 4.00 (0.87–18.33)
Petridou 2002 — 2.02 (1.11–3.68)
Uzcudun 2002 — 3.50 (2.36–6.11)
Lissowska 2003 — 4.25 (1.07–16.90)
Pelucchi 2003 — 5.80 (3.79–8.88)
Sanchez 2003 — 3.28 (1.80–5.99)
Llewellyn 2004 Men — 1.60 (0.81–3.15)
Llewellyn 2004 Women — 1.60 (0.60–4.23)
Castellsague 2004 — 10.29 (4.57–23.17)

0.2 0.5 1 2   5

Relative risk, highest vs lowest exposure category

Figure 4.8.2	Alcoholic drinks and mouth, pharynx, and larynx cancer; cohort and case-control studies

Relative risk (95% CI)

Cohort
Kjaerheim 1998 — 1.26 (1.10–1.44)
Boeing 2002 — 1.24 (1.18–1.30)
Summary estimate — 1.24 (1.18–1.30)

Case control
Martinez 1969 — 1.02 (1.01–1.04)
Martinez 1969 Men — 1.03 (1.01–1.05)
Elwood 1984 — 1.05 (1.04–1.06)
Brownson 1987 — 1.02 (1.02–1.03)
Blot 1988 — 1.05 (1.04–1.06)
Blot 1988 Women — 1.04 (1.02–1.06)
Falk R 1989 — 1.02 (1.00–1.04)
Merletti 1989 Men — 1.01 (0.99–1.04)
Merletti 1989 Women — 1.10 (0.99–1.22)
La Vecchia 1991 — 1.03 (1.01–1.02)
Choi1991 Men — 1.17 (1.08–1.04)
Choi 1991 Women — 1.03 (0.89–1.18)
Franceschi 1992 — 1.02 (1.01–1.03)
Mashberg 1993 — 1.01 (1.00–1.01)
Negri 1993 — 1.02 (1.02–1.03)
Day 1993 White — 1.05 (1.04–1.06)
Day 1993 Black — 1.05 (1.03–1.06)
Ng 1993 Men — 1.02 (1.01–1.04)
Ng 1993 Women — 1.07 (0.99–1.02)
Su 1998 Men — 1.18 (1.01–1.36)
Franceschi 1999 — 1.03 (1.02–1.03)
Hayes 199 Men — 1.03 (1.03–1.04)
Zavras 2001 — 1.02 (1.00–1.04)
Garrote 2001 — 1.02 (1.01–1.03)
Dal Maso 2002 — 1.02 (1.01–1.03)
Pisa 2002 — 1.04 (1.01–1.06)
Lissowska 2002 — 1.04 (1.01–1.08)
Pelucchi 2003 — 1.03 (1.02–1.03)
Castellsague 2004 — 1.01 (1.01–1.02)
Altieri 2004 — 1.03 (1.02–1.03)
Peters 2005 — 1.04 (1.03–1.05)
Summary estimate — 1.03 (1.02–1.04)

0.5   0.75   1   1.5   2

Relative risk, per drink/week

Mouth, pharynx, and larynx

Five cohort studies,[1-6] 89 case-control studies,[7-93] and 4 ecological studies[94-97] investigated alcoholic drinks and mouth, pharynx, and larynx cancers.

Total alcoholic drinks

All five cohort studies showed increased risk for the highest intake group when compared to the lowest (figure 4.8.1),[1-6] which was statistically significant in four.[1 2 4 6] Meta-analysis was possible on two studies, giving a summary effect estimate of 1.24 (95% confidence interval (CI) 1.18–1.30) per drink/week, with no heterogeneity (figures 4.8.2 and 4.8.3).[1 2] All cohort studies adjusted for smoking.

Almost all of the case-control studies showed increased risk for the highest intake group when compared to the lowest (figure 4.8.1),[7-19 21-32 34-70 72-93] which was statistically significant in more than half (as can be seen from the high to low

Figure 4.8.3 Alcoholic drinks and mouth, pharynx, and larynx cancer; cohort studies: dose response

Figure 4.8.4 Alcoholic drinks and mouth, pharynx, and larynx cancer; case-control studies: dose response
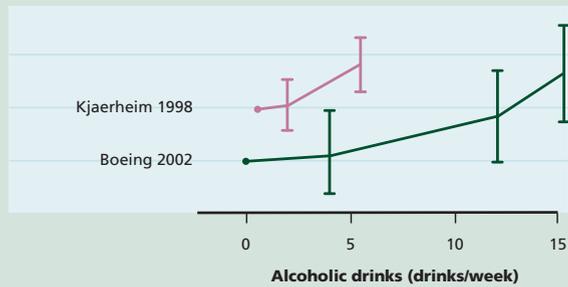
comparison plot).[8-19 21 23-25 28-32 34-36 40-48 52 54-57 59-67 70 72-75 77-86 89-91 93] No studies reported statistically significant contradictory results. Meta-analysis was possible on 25 studies, giving a summary effect estimate of 1.03 (95% CI 1.02–1.04) per drink/week, with high heterogeneity (figures 4.8.2 and 4.8.4).[17 21 26 27 32 34 35 40-42 52 57 60 62 65 67 69 75 78-80 83-85 89] Heterogeneity related to the size, and not the direction, of effect, and is largely explained by varying design and quality of studies.

A continuous curvilinear dose-response relationship was apparent from cohort and case-control data with no obvious threshold (figures 4.8.3 and 4.8.4).

There was some evidence of publication bias as a result of small studies that did not report a significant association being unpublished. However, such studies may suffer from issues of quality.

Ecological studies tended to show increased risk with increased consumption.[94-97]

Beers
Two cohort studies,[1 6] 27 case-control studies,[25 26 32 33 36 42 47 58 62 64 65 68 79 83-85 98-105] and 4 ecological studies[94-96 106] reported separately on beer drinking.

Both cohort studies showed statistically significant increased risk with increased intake; both studies adjusted for smoking.[1 6] Almost all case-control studies also showed increased risk,[25 26 32 33 36 42 47 58 62 64 65 68 83-85 98-104] which was statistically significant in many.[36 42 47 62 68 83-85 98-102] Meta-analysis was possible on six case-control studies, giving a summary effect estimate of 1.06 (95% CI 1.03–1.08), with high heterogeneity. Most studies adjusted for smoking. The ecological studies did not show any consistent or statistically significant effect.[94-96 106]

Wines
Twenty-six case-control studies[25 26 32 33 42 58 62 64 65 68 79 83-85 98 99 101 102 104 105 107-109] and four ecological studies[94-96 110] reported separately on wine drinking.

Most of the case-control studies showed increased risk with increased intake,[25 32 33 58 62 64 68 79 84 85 101 102 105 107-109] which
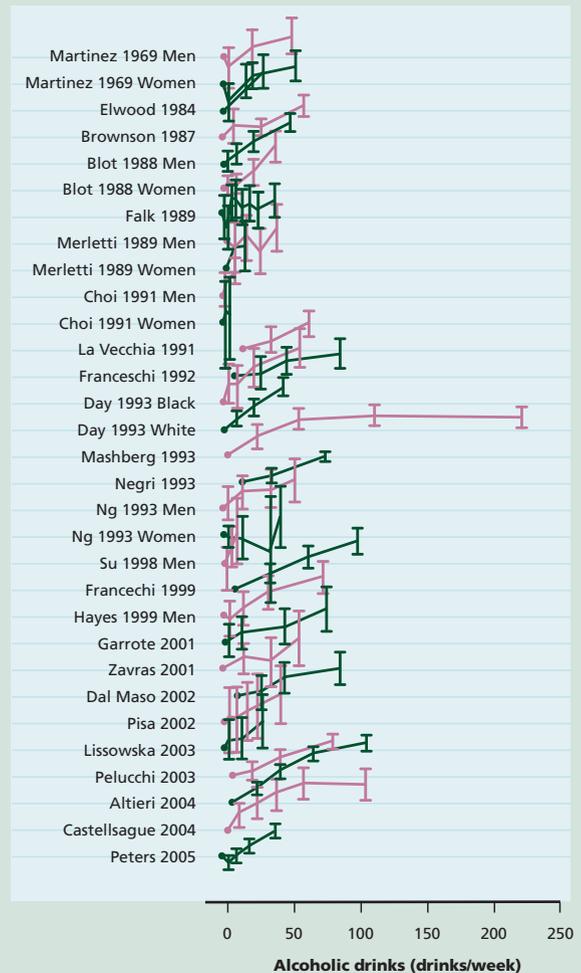
was statistically significant in less than half.[32 33 58 62 68 79 85 108 109] Five studies showed decreased risk,[26 65 83 98 99] which was statistically significant in one.[98 99] Meta-analysis was possible on 11 case-control studies, giving a summary effect estimate of 1.02 (95% CI 1.01–1.03), with high heterogeneity.[32 33 62 68 79 83-85 102 105 109] All studies adjusted for smoking. All four ecological studies showed statistically significant increased risk.[94-96 110]

Spirits
One cohort study,[1] 35 case-control studies,[19 25 26 28 31-33 36 38 42 47 49 50 58 62 64 65 68 79 83-85 98 100-102 104 105 108 109 111-113] and 5 ecological studies[94-96 106 114] reported separately on spirits.

The single cohort study showed a non-significant increased risk with increased intake.[1] Almost all case-control studies

showed increased risk, which was statistically significant in many. Meta-analysis was possible on nine case-control studies, giving a summary effect estimate of 1.03 (95% CI 1.04–1.05), with high heterogeneity. Most studies adjusted for smoking. One ecological study reported a significant increased risk; the others tended to show non-significant increased risk in men and non-significant decreased risk in women.

The general mechanisms through which alcohol could plausibly cause cancer are outlined below. In addition, alcohol acts as a synergistic carcinogen with tobacco. Tobacco may induce specific mutations in DNA that are less efficiently repaired in the presence of alcohol. Alcohol may also function as a solvent, enhancing penetration of other carcinogenic molecules into mucosal cells.

There is ample and consistent evidence, both from case-control and cohort studies, with a dose-response relationship. There is robust evidence for mechanisms operating in humans. The evidence that alcoholic drinks are a cause of mouth, pharynx, and larynx cancers is convincing. Alcohol and tobacco together increase the risk of these cancers more than either acting independently. No threshold was identified.

The Panel is aware that since the conclusion of the SLR, one cohort[115] and four case-control studies[116-119] have been published. This new information does not change the Panel judgement (see box 3.8).

Oesophagus
Eight cohort studies,[1 3 120-125] 56 case-control studies,[33 61 67 80 126-182] and 10 ecological studies[2 94 95 114 183-189] investigated alcoholic drinks and oesophageal cancers.

Total alcoholic drinks
Eight cohort studies,[1 3 120-125] 56 case-control studies,[33 61 67 80 126-137 139-182] and 10 ecological studies[2 94 95 114 183-189] reported on total alcoholic drinks.

Six cohort studies showed increased risk for the highest intake group when compared to the lowest (figure 4.8.5),[1 3 120-122 124] which was statistically significant in four,[1 120 122 124] and in men, but not in women in a fifth study.[121] Two studies showed non-significant decreased risk.[123 125] Effect estimates for all studies are shown in the high to low forest plot (figure 4.8.5). Four studies did not adjust for smoking.[122-125]

Most case-control studies showed increased risk for the highest intake group when compared to the lowest (figure 4.8.5),[33 61 67 80 126 128-137 139 141-148 150-166 169 170 172 174 175 177-182] which was statistically significant in 25.[33 61 67 80 128 129 132 133 135 137 139 141 145 147 148 150 152 153 155-166 170 172 174 175 178-180 182]

A few studies showed decreased risk, but none was statistically significant.[140 149 167 168 171 173 176] Meta-analysis was possible on 20 case-control studies, giving a summary effect estimate of 1.04 (95% CI 1.03–1.05) per drink/week, with high heterogeneity (figures 4.8.6 and 4.8.7).[33 61 67 131 133 137 144 149 150 156 157 160 161 170 178-182] Heterogeneity is related predominantly to size, rather than direction, of effect and may

Figure 4.8.5	Alcoholic drinks and oesophageal cancer; cohort and case-control studies

Relative risk (95% CI)

Cohort

Study	Relative risk (95% CI)
Kono 1987	14.46 (3.00–69.70)
Hirayama 1990	2.28 (1.96–2.65)
Yu 1993	0.50 (0.21–1.20)
Zheng 1995	1.40 (0.62–3.18)
Kinjo 1998 Men	2.40 (1.77–3.25)
Kjaerheim 1998 Women	3.20 (1.64–6.25)
Khjo 1998 Women	2.00 (0.62–6.43)
Sakata 2005	2.40 (1.20–4.80)
Tran 2005	0.92 (0.82–1.03)

Case control

Study	Relative risk (95% CI)
Jozala 1983	26.70 (6.87–10.374)
Tuyns 1982	2.72 (1.03–7.16)
Rossi 1982	13.08 (4.55–37.61)
Tuyns 1983 Men	101.03 (109.9–928.52)
Tuyns 1983 Women	11.04 (1.08–112.57)
Adelhardt 1985	2.95 (1.12–7.76)
Decarli 1987	10.43 (4.37–24.90)
La Vecchia 1989	3.60 (0.93–13.99)
Franceschi 1990	0.90 (0.57–1.42)
De Stefani 1990 Men	5.27 (2.71–10.24)
De Stefani 1990 Women	1.89 (0.71–5.00)
Sankaranarayaran 1991 Men	2.33 (1.52–3.56)
Choi 1991 Men	9.14 (3.79–22.06)
Valsecchi 1992	9.30 (5.11–16.93)
Wang 1992 Men	2.10 (1.06–4.15)
Cheng 1992	11.45 (6.66–19.69)
Tavani 1993	2.30 (0.99–5.34)
Kabat 1993 Men	10.90 (4.88–24.32)
Kabat 1993 Women	13.20 (6.08–28.68)
Parkin 1994	0.80 (0.59–1.08)
Castelletto 1994	8.00 (3.01–21.27)
Hanaoka 1994	6.59 (2.51–17.33)
Tavani 1994	5.40 (1.39–20.91)
Gao 1994 Men	1.40 (1.07–1.84)
Gao 1994 Women	0.60 (0.24–1.53)
Brown 1994 White Men	16.10 (6.68–38.79)
Brown 1994 Black Men	26.90 (11.89–60.85)
Vaughan 1995	9.50 (4.02–22.43)
Cheng 1995	1.50 (0.99–2.27)
Srivastava 1995	3.70 (1.50–9.11)
Gimeno 1995	4.40 (1.86–10.40)
Cheng 1995 Non-smokers	14.43 (3.60–57.82)
Vizcaino 1995	0.90 (0.69–1.18)
Nandakumar 1996 Men	1.80 (1.20–2.70)
Garidou 1996	1.26 (1.09–1.45)
Gammon 1997	7.40 (4.00–13.69)
Dietz 1998	8.60 (3.82–19.38)
Tao 1999	1.54 (0.86–2.76)
Gao 1999	0.78 (0.38–1.62)
Bosetti 2000	12.35 (8.37–18.22)
Levi 2000	15.65 (6.81–35.96)
Nayar 2000	7.81 (3.28–5.61)
Takezaki 2000	8.50 (5.56–13.00)
Takezaki 2001	0.75 (0.46–1.22)
Wu 2001	0.70 (0.47–1.04)
Sharp 2001	0.86 (0.25–2.95)
Dal Maso 2002	13.80 (4.00–47.60)
Gao 2002	1.48 (0.78–2.81)
Boonyaphiphat 2002	5.84 (3.15–10.83)
Engel 2003	9.40 (4.60–19.20)
Chita 2004 men	3.50 (1.72–7.10)
Wang 2004	3.45 (1.73–6.88)
Lee 2005	7.60 (5.20–11.10)
Yang 2005	6.71 (1.92–23.42)
Trivers 2005	1.08 (0.81–1.44)

0.2 0.5 1 2 5 10

Relative risk, highest vs lowest exposure category

162

Figure 4.8.6 | **Alcoholic drinks and oesophageal cancer; cohort and case-control studies**

Relative risk (95% CI)

Cohort
Kjaerheim 1998 — 1.26 (1.10–1.44)

Case control
Tuyns 1983 Men — 1.12 (1.07–1.17)
Tuyns 1983 Women — 1.04 (1.00–1.09)
Decarli 1987 — 1.04 (1.03–1.05)
La Vecchia 1989 — 1.01 (0.99–1.03)
Franceschi 1990 — 1.02 (1.01–1.04)
De Stefani 1990 Men — 1.04 (1.03–1.06)
De Stefani 1990 Women — 1.13 (0.99–1.29)
Sankaranarayanan 1991 Men — 1.02 (1.01–1.03)
Cheng 1992 — 1.08 (1.07–1.09)
Tavani 1993 — 1.03 (1.00–1.06)
Tavani 1994 — 1.02 (1.00–1.04)
Hanaoka 1994 — 1.24 (1.14–1.33)
Brown 1994 Black men — 1.04 (1.03–1.04)
Brown 1994 White men — 1.03 (1.05–1.07)
Castelletto 1994 — 1.05 (1.03–1.07)
Gammon 1997 — 1.07 (1.05–1.08)
Bosetti 2000 — 1.03 (1.03–1.03)
Takezaki 2001 — 1.00 (0.96–1.04)
Sharp 2001 — 1.00 (0.95–1.05)
Boonyaphiphat 2002 — 1.05 (1.04–1.07)
Dal Maso 2002 — 1.03 (1.02–1.04)
Lee 2005 — 0.99 (0.97–1.00)
Yang 2005 — 1.05 (1.03–1.06)
Summary estimate — 1.04 (1.03–1.05)

0.8   1   1.25   1.5

Relative risk, per drink/week

Figure 4.8.7 | **Alcoholic drinks and oesophageal cancer; case-control studies: dose response**

Tuyns 1983 Men
Tuyns 1983 Women
Decarli 1987
De Stefani 1990 Men
De Stefani 1990 Women
Cheng 1992
Tavani 1993
Brown 1994 Black Men
Brown 1994 White Men
Castelletto 1994
Hanaoka 1994
Tavani 1994
Gammon 1997
Bosetti 2000
Cheng 2000
Sharp 2001
Boonyaphiphat 2002
Dal Maso 2002

0   20   40   60   80   100

Alcoholic drinks (drinks/week)

be partially explained by the variation in measurement of alcohol intake, variation in the outcome measured (oesophageal or upper aerodigestive tract), or by inadequate adjustment for smoking in some studies. There is a trend for smaller effect estimates from more recent publications, which could be due to improved methods of adjustment for confounders. Not all studies adjusted for smoking.

There is some evidence of publication bias; with smaller studies tending to report larger effects.

The ecological studies were not consistent.[2 94 95 114 183-189] Two reported statistically significant results, both in the direction of increased risk.[94 186]

Beers
One cohort study,[4] 15 case-control studies,[103 129 143 144 159 170 173 176 190-197] and seven ecological studies[94 95 106 184 187 198 199] reported separately on beer drinking.

The single cohort study showed statistically significant increased risk with increased intake after adjustment for smoking.[4] All case-control studies with the exception of two[173 176] also showed increased risk, which was statistically significant in seven.[103 129 144 159 170 191 193 195-197] Meta-analysis was possible on five case-control studies, giving a summary effect estimate of 1.05 (95% CI 1.03–1.07), with high heterogeneity.[144 159 170 193 197] About half of the studies did not adjust for smoking. The ecological studies were inconsistent and one reported a statistically significant result, which was in the direction of increased risk.[94]

Wines
Ten case-control studies,[143 144 159 161 170 173 190 194 195] one cross-sectional study,[200] and five ecological studies[94 95 106 184 198] reported separately on wine drinking.

All but one of the case-control studies showed increased risk with increased intake,[144] which was statistically significant in seven.[159 161 170 190 195] About half of the studies adjusted for smoking. The single cross-sectional study showed non-significant increased risk.[200] Most ecological

studies were in the direction of increased risk.[94 106 184 198]

Spirits
One cohort study,[4] 15 case-control studies,[139 143-145 159 170 173 181 190 191 194-196 201 202] one cross-sectional study,[200] and five ecological studies[94 95 106 184 198] reported separately on spirits.

The single cohort study showed statistically significant increased risk with increased intake after adjustment for smoking.[4] All of the case-control studies also showed increased risk, which was statistically significant in eight.[139 144 145 191 194 195 201 202] Most studies adjusted for smoking. The single cross-sectional study showed non-significant increased risk.[200] The ecological studies were inconsistent and two reported statistically significant results; both were in the direction of increased risk.[94 106]

The general mechanisms through which alcohol could plausibly cause cancer are outlined below. In addition, alcohol acts as a synergistic carcinogen with tobacco. Tobacco may induce specific mutations in DNA that are less efficiently repaired in the presence of alcohol. Alcohol may also function as a solvent, enhancing penetration of other carcinogenic molecules into mucosal cells.

There is ample and consistent evidence, both from cohort and case-control studies, with a dose-response relationship. There is robust evidence for mechanisms operating in humans. The evidence that alcoholic drinks are a cause of oesophageal cancer is convincing. No threshold was identified.

The Panel is aware that since the conclusion of the SLR, one cohort[203] and four case-control studies[204-207] have been published. This new information does not change the Panel judgement (see box 3.8).

Colorectum
Twenty-four cohort studies investigated alcoholic drinks and colorectal cancer.[124 208-235] Thirteen cohort studies[214 216 219 227 230 232 236-251] and 41 case-control studies investigated ethanol intake and colorectal cancer.

Total alcoholic drinks
Eighteen cohort studies showed increased risk for the highest intake group when compared to the lowest,[124 209 210 212-217 220-223 225-228 233-235] which was statistically significant in four.[209 210 216 227] One study showed non-significant increased risk in men and non-significant decreased risk in women.[211 219] Two studies reported no effect on risk[218 231] and three studies reported decreased risk; none was statistically significant.[208 224 229 230 232] Meta-analysis was possible on six cohort studies, giving a summary effect estimate of 1.01 (95% CI 0.95–1.08) per drink/day, with no heterogeneity (figure 4.8.8).

Alcohol (as ethanol)
Eleven of the cohort studies showed increased risk for the highest intake group when compared to the lowest (figure 4.8.9),[214 216 219 227 230 232 237 239-251] which was statistically significant in six.[219 227 230 240 244 245 251] One study reported no

effect on risk for men and non-significant decreased risk for women,[238] and one study reported no statistically significant association.[236] Meta-analysis was possible on nine cohort studies, of which one reported on colorectal cancer and eight reported on colon cancer, giving a summary effect estimate of 1.09 (95% CI 1.03–1.14) per 10 g/day, with moderate heterogeneity(figures 4.8.10 and 4.8.11).

In a separate meta-analysis of nine studies for rectal cancer, the summary effect estimate was 1.06 (95% CI 1.01–1.12) per 10 g/day, with low heterogeneity (figure 4.8.12). It is apparent from the meta-analysis that the reported effect for men was larger and more often statistically significant than for women. Stratified meta-analyses for colorectal cancer gave summary effect estimates of 1.09 (95% CI 1.02–1.15) for seven studies for men, and 1.00 (95% CI 0.89–1.40) for three studies for women. There was no statistically significant difference with cancer site. There was, however, apparent sexual dimorphism, with a larger effect in men than in women, which explains the bulk of the observed heterogeneity.

Figure 4.8.8 Alcoholic drinks and colorectal cancer; cohort studies

Relative risk (95% CI)

Study	RR (95% CI)
Kato 1999 Women	1.00 (0.82–1.22)
Ford 1997	0.97 (0.82–1.15)
Schoen 1999	1.24 (0.91–1.69)
Chen 2001 Men	1.26 (0.79–2.01)
Flood 2002 Women	1.02 (0.85–1.21)
Pedersen 2003	1.00 (0.91–1.09)
Summary estimate	1.01 (0.95–1.08)

Relative risk, per drink/day

Figure 4.8.9 Ethanol and colorectal cancer; cohort studies

Relative risk (95% CI)

Study	RR (95% CI)
Slattery 1990 Men	2.21 (0.81–6.05)
Slattery 1990 Women	1.66 (0.78–3.52)
Goldbohm 1994	1.10 (0.32–3.81)
Glynn 1996 Men	3.60 (1.27–10.18)
Chyou 1996 Men	1.39 (1.05–1.84)
Murata 1996 Men	3.20 (1.53–6.70)
Harnack 2002 Women	1.08 (0.72–1.62)
Wei 2003 Men	1.55 (1.05–2.28)
Wei 2003 Women	1.14 (0.86–1.52)

Relative risk, highest vs lowest exposure category
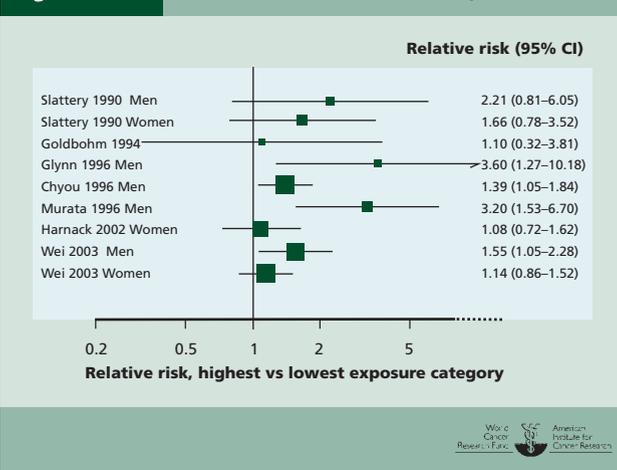
Figure 4.8.10 Ethanol and colon cancer; cohort studies

Relative risk (95% CI)

Wu 1987	1.18 (1.06–1.31)
Kreger 1992 Men	1.00 (0.92–1.09)
Kreger 1992 Women	0.88 (0.71–1.10)
Goldbohm 1994 Men	1.08 (0.95–1.23)
Goldbohm 1994 Women	1.07 (0.90–1.29)
Giovanucci 1995 Men, >646 µg/day folate intake	1.02 (0.64–1.61)
Chyou 1996 Men	1.17 (1.06–1.28)
Murata 1994 Men	1.12 (0.94–1.28)
Colbert 2001 Men	1.03 (0.96–1.12)
Harnack 2002 Women	1.05 (0.80–1.38)
Nakaya 2005 Men	1.25 (1.06–1.47)
Summary estimate	1.09 (1.03–1.14)

Relative risk, per 10 g/day

Figure 4.8.12 Ethanol and colorectal cancer; cohort studies

Relative risk (95% CI)

Kreger 1992 Men	0.98 (0.83–1.15)
Kreger 1992 Women	0.81 (0.48–1.37)
Goldbohm 1994 Men	1.08 (0.92–1.27)
Goldbohm 1994 Women	1.05 (0.78–1.39)
Chyou 1996 Men	1.11 (1.07–1.16)
Murata 1996	1.14 (0.93–1.39)
Colbert 2001 Women	0.99 (0.90–1.07)
Hamack 2002	0.94 (0.54–1.65)
Nakaya 2005	1.15 (0.92–1.44)
Summary estimate	1.06 (1.01–1.12)

Relative risk, per 10 g/day

Figure 4.8.11 Ethanol and colon cancer incidence; cohort studies: dose response

Goldbohm 1994 Men

Goldbohm 1994 Women

Chyou 1996 Men

Ethanol (g/day)

When data were analysed separately for drink type (beers, wines, or spirits), they became insufficient to draw any firm conclusions.

Pooled analysis from 8 cohort studies (over 475 000 participants, followed up for 6 to 16 years, more than 4600 colorectal cancer cases) showed a significant increased risk for the highest intake group when compared to the lowest, with an effect estimate of 1.41 (95% CI 1.16–1.72) for those who consumed 45 g/day or greater.[252] No increased risk was observed below intakes of 30 g/day. No significant heterogeneity was observed by sex or cancer site.

In addition, a published meta-analysis of 27 studies reported a statistically significant increased risk, with a summary effect estimate of 1.10 (95% CI 1.05–1.14) per two drinks/day.

Because of the abundant prospective data from cohort studies, case-control studies were not summarized.

The general mechanisms through which alcohol could plausibly cause cancer are outlined below. In addition, the association between alcohol intake and colorectal cancer risk is modified by acetaldehyde dehydrogenase and alcohol dehydrogenase genetic status.[253 254] Alcohol may induce folate deficiency in the colon and rectum, possibly by reducing absorption of folate or by inhibition of critical enzymes. Also, alcohol may disrupt one-carbon metabolism (see Chapter 2). Intestinal bacteria, because of their high alcohol dehydrogenase activity, can oxidise ethanol in colorectal tissue to produce levels of acetaldehyde up to 1000-fold higher than that in blood.

The more elevated risk related to alcohol intake among men compared with women may be because of the generally lower consumption of alcohol among women. That is, it is possible that men exhibit a greater range in the amount of alcohol drunk, which makes effects easier to detect. Also, preferred beverages may differ between the sexes, or there may be hormone-related differences in alcohol metabolism or susceptibility to alcohol.

There is ample and generally consistent evidence from cohort studies. A dose-response is apparent. There is evidence for plausible mechanisms. The evidence that consumption of more than 30 g/day of ethanol from alcoholic drinks is a cause of colorectal cancer in men is convincing, and probably also in women.

The Panel is aware that since the conclusion of the SLR, four cohort[255-258] and four case-control studies[259-262] have been published. This new information does not change the Panel judgement (see box 3.8).

Breast

Eleven cohort studies,[183 263-271] 31 case-control studies[272-310] and 2 ecological studies[311 312] investigated total alcoholic drinks and breast cancer at all ages. Four cohort studies[313-316] and 19 case-control studies[289 302 317-333] investigated alcoholic drinks. Twenty-five cohort studies,[315 334-364] 29 case-

control studies,[280 282 317 318 332 333 365-391] and 4 ecological studies[392-395] investigated ethanol intake.

Total alcoholic drinks

Six cohort studies showed increased risk for the highest intake group of total alcoholic drinks when compared to the lowest,[263 264 267-271] which was statistically significant in three.[267 269 270] Three studies showed non-significant decreased risk[265 266]; one study showed no effect on risk.[183] Meta-analysis was possible on three cohort studies, giving a summary effect estimate of 1.07 (95% CI 0.89–1.29) per five times/week, with no heterogeneity (figures 4.8.13 and 4.8.14).[263 271]

Two cohort studies reported separately on premenopausal breast cancer.[264 268] Both showed increased risk for the highest intake group when compared to the lowest, which was statistically significant in one.[268] Three cohort studies reported separately on postmenopausal breast cancer.[264 268 269] Two showed increased risk for the highest intake group when compared to the lowest,[264 269] which was statistically significant in one.[269] The other study showed non-significant decreased risk.[268]

Four additional cohort studies investigated alcoholic drinks.[313-316] All four showed non-significant increased risk for breast cancer at unspecified ages. One study also reported statistically significant increased risk for postmenopausal breast cancer and non-significant decreased risk for premenopausal breast cancer.[315]

Most of the 22 case-control studies that reported on all-age breast cancer and total alcoholic drinks showed increased risk for the highest intake group when compared to the lowest,[273 274 280 282-285 287 288 290 295 297 301-303 305-309 318] which was statistically significant in seven.[273 284 285 306 318] A few studies showed decreased risk, none was statistically significant.[276 291 295 298 302 304] Meta-analysis was possible on 10 case-control studies reporting on breast cancer at all ages, giving a summary estimate of 1.05 (95% CI 1.03–1.07) for an increment of five times/week, with high heterogeneity (figures 4.8.13 and 4.8.14).[274 276 284 286 287 296 306 307] No heterogeneity was apparent with menopausal status. Twelve case-control studies reported separately on premenopausal breast cancer.[272 275 277-279 281 282 292-294 297 299 300 306 310 318] Ten showed increased risk,[272 275 277 279 281 292-294 299 300 306 318] which was statistically significant in two.[272 281 294 299 300 306] One study showed no effect on risk[297] and the other study showed non-significant decreased risk.[278 282 310] Six studies reported separately on postmenopausal breast cancer.[277 278 281 282 289 297 306 310] Five of these showed increased risk,[278 281 282 289 306 310] which was statistically significant in one.[306] The other study reported non-significant decreased risk.[297]

In addition, 19 case-control studies investigated alcoholic drinks.[289 302 318-323 325-331 333] Most showed increased risk for the highest intake group when compared to the lowest, which was statistically significant in six.[302 318 321 323 327 329] Two studies showed non-significant decreased risk[317 324]; one study showed no effect on risk.[332] Four studies reported separate results for premenopausal breast cancer.[318 320 322 333] Of these, two studies showed non-significant increased risk,[318 333] one showed statistically significant increased risk in

Figure 4.8.13 — **Alcoholic drinks and breast cancer; cohort and case-control studies**

	Relative risk (95% CI)
Cohort	
Wu 1999	1.38 (0.84–2.26)
Wu 1999	1.08 (0.78–1.50)
Byrne 1996	0.99 (0.77–1.28)
Summary estimate	1.07 (0.89–1.29)
Case control	
La Vecchia 1989	1.10 (1.07–1.13)
Baumgartner 2002	1.07 (0.82–1.38)
Katsoyannis 1994	1.05 (0.97–1.12)
Kinney 2000	1.03 (0.92–1.15)
Lash 2000	1.01 (0.86–1.19)
Rosenberg 1990	0.97 (0.86–1.10)
Viladiu 1996	0.97 (0.93–1.11)
Freudenheim 1995	0.94 (0.79–1.13)
Sneyd 1991	0.94 (0.81–1.09)
Baughmater 2002	0.90 (0.79–1.03)
Summary estimate	1.05 (1.03–1.07)

Relative risk, per 5 times/week

Figure 4.8.14 — **Alcoholic drinks and breast cancer; cohort and case-control studies: dose response**

Alcoholic drinks (times/week)

166
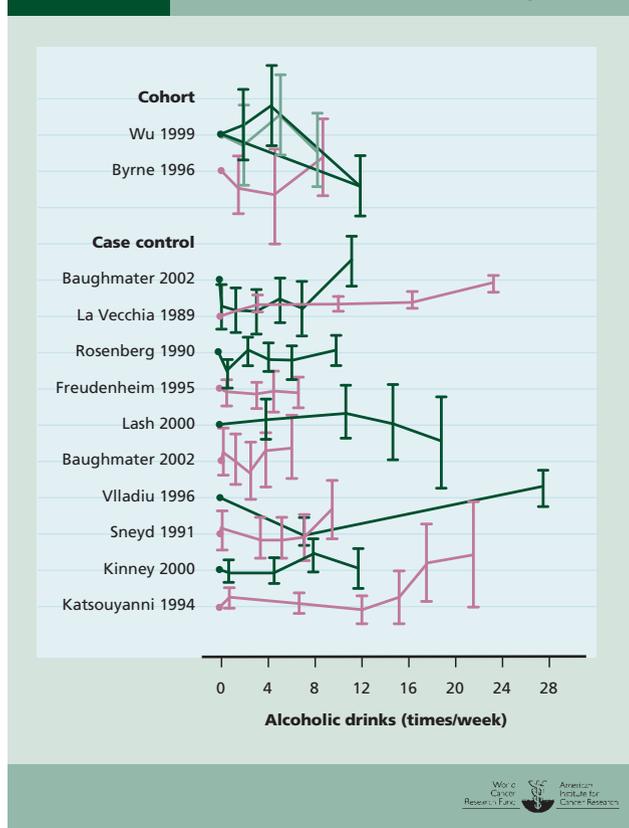
parous women,[322] and one showed non-significant decreased risk.[320] Seven studies reported separately on postmenopausal breast cancer.[289 318 320-322 326 333] All seven studies showed increased risk for the highest intake group when compared to the lowest, which was statistically significant in three,[318 321 333] and in oestrogen-sensitive cancers in a fourth study.[326]

Both ecological studies showed statistically significant, positive associations.[311 312]

When data were analysed separately for drink type (beers, wines, or spirits), they became insufficient to draw any firm conclusions.

Alcohol (as ethanol)

Twelve cohort studies investigated ethanol intake and all-age breast cancer.[315 336 338-341 343-350 352-354 361-364] Eight cohort studies showed increased risk for the highest intake group when compared to the lowest,[315 336 338-341 343 344 346-348 350 352-354 361 362] which was statistically significant in six.[338 341 344 350 352 354 361] Four studies showed decreased risk,[345 349 363 364] which was statistically significant in one.[364] Meta-analysis was possible on nine cohort studies, giving a summary effect estimate of 1.10 (95% CI 1.06–1.14) per 10 g/day, with high heterogeneity (figure 4.8.15). Heterogeneity could be partly explained by differential adjustment for age and reproductive history.

Seven cohort studies reported separately on premenopausal breast cancer.[315 340 343 347 348 352-354 361] Six studies showed increased risk,[340 343 347 348 352-354 361] which was statistically significant in three.[340 348 352] One study showed a non-significant decreased risk.[315] Meta-analysis was possible on five studies, giving a summary estimate of 1.09 (95% CI 1.01–1.17) per 10 g/day, with moderate heterogeneity.[315 340 343 347 352] Eighteen cohort studies reported separately on postmenopausal breast cancer.[315 334 335 337 339 340 342 347 348 351-361] Fifteen studies showed increased risk,[315 335 337 339 342 347 348 351 353-361] which was statistically significant in seven.[315 335 337 339 342 347 357-359] Three studies showed non-significant decreased risk.[334 340 352] Meta-analysis was possible on 11 studies, giving a summary effect estimate of 1.08 (95% CI 1.05–1.10) per 10g/day, with moderate heterogeneity.[315 334 335 339 340 347 352 355 358-360]

Pooled analysis from 6 cohort studies (over 320 000 participants, followed up for up to 11 years, more than 4300 breast cancer cases) showed a significant increased risk with increasing intake, with an effect estimate of 1.09 (95% CI 1.04–1.03) per 10 g/day.[396] No significant heterogeneity was observed by menopausal status.

A separate pooled analysis of 53 case-control studies (more than 58 000 cases and more than 95 000 controls) showed a significant increased risk with increasing intake, with an effect estimate of 7.1 per cent increased risk (95% CI 5.5–8.7%; p < 0.00001) per 10 g/day.[397] No significant heterogeneity was observed by menopausal status.

Eighteen case-control studies investigated ethanol intake and all-age breast cancer.[280 282 317 318 332 365-371 374 378 379 381 383 384 386 387 390 391] Twelve case-control studies showed increased risk for the highest intake group when compared to the lowest,[280 318 332 365 367-369 374 379 381 383 384 386 387 391] which was statistically significant in five.[280 318 368 369 374 381 384] Five studies

**Figure 4.8.15   Ethanol and breast cancer; cohort studies**

Relative risk (95% CI)

	Relative risk (95% CI)
Holmberg 1995	4.32 (1.34–13.89)
Rissanen 2003	2.33 (1.28–4.24)
Dumeaux 2004	1.41 (1.21–1.64)
Willett 1987	1.19 (1.11–1.29)
Lin 2005	1.15 (1.03–1.28)
Hines 2000	1.08 (0.88–1.33)
Rohan 2000	1.03 (0.98–1.09)
Oodman 1997	0.86 (0.67–1.11)
Schatzkin 1989	0.64 (0.43–0.94)
Summary estimate	1.10 (1.06–1.14)

Relative risk, per 10 g/day
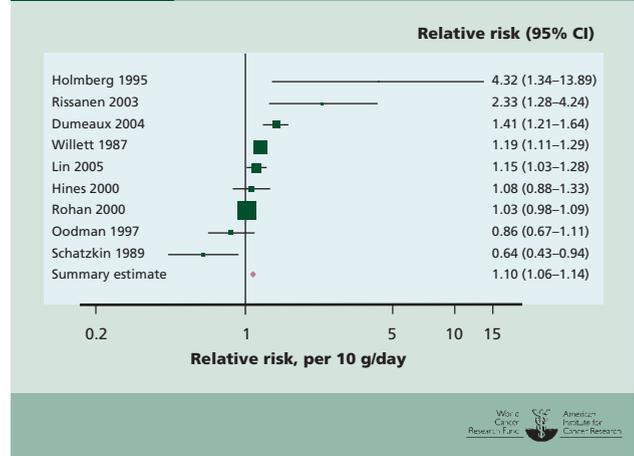
showed decreased risk,[317 366 370 371 378 390] which was statistically significant in one[378]; and one study showed no effect on risk.[282] Meta-analysis was possible on seven case-control studies, giving a summary effect estimate of 1.06 (95% CI 1.04–1.09) per 10 g/day, with moderate heterogeneity (figure 4.8.16).

When case-control data were analysed separately by menopausal status, the meta-analysis for premenopausal breast cancer was consistent with that for all ages (1.08 (95% CI 1.04–1.13) per 10 g/day; nine studies),[317 318 369 373 376 377 380 383 389] but the meta-analysis for postmenopausal breast cancer was not (1.00 (95% CI 0.98–1.01) per 10 g/day; 10 studies).[318 369 372 373 375 380 382 383 385 388]

All four ecological studies showed statistically significant positive associations.[392-395]

The general mechanisms through which alcohol could plausibly cause cancer are outlined below. In addition, most experimental studies in animals have shown that alcohol intake is associated with increased breast cancer risk. Alcohol interferes with oestrogen pathways in multiple ways,

Figure 4.8.16   Ethanol and breast cancer; case-control studies

Relative risk (95% CI)

	Relative risk (95% CI)
Bowlin 1997	1.44 (1.11–1.86)
Rohan 1988	1.21 (0.99–1.48)
Harvey 1987	1.10 (1.02–1.18)
Brandt 2004	1.08 (0.94–1.23)
Ferraroni 1998	1.06 (1.03–1.09)
Trentham-Dietz 2000	1.05 (1.00–1.11)
Webster 1983	1.01 (0.95–1.08)
Summary estimate	1.06 (1.04–1.09)

Relative risk, per 10 g/day
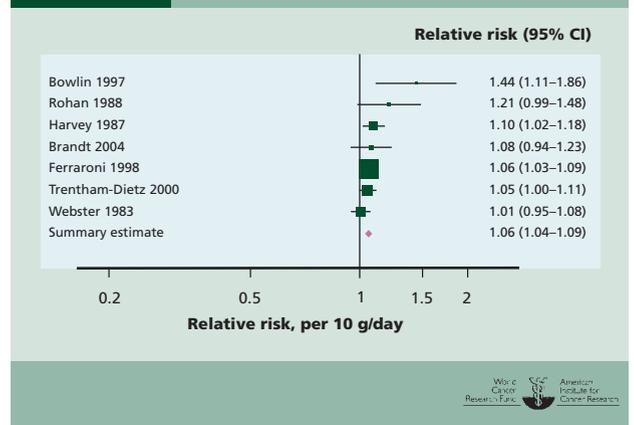
influencing hormone levels and oestrogen receptors.[398]

There is an interaction between folate and alcohol affecting breast cancer risk: increased folate status partially mitigates the risk from increased alcohol consumption.[399]

There is ample, generally consistent evidence from case-control and cohort studies. A dose-response relationship is apparent. There is robust evidence for mechanisms operating in humans. The evidence that alcoholic drinks are a cause of premenopausal and postmenopausal breast cancer is convincing. No threshold was identified.

The Panel is aware that since the conclusion of the SLR, one case-control study[400] has been published. This new information does not change the Panel judgement (see box 3.8).

Liver

Fifteen cohort studies[120 208 220 227 401-422] and 33 case-control studies[158 423-460] investigated alcoholic drinks and liver cancer. Fourteen cohort studies[6 120 227 244 403 404 409 410 412 416 422 461-468] and 21 case-control studies[158 427 431 434 436 440 446 452 456 459 469-485] investigated ethanol intake.

Total alcoholic drinks
Data are available from 15 cohort studies.[120 208 220 227 401-422] Eleven cohort studies showed increased risk for the highest intake group when compared to the lowest,[120 220 227 401-404 407-410 413 414 416 417 420 422] which was statistically significant in two.[120 401] Two studies showed non-significant decreased risk.[405 406 412 418 419] Two studies stated that there was no significant difference but did not provide further data.[411 415 421] Heterogeneity is partially explained by differences in whether and how studies have adjusted for hepatitis virus status. The effect estimates of eight studies are given in the high to low comparison forest plot (figure 4.8.17).

Data are available from 33 case-control studies.[158 423-460] Twenty-eight case-control studies showed increased risk for the highest intake group when compared to the lowest,[158 423-432 434-448 451-456 460] which was statistically significant in 12 (one of these studies reported a non-significant decreased risk in women, but a statistically significant increased risk in men[440]).[158 423 427 429-432 434 439 440 442 444 446 447 454-456] Two studies showed non-significant decreased risk.[449] Three studies stated that there was no significant effect on risk.[433 450 457-459] Meta-analysis was possible on five studies, giving a summary effect estimate of 1.18 (95% CI 1.11–1.26) per drink/week, with high heterogeneity (figure 4.8.18).[158 425 434 449 460]

A dose-response relationship is apparent from case-control but not cohort data.

Alcohol (as ethanol)
Ten cohort studies showed increased risk for the highest intake group when compared to the lowest,[6 120 244 403 404 409 410 416 422 461 465-468] which was statistically significant in five (one of these studies reported a non-significant increased risk in women, but a statistically significant increased risk in men[461]).[6 120 244 416 461 465 468] Three studies in men with cirrhosis showed non-significant decreased risk.[227 412 462 463] One

study stated that there was no significant effect on risk.[464] Meta-analysis was possible on six cohort studies, giving a summary effect estimate of 1.10 (95% CI 1.02–1.17) per 10 g/day or 10 ml/day, with no heterogeneity (figure 4.8.19).

Twenty case-control studies showed increased risk for the highest intake group when compared to the lowest,[158 427 431 434 436 440 446 452 456 469 470 472-475 477-479 481-485] which was statistically significant in 12.[158 427 431 434 440 446 456 474 475 477-479 481 483-485] One study showed non-significant decreased risk.[476] Meta-analysis was possible on 14 case-control studies, giving a summary effect estimate of 1.17 (95% CI 1.09–1.25) per 10 g/day or 10 ml/day, with high heterogeneity (figure

Figure 4.8.17 Alcoholic drinks and liver cancer: cohort and case-control studies

Relative risk (95% CI)

Cohort

Study	Relative risk (95% CI)
Kono 1987	2.36 (1.04–5.35)
Hirayama 1989	1.89 (1.40–2.55)
Ross 1992	1.10 (0.46–2.60)
Goodman 1995 Men	1.11 (0.72–1.71)
Goodman 1995 Women	1.25 (0.78–1.99)
Mutu 1989	1.50 (0.42–5.31)
Yu 1999	1.39 (0.68–2.14)
Evans 2002 Men	0.90 (0.90–1.01)
Evans 2002 Women	0.57 (0.29–1.18)
Wang 2003 HBsAg positive	1.29 (0.78–2.10)
Wang 2003 HBsAg negative	2.00 (0.89–4.51)

Case control

Study	Relative risk (95% CI)
Stemhagen 1983 Men	1.30 (0.64–2.63)
Stemhagen 1983 Women	1.63 (0.92–2.89)
Inaba 1984	3.62 (1.68–7.79)
Austin 1986	2.60 (1.26–5.35)
Harris 1988 Men	1.28 (0.69–2.39)
La Vecchia 1988	1.43 (0.83–2.46)
Harris 1988 Women	1.93 (0.66–5.63)
Tsukuma 1990 Men	2.60 (1.70–3.99)
Olubuyide 1990 Men	1.70 (0.90–3.21)
Olubuyide 1990 Women	1.40 (0.04–50.00)
Hiyama 1990	8.00 (1.30–49.36)
Qureshi 1990	3.04 (0.31–29.54)
Yu 1991 Anti-HCV negative	2.10 (1.20–3.69)
Choi 1991 Men	2.46 (1.16–5.22)
Yamaguchi 1993 HBsAg negative	2.70 (1.81–4.02)
Newton 1996	1.20 (0.50–2.89)
Wang 1996	1.28 (0.98–1.67)
Braga 2000 Men	1.68 (1.14–2.48)
Braga 2000 Women	1.30 (0.42–4.01)
Mukaiya 1998	2.31 (1.20–4.42)
Mandishona 1998	2.00 (0.49–8.10)
Kuper 2000	1.90 (0.91–3.96)
Yu 2002	1.38 (0.68–2.81)
Donato 2002 Men	2.70 (1.09–6.71)
Donato 2002 Women	0.90 (0.33–2.49)
Munaka 2003	1.45 (0.81–2.60)
Tsai 2004	2.55 (1.50–4.33)

0.2 0.5 1 2 5

Relative risk, highest vs lowest exposure category

Figure 4.8.18 Alcoholic drinks and liver cancer; case-control studies

Relative risk (95% CI)

Austin 1986 HBsAg	1.07 (0.86–1.33)
Lu 1988	0.89 (0.77–1.02)
Choi 1991	1.30 (1.19–1.41)
Yu 1991	1.39 (1.08–1.79)
Mukaiya 1998	1.21 (1.01–1.44)
Summary estimate	1.18 (1.11–1.26)

Relative risk, per drink/week

Figure 4.8.19 Ethanol and liver cancer; cohort studies

Relative risk (95% CI)

Oshima 1984	1.24 (1.03–1.50)
Ross 1992	1.20 (0.88–1.63)
Murata 1996	0.99 (0.85–1.16)
Miyakawa 1996 HBV-carrier	0.96 (0.62–1.48)
Khan 2000	1.09 (1.00–1.20)
Sharp 2005	1.26 (0.82–1.93)
Summary estimate	1.10 (1.02–1.17)

Relative risk, per 10 g/day
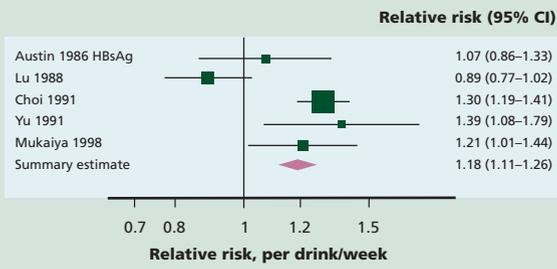
Figure 4.8.20 Ethanol and liver cancer; case-control studies

Relative risk (95% CI)

Infante 1980 Cirrhotic	5.01 (2.42–10.37)
Infante 1980 Non-cirrhotic	6.10 (2.20–16.93)
Yu 1983	1.12 (1.00–1.26)
Inaba 1984	1.81 (1.27–2.59)
Tsukuma 1990	1.17 (1.09–1.29)
Mayans 1990	1.19 (1.09–1.29)
Yamaguchi 1993 Men	1.11 (1.06–1.15)
Arico 1994	0.93 (0.87–1.00)
Pyong 1994 Men	1.40 (1.16–1.69)
Shin 1996	1.05 (0.97–1.15)
Zhang 1998	1.05 (0.95–1.17)
Mukaiya 1998	1.28 (1.05–1.57)
Kuper 2000	1.04 (0.96–1.13)
Hassan 2002	1.16 (1.03–1.30)
Gelatti 2005	1.28 (1.19–1.38)
Summary estimate	1.17 (1.09–1.25)

Relative risk, per 10 g/day

Figure 4.8.21 Ethanol and liver cancer; cohort studies: dose response

Sharp 2005
Ross 1992
Oshima 1984
Murata 1996
Miyakawa 1996 HBV-carrier
Khan 2000

Ethanol (g/day)

4.8.20). Heterogeneity may be due to the inclusion of studies that reported alcoholic behaviour.

A dose-response relationship is apparent from cohort and case-control data (figure 4.8.21).

Beers
Two cohort studies[6 486] and five case-control studies[425 435 444 452 473 479] reported separately on beer drinking.

Both cohort studies showed statistically significant increased risk with increased intake.[6 486] Four case-control studies also showed increased risk,[425 435 444 452 479] which was statistically significant in three.[435 444 452 479] One study reported no effect on risk.[473]

Wines
Three cohort studies[6 410 486] and one case-control study[425] reported separately on wine drinking.

One cohort study showed non-significant increased risk with increased intake.[410] Two studies stated that there was no significant effect on risk.[6 486] The single case-control study showed non-significant increased risk.[425]

Spirits

Two cohort studies[6 486] and five case-control studies[425 444 469 472 479 487] reported separately on spirits.

Both cohort studies showed no significant effect on risk.[6 486] All case-control studies showed increased risk,[425 444 469 472 479 487] which was statistically significant in one[444 479]; and one case-control study showed statistically significant increased risk for consumption of illicit liquor.[487]

Several studies used participants judged to be at high risk of developing liver cancer, that is, people who already had liver cirrhosis. These results are particularly hard to interpret as cirrhosis status affects drinking behaviour. Also the cancer disease path may be different in people with cirrhosis.

Assessment of some studies was hampered by poor exposure assessment, and not all studies adjusted for known confounders such as hepatitis B or C virus.

The general mechanisms through which alcohol could plausibly cause cancer are outlined below. In addition, regular, high levels of alcohol consumption are known to cause liver damage. Tumour promotion has been linked to inflammation in the liver through alcohol-associated fibrosis and hepatitis.[488 489] Alcohol consumption, even at moderate levels, is associated with increases in levels of circulating hepatitis C virus RNA in carriers. Hepatitis C virus infection is highly prevalent among alcoholics with chronic liver disease and appears to accelerate the course of alcoholic liver disease (see chapter 7.8).

There is ample, generally consistent evidence from both cohort and case-control studies. A dose-response relationship is apparent. Alcohol is a cause of cirrhosis that predisposes to liver cancer, but the factors that determine why some people are susceptible to cirrhosis are not known. Alcoholic drinks are a probable cause of liver cancer. No threshold was identified.

The Panel is aware that since the conclusion of the SLR, one case-control study[490] has been published. This new information does not change the Panel judgement (see box 3.8).

Kidney

Three cohort studies[491-493] and 16 case-control studies[308 494-509] investigated alcoholic drinks and kidney cancer. Four cohort studies[6 492 510-513] and five case-control studies[503 504 514-516] investigated ethanol intake.

Total alcoholic drinks

Two cohort studies showed non-significant increased risk for the highest intake group when compared to the lowest.[491 493] One study showed a statistically significant decreased risk.[492] None of the studies was adjusted for smoking; effect estimates were 1.42 (95% CI 0.69–2.9),[493] 1.7 (95% CI 0.8–3.5) for women[491] and 1.2 (95% CI 0.5–2.6) for men,[491] and 0.62 (95% CI 0.41–0.94).[492]

Seven case-control studies showed decreased risk for the highest intake group when compared to the lowest,[308 494 496 499 501-504] of which one was statistically significant[494] and one was statistically significant in women but not in men.[504]

Three studies showed no effect on risk[495 497 509]; three studies stated that there was no significant association[505-507]; two studies showed non-significant increased risk[498 500]; one study showed a non-significant decreased risk in men and a non-significant increased risk in women.[508] Meta-analysis was possible on two studies that adjusted for smoking, giving a summary effect estimate of 0.92 (95% CI 0.71–1.20) per serving/day, with moderate heterogeneity (figure 4.8.22).[496 498]

Alcohol (as ethanol)

All four cohort studies showed decreased risk with increased ethanol intake,[6 492 510-513] which was statistically significant in one.[510 512] Meta-analysis was possible on two unadjusted studies, giving a summary effect estimate of 0.48 (95% CI 0.26–0.90) per serving/day, with no heterogeneity.[492 511]

Three case-control studies showed non-significant decreased risk with increased ethanol intake.[504 514 516] One study showed no effect on risk,[515] and one study stated no significant association.[503] Meta-analysis was possible on two unadjusted studies, giving a summary effect estimate of 0.90 (95% CI 0.77–1.05) per serving/day, with no heterogeneity (figure 4.8.23).[514 515]

There is no known mechanism through which alcohol could decrease kidney cancer risk.

It is unlikely that alcohol increases the risk of kidney cancer, though a protective effect cannot be excluded.

Figure 4.8.22 Ethanol and kidney cancer; case-control studies

Relative risk (95% CI)

	Relative risk (95% CI)
Yuan 1998	1.01 (0.97–1.05)
Parker 2002	0.76 (0.53–1.07)
Summary estimate	0.92 (0.71–1.20)

Relative risk, per unit/day
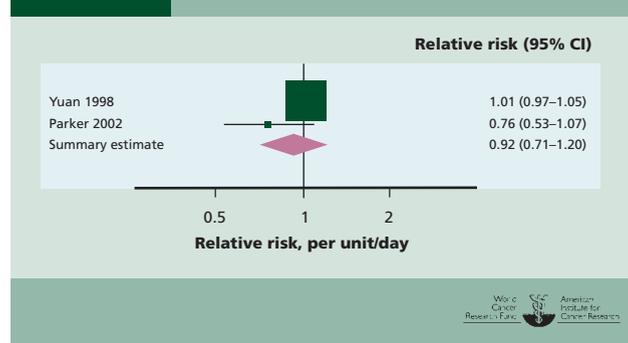
Figure 4.8.23 Alcoholic drinks and kidney cancer; case-control studies

Relative risk (95% CI)

	Relative risk (95% CI)
Mattioli 2002	0.90 (0.76–1.04)
Lindblad 1997	1.00 (0.39–2.59)
Summary estimate	0.90 (0.77–1.05)

Relative risk, per unit/day
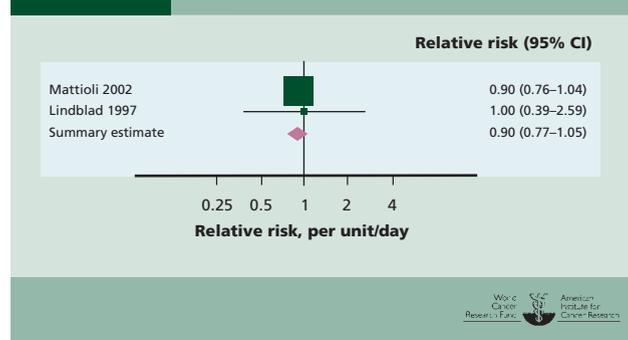
The Panel is aware that since the conclusion of the SLR, one cohort study[517] has been published. This new information does not change the Panel judgement (see box 3.8).

General mechanisms

Evidence suggests that reactive metabolites of alcohol, such as acetaldehyde, may be carcinogenic. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation, and the generation of free-radical oxygen species. Alcohol also acts as a solvent, enhancing penetration of carcinogens into cells. Alcohol has been demonstrated to alter retinoid status in rodent studies and, as a result, cellular growth, cellular differentiation, and apoptosis are adversely altered. For all these pathways, genetic polymorphisms might also influence risk.[398]

Lastly, heavy consumers of alcohol may have diets deficient in essential nutrients, making tissue susceptible to carcinogenesis.

4.8.6 Comparison with previous report

In general, the evidence that alcohol is a cause of a number of cancers has become stronger since the mid-1990s.

The previous report did not find any distinctions between different types of alcoholic drink. This finding is upheld.

The previous report identified a threshold of modest consumption of alcoholic drinks, below which no effect on cancer risk was observed, with the exception of breast cancer. Current evidence does not identify a generally 'safe' threshold.

Current evidence strengthens the previous judgements on colorectal and breast cancers.

4.8.7 Conclusions

The Panel concludes:

Evidence that alcoholic drinks of any type are a cause of various cancers has, on the whole, strengthened.

The evidence that alcoholic drinks are a cause of cancers of the mouth, pharynx, and larynx, oesophagus, colorectum (men), and breast is convincing. They are probably a cause of colorectal cancer in women, and of liver cancer. It is unlikely that alcoholic drinks have a substantial adverse effect on the risk of kidney cancer.

4.9 Food production, preservation, processing, and preparation

Practically all food and drink is changed before it is consumed, for instance by peeling or cooking. The majority of foods and drinks consumed by most people around the world are now modified in many more ways. Products on sale in supermarkets, small shops, and other retail outlets are chilled, pasteurised, canned, bottled, vacuum packed, or otherwise packaged. Most contain a number of ingredients, some of which are also processed. The use of ingredients such as modified starches, added sugars, hydrogenated fats, and also additives used as bulking aids, preservatives, colours, flavours, sweeteners, and for other purposes, is common. In general, rises in consumption of fats, oils, and added sugars occur because of their increased use in processed foods and drinks. Animal and plant products both contain traces of agricultural chemicals. Methods of industrial and domestic food preparation and cooking change the nature of food as eaten.

It is possible that processing and/or preserving methods may alter the nature of food. Different methods of food preservation and processing may be protective, causative, or neutral in their effects on the risk of cancer.

It is for this reason that *the Panel decided* that, as far as practically possible, the evidence on methods of food production, preservation, processing, and preparation (including cooking) should be summarised and judged in the context of the relevant foods and drinks. Most of this evidence is to be found in the previous sections of Chapter 4.

This section summarises other information and findings concerning the ways in which foods and drinks are changed before consumption. These include where data from animal and other experimental studies are not supported by evidence from epidemiological studies. Such studies are often carried out for the purposes of establishing regulations for the safety in use of chemicals known to be toxic, but may use levels of exposure far higher than occur in foods and drinks.

In line with its general criteria for judgement, *the Panel decided* to make no judgements on experimental findings alone that are not supported by epidemiological or other evidence. Nevertheless, *the Panel concurs* that, in general, it seems reasonable to conclude that the changes made to foods and drinks within well regulated, modern food systems, and made to foods and drinks as usually prepared and cooked, are of themselves unlikely to modify the risk of cancer significantly. For this reason, no matrix showing Panel judgements is included in this section.

In line with its general criteria for judgement, *the Panel has decided to* make no judgements on experimental findings from studies using doses of substances at levels far above those found in foods and drinks, many if not most of which are conducted to guide toxicological regulations. *The Panel also concurs* that changes made to processed foods and drinks within well regulated, modern food systems are of themselves unlikely to modify the risk of cancer significantly. For this reason, no matrix showing Panel judgements is included in this section. Those aspects of food production, preservation, processing, and preparation that have been examined in epidemiological as well as experimental settings are discussed and judged in earlier sections of Chapter 4.

This section summarises some of the general methods by which foods and drinks may be changed during their production, preservation, processing, and preparation (including cooking) that may be relevant to the risk of cancer. Almost all foods and drinks are altered — processed, in a general sense of the word — before being consumed.

Reports concerned with the prevention of chronic diseases often mention the added nutritional value of lightly processed cereals (grains), and of vegetables and fruits. But they may not make much distinction between foods and drinks as such, and as modified in production, preservation, processing, and preparation. Previous reports concerned with cancer have concluded that some methods of food and drink modification can produce carcinogens in experimental settings, and that this might reasonably influence cancer risk. Storage conditions that allow contamination of cereals (grains) and other plant foods by aflatoxins, and the preparation of fish Cantonese-style by salting and fermentation, have previously been identified as causes of cancer.

This section covers aspects of food production, preservation, processing, and preparation that are sometimes thought to be relevant to the risk of cancer, but where experimental information (when this exists) is not supported by epidemiological evidence or where there is no such evidence. Where the evidence for foods or drinks is sufficient to judge that they may cause or protect against any cancer, this is summarised and judged in earlier sections of this chapter. For example, see chapter 4.1 for the Panel's findings on aflatoxin contamination; for processed meat and also cooking methods, see chapter 4.3; for salting, see chapter 4.6.

4.9.1 Production

Modern food systems (box 4.9.1) involve various aspects of food production that have some potential to modify the risk of cancer. A clear benefit of these systems of production, distribution, and retail sale, with chilling used at all stages, is

the all-year round supply of fresh vegetables and fruits (see chapter 4.2).

The industrialised farming methods that are part of most modern food systems in most countries use various technologies to maximise production. These include the use of fertilisers, pesticides, and herbicides on food crops; and of veterinary drugs in rearing livestock and in aquaculture. Fertilisers play a part in determining nutrient levels in plants, as well as potentially modifying concentrations of other bioactive microconstituents. Residues of these and other chemicals applied to crops are washed from soils by the rain and can contaminate water supplies. See boxes 4.9.2 and 4.9.3.

Methods or consequences of food production, where epidemiological evidence shows or suggests an effect on the risk of cancer, are summarised and judged earlier in this chapter. These are fungal contamination (chapter 4.1), hot drinks and foods (chapter 4.7), and arsenic contamination (chapter 4.7).

Box 4.9.1	Food systems

Food systems involve the production, preservation, processing, and preparation (including cooking) of food. Gatherer–hunters take food as it is found in nature and modify it by the use of fire. Pastoralists modify the animals that are a source of their food through breeding. Agriculture improves plants for human food use, by selective breeding and planting, and animals too are subject to selective breeding. In Egypt, selectively bred wheat was ground into flour, kneaded with water and other ingredients, and baked into bread as early as 4000 years ago.

Thousands of years before industrialisation, most food and drink consumed by the majority of people was modified in some way in its production. This included preservation by drying, and later other methods such as salting, fermenting, pickling, curing, spicing, and freezing in cold climates; and various methods of preparation and cooking, including boiling and roasting.

Food systems were transformed as part of the industrial and later, the technological revolution. But this was not the point at which foods and drinks became modified for the first time. Rather, many new processes were developed such as sterile bottling and canning. Then, beginning in the late 19th century, steel roller mills were devised for the mass-manufacture of white flour and thus white bread; refrigerated transport using railways and ships made possible the industrial production and international export of meat and dairy products. In the 20th century, commercialisation of the hydrogenation process to turn liquid oils into solid fats made margarine manufacture a big business, and the mass manufacture of soft drinks developed.

What is now known as 'conventional' farming, making extensive use of chemical fertilisers, herbicides, and pesticides, and feed concentrates for animals, developed mainly in the second half of the 20th century. More recent developments in food systems include the use of containers to transport foods and drinks nationally and internationally; the development of supermarkets, of which the biggest are now transnational; and the increasing concentration of food producers, manufacturers, retailers, and caterers.

4.9.1.1 Pesticides and herbicides

The use of synthetic pesticides and herbicides has increased vastly since the middle of the 20th century. Nearly 2500 tonnes of these chemicals were used worldwide in 2001.[1]

The chlorinated pesticide dichloro-diphenyl-trichloro-ethane (DDT) has been banned from use in many countries. Other organochlorine pesticides are now largely being replaced with organophosphorus and carbamate pesticides. These newer types are less persistent in the environment, and have not been found to be carcinogenic in experimental settings.

In many countries, the use of pesticides and herbicides is regulated to minimise residues in foods and drinks, and there are internationally recommended maximum residue limits (box 4.9.3). The use of persistent organic pollutants (organochlorine pesticides, furans, dioxins, and polychlorinated biphenyls) will be banned by 2025 under the United Nations Environment Programme's Stockholm Convention, which entered into force in May 2004.

Many of these contaminants have the potential to accumulate within food systems, and residues of pesticides and herbicides that have been banned from use, or are being phased out, may still be present in foods eaten today. Some contaminants, such as heavy metals and persistent organic compounds, tend to be deposited in fatty tissues and are not easily metabolised or excreted. They accumulate in living creatures, in amounts higher than background levels (for instance, in the soil). Dietary exposure increases with each step up the food chain, as predators consume prey contaminated with these residues.

There are theoretical grounds for concern, which are constantly reviewed by international and national regulatory bodies. However, there is no epidemiological evidence that current exposures are causes of cancers in humans, and so the Panel has made no judgements. Nevertheless, a precautionary approach is wise for women of reproductive age, since vulnerability during embryonic phases of development is increased, and early exposure may result in increased risk at later stages in life.

4.9.1.2 Veterinary drugs

Industrial animal production, as distinct from 'organic' farming (box 4.9.2), requires constant use of antimicrobial drugs to treat and prevent infectious diseases, and promote growth. Residues of these antimicrobials can be found in foods and drinks, normally at levels lower than internationally recommended maximum residue limits (box 4.9.3). When antimicrobials have been found to be carcinogenic in animals, their licence for that use has been withdrawn.

Hormonal anabolic agents are used in animal husbandry in some countries, including the USA, to prevent and terminate pregnancy in cows and to promote growth. Their use has been banned in other countries as well as in the European Union. Hormones designed to stimulate milk production include bovine somatotropin and porcine somatotropin. Many hormones have been found to be multisite carcinogens in experimental settings.[2] These include oestrogens, classed as group 1, human carcinogens, by the International Agency for Research on Cancer (IARC), prog-

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Box 4.9.2   **'Organic' farming**

So-called 'organic' farming is essentially a reversion to, or revival of, methods of agriculture that were the standard until the introduction of farming systems dependent on chemical fertilisers, pesticides, and biocides, in the second half of the 20th century.

Organic farming avoids or largely excludes the use of synthetic fertilisers and pesticides, plant growth regulators, and livestock feed additives. Farmers tend to rely on crop rotation, crop residues, animal manures, and mechanical cultivation to maintain soil productivity, and to supply plant nutrients and control weeds, insects, and other pests. Organic farming is intended to be indefinitely sustainable.

This type of farming has become well established within Europe and is expanding at a steady rate. More than 10 per cent of farms in Austria, Switzerland, and several other countries use organic methods.

The retail market for organic farming in high-income countries has grown about 20 per cent each year since the early 1990s due to increasing consumer demand. Production and distribution have become correspondingly large scale. The variety and availability of processed organic food has increased dramatically, and the cost — which was initially high — is continuing to fall.

Claims that foods produced by organic methods are biologically or nutritionally superior to food produced by intensive methods are not supported by clinical or epidemiological evidence, but some food compositional data indicates higher concentrations of some constituents like vitamin C and dietary fibre. There is evidence that organic products contain fewer residues from chemicals employed in conventional agriculture. However, the subject remains a matter of controversy.

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estins (IARC group 2B, possible human carcinogens), and also testosterone (IARC group 1, human carcinogens).

The toxicity of antimicrobial drugs is constantly reviewed by international and national regulatory bodies. *The Panel notes* the findings on hormonal anabolic agents and also the lack of epidemiological evidence. Because there is no supporting epidemiological or other evidence, the Panel made no judgements.

4.9.1.3 Genetic modification

Plant breeding is a process of genetic exchange which is often undertaken with the purpose of acquiring traits that are either beneficial to humans or increase yield. More recently, the use of new technologies of genetic modification, intrinsic to agriculture and animal husbandry from their beginnings, has raised great public interest and controversy. Many crops are now genetically modified by means of gene transfer within and between species. Potential uses of modern genetic modification technology in food production include changing nutritional composition (for example, beta-carotene in 'golden rice'); increasing the hardiness of crops; improving pest or disease resistance; and increasing herbicide tolerance in crop plants (to allow the use of generic herbicides).

Not all genetic modifications include transgenes, in which a gene from one species is transferred across species, or even

kingdoms — that is to say, from plants to animals. Some genetic modifications involve only inactivating existing genes. For example, tomatoes have been genetically modified to render inactive the enzyme that softens the tomato once ripe; thus, the tomato remains hard despite being ripe. This is beneficial for transport and storage purposes.

The production and use of transgenic and genetically modified foods for humans or animal consumption are regulated in most but not all countries. The regulations require that all genetically modified foods be of equivalent safety as the food they are replacing, both nutritionally and toxicologically.

Any effect of genetically modified foods on risk of human disease might be a result of changes in the types of chemical pesticides or herbicides used, rather than of genetic modification itself. Genetically modified crops may require less use of pesticides and herbicides.

Any effect of modern methods of genetic modification of foods on the risk of cancer is unknown. Because there is no supporting epidemiological or other evidence, the Panel made no judgements.

There is too little evidence to draw any conclusion about the association between methods of production and risk of cancer.

4.9.2 Preservation

Methods of preserving foods have probably been in use since before recorded history began. Gatherer–hunter and peasant–agricultural food systems (see chapter 1.1) include various techniques to preserve foods, which remain in use, such as drying, underground storage, fermenting, smoking, and salting. A range of other methods of preservation accompanies, and is part of, industrialisation and urbanisation. These include canning, bottling, refrigeration, heat treatment, and irradiation.

Methods of food preservation, where epidemiological evidence shows or suggests an effect on the risk of cancer, are summarised and judged earlier in this chapter. These are refrigeration (box 4.6.4); processing meat ('processed meat' refers to red meats preserved by smoking, curing, or salting, or by the addition of chemicals, see box 4.3.1 in chapter 4.3); preserving fish Cantonese-style (see box 4.3.5 in chapter 4.3); and salting (chapter 4.6).

4.9.2.1 Drying

Drying is an ancient method used to preserve cereals (grains), pulses (legumes), fruits, and other plant foods. It is also used to preserve meat and fish, often as part of another preservation process such as salting (see box 4.3.5 in chapter 4.3). Freeze-drying, where the food is frozen and the water extracted, has been in commercial use since the mid-20th century, and is used to preserve fruits, herbs, meat, fish, milk, eggs, coffee, and other foods.

4.9.2.2 Fermenting

Fermentation is an ancient method used to preserve many foods and drinks. It may originally have been discovered by

accident, because foods ferment as a result of the action of bacteria or moulds (yeasts). Fermentation has special features. It characteristically changes the sensory and nutritional qualities of foods and drinks: for example, bacterial fermentation turns milk into yoghurt and cabbage into kimchi (a staple food in Korea) and sauerkraut. Fermentation by yeasts turns sugar into alcohol, and so is an essential part of the process by which cereals (grains), vegetables, fruits, and other plant foods are the basis for beers, wine, and spirits.

4.9.2.3 Canning, bottling
Bottling and canning were first developed around 1800. The process involves heating or cooking fruits, vegetables, meats, and other foods in containers, then sealing them while still hot. Glass bottles were first used, and then cans.

4.9.2.4 Pasteurisation
Heat can be used to preserve milk and fruit juices by pasteurisation, which kills many micro-organisms. This involves various methods of rapid heating to a specific temperature, maintaining that temperature for a set period of time, followed by rapid cooling.

4.9.2.5 Chemical preservation
Chemical preservative additives are added to perishable processed foods. Antimicrobials inhibit the growth of bacteria and fungi. Antioxidants reduce the rate at which lipids are oxidised through exposure to air, which leads to rancidity. A third type blocks the natural ripening processes that continue to occur in plant foods following harvest. The most commonly used antimicrobial preservatives are benzoates, nitrites (see box 4.3.2 in chapter 4.3), and sulphites. There are internationally specified limits for levels of chemical preservatives in foods and drinks.

4.9.2.6 Irradiation
Irradiation was first patented at the beginning of the 20th century as a means of preserving food using ionising radiation. The process has been tested extensively, but there is considerable public suspicion over the safety of irradiated foods. For example, 2-alkylcyclobutanones, which interact with DNA in laboratory settings, are found exclusively in irradiated foods.

Methods of preservation tend to improve food security and enable more reliable availability of food, but may have adverse effects too. Some methods of food preservation such as drying are almost certainly benign, and others like fermentation may have some beneficial effects. The toxicity of preservatives and preservation methods is constantly reviewed by international and national regulatory bodies. Because experimental data are not supported by epidemiological or other evidence, the Panel made no judgements.

There is too little evidence to draw any conclusion about the association between methods of preservation and risk of cancer.

4.9.3 Processing

Food processing transforms basic ingredients into manufactured foods and drinks. In the broad sense of the word, food production, processing, preservation, and preparation are methods of processing. The term 'processing' here is used to refer to techniques and technologies other than methods of preservation that are used by manufacturers of industrialised processed foods. The processes that take place in kitchens (commercial or domestic) are considered in chapter 4.9.4.

Methods of food processing, where there is evidence that they may affect the risk of cancer, are summarised and judged earlier in this chapter. These are hydrogenation (chapter 4.5); refining (chapters 4.1 and 4.6); and the production of alcohol by fermentation (chapter 4.8).

4.9.3.1 Additives
Many if not most processed foods contain additives. These may be synthetic, 'nature-identical', or natural. As well as preservatives, these include bulking aids, colours, flavours, solvents, and many other categories. For general issues of toxicity in use, see box 4.9.3. Additives mentioned here are some of those where issues of carcinogenicity have arisen (also see box 4.9.4).

Flavours
Alkenylbenzenes are a group of naturally occurring flavours, some of which have been found to cause liver cancer in

Box 4.9.3	Regulation of additives and contaminants

Any chemicals that have a useful function in the production, processing, or preservation of foods or drinks may nevertheless be toxic, and possibly mutagenic or carcinogenic. For this reason, food additives and contaminants, such as traces of chemicals used in industrial agricultural production, are subject to international and national surveillance and regulations.

They are a cause for concern and vigilance because some, and in particular agricultural chemicals, are known to be toxic in experimental settings, though at levels well above those found in foods and drinks.

There is little epidemiological evidence on the possible effects of contaminants and additives as present in foods and drinks.

Because contaminants and additives are subject to international and national regulation, there is a vast amount of toxicological information from experiments on laboratory animals and other settings. Failing any other method, it seems reasonable to observe the effects of food additives and contaminants on laboratory animals at levels greatly in excess of any likely to be present in foods and drinks; and based on several assumptions and judgements, to set limits for safety in use. When such limits are used as regulatory limits, they are also subject to surveillance and special investigation when any chemical present in foods and drinks seems to be a cause for special concern.

This area remains controversial. Theoretically, it would be ideal if food supplies contained no trace of any toxic substance, including those that are or may be mutagenic or carcinogenic. However, some foods in nature contain carcinogens and the issue is not confined to methods of industrial food processing.

Box 4.9.4   Water fluoridation

In the early 1940s, people who lived where drinking water supplies had higher naturally occurring fluoride levels were found to have less dental caries than people who lived in areas with lower naturally occurring fluoride levels. This finding is supported by more recent studies.[5]

Where natural fluoride levels are low, fluoride compounds are sometimes added to water supplies in order to reduce dental caries in the general population.

Most cities in the USA now fluoridate their water supplies; most of Europe does not. The advisability of fluoridation is disputed: fluoride can have adverse effects at doses not much above that recommended for prevention of dental caries, and excess can cause dental fluorosis and bone fragility.

Studies in experimental animals have identified an increased risk of osteosarcomas (bone cancers) when exposed to water containing high concentrations of fluoride. A report published in the USA in 2006 considered all the available evidence on fluoride and osteosarcoma and found the overall evidence to be tentative and mixed, and made no recommendations for revising current available fluoride levels in drinking water.[6] A study published later in 2006 suggested an association between drinking fluoridated water and osteosarcoma in adolescent men.[7] However, preliminary analysis of a second set of cases from the same study does not replicate the findings.[8] The US Centers for Disease Control and Prevention continues to support community water fluoridation as a safe and effective public health measure to prevent and control tooth decay.

These findings are not the basis for any judgement.[9]

rodents at levels vastly higher than normal human dietary intakes.[3]

Colours

About 50 colour compounds are permitted for use in foods.[4] The number varies in different countries. Various azo dyes and other colours found to be carcinogenic in experimental settings have been withdrawn from use.

Those dyes now regulated for use in food are judged by UN and other expert committees not to be carcinogenic in the amounts found in foods and drinks. The xanthene colour erythrosine and ammonia caramel (a class 3 carcinogen, according to IARC) cause cancers in rats given high doses, but are judged to be safe as now used.[10]

Solvents

Around 20 solvents are permitted for food use.[4] Two — dichloromethane and trichloroethylene — once used widely for decaffeinating coffee and tea, have been classified by IARC as possibly and probably carcinogenic to humans, respectively. The Joint FAO/WHO Expert Committee on Food Additives has recommended that use of these solvents should be restricted, and that levels in food should be as low as technologically possible.[10] These solvents are now generally not used for decaffeination.

4.9.3.2 Packaging

Foods and drinks can become contaminated with traces of chemicals that migrate from packaging materials such as plastic wrappings and bottles, and metal cans. Migration from food-contact materials can occur during the processing, storage, and preparation of food. The polymers used in plastic packaging are biologically inert, but their monomers such as vinyl chloride, acrylonitrile, and acrylamide can and do migrate into foods. Plasticisers such as phthalates, used in the manufacture of these polymers, can also migrate into foods and drinks. These are mutagenic or carcinogenic in experimental animals. Nonylphenol and bisphenol-A, used in packaging, mimic the action of oestrogens in the body. Synthetic oestrogens in the diet are not readily excreted and may therefore accumulate in the body.

The potential effects of industrial food-processing methods and of additives and contaminants in foods and drinks on carcinogenicity are constantly reviewed by international and national regulatory bodies. In view of the lack of supporting epidemiological or other evidence, the Panel made no judgements. There is too little evidence to draw any conclusion about the association between methods of preservation and risk of cancer.

4.9.4 Preparation

'Preparation' here means domestic cooking or the cooking done in industrial kitchens, by caterers for indirect or direct sale.

Methods of food preparation, where epidemiological evidence shows or suggests an effect on the risk of cancer, are summarised and judged earlier in this chapter. These are grilling (broiling) and barbecuing (charbroiling) animal foods (chapter 4.3), and carcinogenic compounds generated by cooking these foods in a flame or at very high temperatures (see box 4.3.4 in chapter 4.3), and 'fast foods' (Chapter 8).

4.9.4.1 Industrial cooking

Ready-to-heat and ready-to-eat dishes sold in supermarkets and other retail outlets are a massively increasing market. Like 'fast foods' sold for immediate consumption, these are usually energy dense (see Chapter 8). Intense and prolonged industrial cooking of starch-based foods such as crisps (chips), French fries (chips), and other snack foods, generates acrylamides, classified by IARC as 'probably carcinogenic to humans'. At the time when this Report was completed, acrylamides were the subject of special surveillance and study.

4.9.4.2 Steaming, boiling, stewing

These are methods of cooking at up to 100°C. Some labile water-soluble vitamins are destroyed or lost in this process.

4.9.4.3 Baking, roasting

These are methods of cooking at up to 200°C, but not on a direct flame. During baking, the high temperatures are usually reached only on the surface of the food, while the inner parts often remain below 100°C. Traditional forms of roasting usually involve basting foods with oils or fats.

4.9.4.4 Microwaving

Microwaving exposes food to temperatures up to 200°C. Microwaves are a form of electromagnetic radiation. They cause vibration of water molecules, which produces heat. There is no evidence that microwaves have any specific effect on food composition beyond that of heat.

4.9.4.5 Frying, grilling (broiling), barbecuing (charbroiling)

Also see box 4.3.4 in chapter 4.3. Frying, grilling (broiling), and barbecuing (charbroiling) generate temperatures of up to 400°C, and sometimes use a direct flame to cook food. These methods create high levels of carcinogenic compounds. For any cooking involving wood fires, the type of wood used can also be an important factor in determining which chemicals contaminate the food. Hardwoods such as oak and hickory burn cleanly; others such as mesquite generate copious quantities of polycyclic aromatic hydrocarbons.

Because of the experimental evidence of carcinogen production, it is prudent not to consume burned or charred foods frequently or in large amounts. Industrial food preparation methods are regulated. Because there is no supporting epidemiological or other evidence, the Panel made no judgements.

There is too little evidence to draw any conclusion about the association between methods of preparation and risk of cancer.

4.9.5 Interpretation of the evidence

4.9.5.1 General

For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7.

Aspects of food production, preservation, processing, and preparation (including cooking), where epidemiological evidence enables judgements to be made, are summarised, with Panel judgements, in previous sections of this chapter.

4.9.5.2 Specific

Measurement. It is practically impossible to measure small amounts of additives and trace amounts of contaminants in foods and drinks except by analysis. Epidemiological studies using usual methods of dietary assessment are therefore generally uninformative.

Terminology. The terms used for different types of cooking vary around the world. 'Broiling' in the USA is called 'grilling' in other countries. 'Barbecuing' may mean grilling in flame or slow cooking near smoking embers. Results of studies in these areas need to be interpreted with care, given that carcinogenic compounds are particularly generated when meat and other animal and plant foods are cooked in a flame, and even more so when they are burned or charred.

Study design. Practically all studies of the topics covered in this section are laboratory experiments on animals. They are commonly carried out to assess toxicity to determine safety in use, as a basis for food safety regulations. The relevance of such work to the actual levels consumed of substances identified in this section is obscure. Also, it is commonly agreed, as in this Report, that information from animal and other experimental settings, which is unsupported by evidence from epidemiological studies, is not a sound basis for firm judgements.

Confounding. Studies commonly report the difficulty in separating out specific methods of processing or cooking, when foods are characteristically processed and prepared in a number of different ways.

4.9.6 Evidence and judgements

The Panel decided to make no judgements on experimental findings of toxicity that are not supported by epidemiological or other evidence.

The evidence considered by the Panel is in the systematic literature review (SLR). Because the Panel made no judgement on the isolated experimental data, this evidence is not summarised separately here.

The full SLR is contained on the CD included with this Report.

4.9.7 Comparison with previous report

In general, the previous report found that information from animal and other experimental settings unsupported by epidemiological evidence, was not a basis for judgement. In this respect, the view of the Panel responsible for this Report is similar. The findings of the previous report on food additives, microbial contaminants, salt and salted foods, salted fish (Cantonese-style), cured meats, and the grilling and barbecuing of meat, fish, and other foods, were all contained in a chapter on food processing. The previous panel's judgements were mostly similar to those made here, with the important exception of processed meat, which was not considered separately from smoked and cured meats by the previous report. The judgements of this Report on these subjects are made in previous sections of this chapter.

4.9.8 Conclusions

The Panel concludes:
The Panel decided to make no judgements on isolated experimental findings that were not supported by epidemiological or other evidence.

It is not possible to make any definitive judgement in the absence of epidemiological evidence. Nevertheless, *the Panel concurs* that, in general, it seems reasonable to conclude that the changes made to foods and drinks within well regulated, modern food systems, and those made to foods and drinks as usually prepared and cooked, are of themselves unlikely to modify the risk of cancer significantly.

There are important exceptions to this tentative conclusion

and in these cases, the Panel's judgements and conclusions are found in the relevant earlier sections of this chapter. These judgements and conclusions are made in those sections wherever epidemiological and other evidence justifies a judgement of a protective or causative effect, using the agreed criteria, for aspects of food production (including contamination), processing, preservation, and preparation (including cooking).

4.10 Dietary constituents and supplements

DIETARY CONSTITUENTS AND SUPPLEMENTS, AND THE RISK OF CANCER

In the judgement of the Panel, the factors listed below modify the risk of cancer. Judgements are graded according to the strength of the evidence.

	DECREASES RISK		INCREASES RISK	
	Exposure	**Cancer site**	**Exposure**	**Cancer site**
Convincing			**Beta-carotene supplements**[1]	**Lung**
Probable	**Calcium**[2] **Selenium**[3]	**Colorectum** **Prostate**		
Limited — suggestive	Retinol[4] Alpha-tocopherol[2] Selenium[3]	Skin[5] Prostate Lung[3] Colorectum[6]	Retinol supplements[1] Selenium supplements[2]	Lung Skin
Substantial effect on risk unlikely	Beta-carotene[7]: prostate; skin (non-melanoma)			

1 The evidence is derived from studies using high-dose supplements (20 mg/day for beta-carotene; 25 000 international units/day for retinol) in smokers.
2 The evidence is derived from studies using supplements at a dose of 200 µg/day.
3 The evidence is derived from studies using supplements at 200 µg/day. Selenium is toxic at high doses.
4 The evidence is derived from studies using supplements at a dose of 25 000 international units/day.
5 Applies only to squamous cell carcinoma.
6 The evidence is derived from studies using supplements at a dose of 200 µg/day. Selenium is toxic at high doses.
7 The evidence is derived from studies using supplements (at doses of 20, 30, 50 mg for prostate, and doses of 30, 50 mg/day for skin), and foods containing beta-carotene: see chapter 4.2.

For an explanation of all the terms used in the matrix, please see chapter 3.5.1, the text of this section, and the glossary.

Nutritional science conventionally divides foods and drinks into their chemical constituent parts, such as water, carbohydrates, fats, proteins, vitamins, and minerals. Their biological functions are then explored, singly or in combination. It is now increasingly agreed by the nutrition science community that research and also public health can additionally benefit from a more integrated approach, in which the emphasis is placed on foods and drinks. In this Report, the evidence, its summaries, and the Panel's judgements are food-based, wherever possible.

Here, the evidence on macronutrients, micronutrients (isolated in the form of supplements), and bioactive constituents of plant foods (also known as phytochemicals) is summarised and judged.

Overall, *the Panel judges* that the evidence that dietary macronutrients specifically affect the risk of cancer is unimpressive. The evidence, based on observational data and randomised controlled trials of supplements, that certain vitamins and minerals affect the risk of specific cancers is, in some cases, impressive.

The Panel judges as follows:
The evidence that high-dose beta-carotene supplements are a cause of lung cancer in tobacco smokers is convincing. There is limited evidence suggesting that high-dose retinol supplements are a cause of lung cancer in tobacco smokers.

Calcium probably protects against colorectal cancer. At specific doses, selenium probably protects against prostate cancer.

It is unlikely that beta-carotene has a substantial effect on the risk of either prostate cancer or non-melanoma skin cancer.

There is limited evidence suggesting that retinol at specific doses protects against squamous cell carcinoma of the skin. There is also limited evidence suggesting that alpha-tocopherol protects against prostate cancer, and that selenium at specific doses protects against colorectal and lung cancer. There is limited evidence suggesting that selenium supplements are a cause of skin cancer.

Within the remit of this Report, the strongest evidence,

corresponding to judgements of 'convincing' or 'probable', shows that high-dose beta-carotene supplements in tobacco smokers are a cause of lung cancer; that calcium probably protects against colorectal cancer; and that selenium probably protects against prostate cancer. It is unlikely that beta-carotene, or foods containing it, have a substantial effect on the risk of either prostate or skin (non-melanoma) cancer. *The Panel emphasises* **that this evidence and these judgements relate to these micronutrients only at the specified doses.**

Nutrition science in its conventional form as a biological discipline was created in the early 19th century following the identification of carbohydrates, fats, and proteins. As nutrients, these all supply energy and are essential for tissue structure and function, and physical and mental growth and development. Later research has divided these macronutrients into many constituent parts such as monosaccharides and polysaccharides (including non-starch polysaccharides or 'dietary fibre'); saturated and unsaturated fatty acids (which themselves have many fractions); and amino acids. Many of these constituents of the main nutrients are known to have different metabolic, physiological, biochemical, and other effects, in isolation or combination.

Beginning in the early 20th century, a series of substances that do not supply energy were identified also as being vital to life, typically in very small amounts: these are vitamins, minerals, and trace elements. More recently a large number of other substances that are not nutrients, in the sense of being essential components of metabolic processes or cell structure, have been identified as bioactive. Because these are contained in plants, they are commonly known as phytochemicals.

Reports concerned with specifying recommended dietary (or daily) amounts or reference values for nutrients, by their nature, are structured accordingly. Compilations of the chemical composition of foods, used as standard references in epidemiological studies of food, nutrition, and the risk of diseases including cancer, also specify macro- and micro-constituents of foods and drinks, to varied degrees of completeness and accuracy.

Reports concerned with nutritional deficiencies characteristically make recommendations for the relevant micro-constituents. Increasingly though, they often now make recommendations for dietary patterns, diets, and foods and drinks that are high in the microconstituents with which they are concerned. So a report on vitamin A deficiency may specify foods high in carotenoids and retinol, and may also recommend methods of agriculture that emphasise such foods. Reports concerned with prevention of chronic diseases were initially structured in terms of dietary constituents, with only secondary reference to foods. But following a general international agreement that food-based dietary guidelines are more useful, and often better reflect the science, such reports now give more emphasis to foods and drinks, both in their analysis of evidence and in their recommendations.

The policy of this Report is to always emphasise foods and drinks. Thus, earlier sections of this chapter include sum-

maries and judgements of the evidence on dietary fibre, vitamins, minerals, and trace elements as contained in foods, and also on fats, oils, sugars, salt, and alcohol as foods. Also see chapters 4.1 to 4.8. This section is concerned with macronutrients and micronutrients as such, and with non-nutrient bioactive constituents of food (phytochemicals).

4.10.1 Macronutrients

Chemically, macronutrients are classified as carbohydrates, fats, and proteins, and these categories have many sub-classifications. Diets need to include adequate amounts of macronutrients for physical and mental growth and development, and for maintenance of normal tissue structure and function. All macronutrients supply energy. Alcohol also supplies energy, but there is no requirement for it. Also see chapter 4.8.

4.10.1.1 Carbohydrates
Carbohydrates consist of monosaccharide sugars, or larger molecules of these units joined together: disaccharides (two units), oligosaccharides (a few), or polymers (many). For instance, glucose is a monosaccharide and starch is a polymer of glucose units. Polysaccharides are sometimes called 'complex' carbohydrates and sugars 'simple' carbohydrates.

Carbohydrates are generally the largest single source of energy in diets. They supply around 4 kilocalories per gram. They form part of important structural components in the body and, in the form of glucose, are the principal and preferred energy source for metabolism. They also play major roles in several essential cellular and physiological processes. Non-starch polysaccharides are the characterising feature of dietary fibre.

Glycaemic index and glycaemic load are terms used to characterise foods and diets based on their effects on blood glucose levels. Also see box 4.1.3 in chapter 4.1.

Cereals (grains) and products made from them (such as breads, pastas, and breakfast cereals), as well as starchy roots and tubers, are all high in carbohydrates. These foods contain a mixture of complex and simple carbohydrates and other nutrients. Until recently, starches have been the main source of carbohydrate in human diets. With industrialisation and urbanisation, sugars have been added in increasing quantities in food preparation and as an ingredient in processed foods. Diets consumed in some high-income countries now may contain roughly as much carbohydrate in the form of sugars as they do starches. Diets high in complex carbohydrates are usually associated with lower prevalence of obesity, heart disease, and type 2 diabetes.

For summaries and judgements on dietary fibre, see chapter 4.1. For summaries and judgements on sugars, see chapter 4.6. For food processing, see chapter 4.9.

4.10.1.2 Fat
Fats in diets are mostly made up from triglycerides — three fatty acid molecules attached to a glycerol backbone. Triglycerides are lipids, a class of organic compounds characterised by their solubility in organic solvents (such as ether

and chloroform); they are usually insoluble in water. The body stores excess energy as lipids in the form of body fat (also known as adipose tissue). Lipids also form part of the structural components of cellular membranes as well as being precursors of important hormones.

Dietary fats include solid fats and liquid oils. Their physical form at a particular temperature is determined by the chemical structure of their constituent fatty acids. Fats with a high proportion of 'saturated' fatty acids are solid or semi-solid at ambient temperatures; those with a higher amount of 'unsaturated' fatty acids are more likely to be oils. The different degrees of saturation produce various effects in the body. Diets high in saturated fatty acids (and also *trans*-fatty acids) (see chapter 4.5 and box 4.5.1) increase circulating blood concentrations of cholesterol and the risk of cardiovascular disease. The World Health Organization recommends limiting total fat to between 15 and 30 per cent of total daily energy intake and saturated fatty acids to less than 10 per cent.[1]

Fats are the most concentrated energy source, supplying around 9 kcal per gram. They also carry the fat-soluble vitamins (see chapter 4.10.2.1). The body can make all but two of the fatty acids it needs — linoleic acid and alpha-linolenic acid, known as the 'essential' fatty acids. Both are found in vegetables, nuts, and seeds and their oils, in varying quantities. They are also found in meat, eggs, and dairy products, but at lower levels. The long-chain fatty acids found in oily fish (eicosapentaenoic and docosahexaenoic acids) can be made to a limited extent in the body, where they play a role in inflammation.[2] These and related fatty acids are precursors to prostaglandins; these hormone-like compounds have other diverse effects, including roles in blood vessel dilation and constriction, blood clotting, and transmission of nerve impulses.

Nuts, seeds, meat, oily fish, whole milk and dairy products, cooking oils and fats, spreadable fats, and a wide range of manufactured foods all contain varying amounts and types of fats. Those from animal sources usually have a higher proportion of saturated fatty acids, and these are common in processed foods.

For summaries and judgements on fats and oils as foods, see chapter 4.5. For summaries and judgements on foods that are or may be high in fats, see chapters 4.3 and 4.4.

4.10.1.3 Proteins

Proteins are large organic molecules made up of amino acids arranged in a chain. Short chains are called peptides, for instance di- and tripeptides (made up of two and three amino acids respectively). Longer chains are known as oligopeptides, and long chains as polypeptides. Proteins are fundamental structural and functional elements within every cell in the body.

Many proteins are enzymes that catalyse biochemical reactions and are vital to metabolism. Others have structural or mechanical functions, such as the proteins in the cytoskeleton, which give cells their shape and strength. They are also important in cell signalling, immune responses, cell adhesion, and the cell cycle.

Proteins supply around 4 kcal per gram. They are digest-ed into their constituent amino acids, which are then absorbed into the blood. The body has the ability to make some amino acids, but others, so called essential amino acids, must be obtained from foods and drinks.

Dietary sources of protein include meats, milk and cheese, pulses (legumes), nuts, and cereals (grains) and products made from them, such as breads. Animal proteins from eggs, milk, and meat contain all the essential amino acids in the proportions needed by humans; soya protein is the only plant food to do so. Other plant protein sources have differing proportions of various essential amino acids, so diets without animal foods or soya need to include a variety of plant protein sources to provide enough of the essential amino acids.

For summaries and judgements on foods that contain proteins, see chapters 4.1, 4.2, 4.3, and 4.4.

4.10.2 Micronutrients

Micronutrients are essential constituents of diets needed in small quantities compared with macronutrients, and are not sources of energy. These are vitamins, minerals, and trace elements. Deficiency of any dietary constituents classified as a micronutrient causes debility, disease, and eventually death.

Many processed foods are 'fortified' with synthetic vitamins and minerals (box 4.10.1). Others contain various microconstituents such as phytochemicals, and sometimes other ingredients such as bacteria and 'prebiotic' polysaccharides; these products are sometimes termed 'functional foods' (box 4.10.2). Both types of product are often marketed with health claims relating to these added constituents or to the whole food.

4.10.2.1 Vitamins

Vitamins are organic molecules, classed as fat- or water-soluble, that are needed for metabolism but cannot be made in the body and so must be supplied in the diet. They have different specific functions in the body. For example, vitamin K is needed for blood clotting and vitamin C for the production of collagen in connective tissue.

Vitamins A (retinol), D, E, and K are fat-soluble and can only be digested, absorbed, and transported in conjunction with dietary fats. So they are found mainly in fatty foods such as liver and oily fish, milk and dairy products, animal fats (such as butter), and vegetable oils. The main sources of vitamin A are plant foods containing the retinol precursors known as carotenoids, which are converted by the body to retinol (see box 4.2.1 in chapter 4.2). Preformed retinol, which is absorbed better than carotenes in plant foods, is found only in animal products, of which liver is a particularly rich source. Fat-soluble vitamins are stored in the liver and in body fat stores. For this reason, they do not need to be consumed every day. For the same reason, some are toxic in high doses.

Vitamin C and the B vitamins are water-soluble. The B group includes thiamin (vitamin B1), riboflavin (B2), niacin (B3), pyridoxine (vitamin B6), biotin, pantothenic acid,

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Box 4.10.1 Food fortification

Food 'fortification' refers to the addition of nutrients, often in synthetic form, to foods, so that the food contains more of the nutrients added. The term 'enrichment' is sometimes also used.

The United Nations and other international organisations are responsible for major food fortification programmes, designed in particular to reduce rates of deficiency of vitamin A, iodine, iron, and other nutrients, mostly within low-income countries. But common foods have been fortified in many countries since the early 20th century. For example, in some countries margarine and other fat spreads, or milk, have been fortified with vitamins A and D. White flour, and therefore white bread and other products made from it, is commonly fortified with some B vitamins, and also sometimes with calcium and iron.

The term 'fortification' in these and other examples may refer to the partial replacement of nutrients otherwise absent or depleted by food-processing methods. Or it may refer to the addition of nutrients to levels not found in the food in whole form; for example, the addition of calcium to white bread in the UK is to levels higher than those found in wholegrain breads; and salt may not contain iodine.

Many common processed foods and drinks, including some that would otherwise be low in nutrients, are now fortified with various combinations of synthetic nutrients. These include breakfast cereals, biscuits (cookies) and other baked goods, dried milk, milk-based products, and soft drinks, and even confectionery. Many such products are designed to be consumed by children.

In an increasing number of countries, the nutrients consumed in fortified foods and drinks amount to a substantial and growing proportion of total consumption of these nutrients. For example, since 1998 in the USA, grain has been fortified with folic acid, the synthetic equivalent of folate, as a public health measure designed to reduce the incidence of neural tube defects in the fetus. As a result, it is estimated that over one third of all intake of this nutrient in the USA comes from this source, as well as from fortified breakfast cereals.[3]

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folate, and cobalamin (vitamin B12). Excess amounts of water-soluble vitamins are generally not toxic because they are excreted in the urine rather than stored in the body. This also means that they generally have to be consumed more frequently than fat-soluble vitamins. Plant foods are important sources of water-soluble vitamins: for example, cereals (grains), vegetables, fruits, some roots and tubers, and pulses (legumes). They can be destroyed by heat or exposure to the air, or lost by leaching during cooking, for instance when vegetables are boiled (see chapter 4.9.4).

4.10.2.2 Minerals, trace elements

Minerals are inorganic substances. Most foods contain significant amounts of one or more minerals, and these compounds have many specific functions in the body. Some are essential components of enzymes and other proteins (as 'cofactors', such as iron). They are also involved in maintaining normal cell function (sodium, potassium, calcium), and for structure (calcium in bones and teeth). Others include magnesium, phosphorus, and sulphur.

Trace elements are minerals needed by the body in very small amounts. Whether a mineral is defined as a trace element is somewhat arbitrary: iron, zinc, and copper are minerals that may or may not be identified as trace elements. Others include iodine, selenium, chromium, fluoride, boron, cobalt, manganese, molybdenum, and silicon.

4.10.3 Phytochemicals

Phytochemicals are bioactive constituents of plant foods not identified as nutrients because they are not essential in the sense of being vital to life itself. Unlike vitamins and minerals, people do not suffer diseases when their diets are low in phytochemicals. However, consuming them may have beneficial effects on health or active roles in the prevention of diseases. Also see box 4.2.2 in chapter 4.2.

Box 4.10.2 Functional foods

Functional foods are so-called because they are believed or claimed to have special qualities, such as promoting well-being or protecting against disease. What marks them out from 'normal' foods is that they are specifically formulated, manufactured, and marketed as being 'functional' in specified ways, for which claims are made. Some fortified products, such as breakfast cereals and yoghurts, are positioned as functional foods.

The ingredients in functional foods claimed to have special qualities may be added fractions of macronutrients, such as amino acids or fatty acids, or vitamins, minerals, or trace elements. Very often the 'functional' ingredients will be known or claimed to be bioactive in other ways: these include phytochemicals, herbal extracts, and commensal bacteria.

Various phytochemicals have been shown to have antioxidant, anti-carcinogenic, anti-inflammatory, immunomodulatory, and antimicrobial effects in laboratory experiments. But it is not yet clear whether consuming these compounds produces these or other effects in the body.

Phytochemicals have various chemical structures and are grouped into families on this basis. They include flavonoids, isoflavones (phytoestrogens), glucosinolates, terpenes, organosulphur compounds, saponins, capsaicinoids, and phytosterols. Many vegetables, fruits, pulses (legumes), herbs, and teas are high in phytochemicals.

4.10.4 Supplements

Vitamins, minerals, trace elements, and other bioactive substances are available as supplements, usually in pill or powder form. These began to be manufactured and marketed after their functions were identified, and claims made for their general benefits in prevention of disease and promotion of well-being.

Many dietary supplements are classed as foods, although

Levels of supplementation

The effects of bioactive substances vary with the quantities consumed. The amounts of nutrients and other substances in diets depend on the nature and quantity of the foods and drinks that taken together make up diets.

The amounts of nutrients and other substances contained in dietary supplements, in this context usually referred to as doses, may or may not be at levels that can be found in diets. Lower amounts, at levels about the same as those that can be found in diets, are known as 'physiological doses'. Higher amounts, at levels above any that can be found in diets, are known as 'pharmacological doses', or sometimes as 'mega-doses'.

Evidence from trials and studies using supplements are often difficult to compare. One reason for this is that both human and animal studies use supplements in different combinations and concentrations. A nutrient that has one effect at a relatively low or physiological dose may have a different effect at a higher or pharmacological dose. For instance, a nutrient that may evidently be protective at a lower or physiological dose may be toxic or pathogenic at a higher dose.

Randomised controlled trials using various doses of micronutrients have produced evidence of the effects of these supplements in modification of the risk of cancers of some sites. This evidence is summarised and judged in chapter 4.10.6.

some may be regulated medicinal products. Manufacturers of food supplements may market their products using health claims, although in some countries such as the UK, medicinal claims that the product can prevent, cure, or treat a disease may not be made. Herbal products may be permitted to make certain claims based on their history of being used for a particular condition. The regulatory status of dietary supplements varies from country to country.

Some nutrients such as water-soluble vitamins have been thought to be harmless at pharmacological doses; but there is now evidence, including some summarised and judged in this Report, that this is not always the case. Other nutrients, including fat-soluble vitamins and all minerals and trace elements, are known to be toxic at pharmacological doses; some of these, selenium being one example, are known to be toxic at relatively low pharmacological levels (also see box 4.10.3).

Expert reports issued by United Nations agencies and national governments specify levels of nutrients agreed to protect against deficiency diseases, and also (sometimes) agreed to be safe in use.

Many people take dietary supplements. Their use is higher in high-income countries. In the UK, 35 per cent of respondents reported taking dietary supplements. Around 50 per cent of people in the USA take supplements in some form.

4.10.5 Interpretation of the evidence

4.10.5.1 General
For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7.

'Relative risk' (RR) is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.10.5.2 Specific
These specific points apply only to trials using micronutrient supplements.

Measurement. The results of supplement trials can be assumed only to apply to levels and forms of the micronutrient present in the supplement.

Study design. Randomised controlled trials (RCTs) using nutrient supplements provide strong evidence. But the evidence can only be taken to apply to supplements at the doses and in the form given, under the specific experimental conditions. The doses used in trials are often pharmacological, in which case they cannot be taken as directly relevant to the nutrients as contained in foods and diets. Supplements in synthetic forms are sometimes but not always chemically identical to the nutrient as found in food, and so may have different biochemical effects. This may also be because of the level of the dose, because the nutrient is given in isolation or separated from the nutritional matrix as found in foods, or for other reasons.

Confounding. In trials using supplements given in combinations, it is not possible to attribute any effect to an individual nutrient.

4.10.6 Evidence and judgements

The full systematic literature review (SLR) is contained on the CD included with this Report.

4.10.6.1 Carbohydrates
For the evidence on foods containing carbohydrate, including dietary fibre, see chapter 4.1. For the evidence on sugars as a food, see chapter 4.6.

4.10.6.2 Fats
For the evidence on foods containing substantial amounts of fats and oils, see chapters 4.3 and 4.4. For the evidence on fats and oils as foods, see chapter 4.5.

4.10.6.3 Proteins
The evidence from the SLRs did not suggest that proteins specifically modify the risk of cancers of any sites. For the evidence on foods containing protein, see chapters 4.1, 4.3, and 4.4.

4.10.6.4 Vitamin supplements
The evidence presented here is derived from studies of vitamins and beta-carotene (a vitamin A precursor) in supplement form only. Microconstituents in supplement form may have very different effects according to form, dosage, combination with other nutrients, interaction with diets as a whole, and other factors.

4.10.6.4.1 Retinol
Skin

Two RCTs investigated retinol supplements and skin cancer (table 4.10.1).[4][5]

Both trials included only participants at risk of developing non-melanoma skin cancer. The retinoid skin cancer prevention (actinic keratoses) trial (SKICAP-AK) included people with a history of precancerous lesions (actinin keratoses); the retinoid skin cancer prevention (squamous cell carcinoma/basal cell carcinoma) trial (SKICAP-S/B) included people with a history of non-melanoma skin cancer. SKICAP-AK showed non-significant increased risk for basal cell carcinoma, with an effect estimate of 1.14 (95% confidence interval (CI) 0.91–1.43), but it did show a statistically significant decreased risk for squamous cell carcinoma 0.68 (95% CI 0.51–0.92), comparing intervention to placebo.[5] SKICAP-S/B produced no evidence of effect for either basal cell carcinoma (106 cases intervention group: 110 cases placebo group) or squamous cell carcinoma (41 cases each in intervention and placebo group).[4]

Meta-analysis was possible on both trials, giving summary effect estimates of 1.10 (95% CI 0.90–1.34) for basal cell carcinoma and 0.93 (95% CI 0.70–1.23) for squamous cell carcinoma.

The mechanism of anti-tumour action of the retinoids is not completely known but retinol is known to bind to cell receptors with promotion of differentiation, alteration of membranes, and immunological adjuvant effects.[6]

The evidence is sparse and studies were conducted on a narrowly defined population group (people at risk of developing skin cancer). There is limited evidence suggesting that retinol supplements protect against squamous cell skin cancer.

The Panel is aware that since the conclusion of the SLR, one case-control study[7] has been published. This new information does not change the Panel judgement (see box 3.8).

Lung

Two trials (one an RCT, the other a non-randomised trial),[8-11] two cohort studies,[12][13] and two case-control studies[14][15] investigated retinol or vitamin A supplements and lung cancer (table 4.10.2).

The single RCT was the Beta-Carotene and Retinol Efficacy Trial (CARET) trial (table 4.10.2) among current and former smokers (some of whom were asbestos workers) who were given retinyl palmitate and beta-carotene, or placebo. It showed statistically significant increased risk of all lung cancers in the treated subjects, with an effect estimate of 1.28 (95% CI 1.04–1.57). The risk of death from lung cancers was 1.46 (95% CI 1.07–2.00).[9] The risk was especially elevated in those who had the intervention as well as exposure to either asbestos or heavy smoking, although neither subgroup analysis was statistically significant. At follow-up (5 years after trial termination), the effect was reduced and no longer statistically significant, with an effect estimate of 1.12 (95% CI 0.97–1.31).[8]

The other trial, which was not randomised, gave retinol or beta-carotene to asbestos-exposed people and used a matched comparison group, giving an adjusted effect estimate of 0.67 (95% CI 0.33–1.37).[11]

One cohort study was stratified according to smoking status (current, former, and never).[12] In current smokers, high-dose vitamin A supplements (synthetic beta-carotene or retinol) were associated with an increased risk, with an effect estimate of 3.42 (with no CI or value for trend reported), when compared to no supplements. Men who never smoked showed a non-significant decreased risk.[12] The other cohort study showed no effect on risk for men and non-significant decreased risk in women. Effect estimates were 1.0 (95% CI 0.66–1.51) for men and 0.65 (95% CI 0.39–1.06) for women, when comparing supplement use to non-use.[13] One case-control study showed a non-significant increased risk with supplement use,[14] the other showed no effect on risk.[15]

It is possible that the potential protective associations present at dietary intake amounts of vitamins are lost or reversed by pharmacological supplementation and the higher levels that this may supply.

The evidence is sparse and inconsistent. There is limited evidence suggesting that high-dose retinol

Table 4.10.1	Retinol supplements and skin cancer; trials			
Trial name	Number of participants	Intervention	Length of intervention	Length of follow-up
SKICAP-AK Moon 1997	2297 with moderate risk of skin cancer	25000 IU retinol or placebo daily	5 years	3.8 years
SKICAP-S/B Levine 1997	525 with high risk of skin cancer	25000 IU retinol, 5–10 mg isotretinoin or placebo daily	3 years	3 years

Table 4.10.2	Vitamin A supplements and lung cancer; trials			
Trial name	Number of participants	Intervention	Length of intervention	Length of follow-up
Beta-Carotene and Retinol Efficacy Trial (CARET) Goodman 2004 Omenn 1996	18 314 at high risk of developing lung cancer	30 mg beta-carotene and 25 000 IU retinyl palmitate	4 years (trial ended early)	5 years
Western Perth asbestos workers Musk 1998	1203 participants, 996 comparison subjects	Annual supplies of vitamin A (either synthetic beta-carotene or retinol), help in quitting smoking, and dietary advice	Maximum of 4 years	–

supplements are a cause of lung cancer in current smokers.

4.10.6.4.2 Beta-carotene

Lung

Five RCTs[8-10 16-20] and one cohort study[21] investigated beta-carotene supplements and lung cancer (table 4.10.3).

Four studies showed increased risk with a beta-carotene intervention,[16 17 19 20] which was statistically significant in two (during the trial, not at follow-up; smokers).[8-10 16 17] One study showed a non-significant decreased risk.[18] Meta-analysis was possible on three trials, giving a summary effect estimate of 1.10 (95% CI 0.89–1.36) for beta-carotene supplementation versus none, with moderate heterogeneity (figure 4.10.1). Two trials could not be included in the meta-analysis. One trial reported an effect estimate of 1.50 (95% CI 0.43–5.28) for those taking beta-carotene compared to those taking retinol from a total of 10 lung cancers in all participants.[20] The other RCT was the CARET trial (table 4.10.3) among current and former smokers (some of whom were asbestos workers) who were given retinyl palmitate and beta-carotene, or placebo. It showed statistically significant increased risk of all lung cancers in the treated subjects, with an effect estimate of 1.28 (95% CI 1.04–1.57). The risk of death from lung cancers was 1.46 (95% CI 1.07–2.00).[9] The risk was especially elevated in those who had the intervention as well as exposure to either asbestos or heavy smoking, although neither subgroup analysis was statistically

Figure 4.10.1 Beta-carotene supplements and lung cancer; trials

Relative risk (95% CI)

	Relative risk (95% CI)
Virtamo 2003 (ATBC) Men	1.17 (1.02–1.34)
Cook 2000 (PHS) Men	0.90 (0.68–1.18)
Lee 1999 (Women's Health Study)	1.43 (0.83–2.48)
Summary estimate	1.10 (0.89–1.36)

Relative risk, intervention group vs control group
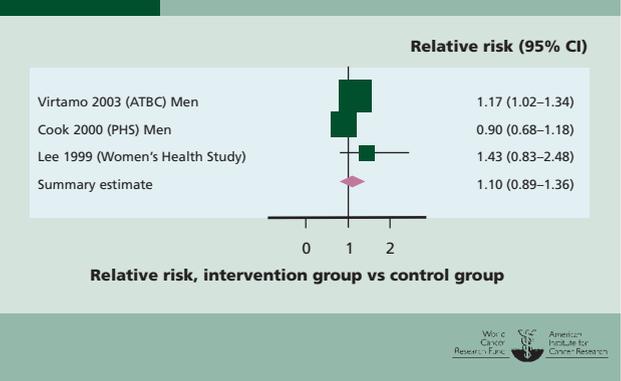
significant. At follow-up (five years after trial termination), the effect was reduced and no longer statistically significant, with an effect estimate of 1.12 (95% CI 0.97–1.31).[8]

One cohort study showed non-significant increased risk for beta-carotene supplementation compared to none in women. The other study showed non-significant decreased risk in men. Effect estimates were 1.23 (95% CI 0.55–2.76; women) and 0.82 (95% CI 0.36–1.85; men).[21]

There is a marked interaction between beta-carotene, heavy smoking and genotype.[22 23] When beta-carotene supplementation among those without the glutathione-S-transferase variant GSTM1 who smoked more than 42 cigarettes per day was compared to beta-carotene supplementation among those without GSTM1 who smoked less than 37 cigarettes per day, a RR of 6.01 (95% CI 1.90–19.08) was observed.[22] After adjusting for age and smoking habits, an RR of 3 (95% CI 1.3–7.1) was observed for the Arg/Arg genotype when 545 μg/l of serum beta-carotene was compared to 45 μg g/l.[23] Glutathione-S transferase 1 and 2 are carcinogen-detoxifying enzymes. People without or with less active forms of these enzymes, due to genetic variation, are less able to metabolise toxins than others and have higher risk of cancer, particularly if they are smokers or exposed to regular doses of toxins through another source.

It is possible that the protective association present at dietary intake amounts of carotenoids is lost or reversed by pharmacological supplementation and the higher levels that this may supply. In one animal study, low-dose beta-carotene was protective against smoking-induced changes in p53, while high doses promoted these changes.[24] A second explanation could be the complex nature of naturally occurring carotenoids and the possibility that the protective associations are not due to the specific agent used in supplement studies, but rather to other carotenoids present in dietary exposure[25] or other associated dietary or health related behaviours.

> There is strong evidence from good quality trials, consistent with cohort studies. An interaction between smoking, genetics, and beta-carotene is apparent. The evidence that beta-carotene supplements cause lung cancer in current smokers is convincing.

Table 4.10.3 Beta-carotene supplements and lung cancer; trials

Trial name	Number of participants	Intervention	Length of intervention	Length of follow-up
Physicians' Health Study (PHS) Cook 2000	22 071	50 mg beta-carotene taken on alternate days	13 years	–
Women's Health Study (WHS) Lee 1999	39 876	50 mg of beta-carotene taken on alternate days	2 years	4 years
ATBC study (male smokers) Virtamo 2003 Albanes 1996	29 133	20 mg of beta-carotene only or with 50 mg of alpha-tocopherol	5–8 years	6–8 years
Western Perth asbestos workers de Klerk 1998	1024	30 mg/day beta-carotene or 25 000 IU/day retinol	Up to 5 years	–
Beta-Carotene and Retinol Efficacy Trial (CARET) Goodman 2004 Omenn 1996	18 314 at high risk of developing lung cancer	30 mg beta-carotene and 25 000 IU retinyl palmitate	4 years (trial ended early)	5 years

Table 4.10.4	Beta-carotene supplements and prostate cancer; trials			
Trial name	Number of participants	Intervention	Length of intervention	Length of follow-up
Beta-Carotene and Retinol Efficacy Trial (CARET) Omenn 1996 Goodman 2004	18 314 at high risk of developing lung cancer	30 mg beta-carotene and 25 000 IU retinyl palmitate	4 years (trial ended early)	5 years
Physicians' Health Study (PHS) Cook 2000	22 071	50 mg beta-carotene taken on alternate days	13 years	–
ATBC Study (male smokers) Virtamo 2003 Heinonen 1998	29 133	20 mg of beta-carotene only or with 50 mg of alpha-tocopherol	5–8 years	6–8 years

Table 4.10.5	Beta-carotene supplements and skin cancer; trials			
Trial name	Number of participants	Intervention	Length of intervention	Length of follow-up
Nambour Skin Cancer Prevention Trial Green 1999	1621	Four treatment groups: daily application of sunscreen and beta-carotene supplementation (30 mg per day); sunscreen plus placebo tablets; beta-carotene only; or placebo only	4.5 years	–
Beta-Carotene Trial Greenberg 1990	1805 (with history of non-melanoma skin cancer)	50 mg daily	5 years	1–5 years
Physicians' Health Study (PHS) Frieling 2000 Hennekens 1999	22 071	50 mg beta-carotene taken on alternate days	12 years	–
Women's Health Study (WHS) Lee 1999	39 876	50 mg of beta-carotene taken on alternate days	2 years	4 years

Prostate

See also chapter 4.2.5.3 for evidence on foods containing beta-carotene. Three RCTs[9 10 16 18 26] and two cohort studies[27 28] investigated beta-carotene supplements (table 4.10.4).

Two trials showed a non-significant increased risk for beta-carotene supplementation compared to none[9 10 16]; the other showed no effect on risk.[18] Effect estimates were 1.26 (95% CI 0.98–1.62) for the 1985 to 1993 follow-up period,[16] 1.01 (95% CI 0.80–1.27),[9 10] and 1.0 (95% CI 0.9–1.1).[18]

One cohort study showed a non-significant increased risk for beta-carotene supplementation compared to none[27]; the other stated that there was no significant association.[28] The single reported effect estimate was 1.17 (95% CI 0.85–1.61).[27]

There is no evidence for any mechanism of action.

There is strong evidence from good quality trials, and from cohort studies, which consistently fails to demonstrate a protective effect. Beta-carotene supplements are unlikely to have a substantial protective effect against prostate cancer. The evidence is too limited to draw a conclusion on a harmful effect.

Skin

See also chapter 4.2.5.3 for evidence on foods containing beta-carotene. Four RCTs[19 29-32] and one cohort study[33] investigated beta-carotene supplements (table 4.10.5).

Non-melanoma skin cancer

Three RCTs investigated non-melanoma skin cancer as an outcome.[29 31 32] Two trials showed non-significant increased risk for beta-carotene supplementation compared to none[31 32]; one trial showed a non-significant decreased risk.[29] The results are shown in the forest plot, separated for basal cell carcinoma and squamous cell carcinoma (figure 4.10.2). Meta-analysis was possible on all three trials, giving a summary effect estimate of 1.00 (95% CI 0.94–1.07) for basal cell carcinoma and 1.01 (95% CI 0.95–1.06) for squamous cell carcinoma.

The single cohort study showed a non-significant decreased risk for beta-carotene supplementation compared to none. The effect estimate was 0.42 (95% CI 0.12–1.47).[33]

Figure 4.10.2 Beta-carotene supplements and non-melanoma skin cancer; trials

Relative risk (95% CI)

Basal cell carcinoma
Greenberg 1990 — 1.04 (0.89–1.21)
Green 1999 — 1.04 (0.79–1.37)
Frieling 2000 — 0.99 (0.92–1.06)
Summary estimate — 1.00 (0.94–1.07)

Squamous cell carcinoma
Greenberg 1990 — 1.22 (0.87–1.72)
Green 1999 — 1.35 (0.84–2.18)
Frieling 2000 — 0.97 (0.84–1.13)
Summary estimate — 1.01 (0.95–1.06)

0.5   1   2

Relative risk, intervention group vs control group
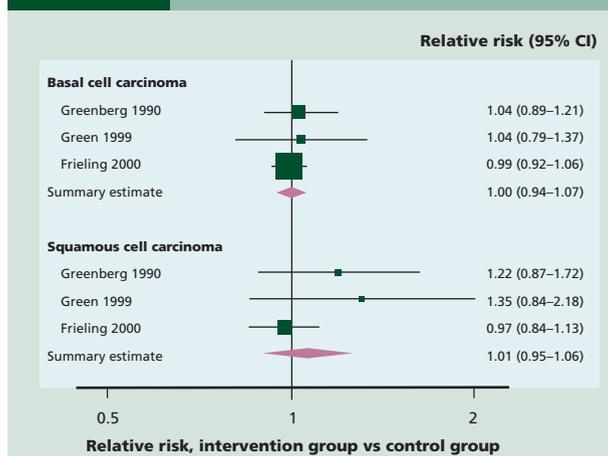
Melanoma skin cancer

The Women's Health Study[19] and Physicians' Health Study[30] investigated melanoma skin cancer as an outcome. Both trials stated that there was no significant effect from beta-carotene supplementation compared to none.[19 30]

There is no evidence for any mechanism of action.

There is strong evidence from good quality trials that consistently fail to show an effect. It is unlikely that beta-carotene has a substantial effect on the risk of non-melanoma skin cancer.

4.10.6.4.3 Alpha-tocopherol
Prostate

One RCT investigated alpha-tocopherol supplements and prostate cancer (table 4.10.6).[16 26]

The ATBC (Alpha-Tocopherol Beta-Carotene) trial was a large RCT of male smokers given 50 mg of alpha-tocopherol and 20 mg of beta-carotene (see table 4.10.6 for details). It showed a statistically significant decreased risk for alpha-tocopherol supplements, with an effect estimate of 0.66 (95% CI 0.52–0.86) for use compared to non-use. Prostate cancer was not a prior-stated outcome for this trial.[16 26]

Data on dietary, serum, or supplemental vitamin E or alpha-tocopherol levels were suggestive of decreased risk, though generally not statistically significant. Data on gamma-tocopherol provided evidence of an association with decreased risk.

Vitamin E exists in eight different forms or isomers: four tocopherols and four tocotrienols. There is an alpha, beta, gamma, and delta form of each. Each form has slightly different biological properties but all are antioxidants. Alpha-tocopherol is thought to be the most biologically active isomer of vitamin E. It inhibits proliferation, can directly activate certain enzymes, and exerts transcriptional control on several genes.[34] Vitamin E has also been shown to inhibit the growth of human prostate tumours induced in mice.[35]

The evidence is sparse. There is limited evidence that alpha-tocopherol supplements protect against prostate cancer in smokers.

Table 4.10.6	Alpha-tocopherol supplements and prostate cancer; trials			
Trial name	Number of participants	Intervention	Length of intervention	Length of follow-up
ATBC Study (male smokers) Virtamo 2003 Heinonen 1998	29 133	20 mg of beta-carotene only or with 50 mg of alpha-tocopherol	5–8 years	6–8 years

Figure 4.10.3 Calcium supplements and colorectal cancer; cohort studies

Relative risk (95% CI)

	Relative risk (95% CI)
Bostick 1993 Women	0.66 (0.43–1.02)
Kampman 1994	0.95 (0.50–1.79)
Wu 2002 Men	0.70 (0.43–1.14)
McCullough 2003 Men	0.60 (0.33–1.10)
McCullough 2003 Women	0.73 (0.30–1.76)
Feskanich 2004 Women	0.87 (0.69–1.11)
Lin 2005 Women	1.30 (0.90–1.87)

Relative risk, highest vs lowest exposure category
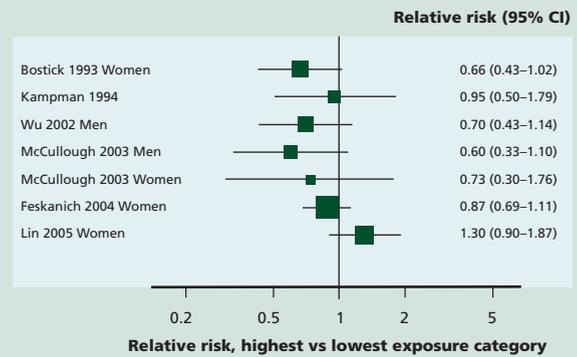
4.10.6.4.4 Calcium
Colorectum

Seven cohort studies investigated calcium supplements and colorectal cancer.[36-43] Three trials[44-49] and four cohort studies[50-53] investigated calcium supplements and colorectal adenomas.

Six cohort studies showed decreased risk for calcium supplements when compared to none,[36-41 43] which was statistically significant in one.[40] One study showed non-significant increased risk.[42] The effect estimates can be seen in the forest plot, apart from one study which reported an effect estimate of 0.76 (95% CI 0.56–0.98) for the highest intake group compared to the lowest (figure 4.10.3).[43]

Pooled analysis from 10 cohort studies (with over 534 000 participants followed up for 6 to 16 years, 4992 cases of colorectal cancer) presented results for calcium from food sources and total calcium which includes supplements. A larger effect was seen for total calcium (0.78, 95% CI 0.69–0.88) than for calcium from food sources (0.86, 95% CI 0.78–0.95).[54]

Because of the abundant prospective data from cohort studies, case-control studies were not summarised.

Adenomas

Two RCTs showed decreased risk of adenomas with calcium supplementation,[44-48] which was statistically significant in one.[44-47] Effect estimates were 0.81 (95% CI 0.67–0.99; 1200 mg calcium; adenoma incidence)[44] and 0.66 (95% CI 0.38–1.17; 4 g calcium; adenoma recurrence).[48]

One additional trial showed a reduced risk of new adenoma growth during a 3-year intervention of a daily mixture of beta-carotene 15 mg, vitamin C 150 mg, vitamin E 75 mg, selenium 101 μg, and calcium (1.6 g daily) as carbonate (p value 0.035), though with no statistically significant effect on the growth of pre-existing adenomas.[49]

Three cohort studies showed decreased risk with calcium supplementation,[50-52] which was statistically significant for one.[50] One study reported no significant association.[53] Meta-

analysis was possible on two of these studies, giving a summary effect estimate of 0.91 (95% CI 0.85–0.98) per 200 mg/day.[50] [52] The other study that gave quantified results reported an effect of 0.76 (95% CI 0.42–1.38).[51]

Calcium is an import micronutrient and intracellular calcium is a pervasive second messenger acting on many cellular functions, including cell growth. It has been widely demonstrated that calcium has direct growth-restraining, and differentiation- and apoptosis-inducing action, on normal and tumour colorectal cells.[55]

There is generally consistent evidence from several cohort studies, and evidence from trials for colorectal adenomas. There is evidence for plausible mechanisms. Calcium probably protects against colorectal cancer.

4.10.6.4.5 Selenium
Prostate
One RCT[56] [57] and two cohort studies[27] [58] investigated selenium supplements and prostate cancer (table 4.10.7).

The RCT was conducted in men with a history of skin cancers. Prostate cancer was not a prior stated outcome and was assessed as a secondary endpoint. Out of 974 participants, approximately half were randomised to receive 200 μg of selenium daily. There were 13 cases of prostate cancer in the selenium group and 35 cases in the control group, giving an effect estimate of 0.37 (95% CI 0.20–0.70) for supplement use compared to non-use, after a mean of 4.5 years of the intervention and a mean of 6.5 years follow-up.[56] The effect was strongest in those with the lowest levels of selenium at the start of the trial.[57]

Both cohort studies showed non-significant decreased risk with selenium supplementation.[27] [58] Effect estimates were 0.94 (95% CI 0.57–1.55)[27] and 0.91 (95% CI 0.57–1.48)[58] for use versus non-use.

Dietary selenium data are supportive of an effect (see chapter 4.2.5.8).

The general mechanisms through which selenium could plausibly protect against cancer are outlined below. In addition, selenoproteins are involved in testosterone production, which is an important regulator of both normal and abnormal prostate growth.

There is strong evidence from trials and cohort studies. Selenium probably protects against prostate cancer.

Table 4.10.8	Selenium supplements and lung cancer; trials			
Trial name	Number of participants	Intervention	Length of intervention	Length of follow-up
NPC Trial Reid 2002	1312 people with a history of non-melanoma skin cancers	200 μg selenium daily (primary endpoint was skin cancer)	Mean 4.5 years	Mean 7.9 years

Lung
One RCT investigated selenium supplements and lung cancer (table 4.10.8).[59]

The Nutritional Prevention of Cancer (NPC) Trial consisted of more than 1300 participants enrolled from several dermatology practices who were treated with 200 μg of selenium. The trial showed a non-significant decreased risk with supplementation, with an effect estimate of 0.74 (95% CI 0.44–1.24) after a mean of 4.5 years of the intervention and a mean of 7.9 years follow-up, adjusted for age and smoking. Subgroup analysis indicated that this risk differed according to baseline plasma selenium level, with an effect estimate of 0.42 (95% CI 0.18–0.96) for those in the lowest tertile compared to no apparent effectiveness for individuals in the higher tertiles of plasma selenium.[59] This suggests that selenium supplementation may decrease cancer risk in those who are deficient in dietary selenium, but that this effect may not extend to those whose intake of selenium is within the recommended levels.

The general mechanisms through which selenium could plausibly protect against cancer are outlined below.

The evidence is sparse. There is limited evidence suggesting that selenium protects against lung cancer.

Skin
One RCT[60-62] and one cohort study[33] investigated selenium supplements and skin cancer (table 4.10.9).

The Nutritional Prevention of Cancer Trial (see above) showed a non-statistically significant increased risk of total non-melanoma skin cancer with supplementation, with an effect estimate of 1.18 (95% CI 0.49–2.85). Subgroup analysis showed an effect estimate of 1.14 (95% CI 0.93–1.39) for

Table 4.10.7	Selenium supplements and prostate cancer; trials			
Trial name	Number of participants	Intervention	Length of intervention	Length of follow-up
NPC Trial Clark 1998 Duffield-Lillico 2003	974 men with a history of non-melanoma skin cancers	200 μg selenium daily (primary endpoint was skin cancer)	Mean 4.5 years	Mean 6.5 years

Table 4.10.9	Selenium supplements and skin cancer; trials			
Trial name	Number of participants	Intervention	Length of intervention	Length of follow-up
NPC Trial Combs 1997 Clark 1996 Duffield-Lillico 2002	1312 people with a history of non-melanoma skin cancers	200 μg selenium daily (primary endpoint was skin cancer)	Mean 4.5 years	Mean 6.4 years

squamous cell carcinoma and 1.10 (95% CI 0.95–1.28) for basal cell carcinoma.[61]

The single cohort study stated that there was no statistically significant association.[33]

> The evidence is sparse and no plausible mechanisms have been identified. **There is limited evidence suggesting that selenium supplements are a cause of skin cancer.**

Colorectum

One RCT[60][62] and one cohort study[63] investigated selenium supplements and colorectal cancer (table 4.10.10).

The single trial included 1312 participants who were randomised to receive 200 μg selenium or a placebo. There were 8 colorectal cancer cases in the intervention group and 19 in the control group, giving an effect estimate of 0.36 (p value for trend 0.025) for use versus non-use.[60] A hazard ratio of 0.46 (95% CI 0.21–1.02) is given after a further 2.5 years follow-up.[62]

The single cohort study showed non-significant decreased risk, with an effect estimate of 0.60 (95% CI 0.27–1.32) for use versus non-use.[63]

Dietary selenium data are supportive of an effect (see chapter 4.2.5.8).

The general mechanisms through which selenium could plausibly protect against cancer are outlined below.

> The evidence is sparse. **There is limited evidence to suggest that selenium protects against colorectal cancer.**

General mechanisms

Dietary selenium deficiency has been shown to cause a lack of selenoprotein expression. Twenty-five selenoproteins have been identified in animals, and a number of these have important anti-inflammatory and antioxidant properties.[64] Four are glutathione peroxidises, which protect against oxidative damage to lipids, lipoproteins, and DNA. These enzymes are rapidly degraded during selenium deprivation. Three are thioredoxin reductases and, amongst other functions, these regenerate oxidised ascorbic acid to its active antioxidant form.

Selenoproteins appear to reach their maximal levels relatively easily at normal dietary selenium intake and not to increase with selenium supplementation. It is,

however, plausible that supraphysiological amounts of selenium might affect programmed cell death, DNA repair, carcinogen metabolism, immune system, and anti-angiogenic effects.[65]

4.10.7 Comparison with previous report

This Report associates nutrients and dietary constituents with foods and drinks wherever possible; and findings and judgements on these as contained in foods and drinks are found in previous sections of this chapter. The previous report included a whole chapter on dietary constituents. It found that starch (probably when it is the staple of poverty diets) possibly protected against colorectal cancer but was possibly a cause of stomach cancer. The evidence from the SLRs undertaken for this Report did not reproduce these findings.

The previous report noted that trials using supplements of various micronutrients such as beta-carotene, vitamin E, and multiple vitamins and minerals had produced mixed results. But it did not make formal judgements as a result of these trials, although one of the report's recommendations was that dietary supplements are probably unnecessary, and possibly unhelpful, for reducing cancer risk. RCTs published since the mid-1990s have strengthened the evidence on the relationship of some dietary supplements and the risk of cancers of some sites.

For comparisons with the previous report concerning dietary constituents here identified as foods (such as sugars, fats and oils, and alcohol) or foods which contain certain constituents (such as dietary fibre, vitamins, minerals, and trace elements), see chapters 4.1 to 4.8.

4.10.8 Conclusions

The Panel concludes:

The evidence that the use of high-dose beta-carotene supplements in tobacco smokers is a cause of lung cancer is convincing. There is limited evidence suggesting that high-dose retinol supplements are a cause of lung cancer in this group. The principal cause of lung cancer is smoking tobacco.

Calcium probably protects against colorectal cancer. At specific doses, selenium probably protects against prostate cancer.

There is limited evidence suggesting that retinol at specific doses protects against squamous cell carcinoma of the skin. There is also limited evidence suggesting that alpha-tocopherol protects against prostate cancer; and also that selenium at specific doses protects against colorectal cancer (at a level of 200 μg/day, the dose used in the studies on which this judgement is based).

There is limited evidence suggesting that selenium supplements are a cause of skin cancer. It is unlikely that beta-carotene supplements, or foods containing it, have a substantial effect on the risk of either prostate cancer or skin (non-melanoma) cancer.

Table 4.10.10	Selenium supplements and colorectal cancer; trials			
Trial name	**Number of participants**	**Intervention**	**Length of intervention**	**Length of follow-up**
NPC Trial Combs 1997 Duffield-Lillico 2002	1312 people with a history of non-melanoma skin cancers	200 µg selenium daily (primary endpoint was skin cancer)	Mean 4.5 years	Mean 6.4 years

4.11 Dietary patterns

The nature, quality, quantities, and proportions of different foods and drinks in diets, and the frequency with which they are habitually consumed, constitute dietary patterns. Populations, communities, and families may share similar dietary patterns, which are determined by various factors such as the ecological niche they inhabit, physical environments in which they live, or by tradition, culture, religion, or choice. Dietary patterns, as well as patterns of physical activity, have co-evolved with humans over millennia and are intimately related to long-term survival of the species within a given environment. The changes in environment including diets and activity patterns over the past century are likely to have affected the risk of chronic diseases, including cancer. Indeed, the impact of food and nutrition on health is not generally determined by individual foods and drinks, specific dietary constituents, or the ways in which foods are modified, for example by processing or cooking. No food or drink is an elixir and few are poisons, unless they are contaminated with pathogenic micro-organisms. It is dietary patterns, with physical activity levels and other factors that influence nutritional requirements, that determine nutritional status and other health outcomes that are of interest to this Report.

Dietary patterns are difficult to characterise and are an infrequent subject for epidemiological and experimental investigations which, by their reductionist approach, typically address specific foods and dietary components. This precisely focused approach may overlook the significance of diets as a whole. There is now increasing interest in the examination of the impact of dietary patterns on well-being and disease outcomes, including the risk of cancer.

***The Panel notes* that existing studies of specific dietary patterns use different definitions and that the evidence they have produced is unclear. Currently, given the agreed criteria for grading evidence in this Report, no judgements can be made on any possible relationship between dietary patterns, as defined in the literature, and the risk of cancer. For this reason, no matrix showing Panel judgements is included in this section. However, a narrative summary provides an analysis of existing evidence relating dietary patterns and cancer-related outcomes.**

For most populations at most times, food systems determine dietary patterns; traditionally, these systems have themselves been largely determined by climate and terrain. Until recently in history, diets have been mostly made up from locally available plant and animal sources, as gathered, hunted, reared, cultivated, preserved, processed, prepared, and consumed. The current dietary patterns of subsistence farmers around the world, in East Africa, Mexico, India, and China for instance, differ mostly not as a matter of communal or family choice, but because different staple crops flourish in different parts of the world. The same applies to communities that live near rivers, lakes, and seas: their dietary patterns are different from those of inland populations largely because fish and seafood are available. Traditional diets in the territories on or close to the Mediterranean littoral are typically high in vegetables, fruits, fish, and seafood. The dietary patterns of pastoralist populations, especially those living in Arctic climates, are high in meat and animal foods. The extreme example of imposed dietary patterns are 'poverty' or 'deficiency' diets, consumed by impoverished communities.

One characteristic of human civilisation is food culture: the development of dietary patterns throughout or within societies as part of general culture. It is thought that dietary patterns have acquired a cultural dimension based on the fact that they have evolved with human populations providing advantages for survival within a given ecological setting. Thus food cultures sometimes have become an expression of some system of belief.

Dietetics, in its original form as a general philosophy of the well-led life, was developed in Greece and then later in western Europe (for example, by the School of Salerno, from the 12th century). Scholars and teachers of dietetics recommended various dietary regimes, which involved dietary patterns selected as a matter of choice. These were often simple or frugal, and not just for personal well-being and freedom from disease, but also as an expression of virtue.[1] More recently, people began to adopt certain dietary patterns in the belief that these could protect against disease.

The urban–industrial food systems that generate the foods and drinks now purchased and consumed by most people in the world are characterised by the increased use of technology in production, manufacture, processing, distribution, and sale. Another key feature is globalisation. Spices have been transported from Asia to Europe for thousands of years; sugar has been shipped around the world for half a millennium; similarly, the export of tropical fruits, meat, and tea became subject to major intercontinental trade in the 19th century. Very many if not most foods, or their ingredients, now travel long distances before reaching their point of sale. Globalised food systems are now shaping dietary patterns in all continents.[2 3]

This chapter summarises some of the dietary patterns that might modify the risk of cancer. Breastfeeding is also men-

tioned here in this context. For evidence and judgement on lactation, see Chapter 6; on being breastfed in relation to weight gain, overweight, and obesity, see Chapter 8.

4.11.1 Traditional and industrial dietary patterns

Dietary patterns are determined by many factors. This first group includes some traditional and industrial dietary patterns, determined mainly by climate and terrain, material resources, technology, and culture.

4.11.1.1 Mediterranean
The traditional food systems of the territories on or near the Mediterranean littoral, in southern-most Europe, the Middle East, and northern-most Africa, are the fount of a number of great cuisines. These were developed by peoples, often from the East, who settled in successive waves within what is now Spain, southern France and Italy, former Yugoslavia, Greece, Turkey, Cyprus, Crete, Lebanon, Israel, Palestine, Egypt, Libya, Algeria, Tunisia, and Morocco. The Mediterranean dietary patterns that have since evolved generally have some common aspects.

Traditional Mediterranean diets are broadly characterised by high consumption of breads and other cereal foods usually made from wheat, and of vegetables and fruits, fish, cheese, olive oil, tree nuts (almonds and walnuts), and (in non-Islamic countries) wine. Extensive use is made of many herbs and spices. Meat is also consumed, but often only on relatively special occasions or in small amounts in combination with other foods in everyday dishes. Coffee, drunk with added sugar (in modern times), is the traditional hot drink. Desserts may also be sweet but overall consumption of sugar is low.

Since the second half of the 20th century, much attention has been given to the 'Mediterranean' diet. This interest is because of evidence associating the dietary patterns of the populations living in this region with low incidence of coronary heart disease.[4] It is usually thought that this association is causal, and that the reasons include high consumption of fresh foods, dietary fibre, vegetables, fruits, and fish; modest consumption of alcoholic drinks; and low intakes of saturated fatty acids. In addition, historically, habitual levels of physical activity have been high.

Recommendations published since the early 1980s on food, nutrition, and the prevention of cancer have similarities with those for the prevention of coronary heart disease. Mediterranean dietary patterns might therefore also be protective against cancer, either generally or of specific sites.

Traditional Mediterranean dietary patterns are gradually becoming less common as the food supplies of the countries of the Mediterranean littoral become increasingly 'western' or 'globalised'.

4.11.1.2 Asian
Traditional Asian cuisines are very diverse. But traditional Asian dietary patterns do have some qualities in common, certainly those of southern and eastern Asian countries including India, Sri Lanka, Thailand, Cambodia, Vietnam, China, and Korea.

Such traditional Asian dietary patterns are of low energy density. The staple cereal (grain) is usually rice, which is also usually the main source of energy. Traditionally, rice paddy is often also used to breed fish. The amounts of vegetables, fruits, and fish in diets vary; consumption is relatively low in impoverished communities, and often high in those that are more prosperous. In the more affluent centres of civilisation, traditional Indian and Chinese cuisines have been and often remain extremely diverse. But they are almost always made up mainly from foods of plant origin, again with very extensive use of herbs and spices. As in the Mediterranean region, large amounts of meat are usually reserved for special occasions. Japan is a maritime nation, and so the traditional dietary pattern is high in fish and seafood and in salt and salt-preserved foods. The maritime regions of other Asian countries have the same dietary patterns. Traditionally, most alcoholic drinks consumed in Asia are made from grains. Most foods are cooked at low temperatures (steaming, boiling), although some high-temperature methods are also used (stir-frying, deep-frying, roasting). Tea is the traditional hot drink in China, India, Sri Lanka, and Japan. Consumption of fat and sugars is traditionally low.

As with Mediterranean dietary patterns, and probably for broadly the same nutritional reasons, traditional southern and eastern Asian dietary patterns are associated with relatively low rates of obesity, type 2 diabetes, coronary heart disease, and some cancers. However, those that are high in salt are associated with elevated rates of hypertension and stroke. Traditional Asian dietary patterns remain the norm in rural and impoverished regions of southern and eastern Asia, but are now gradually becoming increasingly 'western' or 'globalised' in the urban and more prosperous parts of these countries.

These generalisations do not apply to the countries of northern Asia, including those of the former USSR.

4.11.1.3 Plant-based
Plant-based diets are mainly but not necessarily solely made up from foods of plant origin. Characteristically, cereals (whole or minimally processed grains) and other starchy foods, vegetables and fruits, pulses (legumes), herbs and spices, plant oils, and other foods and ingredients of plant origin are the basis of almost all everyday foods and meals. Meat, poultry, fish, milk and dairy products, animal fats, and other foods and ingredients of animal origin are consumed, usually in small amounts on normal days, but often abundantly on special and feast days. Consumption of alcoholic drinks is also usually reserved for special social occasions.

It is estimated that the dietary patterns of most of the world's population — perhaps around 4 billion people — are plant-based. Traditional Mediterranean and southern and eastern Asian dietary patterns (summarised above) are plant-based, as are the dietary patterns of most rural communities in middle- and low-income countries. Most populations that consume plant-based diets do not do so from choice, but because for them, animals are valuable and animal foods are

relatively costly. In some traditions (see chapters 4.11.1.1 and 4.11.1.2), plant-based or vegetarian diets are consumed as an expression of philosophy of life or of religion. These cultures, teachings, or faiths often also include periodic periods of fasting.

The nutritional profiles of plant-based dietary patterns are very variable, depending largely on the degree of variety of the foods consumed, though their energy density is generally low. Traditional plant-based cuisines from all over the world combine cereals (grains) and other starchy foods with beans and other pulses (legumes) as the staple foods. When food supplies are secure they are generally adequate in energy, and also in protein, unless reliant on very low-protein starchy staples such as cassava (manioc). Plant-based diets may be of relatively low energy density, but not necessarily so. Most of the fatty acids in plant-based diets are unsaturated. Levels of vitamins, minerals, trace elements, and phytochemicals vary, again depending on the degree of variety in diets.

Obesity, type 2 diabetes, coronary heart disease, cancers of some sites, and other chronic diseases have been rare or uncommon in those parts of the world where traditional dietary patterns are plant-based. Such diets are now commonly advocated and consumed by health-conscious people in high-income countries, partly on this basis. These diets are also increasingly popular because of the epidemiological and other evidence that components of plant-based dietary patterns are potentially protective against various chronic diseases including some cancers.

4.11.1.4 'Western'
The dietary patterns sometimes classified as 'western' have been generated by industrialised food systems, at first in western Europe, then in the USA. These patterns have also evolved in countries settled mostly by British and western European peoples, including those of the white populations of South Africa, Australia, New Zealand, and enclaves elsewhere in the world. This broad generalisation does not apply to some countries of Latin America, but in general represents the emerging dominant pattern observed in urban centres of the region.

'Western' dietary patterns are energy dense, and are increasingly made up from processed foods.[5] They are high in meat, milk and other dairy products, fatty or sugary foods such as processed meats, pastries, baked goods, confectionery, sugared and often also alcoholic drinks, with variable amounts of vegetables and fruits. The starchy staple foods are usually breads, cereal products, or potatoes. A feature of the global 'nutrition transition' (see chapter 1.2.1) is that 'western' dietary patterns are becoming 'exported' globally with accelerating speed.

'Western' diets defined in this way are associated with overweight and obesity, type 2 diabetes, cardiovascular disease, stroke, some cancers, and other chronic diseases. However, the term 'western diet' is potentially confusing: variations of such diets consumed within 'western' countries can and do have very different nutritional profiles.

4.11.2 Cultural dietary patterns

These dietary patterns are strongly influenced by cultural factors. These include ethical and religious beliefs, and beliefs about health. The distinction is somewhat arbitrary: these patterns are also influenced by climate and terrain, material resources, and technology.

4.11.2.1 Vegetarian and vegan diets
Plant-based dietary patterns need not be vegetarian, except in a loose sense; but vegetarian diets are generally plant-based. The distinction is more one of attitude than nutritional profile. Typically, vegetarians are at least as concerned about the ethics and environmental effects of consuming (and producing) animal foods as they are with their own well-being and protection against disease.

There are many types of vegetarian dietary patterns, and all exclude red meat and processed meat made from red meat. However, people whose intention is to be vegetarian may occasionally eat these meats; and many if not most will consume some foods containing ingredients derived from animals that supply red meat, perhaps inadvertently.

Lacto-ovo vegetarians consume milk and dairy products and also eggs. Vegans consume no foods of animal origin, although some are stricter than others about what they eat. People who avoid red meats may consume poultry and fish, and are sometimes termed 'semi-vegetarian'. The dietary practices of a number of religions are plant-based or vegetarian. Hindus are often vegetarian. Jains are vegan. Rastafarians are semi-vegetarian. Zen macrobiotic food is mostly vegetarian, although the main emphasis is on whole foods. For Seventh-day Adventists, see chapter 4.11.5.5.

Taken together, vegetarian dietary patterns are heterogeneous, as is the nutritional profile of most types of vegetarian diets. Studies of some vegetarians have identified lower rates of obesity and cardiovascular disease, and all-cause mortality. But people who are the subjects of such studies in high-income countries, who are vegetarian as a matter of belief or choice, are frequently of higher socioeconomic status compared with the general population. They are also less likely to smoke and more likely to be physically active (also see chapter 4.11.5.4).

4.11.2.2 Religious
Seventh-day Adventists are a Christian denomination of about 14 million people who, among other ways of life as part of their faith, are sparing in their consumption of meat and meat products; about half are lacto-ovo vegetarians. Most avoid hot condiments and spices, tea and coffee, and alcoholic drinks. Smoking is proscribed. The effect of Seventh-day Adventist ways of life on well-being and health has been the subject of a large number of studies. Rates of chronic diseases are generally lower among Adventists, and this is usually attributed to be their generally healthy ways of life.

Several other religions enjoin their adherents to refrain from consumption of certain foods or beverages — for instance, Islam forbids consumption of pork and alcohol, Judaism pork and other foods, and Hinduism beef.

4.11.2.3 'Healthy'

People who are conscious of the effects of food and nutrition on well-being, and on the risk of disease, may choose to consume 'healthy' diets. Such diets are featured in very many popular television programmes, newspapers, magazines, and books. However, there are as many 'healthy' dietary patterns as there are concepts of what constitutes a healthy diet; and for many people a 'healthy' diet is seen as a diet regime designed to reduce excess body fat. In the USA, the 'Healthy Diet Indicator'[6] and also the 'Healthy Eating Index' are used to assess how well people adhere to the Dietary Guidelines for Americans.

4.11.3 Other dietary patterns

4.11.3.1 Meal frequency

One hypothesis about food, nutrition, and cancer is that risk may be modified by meal patterns. The times of day at which food is eaten vary greatly in different populations. Gatherer–hunters and pastoralists often consume most of their food once a day only, or may not eat large amounts of food every day. Settled agriculturalists may consume two meals at different times of the day, depending on their work.

In urban settings, having three meals a day has been a common pattern. Some may be light meals and some more substantial, but the time of day at which each type is eaten varies in different parts of the world, and also within countries. Some people choose to eat lighter meals or snacks more frequently throughout the day, rather than having three meals. A feature of globalised food supplies and other aspects of modern cultures is the decline of the family meal; instead, an increasing amount of food is eaten alone in the form of quick meals or snacks, in fast-food outlets, in the street, or at home.

4.11.3.2 Breastfeeding

Being breastfed is a type of dietary pattern for infants. In fact it is the only pattern for healthy individuals based on a single food which provides all known essential nutrients for a given period of life. For a general summary of lactation and breastfeeding, see chapter 6.3. For being breastfed, see Chapter 8.

4.11.4 Interpretation of the evidence

4.11.4.1 General

For general considerations that may affect interpretation of the evidence, see chapters 3.3 and 3.5, and boxes 3.1, 3.2, 3.6 and 3.7.

'Relative risk' (RR) is used in this Report to denote ratio measures of effect, including 'risk ratios', 'rate ratios', 'hazard ratios', and 'odds ratios'.

4.11.4.2 Specific

Classification. A major limitation with most studies of dietary patterns is that there is no general agreement on just what constitutes any dietary pattern. For example, 'healthy' diets vary substantially; different types of diets are termed 'vegetarian'; and there are various types of 'Mediterranean' diet. In general, there is considerable scope for variation within any dietary pattern.

Confounding. Patterns of diet are interrelated with other habitual behaviour that may affect the risk of cancer, such as smoking or physical activity; people who habitually consume any type of diet for the sake of their health or for reasons of belief, may also modify other aspects of their way of life. This is likely to confound results that appear to show associations with the risk of cancer.

Study design. The analysis of conventional epidemiological studies tends to focus on specific foods and drinks and specific aspects of diets, rather than the overall pattern.

Reporting bias. People who habitually consume or who try to follow types of diets in the belief that these are healthy may, in studies relying on self-reporting, provide inaccurate records. They may overestimate their consumption of foods like vegetables, fruits, and other foods they believe to be healthy, and underestimate or fail to report consumption of foods and drinks they believe to be unhealthy. This type of reporting bias is a general issue with studies relying on self-reporting, but may be a special issue here. Studies of specific dietary patterns undertaken by scientists who themselves follow these patterns may be seen as biased for this reason.

4.11.5 Evidence and judgements

Epidemiological research concerned with food, nutrition, and the risk of cancer, characteristically examines individual foods and dietary constituents.

There is a growing body of epidemiological work on dietary patterns; these were within the terms of reference of the systematic literature reviews (SLRs) whose findings are the primary basis for the Panel judgements in this Report. However, the evidence on dietary patterns examined in this way, relative to cancers of individual sites, does not permit conclusions to be drawn and *the Panel decided* not to make any judgements. Also see chapter 4.11.4.2.

In the case of dietary patterns, evidence from the SLRs has been supplemented by an informal narrative literature review, and the results are summarised here.

The full SLR is contained on the CD included with this Report.

4.11.5.1 Mediterranean dietary patterns

In a Swedish cohort study, a 2-point increase in a 'Mediterranean' diet score was associated with a 16% (95% confidence interval (CI) 1%–29%) reduced risk of cancer mortality in women aged 40–49, but not among younger women.[7]

An intervention trial investigated the recurrence of colorectal adenomas. This showed that the 'Mediterranean' diet (characterised by high consumption of vegetables, fruit, lean

meat, fish, and olive oil) was associated with a reduced risk of recurrence of colorectal adenomas in women (RR 0.30 (95% CI 0.09–0.98), but not in men. [8]

4.11.5.2 Asian dietary patterns

A Japanese cohort study[9] showed significant associations between certain dietary patterns and the risk of stomach cancer. These were for a 'traditional' Japanese dietary pattern in men (RR 2.88, 95% CI 1.76–4.72) and in women (RR 2.40, 95% CI 1.76–4.72); and for a 'healthy' dietary pattern in women (RR 0.56, 95% CI 0.32–0.96) but not in men. There was no association found with the 'western' dietary pattern. In the same Japanese cohort,[10] 'traditional' and 'western' dietary patterns were both positively associated with colon cancer risk in women, but not in men: 'traditional' RR 2.06 (95% CI 1.10–3.84) and 'western' RR 2.06 (95% CI 1.10–4.45).

The narrative review did not identify any other studies on Asian dietary patterns and the risk of cancer.

For evidence and judgements on salt, salting, and salted food, and the risk of stomach cancer, see chapter 4.6 and chapter 7.5.

4.11.5.3 'Western' dietary patterns

The narrative review identified several studies that have used data from large cohorts, mostly undertaken in the USA, to derive various types of 'western' dietary patterns from dietary intake information. This is done by combining key components of diets into what is then identified as types of dietary pattern that may be related to the risk of cancer risk. Some case-control and ecological studies have also been carried out.

Analysis of data from the Health Professionals Follow-Up Study found no association between a 'western' dietary pattern and prostate cancer risk. In the study, this pattern was characterised as being high in refined cereals (grains), red and processed meats, fat, and sweets.[11] Similarly, for breast cancer, another large cohort study reported no association between a 'western' dietary pattern and breast cancer risk.[12]

A 'drinker' dietary pattern, characterised as being high in beer, wine, and spirits, was identified as being associated with a moderately increased risk of breast cancer (RR 1.27, 95% CI 1.06–1.52).

A case-control study from Uruguay reported an association with increased breast cancer risk and a 'western' diet; associations with decreased risk were found for 'traditional', 'stew', and 'healthy' dietary patterns.[13] Another case-control study from Uruguay reported an association with increased stomach cancer risk and a 'starchy' pattern; associations with decreased risk were found for 'healthy' and 'mixed' patterns.[14]

A Swedish case-control study found that a diet high in meat, red meat, high-fat dairy products, high-fat gravy, and sweets was significantly associated with increased risk of gastric cardia adenocarcinoma and oesophageal adenocarcinoma. It also found that a 'drinker' pattern (high intakes of beer, spirits/liquor, and French fries) was significantly associated with the risk of squamous cell carcinoma of the oesophagus.[15]

One of the first studies to investigate diet and cancer using factor analysis was a Japanese study looking at gallbladder/biliary tract cancer mortality using data collected between 1958 and 1975.[16] Western-style diets high in foods with high levels of fats and proteins were associated with decreased risk. For breast cancer mortality in Japan, another ecological study found that westernised diets high in both animal and saturated fats were associated with increased risk.[17]

Another Japanese cohort study showed no association between a western dietary pattern and stomach cancer risk.[9] For colon cancer risk in the same Japanese cohort, 'western' as well as 'traditional' dietary patterns were associated with increased colon cancer risk in women, RR 2.06 (95% CI 1.10–3.84) and RR 2.06 (95% CI 1.10–4.45) respectively, but not in men.[10]

Three dietary patterns were identified from analysis of a Swedish cohort: 'healthy', including wholegrains, vegetables, fruits, tomatoes, poultry, and fish; 'western', including refined grains, fried potato, meat, processed meat, high-fat dairy products, margarine/butter, sweets and soft drinks; and 'drinker', including beer, wine, spirits, and snacks. The only pattern significantly associated with increased risk of renal cell carcinoma was the 'drinker' pattern (RR 0.56, 95% CI 0.34–0.95).[18]

An analysis of the Nurses' Health Study cohort also showed no evidence of an association between breast cancer risk and either a 'prudent' or a 'western' dietary pattern.[19] Similarly, no associations were reported between these dietary patterns and pancreatic cancer in a US cohort study.[20]

Two 'western' dietary patterns were identified from a US cohort. These were a 'prudent' type, characterised as being high in wholegrains, vegetables, fruits, low-fat dairy products, poultry, and fish; and a 'typical' type, characterised as being high in refined cereals (grains), red and processed meats, high-fat dairy products, sweets, and desserts. Neither was associated with overall breast cancer risk. However, the typical western pattern was associated with higher risk of breast cancer among smokers (RR 1.44, 95% CI 1.02–2.03).[21]

A Canadian case-control study identified an association between prostate cancer risk and a 'processed' dietary pattern, characterised as being high in refined cereals (grains), white bread, onions and tomatoes, red meat, processed meat, organ meats, vegetable oil and juice, soft drinks, and bottled water. No significant associations were found with 'healthy living', 'traditional western', or 'beverages' patterns.[22]

A case-control study conducted in central Italy identified a 'vitamin-rich' as well as a 'traditional' dietary pattern; both were strongly associated with decreased risk of stomach cancer.[23]

For colon cancer, a case-control study reported a protective effect of a 'prudent' western dietary pattern and increased risk with a 'typical' western pattern.[24] Another reported a protective effect of a western 'physical activity' pattern.[25]

Analysis of data from the French European Prospective Investigation into Cancer and Nutrition (EPIC) cohort showed a significant association between two 'western' dietary patterns and increased risk of colorectal cancer. The

first, RR 1.39 (95% CI 1.00–1.94), included cereal products, potatoes, processed meat, eggs, cheese, butter, sweets, cakes, pizzas and pies, and sandwiches. The second was a 'drinker' pattern, RR 1.42 (95% CI 1.10–1.83), including processed meat, alcoholic beverages, sandwiches, and snacks. A 'meat-eater' pattern, including meat, poultry, and margarine, was non-significantly associated with increased risk of colorectal cancer, RR 1.58 (95% CI 0.98–2.53).[26]

In an Italian cohort study, four dietary patterns were identified: 'western', 'canteen', 'prudent', and 'salad vegetables'. The 'salad vegetables' pattern was associated with lower risk of breast cancer, (RR 0.66, 95% CI 0.47–0.95).[27] Another US cohort study reported no association between either a 'vegetable–fish/poultry–fruit' or a 'beef/pork–starch' pattern and postmenopausal breast cancer. But it found a significant association with decreased risk of invasive breast cancer and a 'traditional southern' pattern, including legumes, salad, and a low intake of mayonnaise salad dressing (RR 0.78, 95% CI 0.65–0.95).[28]

In the Netherlands Cohort Study on Diet and Cancer, factor analysis identified five types of western dietary patterns. Both the 'salad vegetables' and the 'sweet foods' patterns were associated with decreased risk of lung cancer: RR 0.75 (95% CI 0.55–1.01) and RR 0.62 (95% CI 0.43–0.89), respectively. The other three patterns were not significantly associated with lung cancer risk. These were 'pork, processed meats, and potatoes', 'brown for white bread substitution', and 'cooked vegetables'.[29]

One study found that associations between dietary patterns and colorectal cancer were not consistent across European countries. As part of the Dietary Patterns and Cancer (DIETSCAN) project, factor analysis of three European cohorts identified five dietary patterns. Two of these, 'vegetables' and 'pork, processed meats, and potatoes', were common across all three cohorts. The second dietary pattern was associated with increased risk of colon cancer in one cohort of women (RR 1.62, 95% CI 1.12–2.34), and with increased risk of rectal cancer in one cohort of men (RR 2.21, 95% CI 1.07–4.57). Neither pattern was associated with the risk of colorectal cancer in the third cohort.[30]

For thyroid cancer, a case-control study showed that various western dietary patterns of 'fruits', 'raw vegetables', and 'mixed raw vegetables and fruits' were associated with reduced risk of thyroid cancer (RR 0.68, 0.71, and 0.73, respectively). However, a pattern of 'fish and cooked vegetables' was associated with an increased risk (RR 2.79).[31]

Another case-control study showed that a 'dessert' pattern and a 'beef' pattern were associated with increased risk of kidney cancer. A 'juices' factor was associated with increased risk of this cancer in men and an 'unhealthy' pattern with increased risk in women.[32]

One case-control study from Uruguay reported an association with increased risk of oral and pharyngeal cancers and a 'stew' pattern, characterised by cooked vegetables, potato and sweet potato, and boiled meat. It also found a decreased risk of these cancers associated with a 'vegetables and fruits' pattern, characterised by raw vegetables, citrus fruits, other fruits, liver, fish, and desserts.[33]

A case-control study of pancreatic cancer risk showed no association with 'western' and western 'drinker' patterns, but an association with decreased risk and a 'fruits and vegetables' pattern.[34]

A Canadian case-control study found that four dietary patterns were associated with increased risk of kidney cancer: a 'dessert' pattern in both men and women; a 'beef' pattern and a 'juices' pattern in men; and an 'unhealthy' pattern among women.

4.11.5.4 Vegetarian dietary patterns
The narrative review identified several studies that have investigated the relationship between vegetarian diets and the risk of cancer. These often did not adjust for potentially confounding factors. One study found that when adjusted for age only, women who said they consumed vegetarian diets seemed to increase the risk of breast cancer (1.65, 95% CI 1.01–2.7) (vegetarian versus non-vegetarian).[35]

Plausible biological mechanisms have been identified by which vegetarian diets might specifically reduce the risk of cancers of the colon, breast, and prostate (also see chapter 4.2). Any effect of vegetarian diets is likely to be due not only to the exclusion of meat, but also to the inclusion of a larger number and wider range of plant foods, containing an extensive variety of potential cancer-preventive substances.

4.11.5.5 Seventh-day Adventist diets
The SLRs identified a number of cohort studies on the relationship between Seventh-day Adventist diets — and also general ways of life — and the risk of cancer. Two investigated oesophageal cancer,[36 37] seven stomach cancer,[37-43] two kidney cancer,[37 42] one breast cancer[44] and three prostate cancer.[37 41 45] For oesophageal, kidney, breast and prostate cancer, results were mixed and usually not statistically significant, although they were slightly suggestive of reduced risk.

For stomach cancer, meta-analysis of five cohort studies[37-40 42] gave a summary effect estimate of 0.60 (95% CI 0.44–0.80), with low heterogeneity, with non-included studies also reporting reduced risks. None of the studies that reported reduced risk was adjusted for known confounding factors such as smoking.

As not smoking is a feature of Seventh-day Adventism, *the Panel concluded* that data on the dietary patterns associated with this faith are limited and no conclusion can be reached for any cancer site.

No conclusions can be based on this evidence, because the data are too limited and not comparable across studies.

4.11.5.6 Meal frequency
The SLRs identified 20 case-control studies[46-65] that investigated irregular eating and stomach cancer. All but 1 reported increased risk estimates and 15 were statistically significant. Meta-analysis of 16 case-control studies[50-65] gave a summary effect estimate of 2.76 (95% CI 2.10–3.64) for irregular as opposed to regular eating (p < 0.001), but with high heterogeneity.

However, the reference period was generally some years before cancer diagnosis. Irregular eating can be taken to mean frequent snacking or small meals, or missing main

meals. But none of these studies defined 'irregular eating' or quantified the frequency with which meals might be skipped.

Eight case-control studies investigated meal frequency and colorectal cancer.[66-80] Most showed increased risks with increased frequency of meals. Meta-analysis of 11 estimates from 7 of these studies[67-69 76 78-80] gave a summary effect estimate of 1.10 (95% CI 1.02–1.19), with high heterogeneity.

This evidence is also unclear. No cohort studies have been identified as examining meal frequency. People who have stomach or colorectal problems are likely to eat irregularly. There is also high probability of confounding, as regular eating patterns are associated with generally healthy behaviour.

The significance of these findings on meal frequency and stomach and colorectal cancer is unclear, in part because of the high probability of confounding. For this reason, no judgement is made.

4.11.5.7 Being breastfed

The SLRs produced no evidence on any relationship between having been breastfed and the risk of cancer in adult life. However, the reviews did produce evidence on the relationship between lactation and cancer in women, and also between having been breastfed and the risk of overweight and obesity in childhood and thereafter. See chapters 6.3.3 and 8.8.3.

4.11.6 Comparison with previous report

The previous report reviewed evidence on vegetarian and mostly-vegetarian dietary patterns of various types, including Seventh-day Adventist and macrobiotic diets. The report concluded that various types of vegetarian dietary pattern seem to decrease the incidence of cancer in general, as well as of some specific sites. It also concluded that semi-vegetarian diets that include small amounts of meat and foods of animal origin may also be beneficial. This conclusion was not made as a formal judgement.

The previous report identified 'poverty' or 'deficiency' patterns of diet. These are monotonous, very high in refined cereal foods (such as rice), with only small amounts of other foods. This was partly in response to its finding that refined cereals (grains) were a possible cause of oesophageal cancer and that starch was a possible cause of stomach cancer. In explanation, the panel responsible for that report concluded that any increase in the risk of cancer here was likely to be caused by poverty/deficiency dietary patterns, not by the specific food or dietary constituent.

The first recommendation of the previous report was in effect for: 'nutritionally adequate and varied diets, based primarily on foods of plant origin'. This was based partly on the evidently protective effects of vegetables and fruits, and also on the general balance of evidence. The panel emphasised that 'plant-based diets' do and may include relatively modest amounts of foods of animal origin.

4.11.7 Conclusions

The Panel concludes:
Currently, no firm judgements can be made on any possible relationship between dietary patterns and the risk of cancer.