CHAPTER 7

Cancers

Every year an estimated 11 million people are diagnosed with cancer (excluding skin cancers) and nearly 7 million people are recorded as dying from cancer. Projections for 2030 predict that these figures will double. Cancer is increasing at rates faster than the increase in global population. It is becoming more common in high-income but also — and most of all — in middle- and low-income countries, absolutely and also relative to other diseases.

The scientific community is convinced that inherited high susceptibility to cancer accounts for only a small proportion of cases. Although we are all more or less susceptible to various diseases, most adult cancers are caused mainly by environmental factors. This means that most cancers are at least in theory preventable.

One important cause of cancer is smoking, or other exposure to, tobacco. Infection, infestation, solar radiation, and other factors are also important. Food and nutrition, physical activity, body composition, and other associated factors are also individually and collectively important modifiers of cancer risk. But there is a difference. Smoking and exposure to tobacco, and these other factors, are all causes of cancer. By contrast, this and the previous chapters show that food and nutrition, and physical activity can protect against cancer. When we are able to do so, we can choose ways of life that protect both ourselves and the next generation against cancer. So our nutritional state — what we eat and drink, how active we are, and how much body fat we carry — not only as adults but also from and before birth, vitally affects our risk of many cancers.

This chapter follows those on foods and drinks, physical activity, and body composition, growth, and development. Its purpose is to summarise the evidence derived from independently commissioned and presented systematic literature reviews (SLRs), and the Panel's judgements and conclusions, as they relate to cancers of 17 sites. Together, these amount to roughly 80 per cent of the incidence of, and deaths from, all cancers worldwide. Evidence on a number of other cancers is also summarised briefly, based on narrative reviews.

The sequence of the sections of this chapter corresponds roughly with the body's systems, or with sites that have anatomical, metabolic, hormonal, or other features in common, and generally follows the sequence of the previous report.

The structure of all the sections, where evidence derives from these systematic reviews, is identical. After brief introductions, matrices display the Panel's judgements. In this chapter, the Panel's judgements also include the 'Limited — no conclusion' category, where evidence is, in the Panel's view, of such poor quality, or too sparse, confused, or conflicting, to allow a conclusion. Footnotes to these matrices include important explanations or qualifications.

Then follow subsections on trends, incidence, and survival; pathogenesis; and other established causes. The next subsection concerns interpretation of the evidence, in which issues and problems related to specific cancer sites are summarised.

'Evidence and judgements' are the central subsections throughout this chapter. Here, the evidence from the SLRs, reported more extensively with graphics in Chapters 4, 5, and 6, is also summarised. The sequence of these subsections is the same as that of Chapters 4–6. The strongest evidence on protection from cancer comes first, followed by the strongest evidence on causation, and so on. Within each passage, summaries of the statistically most powerful epidemiological studies come first, followed by other epidemiological studies, and then summaries of the experimental literature and evidence of biological plausibility. This is followed by the Panel's judgements, which take into account matters of quality and interpretation.

Then follows a subsection comparing the judgements of this Report with those of the previous report, with indications of why these differ when they do. All sections conclude with the Panel's judgements for each cancer site.

7.1 Mouth, pharynx, and larynx

Cancers of the mouth, pharynx, and larynx, taken together, are the seventh most commonly occurring types of cancer worldwide. These cancers are three times more common in men than in women. Over 550 000 cases were recorded in 2002, accounting for around 5 per cent of cancer cases overall. In general, the rates of these cancers are decreasing. These cancers tend to recur. Survival rates are variable and average around 50 per cent at 5 years. Cancers of the mouth, pharynx, and larynx are the seventh most common cause of death from cancer.

Overall, *the Panel judges* that food and nutrition play an important role in the prevention and causation of cancers of the mouth, pharynx, and larynx.

***The Panel judges* as follows:**

The evidence that alcoholic drinks are a cause of cancers of the mouth, pharynx, and larynx is convincing. The risk is multiplied when drinkers of alcohol also smoke tobacco.

Non-starchy vegetables, fruits, and also foods containing carotenoids probably protect against these cancers.

There is limited evidence suggesting that maté, a herbal infusion traditionally drunk scalding hot through a metal straw in parts of South America, is a cause of oral cancer.

The main single cause of these cancers is smoking tobacco. It has been estimated that up to half of these cancers are preventable by appropriate diets and associated factors.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that alcoholic drinks are a convincing cause of these cancers; and that non-starchy vegetables, fruits, and foods containing carotenoids are probably protective.

There are several different tissues and organs in and around the mouth, pharynx, and larynx. These include the lips, the tongue, the inside lining of the cheeks (buccal mucosa), the floor of the mouth, the gums (gingiva), the palate, and the salivary glands. The pharynx (or throat) is the muscular cavity leading from the nose and mouth to the larynx, which includes the vocal cords.

Ninety per cent of cancers of the mouth, pharynx, and larynx are squamous cell carcinomas, the type discussed here. Cancers of the oropharynx (including the tonsils) and the hypopharynx are also included. For cancer of the nasopharynx, the cavity from the back of the mouth to the nose, see 7.2.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCERS OF THE MOUTH, PHARYNX, AND LARYNX

In the judgement of the Panel, the factors listed below modify the risk of cancers of the mouth, pharynx, and larynx. Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing		**Alcoholic drinks**
Probable	**Non-starchy vegetables[1]** **Fruits[1]** **Foods containing carotenoids[2]**	
Limited — suggestive		Maté[3]
Limited — no conclusion	Cereals (grains) and their products; starchy roots, tubers, and plantains; dietary fibre; pulses (legumes); meat; poultry; fish; eggs; milk and dairy products; total fat; animal fats; plant oils; coffee; tea; frying; grilling (broiling) and barbecuing (charbroiling); protein; vitamin A; retinol; thiamin; riboflavin; niacin; folate; vitamin C; vitamin E; calcium; iron; selenium; body fatness; energy intake	
Substantial effect on risk unlikely	None identified	

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 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.

7.1.1 Trends, incidence, and survival

Rates of cancers of the mouth and pharynx (age adjusted) are stable or decreasing in many high-income countries. There was a sharp increase between 1950 and 1980 in several European countries, such as Germany and France, although this has since reached a plateau and started to decrease. Laryngeal cancer rates appear to have been generally stable or decreasing since 1970.[1]

Age-adjusted incidence rates of oral cancers range from 20–40 per 100 000 people in parts of south-central Asia, Europe, Oceania, and southern Africa, to less than 3 per 100 000 in parts of eastern Asia, northern and western Africa, and Central America. Pharyngeal cancers (other than those of the nasopharynx) follow broadly similar incidence patterns, although the overall incidence is lower, with highs of more than 10 per 100 000 in south-central Asia and western Europe, to a low of less than 1 per 100 000 in northern Africa. Age-adjusted incidence rates of laryngeal cancer range from more than 10 per 100 000 in South America, south-central and western Asia, and southern, central, and western Europe to less than 1 per 100 000 in many African countries.[2] Rates are higher in men than in women by approximately three to one.[2] In the USA, rates are higher among African-American people than in white people.[3]

Risk increases with age, and diagnoses of these three types of cancer are most common in people aged 50 or over.[4]

Although cure rates are high for early-stage cancers of the mouth, pharynx, and larynx, second primary tumours are relatively common at these sites.[5] More than 60 per cent of patients do not seek medical advice until the disease is at an advanced stage; in these cases, long-term survival rates are poor, especially if the cancer site is inaccessible.[4] Five-year survival rates are around 60 per cent in the USA and 50 per cent in the UK.[3 6] These cancers account for just over 5 per cent of all cancer incidence, but just under 5 per cent of all cancer deaths.[2] Also see box 7.1.1.

Box 7.1.1 Cancer incidence and survival

The cancer incidence rates and figures given in this Report are those reported by cancer registries, now established in many countries. These registries record cases of cancer that have been diagnosed. However, many cases of cancer are not identified or recorded: some countries do not have cancer registries; regions of some countries have few or no records; records in countries suffering war or other disruption are bound to be incomplete; and some people with cancer do not consult a physician. Altogether, this means that the actual incidence of cancer is higher than the figures given here.

The cancer survival rates given in this chapter and elsewhere are usually overall global averages. Survival rates are generally higher in high-income countries and other parts of the world where there are established services for screening and early detection of cancer and well established treatment facilities. Survival also is often a function of the stage at which a cancer is detected and diagnosed. The symptoms of some internal cancers are often evident only at a late stage, which accounts for relatively low survival rates. In this context, 'survival' means that the person with diagnosed cancer has not died 5 years after diagnosis. Also see chapter 9.

7.1.2 Pathogenesis

Mouth, pharynx, and larynx cancers, like other types, are the result of genetic alterations that lead to small, localised lesions in the mucous membranes that grow in an abnormal way (dysplasia). These lesions may then progress to carcinoma in situ, and then become invasive cancers.

Exposure to carcinogens, such as those in tobacco, can be prolonged and consistent. The mouth and pharynx are directly exposed to both inhaled carcinogens and those that are ingested by drinking and chewing — including, in the case of chewing tobacco and betel quid, when it is spat out after chewing. Chronic damage and inflammation caused by stomach acid are also implicated; some studies have found that laryngopharyngeal reflux (where stomach acid flows upwards to the larynx and/or pharynx) is associated with laryngeal cancers.[7 8]

Cancers of the mouth, pharynx, and larynx frequently show multiple, independent, malignant foci — with second primary cancers occurring relatively frequently. This phenomenon occurs when an entire region of tissue is repeatedly exposed to carcinogens. Around 90 per cent of oral cancers occur after exposure to tobacco or alcohol, or a combination of both.[9]

7.1.3 Other established causes

7.1.3.1 General

(Also see chapter 2.4.)

Throughout this chapter, this section lists factors outside the scope of this Report, identified as established causes of cancer by the World Health Organization International Agency for Research on Cancer, and other authoritative bodies. These factors are as listed in chapter 2.4: tobacco use; infectious agents; radiation; industrial chemicals; and some medications. Other diseases may also increase the risk of cancer. In the same way, life events that modify the risk of cancer — causative and protective — are also included.

'Established' effectively means 'beyond reasonable doubt' — roughly the equivalent of the judgement of 'convincing' used in this Report. Occasionally, authoritative findings that perhaps fall short of 'established' are also included here.

Where possible, a note of interactive or multiplicative effects with food, nutrition, and the other factors covered by this Report is added, as is any indication of scale or relative importance. The factors here are almost all causative, whereas much of the evidence on food, nutrition, physical activity, and related factors shows or suggests protection against cancer.

7.1.3.2 Specific

Other diseases. There is substantial evidence that gastric reflux increases the risk of oral cancers.

Tobacco use. Smoking, and other use of and exposure to tobacco, is the most important cause of oral cancers, including those of the mouth, pharynx, and larynx. These factors are estimated to cause around 60 per cent per cent of all laryngeal cancers. While alcoholic drinks are an independent cause of these cancers, risk is multiplied if drinkers smoke tobacco and if smokers drink .[10] Chewing of betel quid (with or without added tobacco) also causes oral cancers.[11]

Infection and infestation. Human papilloma viruses (HPVs) are a cause of oral cancers.[12-14]

7.1.4 Interpretation of the evidence

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

7.1.4.2 Specific

Considerations specific to cancers of the mouth, pharynx, and larynx include:

Classification. Some studies did not report separately on cancers of the mouth, pharynx, or larynx, but grouped these cancers with others as 'head and neck cancers' or 'upper aerodigestive tract cancers'. The term 'head and neck cancer' includes all of these sites plus cancers of the middle ear, the nasal cavity, and the paranasal sinuses. The term 'upper aerodigestive tract cancer' includes all head and neck cancers and oesophageal cancer (see 7.3).

Confounding. High-quality studies adjust for smoking but may still be subject to residual confounding. Because of the size of the effect of smoking, and the tendency for the diets of smokers to be low in vegetables and fruits, and for smokers to have relatively lower body mass indices, residual confounding is a particular concern for these exposures. Wherever possible, detailed stratification of the data according to smoking status was obtained.

7.1.5 Evidence and judgements

In total, 238 publications were included in the systematic literature review (SLR) for cancers of the mouth, pharynx, and larynx. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.1.5.1 Non-starchy vegetables

(Also see chapter 4.2.5.1.)

A total of 31 case-control studies and 3 ecological studies examined non-starchy vegetables. Other groupings examined were non-starchy vegetables and fruits (in combination) (1 cohort, 6 case-control); raw vegetables (23 case-control); cruciferous vegetables (1 cohort, 14 case-control, and 1 ecological); green, leafy vegetables (1 cohort, 10 case-control); carrots (3 cohort, 18 case-control); and tomatoes (1 cohort, 12 case-control). Most of the studies for the exposures grouped under non-starchy vegetables showed a decreased risk with increased intake. Meta-analysis showed a 28 per cent decreased risk per 50 g per day (figure 4.2.2). The dose-response relationship suggested that the greatest effect was produced by the first increment; that is, that some vegetable consumption confers a protective effect compared with none (figure 4.2.3). However, it is not clear that the effect continues in a linear fashion. It is possible that this is an artificial phenomenon produced by residual confounding due to smoking. There is some unexplained heterogeneity.

This is a wide and disparate category, and many different plant food constituents are represented that could contribute to a protective effect of non-starchy vegetables. These include dietary fibre, carotenoids, folate, selenium, glucosinolates, dithiolthiones, indoles, coumarins, ascorbate, chlorophyll, flavonoids, allylsulphides, flavonoids, and phytoestrogens, some of which are potentially antioxidants. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. It is difficult to unravel the relative importance of each constituent and is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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[15 16] and two case-control studies[17 18] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.1.5.2 Fruits

(Also see chapter 4.2.5.2.)

A total of 1 cohort study, 35 case-control studies, and 2 ecological studies investigated fruits. Other groupings examined were citrus fruits (1 cohort, 23 case-control, 1 ecological), and non-starchy vegetables and fruits (in combination) (1 cohort, 6 case-control). Most studies showed decreased risk. Meta-analysis showed a 18 per cent decreased risk per 100 g per day for general fruits, or 24 per cent per 50 g per day for citrus fruits (figures 4.2.17 and 4.2.18). The dose-response relationship suggested that the greatest effect was produced by the first increment; that is, that some fruit consumption confers a protective effect compared to none. However, it is not clear that the effect continues in a linear fashion (figures 4.2.19 and 4.2.20). It is possible that this is an artificial phenomenon produced by residual confounding due to smoking.

Studies that reported on combined intake of non-starchy vegetables and fruits showed evidence of an association with decreased risk (see 7.1.5.1).

Fruits are sources of vitamin C and other antioxidants such as carotenoids, phenols, and flavonoids, as well as other potentially bioactive phytochemicals. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. It is difficult to unravel the relative importance of each constituent, and is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

The evidence, including that 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[15 16] and one case-control study[18] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.1.5.3 Foods containing carotenoids

(Also see chapter 4.2.5.3.)

Two cohort studies investigated total serum carotenoids, 10 case-control studies investigated pro-vitamin A carotenoids, and 2 case-control studies investigated total dietary carotenoids. Other groupings examined were dietary alpha-carotene (1 cohort); serum alpha-carotene (3 cohort); dietary beta-carotene (1 cohort, 7 case-control); serum beta-carotene (3 cohort, 2 case-control); dietary lycopene (1 cohort, 4 case-control); and serum lycopene (1 cohort, 1 case-control). All of the serum studies and most of the dietary studies showed decreased risk with increased measures of carotenoids. Meta-analysis was not possible. Information comes predominantly from dietary sources, not supplements; therefore no effect can be attributed to carotenoids separate from foods.

In trials, carotenoids have been effective at reducing cellular damage within the mouth, which may act as a precursor to cancers in this region. Carotenoids are antioxidants. Oxidative damage is linked to the formation of tumours through several mechanisms. Oxidative stress damages DNA. This might be prevented or limited by dietary antioxidants found in fruits and vegetables.

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[15] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.1.5.4 Maté

(Also see chapter 4.7.5.6.1.)

Six case-control studies were examined. All reported increased risk from drinking maté, which was statistically significant in four.

There is some biological plausibility. Maté is a herbal infusion traditionally drunk very hot through a metal straw. This produces heat damage in the mouth, pharynx, and larynx. Repeated damage of this nature could lead to cancer. Chemical carcinogenesis from constituents of maté has also been postulated.[19 20]

The evidence is sparse. There is limited evidence suggesting that maté is a cause of mouth, pharynx, and larynx cancers.

7.1.5.5 Alcoholic drinks

(Also see chapter 4.8.5.1.)

Five cohort studies, 89 case-control studies, and 4 ecological studies investigated alcoholic drinks. All cohort studies and nearly all case-control studies showed increased risk. Meta-analysis of cohort data showed a 24 per cent increased risk per drink/week; case-control data showed a 3 per cent increased risk per drink/week (figure 4.8.2). The cohort studies showed a curvilinear dose-response relationship.

It is biologically highly plausible that alcoholic drinks are a cause of mouth, pharynx, and larynx cancers. IARC classifies alcohol as a Class 1 carcinogen. Reactive metabolites of alcohol such as acetaldehyde can be carcinogenic. There is also an interaction with smoking. 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. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation, and the generation of free radical oxygen species. High consumers of alcohol may also have diets low in essential nutrients, making tissues susceptible to carcinogenesis.

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[15] and four case-control studies[21-24] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.1.5.6 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) and their products; starchy

roots, tubers, and plantains; pulses (legumes); foods containing dietary fibre; meat; poultry; fish; eggs; milk and dairy products; total fat; foods containing animal fat; plant oils; coffee; tea; frying, grilling (broiling), and barbecuing; protein; vitamin A; retinol; thiamin; riboflavin; niacin; folate; vitamin C; vitamin E; iron; calcium; selenium; energy intake; and body fatness.

Fourteen case-control studies examined body fatness, as measured by body mass index (BMI). Meta-analysis produced a statistically significant decreased risk with increased BMI, and a dose-response relationship, but reverse causality was implicated. That is, cancers of the mouth, pharynx, and larynx cause significant weight loss, often before diagnosis. Smoking is also associated with low BMI. For these reasons, the data were judged insufficient to allow any conclusion to be drawn.

7.1.6 Comparison with previous report

The main differences between this Report and the previous report are summarised here, together with any reasons for these differences. When the findings here and in the previous report are similar, this is usually not mentioned. Minor differences are not always mentioned.

7.1.6.1 General

The criteria used by the previous report for gauging the strength of the evidence were not identical to the criteria used for this Report. In particular, a judgement of 'convincing' causal association was not conditional on supportive evidence from prospective studies. This Report does make that requirement. It also emphasises the special importance of randomised controlled trials when applied appropriately, especially where the results are positive. In these respects, the criteria used for this Report are more stringent. See box 3.8 in chapter 3.

7.1.6.2 Specific

The previous report separated cancers of the mouth and pharynx from cancer of the larynx. The panel responsible for the previous report judged the evidence that vegetables and fruits protect against cancers of the mouth and pharynx to be convincing. It also judged that these foods probably protect against cancer of the larynx. Vitamin C was judged to be possibly protective against cancers of the mouth and larynx. There is still little information from cohort studies, which weakens the evidence base.

Evidence accumulated since the mid-1990s confirms the previous judgement that the evidence that alcoholic drinks are a cause of oral cancers is convincing. And in the previous report, the evidence that maté is a cause of oral cancers was judged possible for cancers of the mouth and pharynx.

7.1.7 Conclusions

The Panel concludes:

The evidence that alcoholic drinks are a cause of cancers of the mouth, pharynx, and larynx is convincing. The risk is multiplied when drinkers of alcohol also smoke tobacco.

Non-starchy vegetables, fruits, and foods containing carotenoids probably protect against these cancers.

There is limited evidence suggesting that maté, a herbal infusion, when drunk scalding hot through a metal straw, as is traditional in some parts of South America, is a cause of oral cancer.

The main cause of these cancers is smoking and other use of and exposure to tobacco.

7.2 Nasopharynx

Cancer of the nasopharynx is the 23rd most common type of cancer worldwide. About 80 000 cases were recorded in 2002, accounting for less than 1 per cent overall. In most parts of the world, this cancer is rare. It is relatively common on and near the southern Chinese littoral, and among communities who have migrated from that part of China to other countries. It is twice as common in men as in women. It is the 20th most common cause of death from cancer.

Overall, *the Panel judges* that there is a specific role for Cantonese-style salted fish in the causation of cancer of the nasopharynx.

***The Panel judges* as follows:**
Cantonese-style salted fish is probably a cause of nasopharyngeal cancer. This judgement does not apply to fish salted or fermented by any other method.

There is limited evidence suggesting that non-starchy vegetables and fruits protect against this cancer.

Other causes of this cancer include tobacco smoking and infection with the Epstein-Barr virus.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that Cantonese-style salted fish is a probable cause of this cancer.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE NASOPHARYNX

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		**Cantonese-style salted fish[1]**
Limited — suggestive	Non-starchy vegetables[2] Fruits[2]	
Limited — no conclusion	Cereals (grains) and their products; nuts and seeds; herbs, spices, and condiments; meat; fish; shellfish and seafood; eggs; plant oils; tea; alcohol; salted plant food; Chinese-style pickled cabbage; pickled radish; pickled mustard leaf; Chinese-style preserved salted eggs; fermented tofu and soya products	
Substantial effect on risk unlikely	None identified	

1 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.
2 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.

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.

The nasopharynx is the top portion of the pharynx, the muscular cavity leading from the nose and mouth to the larynx.

Cancers in this area arise predominantly from epithelial cells, with squamous cell carcinomas being the most common. Carcinomas constitute 75–90 per cent of nasopharyngeal cancers in low-risk populations, and virtually 100 per cent in high-risk populations.[25] Nasopharyngeal squamous cell carcinomas are included here; other types are not.

7.2.1 Trends, incidence, and survival

Age-adjusted rates of nasopharyngeal cancer are decreasing in areas of high incidence, such as Hong Kong and Singapore.[25]

This cancer is predominantly a disease of low-income countries, with overall rates more than three times higher in middle- to low- than in high-income countries. Incidence is also higher in certain ethnic groups — for instance Chinese and also Malay and Filipino people living in south-eastern Asia.

Around the world, age-adjusted incidence rates range from 20–30 per 100 000 people in parts of Hong Kong and south-eastern Asia, to less than 1 per 100 000 across most of the Americas and Europe.

This cancer also occurs in northern Africa, parts of the Middle East, and Micronesia and Polynesia. However, the highest rates are among Cantonese people who live in the central region of Guangdong Province in southern China, which includes Hong Kong.[25] Migrant populations from this province carry the risk levels of the original population, but this decreases over generations.[26] Rates are approximately twice as high in men as in women.[2]

The age profile of nasopharyngeal cancer is different in areas of high compared with low incidence. Risk increases with age in most of the world, but in Guangdong Province it peaks between the ages of 45 and 54. In populations where there is a moderate incidence of this cancer, risk peaks in young adults.[25] Overall 5-year survival rates are around 50 per cent.[27] Also see box 7.1.1.

There are two variants of nasopharyngeal squamous cell carcinoma: keratinising and non-keratinising. The non-keratinising variant can be further divided into differentiated or undifferentiated. In North America, the proportions of each are 25, 12, and 63 per cent, respectively. In southern China, the distribution is different: 2, 3, and 95 per cent.[27]

Box 7.2.1 Epstein-Barr virus

Most adults are infected with the Epstein-Barr virus, but relatively few will ever develop the cancers of which this virus is a contributory or necessary cause. Other factors beyond infection with the virus are needed to lead to the development of cancer. Environmental factors including some dietary factors are thought to render precancerous epithelial cells sensitive to Epstein-Barr virus infection, which then triggers malignancy.[29]

Epstein-Barr virus is a DNA virus of the herpes family. It primarily infects B lymphocytes (white blood cells that produce antibodies), though it can also infect epithelial cells. Infection usually occurs in childhood and does not usually produce symptoms, but in adults it can cause infectious mononucleosis or glandular fever. It is particularly associated with undifferentiated nasopharyngeal carcinoma, the most prevalent type.[30 31]

In nasopharyngeal carcinoma, all of the tumour cells carry viral DNA in a monoclonal form. This means that Epstein-Barr virus infection must have occurred quite early in the cancer process, before rapid growth.[32] It is not normally possible to detect Epstein-Barr virus infection in non-cancerous nasopharyngeal cells.[31]

7.2.2 Pathogenesis

Variation in the distribution of keratinising squamous cell carcinoma and the two forms of non-keratinising carcinoma in North America and southern China, together with the different age profiles in the two regions, suggests that different disease paths may occur in high-incidence populations.

Patches of dysplasia are the first recognisable precancerous lesions; latent infection with the Epstein-Barr virus (see box 7.2.1) leads to severe dysplasia. The subsequent genetic and chromosomal changes in these lesions lead to invasive carcinoma.[28]

7.2.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Tobacco use. Smoking tobacco is a cause of nasopharyngeal cancer.

Occupational exposure. Occupational exposure to formaldehyde is also a cause of this cancer.[33-35]

Infectious agents. Epstein-Barr virus infection is a cause of nasopharyngeal cancer (see box 7.2.1).[30] It may be necessary but is not a sufficient cause.

7.2.4 Interpretation of the evidence

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

7.2.4.2 Specific

Considerations specific to cancer of the nasopharynx and to Cantonese-style salted fish, include:

Classification. The term 'salted' is an incomplete and perhaps misleading term, given that the fish is also fermented. See the footnote of the matrix for this section, and also 7.2.5.3.

Confounding. It is not possible to exclude a genetic component. Those at highest risk are Cantonese-speaking communities living in or originally from Guangdong Province.

Production, preservation, processing, preparation. The method of salting or the type of fish salted varies between regions. The presence of nitrates and nitrosamines (see box 4.3.2) in the fish also varies.

7.2.5 Evidence and judgements

In total, 74 publications were included in the SLR for nasopharyngeal cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.2.5.1 Non-starchy vegetables

(Also see chapter 4.2.5.1.)

Five case-control studies and two ecological studies investigated non-starchy vegetables; a further four case-control studies investigated green vegetables. Preserved vegetables were excluded from all categories. Nearly all of the studies showed decreased risk with increased intake.

This is a wide and disparate category, and many different plant food constituents are represented that could contribute to a protective effect of non-starchy vegetables. These include dietary fibre, carotenoids, folate, selenium, glucosinolates, dithiolthiones, indoles, coumarins, ascorbate, chlorophyll, flavonoids, allylsulphides, flavonoids, and phytoestrogens, some of which are potentially antioxidants. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. It is difficult to unravel the relative importance of each constituent and it is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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

7.2.5.2 Fruits

(Also see chapter 4.2.5.2.)

Six case-control studies investigated general fruits and a further five case-control studies investigated citrus fruits. Preserved fruits were excluded from all categories. Most of the studies for general fruits and all of the studies for citrus fruits showed a decreased risk.

This is a wide and disparate category, and many different plant food constituents are represented that could contribute to a protective effect of fruits. These include dietary fibre, carotenoids, folate, selenium, glucosinolates, dithiolthiones, indoles, coumarins, ascorbate, chlorophyll, flavonoids, allylsulphides, flavonoids, and phytoestrogens, some of which are potentially antioxidants. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. 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. In addition, some components of citrus fruits have been shown directly to inhibit Epstein-Barr virus activation.[36]

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

7.2.5.3 Cantonese-style salted fish

(Also see chapter 4.3.5.3.1.)

One cohort study and 21 case-control studies of adult diets were examined. The single cohort study and most of the case-control studies showed increased risk with higher intake. Meta-analysis showed a 28 per cent increased risk per time eaten per week (figure 4.3.9). There is some heterogeneity, not all readily explained. Childhood diet data implicate an increased risk with early-life exposure.

Cantonese-style salted fish is dried in natural conditions outdoors. As prepared on the southern Chinese littoral, it is characterised by treatment with less salt than used on the northern littoral; it is also subject to fermentation during the drying process in the warm, damp climate of southern China.

The high content of nitrate and nitrosamines may account for some of the increased risk associated with salted fish intake. Nitrosamines are known mutagens and animal carcinogens that induce gene mutation. The direct role of nitrosamines in the carcinogenic process is supported by the increased risk for nasopharyngeal cancer development in people who have a variant allele of CYP2E1. This enzyme is expressed in the nasopharynx and is involved in the metabolic activation of nitrosamines to carcinogenic adducts.[37] Additional evidence has suggested a component of salted fish may contain Epstein-Barr virus-activating substances, although the specific agents of action have not been identified.[38]

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 a cause of nasopharyngeal cancer.

7.2.5.4 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) and their products; nuts and seeds; meat; fish; shellfish and seafood; eggs; herbs, spices, and condiments; tea; alcohol; plant oils; salted plant foods; Chinese-style pickled cabbage; pickled radish; pickled mustard leaf; Chinese-style preserved salted eggs; and fermented tofu/soya products.

7.2.6 Comparison with previous report

7.2.6.1 General

See 7.1.6.1, and box 3.8.

7.2.6.2 Specific

The previous report judged the evidence that Cantonese-style salted fish is a cause of nasopharyngeal cancer to be convincing. No further cohort studies have been conducted since the mid-1990s.

7.2.7 Conclusions

The Panel concludes:

Cantonese-style salted fish is probably a cause of nasopharyngeal cancer. This does not apply to fish salted or fermented by any other method.

There is limited evidence suggesting that non-starchy vegetables, and also fruits, protect against this cancer.

7.3 Oesophagus

Cancer of the oesophagus is the eighth most common type of cancer worldwide. Around 460 000 cases occurred in 2002, accounting for over 4 per cent overall. There are two common types of oesophageal cancer, adenocarcinoma and squamous cell carcinoma, which have different patterns of occurrence. In general this cancer is not increasing, except for adenocarcinomas, which are increasing in high-income countries. Oesophageal cancer is twice as common in men as in women. It is usually fatal and is the sixth most common cause of death from cancer.

Overall, *the Panel judges* that food and nutrition and body fatness play an important role in the prevention and causation of cancer of the oesophagus.

***The Panel judges* as follows:**

The evidence that alcoholic drinks are a cause of cancer of the oesophagus is convincing. The risk is multiplied when drinkers of alcohol also smoke tobacco. The evidence that greater body fatness is a cause of oesophageal adenocarcinoma is also convincing. Maté, a herbal infusion, when drunk scalding hot through a metal straw, as is traditional in parts of South America, is probably a cause of this cancer.

Non-starchy vegetables, fruits, and foods containing beta-carotene and/or vitamin C probably protect against oesophageal cancer.

There is limited evidence suggesting that foods containing dietary fibre, folate, pyridoxine, or vitamin E protect against this cancer, and that red meat, processed meat, and high-temperature drinks are causes of this cancer.

See chapter 8 for evidence and judgements on factors that modify the risk of body fatness, including physical activity and sedentary ways of life, the energy density of foods and drinks, and breastfeeding.

Other causes of this cancer include smoking tobacco and chewing betel quid. It has been estimated that most cases of oesophageal cancer are preventable by appropriate diets and associated factors, together with not smoking.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that alcoholic drinks and body fatness are a cause of this cancer (adenocarcinoma only); that non-starchy vegetables, fruits, and foods containing beta-carotene and/or vitamin C are probably protective; and that maté, as traditionally drunk in parts of South America, is probably a cause of this cancer.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE OESOPHAGUS

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

	DECREASES RISK	INCREASES RISK
Convincing		**Alcoholic drinks** **Body fatness[1]**
Probable	**Non-starchy vegetables[2]** **Fruits[2]** **Foods containing beta-carotene[3]** **Foods containing vitamin C[3]**	**Maté[4]**
Limited — suggestive	Foods containing dietary fibre[3] Foods containing folate[3] Foods containing pyridoxine[3 5] Foods containing vitamin E[3]	Red meat[6] Processed meat[7] High-temperature drinks
Limited — no conclusion	Cereals (grains) and their products; starchy roots, tubers, and plantains; pulses (legumes); soya and soya products; herbs, spices, and condiments; poultry; fish; eggs; milk and dairy products; total fat; saturated fatty acids; monounsaturated fatty acids; polyunsaturated fatty acids; sugary foods and drinks; salt; salting; fermenting; pickling; smoked and cured foods; nitrates and nitrites; frying; grilling (broiling) and barbecuing (charbroiling); protein; vitamin A; retinol; thiamin; riboflavin; calcium; iron; zinc; pro-vitamin A carotenoids; beta-cryptoxanthin; Seventh-day Adventist diets; adult attained height; energy intake	
Substantial effect on risk unlikely	None identified	

1 For oesophageal adenocarcinomas only.
2 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
3 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 box 4.1.2 and chapter 4.2).
4 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.
5 Vitamin B6.
6 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
7 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.

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.

The oesophagus is the muscular tube through which food passes from the pharynx to the stomach.

The oesophagus is lined over most of its length by squamous epithelial cells, where squamous cell carcinomas occur. The portion just above the gastric junction (where the oesophagus meets the stomach) is lined by columnar

epithelial cells, from which adenocarcinomas can develop.[4] Adenocarcinoma of the oesophagus shows similarities with adenocarcinoma of the gastric cardia (see 7.5). Each type accounts for around half of all cases and both types are included in this Report.

7.3.1 Trends, incidence, and survival

Age-adjusted rates of oesophageal squamous cell carcinomas are generally declining, although in some high-income regions, overall rates of oesophageal cancer are increasing. For instance, the incidence of oesophageal adenocarcinoma is rising rapidly in Europe and North America.[39] In the USA, adenocarcinomas in white men increased fivefold between 1974 and the end of the 20th century, making it the fastest increasing cancer studied in that country.[40]

Oesophageal cancer is, however, mainly a disease of low-income countries, occurring around four times more commonly in low- to middle- than in high-income countries. Around the world, age-adjusted incidence rates range from more than 20 per 100 000 people in parts of eastern and southern Africa and eastern and south-central Asia to less than 5 per 100 000 in northern, western, and middle Africa, Central America, and south-eastern Asia. Localised peaks in incidence have been reported to exceed 100 per 100 000. For instance, in rural Linxian, China, oesophageal cancer is the leading cause of death.[41] In the USA, rates are higher among African-American people than in white people. Worldwide, rates are higher in men than in women, by around five to two. In most populations, risk increases with age, with few cases diagnosed in people under 40.

Oesophageal cancer does not usually produce symptoms at the early stages, so the disease is generally at an advanced stage when diagnosed. Survival rates are poor: around 10 per cent at 5 years.[3 6] This type of cancer accounts for a little over 4 per cent of all cancer incidence, but almost 6 per cent of all cancer deaths worldwide. Also see box 7.1.1.

7.3.2 Pathogenesis

The epithelial cells lining the oesophagus are exposed directly to carcinogens in food. Repeated exposures, for instance, to burns from very high-temperature drinks or irritation from the direct action of alcohol, may cause inflammation.

The role of irritation and inflammation in the development of oesophageal cancer is supported by the finding that gastro-oesophageal reflux (where stomach acid flows upwards to the oesophagus) increases the risk of adenocarcinomas by as much as 40-fold.[42] Barrett's oesophagus is a probable intermediate stage between gastro-oesophageal reflux disease, with repeated gastro-oesophageal reflux, and developing oesophageal adenocarcinoma.[43] Barrett's oesophagus is an acquired condition in which squamous cells are replaced by columnar epithelial cells; autopsy studies suggest that it usually remains undiagnosed.[44] The increasing use of endoscopes to investigate abdominal symptoms has resulted in the earlier detection of a small proportion of adenocarcinomas in people with Barrett's oesophagus.[4]

Some people have an abnormally strong lower oesophageal sphincter (a condition called oesophageal achalasia), which means swallowed food is retained in the oesophagus. It causes a 15-fold increase in the risk of squamous cell carcinomas, which may be due to chronic irritation of the lining of the oesophagus or its increased contact with food-borne carcinogens.[45 46]

Tylosis A is the late-onset, inherited familial disease where the outer horny layer of the skin thickens, affecting the palms and soles (hyperkeratosis). Palmar and plantar hyperkeratosis is the single proven genetic abnormality associated with a 25 per cent lifetime incidence of squamous cell cancer of the oesophagus.[47]

7.3.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Other diseases. Gastric reflux and oesophageal achalasia both increase the risk of, and thus can be seen as a cause of, this cancer. Barrett's oesophagus can be seen as a precancerous condition.

Tobacco use. Smoking is a cause both of oesophageal squamous cell carcinoma and of adenocarcinomas, increasing the risk approximately twofold.[10 39] Smoking is estimated to cause around 40 per cent of all cases. Chewing betel quid (on its own and also with tobacco quid) is also a cause of oesophageal cancers.[11]

Infectious agents. HPV (see box 7.13.1) is also a cause of this cancer, and is estimated to be a cause of almost 25 per cent of squamous cell carcinomas. Like other infectious agents, it may be a necessary cause but is not a sufficient cause. It may also play a role in the divergent geographical distributions of this cancer.[48]

7.3.4 Interpretation of the evidence

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

7.3.4.2 Specific

Considerations specific to cancer of the oesophagus include:

Classification. There are different types of oesophageal cancer. Squamous cell carcinomas have different geographical and time trends from adenocarcinomas. Each follows a different disease path, and may have different associated risk factors. However, there were only sufficient data to conduct separate analyses for body fatness. Therefore the ratio of

squamous cell carcinomas to adenocarcinomas in each study is a potential cause of heterogeneity in all other summaries. The oesophageal-gastric junction and gastric cardia are also lined with columnar epithelial cells. Cancers in these areas are often grouped with oesophageal cancers, although they may also be classed as stomach cancers (see 7.5).[4] Different approaches or definitions in different studies are another potential source of heterogeneity.

Confounding. Smoking is the main single cause of this cancer. High-quality studies adjust for smoking.

7.3.5 Evidence and judgements

In total, 262 publications were included in the SLR for oesophageal cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.3.5.1 Foods containing dietary fibre

(Also see chapter 4.1.5.3.)

One cohort study, nine case-control studies, and two ecological studies investigated dietary fibre. Most were suggestive of a relationship with decreased oesophageal cancer incidence. Data come predominantly from dietary sources, not supplements; therefore no specific effect can be attributed specifically to dietary fibre itself, which is interpreted simply as a marker of consumption of foods containing it.

It is not clear whether there is an as yet unknown mechanism through which dietary fibre could exert a direct effect on oesophageal cancer, or whether the effect is mediated through other constituents of the foods (such as cereals (grains), 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.

7.3.5.2 Non-starchy vegetables

(Also see chapter 4.2.5.1.)

A total of 5 cohort studies, 37 case-control studies, and 6 ecological studies investigated non-starchy vegetables. Other groupings examined were vegetable and fruit consumption (combined) (8 case-control), raw vegetables (16 case-control), cruciferous vegetables (1 cohort, 5 case-control), allium vegetables (1 cohort, 8 case-control), green, leafy vegetables (1 cohort, 11 case-control), and tomatoes (1 cohort, 9 case-control). All of the studies of raw vegetables and most of the other studies showed decreased risk with increased intake. Meta-analysis of case-control data showed a 31 per cent decreased risk per 50 g of raw vegetables per day (figures 4.2.6 and 4.2.7). Raw vegetables have a more consistent definition than non-starchy vegetables, which may include preserved vegetables and a variety of cooking methods, leading to increased heterogeneity.

This is a wide and disparate category, and many different plant food constituents are represented that could contribute to a protective effect of non-starchy vegetables. These include dietary fibre, carotenoids, folate, selenium, glucosinolates, dithiolthiones, indoles, coumarins, ascorbate, chlorophyll, flavonoids, allylsulphides, flavonoids, and phytoestrogens, some of which are potentially antioxidants. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. It is difficult to unravel the relative importance of each constituent and it is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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 (see chapter 4.2.5.1). Non-starchy vegetables probably protect against oesophageal cancer.

The Panel is aware that since the conclusion of the SLR, one cohort[49] and two case-control studies[17 50] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.3.5.3 Fruits

(Also see chapter 4.2.5.2.)

A total of 4 cohort studies, 36 case-control studies, and 7 ecological studies investigated fruits; and 1 cohort study, 16 case-control studies, and 1 ecological study investigated citrus fruits. All of the cohort studies and most of the other studies showed decreased risk with increased intake. Meta-analysis of case-control data showed a 22 per cent decreased risk per 50 g of fruit per day, and 30 per cent decreased risk per 50 g of citrus fruit per day (figures 4.2.22 and 4.2.24). A dose-response relationship was apparent. Heterogeneity could not be fully explained.

Fruits are sources of vitamin C and other antioxidants, such as carotenoids, phenols, and flavonoids, as well as other potentially bioactive phytochemicals. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage.

It is difficult to unravel the relative importance of each constituent and it is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

The evidence, including that 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[49] and two case-control studies[50 51] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.3.5.4 Foods containing folate

(Also see chapter 4.2.5.4.)

Eight case-control studies investigated dietary folate and two case-control studies investigated red-cell and plasma folate. All studies showed a relationship with decreased cancer incidence. Data come predominantly from dietary sources, not supplements; therefore no effect can be attributed to folate separate from foods.

Folate plays an important role in the synthesis, repair, and methylation of DNA. Abnormal DNA methylation has been linked to aberrant gene expression and to cancers at several sites. Folate may also reduce HPV proliferation in cells.

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[52] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.3.5.5 Foods containing pyridoxine (vitamin B6)

(Also see chapter 4.2.5.5.)

Six case-control studies investigated foods containing pyridoxine and oesophageal cancer.

All six studies showed a relationship between pyridoxine consumption and reduced risk of oesophageal cancer, with none reporting contrary results.

Together with folate and cobalamin (vitamin B12), vitamin B6 is involved in one-carbon metabolism and 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[52] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.3.5.6 Foods containing vitamin C

(Also see chapter 4.2.5.6.)

One cohort study, 19 case-control studies, and 3 ecological studies investigated vitamin C. The single cohort study and nearly all of the case-control studies showed decreased risk with increased intake.

Vitamin C traps free radicals and reactive oxygen molecules, protecting DNA from mutagenic attack, protecting against lipid peroxidation, reducing nitrates, and stimulating the immune system.

A substantial amount of consistent evidence is available, both from cohort and from 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[53] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.3.5.7 Foods containing vitamin E

(Also see chapter 4.2.5.7.)

One cohort study, nine case-control studies, and one ecological study investigated dietary vitamin E; three cohort studies and four case-control studies investigated serum vitamin E. All cohort studies and most case-control studies showed decreased risk with increased intake; serum case-control data were inconsistent.

Vitamin E is a family of eight compounds collectively referred to as tocopherols. They can act as antioxidants and free radical scavengers; however, few animal studies support an anti-cancer effect.

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.

7.3.5.8 Foods containing beta-carotene

(Also see chapter 4.2.5.3.)

Ten case-control studies investigated dietary beta-carotene; three cohort studies and one case-control study investigated serum beta-carotene; and one cohort study and three case-control studies investigated dietary pro-vitamin A carotenoids. Most of these studies showed a relationship with decreased risk.

Data come predominantly from dietary sources, not supplements; therefore no effect can be attributed to carotenoids separate from foods.

Carotenoids are antioxidants, which can prevent lipid oxidation and related oxidative stress. Some, such as beta-carotene, are also pro-vitamin A carotenoids.

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.

7.3.5.9 Red meat

(Also see chapter 4.3.5.1.1.)

Twelve case-control studies investigated red meat. Most were suggestive of increased risk.

There are several potential underlying mechanisms for a positive association of red meat consumption with oesophageal cancer, including the generation of potentially carcinogenic *N*-nitroso compounds (see box 4.3.2). Some meats are also cooked at high temperatures, resulting in the production of heterocyclic amines and polycyclic aromatic hydrocarbons (see box 4.3.4). Red meat contains haem iron. Free iron can lead to the production of free radicals (see box 4.3.3).

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[54] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.3.5.10 Processed meat

(Also see chapter 4.3.5.1.2.)

Two cohort studies and eight case-control studies investigated processed meat. Both cohort studies were suggestive of increased risk; case-control data were inconsistent. The definition of processed meat varies (see box 4.3.1), which may increase heterogeneity.

Nitrates are produced endogenously in gastric acid and are added as preservatives to processed meats (see box 4.3.2). This may contribute to production of *N*-nitroso compounds and increased exposure. These compounds are suspected mutagens and carcinogens.[55]

Many processed meats also contain high levels of salt and nitrite. Meats cooked at high temperatures can contain heterocyclic amines and polycyclic aromatic hydrocarbons (see box 4.3.4). Haem promotes the formation of *N*-nitroso compounds and also contains iron. Free iron can lead to the production of free radicals (see box 4.3.3).

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[54] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.3.5.11 Maté

(Also see chapter 4.7.5.6.1.)

Eight case-control studies and one ecological study investigated maté. Most were suggestive of an increased incidence with higher maté consumption. Meta-analysis of case-control data showed a 16 per cent increased risk per cup/day (figure 4.7.5). A dose-response relationship was apparent.

There is some biological plausibility. Maté is a tea-like beverage typically drunk very hot through a metal straw. This produces heat damage in the oesophagus. Repeated damage of this nature can lead to cancer (see chapter 2.4.1.3). Chemical carcinogenesis from constituents of maté has also been postulated.[19 20]

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.

7.3.5.12 High-temperature foods and drinks

(Also see chapter 4.7.5.7.)

Three cohort studies and 15 case-control studies investigated high-temperature foods and drinks. Most were suggestive of a relationship between them and increased incidence of oesophageal cancer but many were inadequately adjusted for alcohol and smoking.

High-temperature foods and drinks can produce heat damage in the oesophagus. Repeated damage of this nature can predispose to the development of oesophageal cancer.

The evidence is inconsistent. There is limited evidence suggesting that high-temperature drinks are a cause of oesophageal cancer.

The Panel is aware that since the conclusion of the SLR, two case-control studies[50 51] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.3.5.13 Alcoholic drinks

(Also see chapter 4.8.5.1.)

Eight cohort studies, 56 case-control studies, and 10 ecological studies investigated alcoholic drinks. Most studies showed a relationship between increased consumption and increased cancer incidence. Meta-analysis of case-control data showed a 4 per cent increased risk per drink/week (figure 4.8.6). A dose-response relationship is apparent from case-control data, with no clear threshold.

It is biologically highly plausible that alcoholic drinks are a cause of oesophageal cancer. Reactive metabolites of alcohol such as acetaldehyde can be carcinogenic. 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. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation, and the generation of free radical oxygen species. Lastly, heavy consumers of alcohol may have diets low in essential nutrients, making tissues susceptible to carcinogenesis.

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[56] and four case-control studies[50 51 53 57] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.3.5.14 Body fatness

(Also see chapter 6.1.3.1.)

A sufficient number of studies investigated BMI to allow squamous cell carcinomas and adenocarcinomas to be analysed separately. While results were inconsistent for squamous cell carcinomas and for all oesophageal cancers, adenocarcinomas, when analysed separately, showed a consistent increased risk with greater BMI. Three cohort studies and eight case-control studies investigated body fatness, as measured by BMI and adenocarcinomas. All of the cohort studies and most of the case-control studies showed increased risk with increased BMI. Meta-analysis of case-control data showed a 55 per cent increased risk per 5 kg/m^2 (figure 6.1.2). A dose-response relationship is apparent. This is consistent with known geographical and time trends for both BMI and adenocarcinomas.

It is biologically plausible that body fatness is a cause of

oesophageal cancer. High body fatness is associated with increased gastro-oesophageal reflux and Barrett's oesophagus. It also directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (see box 2.4) Body fatness stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers (see chapter 2.4.1.3).

The epidemiology is consistent with evidence of a dose-response relationship. There is evidence for plausible mechanisms that operate in humans. The evidence that greater body fatness is a cause of oesophageal adenocarcinoma is convincing.

The Panel is aware that since the conclusion of the SLR, two cohort[58 59] and five case-control studies[51 53 60-62] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.3.5.15 Other exposures

Other exposures were evaluated. However, the data were either too sparse, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) or their products; starchy roots, tubers, and plantains; pulses (legumes); soya and soya products; herbs, condiments or spices; poultry; fish; eggs; milk and dairy products; sugary foods and drinks; fermenting; pickling; salt; salting; smoked and cured foods; nitrates and nitrites; frying, grilling (broiling), and barbecuing; total fat; saturated fatty acids; monounsaturated fatty acids; polyunsaturated fatty acids; protein; vitamin A; retinol; pro-vitamin A carotenoids; beta-cryptoxanthin; thiamin; riboflavin; iron; calcium; zinc; energy intake; adult attained height; and Seventh-day Adventist diets.

7.3.6 Comparison with previous report

7.3.6.1 General

See section 7.1.6.1 of this chapter, and box 3.8 in chapter 3.

7.3.6.2 Specific

The previous report judged the evidence that vegetables and fruits protect against oesophageal cancer to be convincing. Data published since then have been somewhat less consistent.

At the time of the previous report, the evidence on body fatness was unclear, because data on adenocarcinomas was inadequate and not analysed separately.

The previous report judged it possible that carotenoids or vitamin C protect against this cancer. The evidence base for foods containing these nutrients is now stronger. The previous report judged it possible that maté and other very hot drinks cause oesophageal cancer. The evidence on maté is now stronger.

7.3.7 Conclusions

The Panel concludes:
The evidence that alcoholic drinks and body fatness (adenocarcinomas only) are causes of cancer of the oesophagus is convincing. The risk is multiplied when drinkers of alcohol also smoke tobacco.

Non-starchy vegetables, fruits, and foods containing beta-carotene and/or vitamin C probably protect against oesophageal cancer.

Maté, a herbal infusion, when drunk scalding hot through a metal straw as is traditional in South America, is probably a cause of this cancer.

There is limited evidence suggesting that foods containing dietary fibre, folate, pyridoxine, or vitamin E protect against this cancer; and that red meat, processed meat, and high temperature drinks are causes of this cancer.

7.4 Lung

Cancer of the lung is the most common type of cancer worldwide (excluding non-melanoma skin cancer). Around 1.4 million cases were recorded in 2002, accounting for over 12 per cent of all cancers. Three-quarters of all cases occur in men. The disease is most common in high-income countries and is increasing in some low-income countries such as China. It is almost always fatal, and is the chief cause of death from cancer: nearly 18 per cent of all deaths from cancer are from this type.

Overall, *the Panel emphasises* that the principal cause of lung cancer is smoking tobacco.

***The Panel judges* as follows:**

The evidence that arsenic in drinking water and (in smokers only) pharmacological doses of beta-carotene are a cause of this cancer is convincing.

Fruits, and also foods containing carotenoids, probably protect against lung cancer.

There is limited evidence suggesting that non-starchy vegetables, selenium and foods containing it, foods containing quercetin, and physical activity protect against lung cancer.

There is also limited evidence suggesting that red meat, processed meat, total fat, butter, pharmacological doses of retinol (smokers only), and low body fatness are causes of lung cancer.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that arsenic in drinking water and pharmacological doses of beta-carotene (smokers only) are causes of lung cancer; and that fruits and foods containing carotenoids probably protect against this cancer.

The lungs are part of the aerodigestive system. They contain hundreds of lobules, and each lobule contains a bronchiole, its branches, and clusters of alveoli. This is where carbon dioxide (a product of respiration) is removed from the blood and replaced with oxygen, to fuel further respiration, producing energy.

About 90–95 per cent of lung cancers are either small-cell carcinoma or non-small-cell carcinoma. The latter has three major subtypes: squamous cell carcinoma, adenocarcinoma, and large-cell carcinoma.[4] Squamous cell carcinomas account for 30–35 per cent, adenocarcinomas 30–45 per cent, and large-cell carcinomas about 9 per cent of all lung cancers. Small cell lung cancer (SCLC) accounts for 10–15 per cent of all lung cancers; this form is considered a distinct clinical pathological entity due to its characteristic aggressive biology, diffuse nature, propensity for early metastasis, and overall poor prognosis. Mesothelioma, which affects the pleura (layer of cells covering the lung and chest cavity), is almost always caused by previous exposure to asbestos.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE LUNG

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

	DECREASES RISK	INCREASES RISK
Convincing		**Arsenic in drinking water[1]** **Beta-carotene supplements[2]**
Probable	**Fruits[3]** **Foods containing carotenoids[4]**	
Limited — suggestive	Non-starchy vegetables[3] Foods containing selenium[4] Foods containing quercetin[4] Selenium[5] Physical activity[6]	Red meat[7] Processed meat[8] Total fat Butter Retinol supplements[2] Low body fatness
Limited — no conclusion	Cereals (grains) and their products; starchy tubers; dietary fibre; pulses (legumes); poultry; fish; eggs; milk and dairy products; total fat; animal fats; plant oils; soft drinks; coffee; tea; alcohol; preservation, processing, and preparation; carbohydrate; protein vitamin A; thiamin; riboflavin; niacin; vitamin B6; folate; vitamin C; vitamin E; multivitamins; calcium; copper; iron; zinc; pro-vitamin A carotenoids; lycopene; flavonoids; culturally-defined diets; body size, shape, and composition (except low body fatness); energy intake	
Substantial effect on risk unlikely	None identified	

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 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.
3 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
4 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).
5 The evidence is derived from studies using supplements at a dose of 200 µg/day.
6 Physical activity of all types: occupational, household, transport, and recreational.
7 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
8 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.

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.

7.4.1 Trends, incidence, and survival

Smoking and other exposure to tobacco smoke are the principal causes of lung cancer. The trend and incidence patterns are explained largely by these exposures. Age-adjusted rates of lung cancer are decreasing in many high-income countries due to decreased smoking. Global and regional trends in incidence have mirrored the prevalence of smoking, with a time lag of around 35 years.[63] Lung cancer was rare until the end of the 19th century, with only 140 cases reported in the world literature before 1898, and only 374 by 1912.[63] Incidence peaked in most high-income countries in the second half of the 20th century, and later for women than men.

The relative incidence of the various types of lung cancer is gradually changing. Between 1980 and 2000, the proportion of squamous cancers decreased as the proportion of adenocarcinomas increased, possibly due to changes in smoking habits or products.[64] Adenocarcinoma is now the most frequently diagnosed type in the USA and Japan; while it is also showing signs of increasing in Europe, squamous cell carcinoma continues to be the predominant type.

Lung cancer is mainly a disease of high-income countries, where the smoking epidemic began earlier, and overall rates are nearly double those in middle- to low-income countries. Around the world, age-adjusted incidence ranges from more than 60 per 100 000 people in North America and across much of Europe, to less than 5 per 100 000 in much of middle Africa. Within Europe, rates are highest in eastern European countries. In the USA, rates are higher among African-American people than in white people. Worldwide, rates are higher in men than in women, by around three to one. The incidence of lung cancer increases with age. Rates will continue to rise in middle- and low-income countries as tobacco smoking increases.

The early stages of lung cancer do not usually produce symptoms, so the disease is generally at an advanced stage when it is diagnosed. Survival rates are poor, around 10 per cent at 5 years, and are usually higher in women than men.[3 6] SCLC has a worse prognosis than non-SCLC (a survival rate of only around 5 per cent at 5 years), because SCLC has a tendency to metastasise (spread) early, and surgery is not usually successful.[4 65] Lung cancer accounts for somewhat over 12 per cent of all cancer incidence, but for nearly 18 per cent of all cancer deaths. Also see box 7.1.1.

7.4.2 Pathogenesis

Carcinogens in tobacco smoke, or other inhaled particles such as coal tar or asbestos, can interact directly with the DNA of lung cells. Because the whole lung is exposed to inhaled carcinogens, several sites may accumulate different cancerous changes, leading to multiple cancers originating in different types of cell.[4]

Inflammation may also play a role in the development of lung cancer, with cancerous changes occurring as a response to chronic exposure to irritants and repeated injury. Columnar epithelial cells are replaced with stratified squamous epithelial cells, which may also increase cancer risk. The division of these new cells increases, and this eventually is followed by dysplasia of the lung mucosa. When this process involves the full thickness of the mucosa, these dysplastic lesions become carcinoma in situ. Further invasion to the depth of the basement membrane, and the subsequent infiltration of the underlying stroma by malignant cells, signals invasive cancer. This process may take 10–20 years.[4]

People with adenocarcinomas may have an associated history of chronic lung disease, such as scleroderma, rheumatoid disease, sarcoidosis, or tuberculosis.[4]

7.4.3 Other established causes

(Also see chapter 2.4 and section 7.1.3.1.)

Tobacco use. Smoking is the principal cause of lung cancer; it is estimated to be responsible for 85 per cent of all types of this cancer.[66] In populations with a history of long-term cigarette use, the proportion has reached 90 per cent.[10] Involuntary exposure to tobacco smoke ('passive smoking') is also a cause of lung cancer, including in people who have never smoked.[10]

Industrial chemicals. Carcinogens that are causes of lung cancer include aluminium; arsenic; asbestos (both lung cancer and mesothelioma); chloromethyl methyl ether and/or bis-chloromethyl ether; coal-tar fumes; erionite (mesothelioma); pollutants from iron and steel founding; untreated mineral oils; mustard gas; soot; talc containing asbestiform tremolite; and vinyl chloride.[67]

7.4.4 Interpretation of the evidence

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

7.4.4.2 Specific

Considerations specific to cancer of the lung include:

Measurement. Due to low survival rates, both incidence and mortality can be assessed. Low survival times and rates decrease the reliability of case-control studies, which often rely on proxy reporting.

Confounding. Smoking tobacco is the predominant cause of lung cancer, and smokers tend also to have less healthy diets, more sedentary ways of life, and to be leaner than non-smokers. Therefore a central task in assessing the results of dietary studies is to evaluate the degree to which observed associations in smokers may be due to confounding/residual confounding by cigarette smoking; that is, not a direct result of the dietary exposure examined. A high proportion of the studies assessed below are appropriately adjusted for smoking.

7.4.5 Evidence and judgements

In total, 561 publications were included in the SLR for lung cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.4.5.1 Non-starchy vegetables

(Also see chapter 4.2.5.1.)

A total of 17 cohort studies, 27 case-control studies, and 6 ecological studies investigated total vegetables. Other groupings examined were non-starchy vegetables specifically (3 cohort, 1 case-control); green, leafy vegetables, excluding cruciferous (5 cohort, 17 case-control); non-starchy root vegetables and tubers (2 cohort); and carrots (6 cohort, 21 case-control, 1 ecological). Most studies showed decreased risk with increased intake. Data are particularly consistent when stratified for carrots. A pooled analysis of 8 cohort studies (more than 430 000 participants, followed up for 6–16 years, with more than 3200 lung cancer cases) showed a non-significant decreased risk for the groups that ate the most vegetables. There was considerable heterogeneity, not all readily explained.

This is a wide and disparate category, and many different plant food constituents are represented that could contribute to a protective effect of non-starchy vegetables. These include dietary fibre, carotenoids, folate, selenium, glucosinolates, dithiolthiones, indoles, coumarins, ascorbate, chlorophyll, flavonoids, allylsulphides, flavonoids, and phytoestrogens, some of which are potentially antioxidants. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. It is difficult to unravel the relative importance of each constituent and it is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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

7.4.5.2 Fruits

(Also see chapter 4.2.5.2.)

Twenty-five cohort studies, 32 case-control studies, and 7 ecological studies investigated fruit consumption. Most of these showed decreased risk with increased intake. Meta-analysis of cohort data showed a 6 per cent decreased risk per 80 g serving/day; meta-analysis of case-control data showed a 20 per cent decreased risk per serving/day (figure 4.2.25). A pooled analysis of 8 cohort studies (more than 430 000 participants, followed up for 6–16 years, with more than 3200 lung cancer cases) showed a 23 per cent decreased risk for the groups that ate the most fruit. There is considerable heterogeneity, perhaps explained by the broad and disparate nature of this category.

Fruits are sources of vitamin C and other antioxidants, such as carotenoids, phenols, and flavonoids, as well as other potentially bioactive phytochemicals. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. In addition, flavonoids found in fruit directly inhibit the expression of a cytochrome P450 enzyme. This helps to metabolise toxins and has been associated with increased risk of lung cancer, primarily in smokers.[68] It is difficult to unravel the relative importance of each constituent, and it is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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[69] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.4.5.3 Foods containing carotenoids

(Also see chapter 4.2.5.3.)

A total of 11 cohort studies, 16 case-control studies, and 1 ecological study investigated total dietary carotenoids; 4 cohort studies and 5 case-control studies investigated serum or plasma carotenoids. Other groupings examined were dietary beta-cryptoxanthin (7 cohort, 8 case-control, 1 ecological), and serum/plasma beta-cryptoxanthin (6 cohort, 1 case-control). Nearly all cohort studies and most case-control studies showed decreased risk with increased intake. Meta-analysis of cohort data showed a 2 per cent decreased risk per 1 mg dietary carotenoid intake per day, or per 10 μg beta-cryptoxanthin intake per day (figure 4.2.28). A pooled analysis of 7 cohort studies (almost 400 000 participants, followed up for 7–16 years, with more than 3100 lung cancer cases) showed a 24 per cent decreased risk for the groups that consumed the most beta-cryptoxanthin. Several case-control studies did not adjust for smoking. Data come predominantly from dietary sources, not supplements; therefore no effect can be attributed to carotenoids separate from foods.

Carotenoids are antioxidants, which can prevent lipid oxidation and related oxidative stress. Some, such as beta-carotene, are also pro-vitamin A carotenoids.

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.

7.4.5.4 Foods containing selenium

(Also see chapter 4.2.5.8.)

Two cohort studies, 2 case-control studies, and 2 ecological studies investigated dietary selenium; 10 cohort studies, 7 case-control studies, and 4 ecological studies investigated

plasma or serum selenium; and 3 cohort studies investigated selenium levels in nails. Most studies showed decreased risk with increased intake. Meta-analysis of cohort data on plasma or serum selenium produced evidence of decreased risk with a clear dose-response relationship.

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. Four are glutathione peroxidases, which protect against oxidative damage to biomolecules such as lipids, lipoproteins, and DNA. Three are thioredoxin reductases and, among other functions, these regenerate oxidised ascorbic acid to its active antioxidant form.

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

7.4.5.5 Foods containing quercetin

(Also see chapter 4.2.5.9.)

Two cohort studies and three case-control studies investigated quercetin intake. Both cohort studies showed statistically significant decreased risk for the highest intake groups. Data from case-control studies were more heterogeneous.

Quercetin is a flavonoid which directly inhibits expression of a cytochrome P450 enzyme that helps to metabolise toxins, resulting in decreased DNA damage in laboratory experiments.[70]

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

7.4.5.6 Red meat

(Also see chapter 4.3.5.1.1.)

One cohort study and nine case-control studies investigated red meat. The single cohort study and most of the case-control studies showed increased risk with increased intake.

Red meat contains haem iron (see box 4.3.3). Free iron can lead to the production of free radicals. When cooked at high temperatures, red meat can also contain heterocyclic amines and polycyclic aromatic hydrocarbons (see box 4.3.4).

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

7.4.5.7 Processed meat

(Also see chapter 4.3.5.1.2.)

Four cohort studies and 10 case-control studies investigated processed meat, most of which showed increased risk with increased intake.

N-nitroso compounds are suspected mutagens and carcinogens that are found in processed meats, and produced in the stomach from nitrates, including those used to preserve meats.[55] Many processed meats also contain high levels of salt and nitrite (see box 4.3.2). When cooked at high temperatures, meats can also contain heterocyclic amines and polycyclic aromatic hydrocarbons (see 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 (see box 4.3.3).

There is limited, inconsistent evidence suggesting that processed meat is a cause of lung cancer.

7.4.5.8 Total fat

(Also see chapter 4.5.5.1.)

Nine cohort studies, 17 case-control studies, and 4 ecological studies investigated total fat intake. Most studies showed increased risk with increased intake, although cohort data were less suggestive of an effect, and few studies were statistically significant. No evidence for plausible mechanisms was found.

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 principle cause of lung cancer is smoking tobacco.

7.4.5.9 Butter

(Also see chapter 4.5.5.1.1.)

Two cohort studies and eight case-control studies investigated butter consumption. Most studies showed increased risk with increased intake, but cohort data were inconsistent. No evidence for plausible mechanisms was found.

There is a limited amount of inconsistent evidence suggesting that consumption of butter is a cause of lung cancer.

7.4.5.10 Arsenic in drinking water

(Also see chapter 4.7.5.1.1.)

Two cohort studies, 2 case-control studies, and 12 ecological studies investigated arsenic in drinking water. All cohort and case-control studies, and most ecological studies, showed a relationship between increased levels of arsenic in drinking water and increased incidence. Meta-analysis was not possible, but effect estimates tended to be large (an increased risk of over 300 per cent for the highest levels).

Soluble arsenic in drinking water induces lung cancers in animal models.[71] In humans, arsenic is a chromosomal mutagen (an agent that induces mutations involving more than one gene, typically large deletions or rearrangements). It can also act as a synergistic co-mutagen. Arsenic exposure also causes chronic lung disease.[71] The Joint FAO/WHO Expert Committee on Food Additives has set a provisional tolerable weekly intake of 0.015 mg/kg of body weight.[72]

The evidence is ample and consistent, 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 in drinking water is a cause of lung cancer is convincing.

7.4.5.11 Retinol supplements (in smokers)

(Also see chapter 4.10.6.4.1.)

Two trials (one randomised controlled, one non-randomised), two cohort studies, and two case-control studies investigated retinol or retinol supplements. The single randomised controlled trial, performed in current and former smokers only, showed a statistically significant increased risk with a high-dose supplement. There was a suggestion of further elevated incidence in heavy smokers and asbestos workers. The non-randomised trial was inconclusive. One cohort, also stratified by smoking status, showed a relationship with increased incidence only in current smokers. All other studies failed to stratify by smoking status and were inconclusive.

It is possible that some protective effect present at dietary intake amounts of vitamins is lost or reversed by the higher levels supplied by pharmacologic supplementation.

The evidence is sparse and inconsistent. There is limited evidence suggesting that high-dose vitamin A supplements are a cause of lung cancer in current smokers.

7.4.5.12 Beta-carotene supplements (in smokers)

(Also see chapter 4.10.6.4.2.)

Four randomised controlled trials and two cohort studies investigated beta-carotene supplements. Of these, one randomised controlled trial was performed in smokers. This study showed a statistically significant increased risk of 17 per cent with a daily 20 mg beta-carotene supplement. It also suggested that heavy smoking elevated the risk further. Other trials and studies, either in non-smokers or not stratified according to smoking status, were inconclusive.

There is a marked interaction between beta-carotene, heavy smoking, and glutathione *S*-transferase (GST) genotype. GST is a carcinogen-detoxifying enzyme (see chapter 2.5). Beta-carotene supplementation among people without GSTM1 (one of the variants of the GST gene) 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 relative risk of 6.01 (95% confidence interval 1.90–19.08) was observed.

It is possible that a protective association present at dietary intake amounts of carotenoids is lost or reversed by the higher levels that pharmacological supplementation may supply. In one animal study, low-dose beta-carotene was protective against smoking-induced changes in the tumour-suppressor p53 gene (see box 2.2), while high doses promoted these changes.[73] A second explanation could relate to disturbance of the complex nature of naturally occurring carotenoids. It is possible that the protective associations are not due to the specific agent used in supplement studies, but rather to other carotenoids present in dietary exposure,[74] or other associated dietary or health-related behaviour.

There is strong evidence from good-quality trials, consistent with cohort studies. An interaction between smoking, genotype, and beta-carotene is apparent. The evidence that beta-carotene supplements cause lung cancer in current smokers is convincing.

7.4.5.13 Selenium supplements

(Also see chapter 4.10.6.4.5.)

One randomised controlled trial investigated selenium supplements and lung cancer.

The single trial of more than 1300 participants given 200 μg/day of selenium for 13 years showed a non-significant decreased risk with supplementation, adjusted for age and smoking. Subgroup analysis indicated that this risk differed according to baseline plasma selenium level, with a statistically significant decreased risk for those with the lowest initial plasma selenium. This is suggestive that selenium supplementation may decrease cancer risk in those who have poor selenium status, but that this effect may not extend to those who do not.

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. Four are glutathione peroxidases, which protect against oxidative damage to biomolecules such as lipids, lipoproteins, and DNA. Three are thioredoxin reductases and, among other functions, these regenerate oxidised ascorbic acid to its active antioxidant form.

The evidence is sparse. There is limited evidence suggesting that selenium protects against lung cancer.

7.4.5.14 Physical activity

(Also see chapter 5.4.4.)

In total, 5 cohort studies investigated total physical activity; 2 cohort studies investigated non-recreational activity; 4 cohort studies and 2 case-control studies investigated occupational activity; and 11 cohort studies and 4 case-control studies investigated recreational activity. Overall, most studies showed decreased risk with increased physical activity. No studies showed a statistically significant increased risk. Of the categories analysed, consistent protective relationships were reported for total physical activity, non-recreational activity, and recreational activity. Increased heterogeneity in occupational physical activity may be due to either the extreme variation in exposure definition, or the generally lower levels of occupational activity, meaning that, as a percentage of daily activity, occupational activity is of reduced importance in many high-income countries (where these studies were generally performed).

Sustained, moderate physical activity raises metabolic rate and increases maximal oxygen uptake. In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity (the amount of work that it can perform), as well as reducing blood pressure and insulin resistance.

There is evidence from prospective and case-control studies showing lower risk of lung cancer with higher levels of physical activity, but there is no evidence of plausible mechanisms. The relationship between activity, BMI, and lung cancer makes the evidence difficult to interpret. There is limited evidence suggesting that physical activity protects against lung cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[75] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.4.5.15 Body fatness

(Also see chapter 6.1.3.1.)

Twenty-one cohort studies, 24 case-control studies, and 1 ecological study investigated body fatness, as measured by BMI. Nearly all of the cohort and case-control studies showed decreased risk with increased BMI. Meta-analysis of cohort and case-control data provided evidence of a statistically significant reduced risk, with no heterogeneity in cohort data.

Smoking is the principal cause of lung cancer and may also be associated with lower BMI. There is a high potential for confounding due to tobacco smoking, and residual confounding is therefore possible. In addition, it is possible that people with undiagnosed lung cancer may lose weight, so giving a spurious association (reverse causation).

There is no known mechanism through which greater body fatness could plausibly protect against lung cancer, or through which low body fatness could increase risk.

Although the epidemiological evidence suggests an inverse relationship, this could be caused by confounding by cigarette smoking or reverse causation due to weight loss from undiagnosed cancer. There is limited evidence suggesting that low body fatness is a cause of lung cancer.

7.4.5.16 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) or their products; starchy tubers; pulses (legumes); meat; poultry; fish; eggs; animal fats; milk and dairy products; soft drinks; coffee; tea; alcohol; processing, preservation, and preparation; carbohydrate; dietary fibre; total fat; protein; vitamin A; retinol; pro-vitamin A carotenoids; lycopene; thiamin; riboflavin; niacin; vitamin B6; folate; vitamin C; vitamin E; multivitamins; iron; zinc; copper; calcium; selenium; flavonoids; energy intake; plant oils; body size, shape, and composition (except low body fatness); and culturally defined diets.

7.4.6 Comparison with previous report

7.4.6.1 General

See section 7.1.6.1 of this chapter, and box 3.8 in chapter 3.

7.4.6.2 Specific

The previous report judged the evidence that vegetables and fruits protect against lung cancer to be convincing. Evidence, particularly from cohort studies published since the mid-1990s, is more consistent for fruits than for vegetables.

The findings of the previous report for carotenoids, and for pharmaceutical doses of beta-carotene given to smokers, were identical to the current findings (for foods containing carotenoids), although the previous report did not include a matrix entry for beta-carotene supplements. The previous report did not review arsenic.

7.4.7 Conclusions

The Panel concludes:

The evidence that arsenic in drinking water and (in smokers only) pharmacological doses of beta-carotene are causes of lung cancer is convincing.

Fruits, and also foods containing carotenoids, probably protect against lung cancer.

There is limited evidence suggesting that non-starchy vegetables, selenium and foods containing it, foods containing quercetin, and physical activity protect against lung cancer.

There is also limited evidence suggesting that red meat, processed meat, total fat, butter, pharmacological doses of retinol (in smokers only), and low body fatness are causes of lung cancer.

Smoking tobacco is the main cause of lung cancer.

7.5 Stomach

Cancer of the stomach is the fourth most common type of cancer worldwide. Almost one million cases were recorded in 2002. Two out of three cases occur in men. Overall, it is decreasing rapidly in high-income countries, but remains very common elsewhere in the world. It is usually fatal and is the second most common cause of death from cancer.

Overall, *the Panel judges* that food and nutrition play an important role in the prevention and causation of stomach cancer.

***The Panel judges* as follows:**
Non-starchy vegetables, including specifically allium vegetables, as well as fruits probably protect against stomach cancer.

Salt, and also salt-preserved foods, are probably causes of this cancer.

There is limited evidence suggesting that pulses (legumes), including soya and soya products, and also foods containing selenium protect against stomach cancer.

There is also limited evidence suggesting that chilli, processed meat, smoked foods, and grilled (broiled) and barbecued (charbroiled) animal foods are causes of stomach cancer.

Infection with the bacterium *Helicobacter pylori* is established as a necessary cause of almost all cases of stomach cancer. It has been estimated that most cases of this cancer are preventable by appropriate diets and associated factors.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable",shows that non-starchy vegetables, allium vegetables, and fruits protect against stomach cancer; and that salt and also salt-preserved foods are causes of this cancer.

The stomach is the sac-like part of the digestive system between the oesophagus and the small intestine. The body of the stomach is lined by a mucous membrane consisting of columnar epithelial cells and glands, surrounded by muscle.

There are two main types of stomach cancer. Distal gastric cancers (those of the lower portion of the stomach) are the predominant type. The other type is cancer of the gastric cardia or of the gastro-oesophageal junction.[4] The latter are sometimes grouped with oesophageal adenocarcinomas.

Distal gastric cancers may be classified depending on their appearance under the microscope as intestinal or diffuse (from mucus-producing cells). The former is more common and predominates in areas of high incidence; the latter has a poorer prognosis, tends to occur at a younger age, and may also occur in the cardia.[76] More than 95 per cent of gastric cancers are adenocarcinomas.[77]

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE STOMACH

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable	**Non-starchy vegetables[1]** **Allium vegetables[1]** **Fruits[1]**	**Salt[2]** **Salted and salty foods**
Limited — suggestive	Pulses (legumes)[3] Foods containing selenium[4]	Chilli[1] Processed meat[5] Smoked foods[6] Grilled (broiled) or barbecued (charbroiled) animal foods[6]
Limited — no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; starchy roots, tubers, and plantains; nuts and seeds; herbs, spices, and condiments; meat (unprocessed); poultry; eggs; milk and dairy products; fats and oils; total fat; fatty acid composition; cholesterol; sugars; sugar (sucrose); fruit juices; coffee; tea; alcohol; dietary nitrate and nitrite, *N*-nitrosodimethylamine; drying or dried food; protein; thiamin; riboflavin; vitamin C; vitamin D; multivitamin/mineral supplements; calcium; iron; selenium supplements; carotenoids; culturally defined diets; meal frequency; eating speed; body fatness; energy intake	
Substantial effect on risk unlikely	None identified	

1 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
2 'Salt' here means total salt consumption, from processed foods, including salty and salted foods, and also salt added in cooking and at the table.
3 Including soya and soya products.
4 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).
5 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
6 The evidence is mostly from meats preserved or cooked in these ways.

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.

World Cancer Research Fund | American Institute for Cancer Research

7.5.1 Trends, incidence, and survival

Age-adjusted rates of stomach cancer are decreasing, and in 2002 (in many countries) were half what they were 30 years earlier. However, during the same period, two types of cancer affecting the upper (proximal) section of the stomach — those of the gastro-oesophageal junction and gastric cardia

— increased, notably in high-income countries.[78] The decline in stomach cancer incidence is likely to have been due partly to the increased availability of refrigeration (see box 4.6.4). This has had the effect of increasing availability and consumption of fresh foods such as vegetables and fruits, and decreasing consumption of foods preserved by salt and other relevant methods.[79 80]

Age-adjusted incidence rates range from more than 60 per 100 000 people in Japan and other countries in eastern Asia, to less than 10 per 100 000 in much of Africa and North America. Chile and other Latin American countries, as well as Portugal and eastern Europe, have moderately high rates of 30 per 100 000. Rates are also higher in some ethnic groups, for instance, Asian and Pacific Islanders living in the USA, and African-American, and Hispanic-American people; rates are also twice as high in men as women. Rates of different types of stomach cancer also vary, both geographically and between ethnic groups. Cancers affecting the lower (distal) section of the stomach are most common in low- to middle-income countries and in people of African origin; proximal tumours are predominant in high-income countries and in white people.[78] Risk increases with age; stomach cancer is rarely diagnosed in people under 50.

The 5-year survival rate for stomach cancer is approximately 20 per cent.[3 6] Survival rates are higher in countries which have screening programmes that lead to early detection, and where distal cancer (which has a better prognosis) predominates.[81] Stomach cancer accounts for nearly 9 per cent of all cancer incidence, but somewhat over 10 per cent of all cancer deaths worldwide. Also see box 7.1.1.

Box 7.5.1 *Helicobacter pylori*

H pylori is a bacterium that lives in the human stomach. Infection does not usually produce symptoms, and spreads through saliva and faecal material. Prevalence increases with age, but differs dramatically among populations.[82] In the USA, prevalence is less than 20 per cent at 20 years old and about 50 per cent at 50 years, which may be typical of high-income countries,[83] while in Korea, it is 50 per cent at 5 years and 90 per cent at 20 years, and in Japan it reaches 85 per cent by middle age.[84]

H pylori colonises the gastric mucosa and elicits both inflammatory and immune lifelong responses, including the release of various bacterial and host-dependent cytotoxic substances.[85] *H pylori* infection greatly reduces the bioavailability of vitamin C. This may play a role in the development of stomach cancer in the presence of dietary and other factors that are a cause of this cancer. In studies of precancerous lesions or gastric atrophy, eradication of *H pylori* promoted regression of these cancer precursors.[86-88]

Some people develop stomach cancer without apparent infection with *H pylori.* Reported percentages of non-cardia cancers that test positive for *H pylori* range from approximately 60 to 95 per cent, averaging around 86 per cent,[89] but those with distal stomach cancer who test negative for *H pylori* may have undergone a loss of infection associated with the atrophic gastritis, and consequently a decline in antibody titre. It can be regarded as a necessary cause for those stomach cancers arising in the distal region of the stomach.[90]

The longer the time of infection, and the greater the impact on the gastric mucosa, the more likely it is that stomach cancer will develop and take a severe form. The exact site of the cancer is most likely to be where the mucosa is most affected.[91] Those who develop extensive gastritis and gastric atrophy are at increased risk of developing cancer.[81]

7.5.2 Pathogenesis

Changes in the stomach mucosa, brought about by a variety of environmental factors and ageing, can eventually lead to atrophic gastritis. The chronic form of this condition, and the resulting changes in the characteristics of the stomach cells, appear to be precursor conditions to the development of distal stomach cancer.[4] Food carcinogens can also potentially interact directly with the epithelial cells that line the stomach. However, cancer can also develop without these precursors, particularly when the bacterium *H pylori* is present in the stomach (see box 7.5.1).[81]

Three independent cohort studies have shown the progression of gastritis from the non-atrophic to the atrophic form. Epidemiological studies of atrophic gastritis have also shown an association with dietary factors, especially a high intake of salt (mostly in the form of salty and salted foods).[90]

N-nitrosamines are known carcinogens produced in the stomach from nitrate in foods, and via nitrite from endogenous nitric oxide production in chronic inflammation (see box 4.3.2). They may be potential causes of stomach cancer[92] (see chapter 2.4.2.6).

Cancers of the gastric cardia show many similarities to oesophageal cancer (see 7.3.1). There is a clear association between Barrett's oesophagus and adenocarcinoma of the lower (distal) oesophagus and of the gastric cardia, caused by chronic acid damage.

The diffuse type of distal stomach cancers (those that develop from mucus-producing cells) show some genetic predisposition, with an increased risk for people with blood group A. Genetic predisposition is thought to be a factor in 5–10 per cent of diffuse cancers.[93] Stomach cancer is part of the spectrum of cancers associated with the germ line mismatch repair (MMR) gene alterations that give rise to hereditary nonpolyposis colorectal cancer (HNPCC).[77] Also see chapter 7.9.2.

7.5.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Infection and infestation. The bacterium *H pylori* is an important cause of distal stomach cancers (see box 7.5.1). Also, Epstein-Barr virus is carcinogenic to humans and has been linked to stomach cancers (particularly gastric lymphoepithelial carcinomas and a smaller proportion of gastric adenocarcinomas) in some studies.[30]

Industrial chemicals. Industrial exposure to ethylene oxide is carcinogenic to humans and has led to increased risk of stomach cancer in some studies.[94]

7.5.4 Interpretation of the evidence

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

7.5.4.2 Specific

Considerations specific to cancer of the stomach include the following.

Classification. Most evidence relates to distal stomach cancers, although cancers of the gastric cardia and gastro-oesophageal junction might be included in an outcome of 'stomach cancer'. It is now well recognised that proximal and distal stomach cancers are quite different, but relatively few studies stratified results on the basis of subsite. For many early studies, most stomach cancer was probably distal in origin, so the lack of stratification was less important. As the incidence and overall proportion of proximal cancer have increased in recent years in high-income countries, there is a greater likelihood that the general term 'stomach cancer' will represent a combination of the two subsites and therefore results will be less informative.

Measurement. Owing to low survival rates, both incidence and mortality can be assessed. Low survival times and rates decrease the reliability of case-control studies, which often rely on proxy reporting.

Confounding. *H pylori* infection is a necessary cause of distal stomach cancer. This has only been established relatively recently. Only recent studies have incorporated *H pylori* status into their design and have adjusted or stratified for infection.

7.5.5 Evidence and judgements

In total, 722 publications were included in the SLR for stomach cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.5.5.1 Non-starchy vegetables

(Also see chapter 4.2.5.1.)

A total of 10 cohort studies, 45 case-control studies, and 19 ecological studies investigated total vegetables. Other groupings examined were green-yellow vegetables (11 cohort, 21 case-control, 8 ecological); green, leafy vegetables (6 cohort, 13 case-control, 2 ecological); tomatoes (3 cohort, 19 case-control); white or pale vegetables (2 cohort, 6 case-control); raw vegetables (6 cohort, 25 case-control, 3 ecological); or non-starchy vegetables and fruits (5 cohort, 6 case-control). Most studies showed decreased risk with increased intake. However, cohort data were less consistent than case-control data. Meta-analysis of cohort data showed a 19 per cent decreased risk per 50 g green-yellow vegetables/day; no other subcategory analyses were statistically significant. Case-control data showed a 15 per cent decreased risk per 50 g vegetables/day (figures 4.2.8. and 4.2.9); a 21 per cent decreased risk per 50 g green-yellow vegetables/day; a 57 per cent decreased risk per 50 g green, leafy vegetables/day; a 30 per cent decreased risk per 50 g tomatoes/day; and a 25 per cent decreased risk per 50 g raw vegetables/day (figure 4.2.12). There was unexplained heterogeneity.

This is a wide and disparate category, and many different plant food constituents are represented that could contribute to a protective effect of non-starchy vegetables. These include dietary fibre, carotenoids, folate, selenium, glucosinolates, dithiolthiones, indoles, coumarins, ascorbate, chlorophyll, flavonoids, allylsulphides, flavonoids, and phytoestrogens, some of which are potentially antioxidants. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. It is difficult to unravel the relative importance of each constituent and it is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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. Non-starchy vegetables probably protect against stomach cancer.

The Panel is aware that since the conclusion of the SLR, one case-control study[95] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.5.5.2 Allium vegetables

(Also see chapter 4.2.5.1.1.)

A total of 2 cohort studies, 27 case-control studies, and 2 ecological studies investigated allium vegetables; and 1 cohort study, 16 case-control studies, and 2 ecological studies investigated garlic. There was also one relevant intervention study that combined allitridium (a garlic extract containing triallylsulphides) and selenium supplements. Most of the studies showed decreased risk with increased intake. Meta-analysis of cohort data showed a 23 per cent decreased risk per 50 g allium vegetables/day. Meta-analysis of case-control data showed a 20 per cent decreased risk per 50 g allium vegetables/day (figure 4.2.14), and a 59 per cent decreased risk per serving of garlic/day. The single trial of combined selenium and allitridium supplements showed a statistically significant decreased risk in men but not women, after 5 years of follow-up.

Allium vegetables, particularly garlic, have antibiotic properties. Although this may act directly against *H pylori,* studies in humans have not shown this effect. 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 idea.

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.

7.5.5.3 Fruits

(Also see chapter 4.2.5.2.)

Sixteen cohort studies, 51 case-control studies, and 23 ecological studies investigated fruits. Most studies showed decreased risk with increased intake, but there was unexplained heterogeneity. Cohort studies suggested a non-significant relationship with decreased risk. Meta-analysis of case-control data showed a 17 per cent decreased risk per 50 g fruits per day (figure 4.2.27).

Fruits are sources of vitamin C and other antioxidants, such as carotenoids, phenols, and flavonoids, as well as other potentially bioactive phytochemicals. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. In addition, flavonoids found in fruits directly inhibit the expression of a cytochrome P450 enzyme, which helps to metabolise toxins and has been associated with increased risk of lung cancer, primarily in smokers.[68] It is difficult to unravel the relative importance of each constituent and it is likely that a protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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[95-97] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.5.5.4 Pulses (legumes) including soya and soya products

(Also see chapter 4.2.5.10.)

A total of 3 cohort studies, 22 case-control studies, and 16 ecological studies investigated pulses (legumes) and stomach cancer; and 2 cohort studies, 9 case-control studies, and 2 ecological studies investigated soya and soya products. All of the cohort studies and most of the case-control studies showed decreased risk with increased intake. Ecological studies showed decreased risk for soya and soya products, but were inconsistent for pulses (legumes).

Meta-analysis of cohort studies showed a non-significant relationship with decreased risk. Meta-analysis of case-control studies produced evidence for a relationship with decreased risk.

Pulses (legumes), particularly soya, contain high levels of isoflavones that have shown anti-cancer properties in laboratory experiments. Saponins and other bioactive constituents of soya (and to a lesser extent, other pulses) may also have anti-cancer properties, although these are less well demonstrated.

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.

7.5.5.5 Foods containing selenium

(Also see chapter 4.2.5.8.)

One case-control study and 5 ecological studies investigated dietary selenium; 3 cohort studies, 9 case-control studies and 3 ecological studies investigated blood selenium; and 1 cohort study and 1 case-control study investigated selenium in toenails or hair. All of the studies for blood, nail, or hair selenium levels showed decreased risk with increased selenium intake. Meta-analysis of cohort data showed a non-significant decreased risk, and meta-analysis of case-control data produced statistically significant evidence of decreased risk.

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. Four are glutathione peroxidases, which protect against oxidative damage to biomolecules such as lipids, lipoproteins, and DNA. Three are thioredoxin reductases, which, among other functions, regenerate oxidised ascorbic acid to its active antioxidant form. Selenoproteins with powerful antioxidant activity may provide protection against the inflammatory effect of *H pylori* that can lead to gastric cancer in infected individuals.

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.

7.5.5.6 Chilli

(Also see chapter 4.2.5.12.1.)

Fourteen case-control studies investigated chilli use. Most of these reported increased risk with increased use, although results were heterogeneous and data were not suitable for meta-analysis.

Anecdotally, chilli may be used to disguise 'off' flavours in foods, so 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 (also see chapter 2.4.1.3).

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.

7.5.5.7 Processed meat

(Also see chapter 4.3.5.1.2.)

Eight cohort studies, 21 case-control studies, 1 cross-sectional study, and 1 ecological study investigated processed meat. Most of these showed increased risk with higher intake. Meta-analysis of cohort data showed a non- signifi-

cant relationship with increased risk. Meta-analysis of case-control data produced evidence of a statistically significant dose-response relationship. Heterogeneity is likely to be caused by the diverse nature of definitions for processed meat in different studies.

Nitrates are produced endogenously in gastric acid, and are added as preservatives to processed meats. They may contribute to *N*-nitroso compound production and exposure. *N*-nitroso compounds are suspected mutagens and carcinogens (see box 4.3.2).[55] Many processed meats also contain high levels of salt and nitrite. Meats cooked at high temperatures can contain heterocyclic amines and polycyclic aromatic hydrocarbons (see box 4.3.4). Haem promotes the formation of *N*-nitroso compounds and also contains iron. Free iron can lead to the production of free radicals (see box 4.3.3).

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[98] and two case-control studies[95 99] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.5.5.8 Smoked foods

(Also see chapter 4.3.5.7.)

Seventeen case-control studies and two ecological studies investigated smoked foods. Most of these showed increased risk with increased intake, with none reporting statistically significant reduced risk.

Definitions of smoked foods varied between studies, although most included smoked meats and/or fish. Smoked foods are often salted. High rates of mortality from stomach cancer are found in countries such as Iceland, Hungary, and Latvia, where diets include a regular intake of meat and/or fish preserved by smoking.

Smoked foods, particularly meats, may contain polycyclic aromatic hydrocarbons, depending on the fuel burned to produce the smoke.[100] (Also see box 4.3.4.) Smoked meats are also often salted or cured, meaning that they are likely to raise endogenous production of *N*-nitroso compounds in the stomach (see box 4.3.2). These are suspected causes of stomach cancer.

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[95 96 99] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.5.5.9 Grilled (broiled) or barbecued (charbroiled) animal foods

(Also see chapter 4.3.5.8.)

Three cohort studies and 12 case-control studies investigated grilled (broiled) or barbecued (charbroiled) foods (these were predominantly meats or fish, although not all studies specified the foods studied). Most studies showed increased risk with increased intake.

Cooking methods involving grilling above a heat source and barbecuing can produce marked differences in levels of carcinogens in foods cooked in these ways (see chapter 4.9.4). For example, fat dripping on hot surfaces can form polycyclic aromatic hydrocarbons and heterocyclic amines (see box 4.3.4), while oven grilling prevents this from happening, resulting in much lower levels of these compounds in the cooked foods.

There is limited, inconsistent evidence, mostly from case-control studies, that grilled (broiled) or barbecued (charbroiled) animal foods are causes of stomach cancer.

7.5.5.10 Salt

(Also see chapter 4.6.5.2.)

Three cohort studies, 21 case-control studies, and 12 ecological studies investigated total salt use. Other groupings examined were salt added at the table (2 cohort, 13 case-control) and sodium intake (1 cohort, 8 case-control). Most studies showed increased risk with increased intake, but there is some unexplained heterogeneity. Meta-analysis of case-control data showed an 18 per cent increased risk per gram of sodium per day; the meta-analyses for total salt indicated increased risk but were not statistically significant (figure 4.6.1).

Assessment of salt intake is complicated as the small proportion added during preparation or at the table is very variable and difficult to quantify. Higher-quality studies, which are better adjusted, tend to report a greater or more significant effect. However, residual confounding is possible: salt intake may be inversely related to the availability of refrigeration in a population, and so to socioeconomic status, which is itself related to stomach cancer risk.

Salt has been shown to directly damage the stomach lining in animal trials. It has also been shown to increase endogenous *N*-nitroso compound formation (see box 4.3.2). Salt may enhance the action of carcinogens in the stomach. In addition, salt intake may facilitate *H pylori* infection.[101]

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[102] and two case-control studies[95 99] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.5.5.11 Salted and salty foods

(Also see chapter 4.6.5.2.1.)

Four cohort studies, 17 case-control studies, and 1 ecological study investigated salty or salted foods. Nearly all of the

studies showed increased risk with increased intake. Meta-analysis of cohort data showed a non-significant increased risk; meta-analysis of case-control data showed a 5.2-fold increased risk per serving per day (figure 4.6.2). Heterogeneity may be partly explained by variation between studies in the precise foods being assessed.

As stated above, assessment of salt intake is complicated. Again, higher-quality studies report a greater or more significant effect.

Again, salt has been shown to directly damage the stomach lining in animal trials. It has also been shown to increase endogenous *N*-nitroso compound formation (see box 4.3.2).

The evidence, both from 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 probable causes of stomach cancer.

The Panel is aware that since the conclusion of the SLR, two case-control studies[95 99] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.5.5.12 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) and their products; starchy roots, potatoes, and other tubers; plantains; nuts and seeds; herbs, spices, and condiments; meat; poultry; eggs; fats and oils; milk and dairy products; sugar; fruit juices; coffee; tea; alcohol; nitrosodimethylamine/dietary nitrate/nitrite; drying or dried food; dietary fibre; sugars; total fat; fatty acid composition; cholesterol; protein; carotenoids; thiamin; riboflavin; vitamin C; vitamin D; multivitamin/mineral supplements; selenium supplements; iron; calcium; energy intake; body fatness; culturally defined diets; meal frequency; and eating speed.

7.5.6 Comparison with previous report

7.5.6.1 General

See 7.1.6.1, and box 3.8.

7.5.6.2 Specific

The previous report judged the evidence that vegetables and fruits protect against stomach cancer to be convincing. Since then, the evidence from cohort studies has been rather equivocal, whereas evidence from case-control studies remains strong and consistent. Previously, the compounds found in allium vegetables were judged possibly to protect against stomach cancer; more recent evidence for allium vegetables is stronger.

The previous report found the evidence that refrigeration protects against stomach cancer to be convincing. Also see box 4.6.4.

Before the mid-1990s there were no published trials of selenium supplements. Two trials are now available, as well as increased numbers of cohort and case-control studies, but the evidence is still limited and only suggestive of a protective effect.

7.5.7 Conclusions

The Panel concludes:

Non-starchy vegetables, and specifically allium vegetables, as well as fruits probably protect against stomach cancer.

Salt and salt-preserved foods are probably causes of this cancer.

There is limited evidence suggesting that pulses (legumes) including soya and soya products and foods containing selenium protect against stomach cancer.

There is also limited evidence suggesting that chilli, processed meat, smoked foods, and grilled (broiled) and barbecued (charbroiled) animal foods are causes of stomach cancer.

Infection with the bacterium *H pylori* is a necessary but not sufficient cause of stomach cancer.

7.6 Pancreas

Cancer of the pancreas is the thirteenth most common type of cancer worldwide. About 230 000 cases were recorded in 2002, accounting for around 2 per cent of cancers overall. The incidence is somewhat more common in men than in women. It is generally increasing, particularly in high-income countries, where it is most frequent. It is rare in Africa and Asia. This cancer is almost always fatal and is the ninth most common cause of cancer death.

Overall, *the Panel is impressed* by the strength of the evidence that body fatness, abdominal fatness, and the factors that lead to greater adult attained height, or its consequences, are causes of cancer of the pancreas.

***The Panel judges* as follows:**

The evidence that body fatness is a cause of cancer of the pancreas is convincing; abdominal fatness is probably a cause of this cancer.

Foods containing folate probably protect against this cancer.

The factors that lead to greater adult attained height, or its consequences, are probably a cause of pancreatic cancer.

It is unlikely that coffee has any substantial effect on the risk of this cancer.

There is limited evidence suggesting that fruits and physical activity protect against this cancer, and that red meat is a cause of this cancer.

See chapter 8 for evidence and judgements on factors that modify the risk of body fatness and abdominal fatness, including physical activity and sedentary ways of life, the energy density of foods and drinks, and breastfeeding.

Tobacco smoking is an established cause of this cancer.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that body fatness and (probably) abdominal fatness are both causes of cancer of the pancreas, and that the factors that lead to greater adult attained height, or its consequences, are probably also a cause of this cancer. Foods containing folate are probably protective. It is unlikely that coffee has any substantial effect on the risk of this cancer.

The pancreas is an elongated gland located behind the stomach. It contains two types of tissue, exocrine and endocrine. The exocrine pancreas produces digestive enzymes that are secreted into the small intestine. Cells in the endocrine pancreas produce hormones including insulin and glucagon, which influence glucose metabolism.

Over 95 per cent of pancreatic cancers are adenocarcinomas of the exocrine pancreas, the type included in this Report.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE PANCREAS

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

	DECREASES RISK	INCREASES RISK
Convincing		**Body fatness**
Probable	**Foods containing folate[1]**	**Abdominal fatness** **Adult attained height[2]**
Limited — suggestive	Fruits[3] Physical activity[4]	Red meat[5]
Limited — no conclusion	Cereal (grains) and their products; dietary fibre; vegetables; pulses (legumes); soya and soya products; processed meat; poultry; fish; eggs; milk and dairy products; total fat; butter; plant oils; margarine; cholesterol; sugar (sucrose); black tea; green tea; alcohol; nitrate and nitrite; total carbohydrate; folic acid supplements; vitamin C; vegetarianism; age at menarche; lactation; energy intake	
Substantial effect on risk unlikely	Coffee	

1 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).
2 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).
3 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
4 Physical activity of all types: occupational, household, transport, and recreational.
5 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.

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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7.6.1 Trends, incidence, and survival

Age-adjusted rates of pancreatic cancer have been generally stable since the 1970s, following an approximate three-fold rise over the preceding 50 years in the countries for which data are available.[103 104]

This is mainly a disease of high-income countries, where overall rates are nearly three times higher than in middle- and low-income countries. Around the world, age-adjusted incidence rates range from 10–15 per 100 000 people in parts of northern, central, and eastern Europe to less than 1 per 100 000 in areas of Africa and Asia, although rates are

relatively high in some countries in these areas, for example, Japan and Korea. In the USA, rates are higher among African-American people than in white people.[3] The risk of pancreatic cancer increases with age, with most diagnoses made in people between the ages of 60 and 80.

The early stages of this cancer do not usually produce symptoms, so the disease is generally advanced when it is diagnosed. Survival rates are therefore low — around 4 per cent at 5 years. This cancer accounts for around 2 per cent of all cancer incidence, but somewhat over 3 per cent of all cancer deaths.[4] Also see box 7.1.1.

7.6.2 Pathogenesis

The ductal cells in the head of the pancreas are exposed to pancreatic secretions, as well as bile, and environmental carcinogens can reach these cells through those fluids or in the blood (see 7.7).

The pancreas is relatively inaccessible to routine medical examination, so the progression of this cancer through precursor lesions is not well understood. However, inflammation is implicated in this process through chronic pancreatitis, which is a risk factor for pancreatic cancer. The role of infection with *H pylori* (see box 7.5.1) is the subject of ongoing research.[105] Conditions that lead to high insulin levels in pancreatic secretions, such as insulin resistance and type 2 diabetes, may increase the risk of this cancer.[106]

More than 90 per cent of pancreatic cancer cases are sporadic (due to spontaneous rather than inherited mutations), although a family history increases risk, particularly where more than one family member is involved.[105] Around 75–90 per cent of pancreatic cancer cases involve a point mutation in the K-ras oncogene[107] (see box 2.2 in chapter 2).

7.6.3 Other established causes

(Also see chapters 2.4 and 7.1.3.1.)

Tobacco use. Approximately 25 per cent of cases of pancreatic cancer are attributable to tobacco smoking.

7.6.4 Interpretation of the evidence

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

7.6.4.2 Specific

Considerations specific to cancer of the pancreas include:

Measurement. Owing to very low survival rates, both incidence and mortality can be assessed. Low survival times and rates decrease the reliability of case-control studies, which often rely on proxy reporting.

Confounding. High-quality studies adjust for smoking.

7.6.5 Evidence and judgements

In total, 318 publications were included in the SLR for this cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.6.5.1 Fruits

(Also see chapter 4.2.5.2.)

Six cohort studies, 16 case-control studies, and 8 ecological studies investigated fruits. All cohort studies and most other studies showed decreased risk with increased intake. Meta-analysis of cohort data showed a non-significant decreased risk. Meta-analysis of case-control data showed a statistically significant decreased risk.

Fruits are sources of vitamin C and other antioxidants, such as carotenoids, phenols, and flavonoids, as well as other potentially bioactive phytochemicals. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. In addition, flavonoids found in fruit directly inhibit the expression of the cytochrome P450 enzyme, which helps to metabolise toxins and has been associated with increased risk of lung cancer, primarily in smokers.[68] It is difficult to unravel the relative importance of each constituent and is likely that a protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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[108] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.6.5.2 Foods containing folate

(Also see chapter 4.2.5.4.)

Three cohort studies, two case-control studies, and one ecological study investigated folate from foods and/or folic acid from supplements. Meta-analysis of all three cohort studies showed a non-significant decreased risk, with high heterogeneity. When stratified according to the source, both dietary studies showed a non-significant decreased risk, and three studies of supplements showed a non-significant increased risk. One cohort study also analysed serum folate levels, showing a significant decreased risk of 55 per cent for the highest levels compared with the lowest. Both the case-control studies and the ecological study showed decreased risk with increased intake. Folic acid supplements do not show a protective effect.

Folate plays an important role in the synthesis and repair of DNA. There is a known interaction between folate and

alcohol and the risk of some cancers (see chapter 4.8). Folate intake is strongly correlated with intake of non-starchy polysaccharide or dietary fibre.

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[109] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.6.5.3 Red meat

(Also see chapter 4.3.5.1.1.)

Seven cohort studies and four case-control studies investigated red meat. Nearly all of the studies showed increased risk with increased intake.

Red meat contains haem iron. Free iron can lead to the production of free radicals (see box 4.3.3). When cooked at high temperatures, red meat can also contain heterocyclic amines and polycyclic aromatic hydrocarbons (see box 4.3.4).

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.

The Panel is aware that since the conclusion of the SLR, one cohort study[110] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.6.5.4 Coffee

(Also see chapter 4.7.5.4.)

Eighteen cohort studies, 37 case-control studies, and 11 ecological studies investigated coffee. Analysis of cohort data showed an effect estimate close to null with low heterogeneity. Data for case-control studies were less consistent.

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 a substantial effect on the risk of pancreatic cancer.

7.6.5.5 Physical activity

(Also see chapter 5.4.5.)

A total of three cohort studies and one case-control study investigated total physical activity; three cohort studies and two case-control studies investigated occupational activity; and nine cohort studies and three case-control studies investigated recreational activity. Several studies also examined walking and transportation. Most of the studies showed decreased risk with increased physical activity, though there was heterogeneity in the direction of effect and no clear dose-response relationship.

Sustained moderate physical activity raises the metabolic rate and increases maximal oxygen uptake. In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity (the amount of work that it can perform), as well as reducing blood pressure and insulin resistance. In addition, low levels of physical activity decrease gastrointestinal transit times. This alters bile content and secretion, as well as affecting pancreatic activity.[111]

There is evidence from prospective studies showing lower risk of pancreatic cancer with higher levels of various types of physical activity, but it is rather inconsistent. There is limited evidence suggesting that physical activity protects against pancreatic cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[112] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.6.5.6 Body fatness

(Also see chapter 6.1.3.1.)

Twenty-three cohort studies and 15 case-control studies investigated body fatness, as measured by BMI. Most cohort studies showed increased risk with increased body fatness, but case-control studies were inconsistent. Meta-analysis of cohort data showed a 14 per cent increased risk per 5 kg/m^2 (figure 6.1.4). Heterogeneity appeared to be explained by a number of studies failing to adjust for smoking, which is separately associated with both BMI and pancreatic cancer.

It is biologically plausible that body fatness is a cause of pancreatic cancer. There is an established connection between increasing BMI or body fatness and insulin resistance and diabetes. The risk of this cancer is increased in people with insulin resistance or diabetes. It also directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (see box 2.4). Body fatness stimulates the inflammatory response, which may contribute to the initiation and progression of several cancers (see chapter 2.4.1.3).

There is ample epidemiological evidence, which is generally consistent, and there is a dose-response relationship. There is evidence for plausible mechanisms that operate in humans. The evidence that greater body fatness is a cause of pancreatic cancer is convincing.

The Panel is aware that since the conclusion of the SLR, two cohort studies[58 112] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.6.5.7 Abdominal fatness

(Also see chapter 6.1.3.2.)

Three cohort studies investigated waist circumference, two cohort studies investigated waist to hip ratio, and one cohort study investigated patterns of weight gain, all of which showed increased risk with increasing measures of abdominal fatness. Half of all studies were statistically significant.

The general mechanisms through which abdominal fatness could plausibly cause cancer are outlined in chapter 6.1.3 (also see box 2.4). The hormonal and other biological effects

of being overweight or obese are outlined in chapter 8. Many of these, such as increased circulating oestrogens and decreased insulin sensitivity, are associated with abdominal fatness independently of overall body fatness.

There is a substantial amount of epidemiological evidence that is generally consistent, and there is evidence for plausible mechanisms. Abdominal fatness is a probable cause of pancreatic cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[112] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.6.5.8 Adult attained height

(Also see chapter 6.2.3.1.)

Eight cohort studies, 12 case-control studies, and 1 ecological study investigated adult attained height. Most cohort studies and the single ecological study showed increased risk with greater adult attained height. Case-control studies were inconsistent. Meta-analysis of cohort data showed an 11 per cent increased risk per 5 cm of height (figure 6.2.5). There was considerable heterogeneity in case-control data, not all readily explained. However, the cohort studies showed a linear dose-response relationship (figure 6.2.6).

The general mechanisms through which the factors that lead to greater adult attained height, or its consequences, could plausibly influence cancer risk are outlined in chapter 6.2.1.3 (for more detail see box 2.4). Many of these, such as early-life nutrition, altered hormone profiles, and the rate of sexual maturation, could plausibly increase cancer risk.

There is ample prospective epidemiological evidence, though there is some inconsistency. There is evidence for a dose-response relationship, and evidence for plausible mechanisms. The factors that lead to greater adult attained height, or its consequences, are probably a cause of pancreatic cancer. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

The Panel is aware that since the conclusion of the SLR, one cohort study[112] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.6.5.9 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) and their products; vegetables; pulses (legumes); soya and soya products; processed meat; poultry; fish; eggs; milk and dairy products; butter; margarine; black tea; green tea; alcoholic drinks; nitrate/nitrite; total carbohydrate; dietary fibre; sucrose; total fat; cholesterol; folic acid supplements; plant oils; energy intake; age at menarche; vegetarianism; and lactation.

In the case of alcoholic drinks, although low-to-moderate levels of drinking were unlikely to have an effect on risk, it could not be excluded that heavy drinking might have an effect.

7.6.6 Comparison with previous report

7.6.6.1 General

See 7.1.6.1, and box 3.8 in chapter 3.

7.6.6.2 Specific

Apart from vegetables and fruits, the strongest evidence and judgements here are remarkably different from the previous report. Much of the evidence on body fatness, abdominal fatness, attained adult height (tallness), and physical activity is recent.

7.6.7 Conclusions

The Panel concludes:

The evidence that body fatness is a cause of cancer of the pancreas is convincing; abdominal fatness is probably a cause of this cancer.

Foods containing folate (but not folic acid supplements) probably protect against pancreatic cancer.

The factors that lead to greater adult attained height, or its consequences, are probably a cause of this cancer. Greater height is unlikely to directly modify the risk of cancer; it is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth.

It is unlikely that coffee has any substantial effect on risk. There is limited evidence suggesting that fruits and also physical activity protect against this cancer, and that red meat is a cause of this cancer.

7.7 Gallbladder

Cancer of the gallbladder accounts for somewhat over 2 per cent of all cancer incidence and rates are generally declining. The highest rates occur in eastern Asia and eastern Europe, but it is rare in Africa. This cancer is usually fatal and is the 17th most common cause of cancer death.

***The Panel judges* as follows:**
Body fatness is probably a cause of cancer of the gallbladder and people with gallstones are more likely to develop gallbladder cancer.

See chapter 8 for evidence and judgements on factors that modify the risk of body fatness, including physical activity and sedentary ways of life, the energy density of foods and drinks, and breastfeeding.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that body fatness is probably a cause of gallbladder cancer, both directly and indirectly, through the formation of gallstones.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE GALLBLADDER

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		**Body fatness**[1]
Limited — suggestive		
Limited — no conclusion	Peppers (capsicums); fish; coffee; tea; alcohol; vitamin C.	
Substantial effect on risk unlikely	None identified	

1 Directly and indirectly, through the formation of gallstones.

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.

The gallbladder is a small sac-like organ that forms part of the biliary tract. Bile, produced in the liver, flows into the gallbladder, where it is stored and concentrated until released into the small intestine.

More than 90 per cent of gallbladder cancers are adenocarcinomas, while only a small proportion are squamous cell carcinomas.[4]

7.7.1 Trends, incidence, and survival

Age-adjusted rates of gallbladder cancer are decreasing.[1] Even in many of the countries where incidence had been relatively high, such as in eastern Asia and eastern Europe, rates have decreased and continued to fall, following a dramatic rise in the 1970s and 1980s.

There is no clear geographical pattern to the distribution of gallbladder cancer. Age-adjusted incidence rates range from 5–10 per 100 000 people in parts of eastern Asia and eastern Europe to less than 1 per 100 000 in parts of Africa. In the USA, rates are higher among both Native- and Hispanic-American people than in white people.[113] Around most of the world, gallbladder cancer is slightly more common in women than men. In Japan and Korea, this trend is reversed, with around 60 per cent of cases in men.[103] Risk increases with age, with more than two thirds of cases occurring in people aged 65 years or older.[114]

Gallbladder cancer is usually advanced at diagnosis. Survival rates are poor: at 5 years less than 12 per cent for advanced disease, but this is much higher (by up to 20 per cent) when the cancer is caught early. Gallbladder cancer accounts for just over 2 per cent of all cancer incidence, and the same proportion of all cancer deaths. Also see box 7.1.1.

7.7.2 Pathogenesis

The pathogenesis of gallbladder cancer is not well understood, partly because it is often diagnosed at a late stage.

Having gallstones increases the risk of this cancer. The associated inflammation decreases the speed at which bile empties from the gallbladder; gallstones may also have a direct effect by blocking the transit of bile.[115] Gallstones, like gallbladder cancers, are more common in women than men, and the risk of cancer is proportional to the size of the gallstones.[116] However, other factors must also be involved: in high-income countries up to 1 person in 10 has gallstones (many asymptomatic),[117] whereas gallbladder cancer is diagnosed in only around 1 in 50 000.

Many toxins, whether they come from diet, smoke inhalation, or other environmental sources (and their metabolic products) are excreted and concentrated in the bile.

Early stages of the disease include plaque-like lesions and small ulcerations in the mucosal lining of the gallbladder, which are associated with chronic inflammation (cholecystitis). This may progress to carcinoma in situ, and then to invasive tumours. This process probably takes at least 20 years (cholecystitis is seldom seen in people under 40), hence the age profile of gallbladder cancer. Chronic inflam-

mation caused by other factors (such as in 'porcelain gallbladder' or from chronic bacterial infection) may be a necessary stage in the development of gallbladder cancer, although the evidence is not conclusive.[4 118 119]

A congenital deformity to the pancreatic ducts is associated with most gallbladder cancers in eastern Asia.[120] This may account for the different epidemiology in this region, and could imply a distinct pathogenesis with different risk factors. Mutations of the tumour-suppressor p53 gene are frequent in gallbladder cancers (see box 2.2).[121]

7.7.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1 of this chapter.)

Other diseases. Having gallstones increases the risk of gallbladder cancer and can be identified as a cause of this cancer.

Other causes are not established; see 7.7.2.

7.7.4 Interpretation of the evidence

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

7.7.4.2 Specific

Considerations specific to cancer of the gallbladder include:

Confounding. Having gallstones increases the risk of gallbladder cancer. Exposures with an apparent link to gallbladder cancer may act indirectly, through gallstones, or directly, either after gallstone formation or in their absence. It is not yet possible to separate these effects. See 7.7.7.

7.7.5 Evidence and judgements

In total, 48 publications were included in the SLR for gallbladder cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.7.5.1 Body fatness

(Also see chapter 6.1.3.1.)

Five cohort studies, seven case-control studies, and two cross-sectional studies investigated body fatness, as measured by BMI. Most studies showed increased risk with increased body fatness. Meta-analysis of cohort data showed a 23 per cent increased risk per 5 kg/m^2; meta-analysis of case-control data showed a 19 per cent increased risk per 5 kg/m^2. Heterogeneity could be partly attributed to differences in the study participants' ethnicity or sex, or to the number of adjustments made in the study.

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (see box 2.4). It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers (see chapter 2.4.1.3). In addition, obesity is a known cause of gallstone formation, and having gallstones increases the risk of gallbladder cancer, possibly through bile cholesterol supersaturation.

Because having gallstones is a cause of gallbladder cancer, *the Panel also reviewed* the dietary causes of gallstones, especially in relation to body fatness. Having a relatively high BMI increases the risk of gallstones in a linear fashion; waist circumference is associated with gallstone risk in men, independently of BMI. Gallstone formation is associated with repeated dieting, especially where it involves rapid weight loss, such as that from very low-energy diets and bariatric surgery.

There is a substantial amount of generally consistent epidemiological evidence with some evidence of a dose-response relationship. There is evidence for several plausible mechanisms. Greater body fatness is a probable cause of gallbladder cancer, directly and also indirectly through the formation of gallstones.

7.7.5.2 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These included capsicums, fish, coffee, tea, alcohol, and vitamin C.

7.7.6 Comparison with previous report

7.7.6.1 General

See 7.1.6.1, and box 3.8 of chapter 3.

7.7.6.2 Specific

Since publication of the previous report, the evidence that body fatness is an indirect and a direct cause of gallbladder cancer has strengthened.

7.7.7 Conclusions

The Panel concludes:

Greater body fatness is probably a cause of cancer of the gallbladder. People with gallstones are more likely to develop gallbladder cancer.

7.8 Liver

Cancer of the liver is the sixth most common type of cancer worldwide. Around 625 000 cases were recorded in 2002, accounting for around 6 per cent of all cancers. About half of all cases occur in China, and it is more common in middle- and low-income countries. It is almost always fatal, and is the third most common cause of death from cancer, accounting for around 9 per cent of all deaths.

Overall, *the Panel notes* that toxic compounds are the main causes of primary liver cancer related to foods and drinks.

***The Panel judges* as follows:**
The evidence that aflatoxins, which contaminate mostly cereals (grains) and pulses (legumes) stored in hot, wet conditions, are a cause of liver cancer is convincing. Alcoholic drinks are probably a direct cause of this cancer. There is limited evidence suggesting that fruits are protective, and that body fatness is a cause of this cancer.

Other causes of this cancer include infection with hepatitis viruses B or C, the development of cirrhosis from any cause, and infestation with liver flukes.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that aflatoxins, and probably alcoholic drinks, are causes of liver cancer.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE LIVER

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

	DECREASES RISK	INCREASES RISK
Convincing		**Aflatoxins[1]**
Probable		**Alcoholic drinks[2]**
Limited — suggestive	Fruits[3]	Body fatness
Limited — no conclusion	Cereals (grains) and their products[1]; non-starchy vegetables; peanuts (groundnuts)[1]; fish; salted fish; water source; coffee; tea	
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 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 susceptibility factors.
3 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.

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.

The liver is the body's largest organ. It processes and stores nutrients, and produces cholesterol and proteins such as albumin, clotting factors, and the lipoproteins that carry cholesterol. It also secretes bile and performs many metabolic functions, including detoxification of several classes of carcinogen.

Different types of tumour occur in the liver. Each has potentially different causes and natural history. Around 75–90 per cent of liver cancers are hepatocellular carcinoma. This starts in hepatocytes, which are the commonest type of liver cell, and has various subtypes. Cholangiocarcinomas account for 10–20 per cent of primary liver cancers. These cancers start in the small bile ducts (tubes that carry bile to the gallbladder) within the liver. Hepatoblastoma and angiosarcoma are less common types of liver cancer. Hepatocellular carcinoma is the main type included here. Secondary tumours of the liver are not included.

7.8.1 Trends, incidence, and survival

Age-adjusted rates of liver cancer are either increasing or stable in most countries for which data are available.[6 122] However, a recent report on trends in the USA between 1975 and 2001 suggested that these increases may now be reversing.[3]

This is predominantly a disease of middle- to low-income countries, where overall rates are more than double those in high-income countries. Around the world, age-adjusted incidence rates range from more than 40 per 100 000 people in eastern Asia and parts of Africa to less than 5 per 100 000 in the Americas and northern Europe.[2] In the USA, rates are higher among African-American and Hispanic-American people, and Asian and Pacific Islanders, than in white people.[3] Globally, rates are higher in men than women by five to two.

Risk tends to increase with age, although the disease develops at a younger age (typically around the age of 40, or below) in people living in Asia and Africa compared with those in high-income countries.[123]

Box 7.8.1 Hepatitis viruses

Hepatitis B and hepatitis C viruses are causes of liver cancer. The former appears to act directly by damaging cells and their DNA. The latter shows an indirect effect, mediated by cirrhosis. For both, there is potential for nutrition status to have an effect at several stages: susceptibility to and duration of infection, liver damage, DNA damage, and cancer progression.[129]

Around 7–8 per cent of the world's population is estimated to be infected with hepatitis B virus. It is mostly spread by blood and sexual transmission. In endemic areas, the carrier rate may be 10–20 per cent.[130] It is often acquired at birth or in childhood, and is endemic in areas of Africa and Asia. Chronic hepatitis B virus carriers have a 100-fold greater chance of developing liver cancer than non-carriers. Those infected in adulthood have a lower risk of this cancer than those infected in childhood because there is less time for the virus to cause inflammation.[130] Vaccination against hepatitis B virus has been shown to reduce the prevalence of liver cancer by 60 per cent.[131]

Liver cancer in hepatitis B virus carriers is not necessarily connected with cirrhosis: up to 40 per cent of associated liver cancer cases are non-cirrhotic. Hepatitis B virus carries its genetic code as DNA rather than RNA. Viral DNA can insert itself into liver cells and alter their DNA.

Around 3 per cent of the world's population is estimated to be infected with hepatitis C virus. It is more prevalent in high-income countries. Approximately 80 per cent of these infections become chronic, of which 15–20 per cent develops into cirrhosis. Of those, 1–4 per cent develops into liver cancer each year. Interruption of the sequence of chronic hepatitis developing into cirrhosis prevents liver cancer. Also, there is an interaction between hepatitis C virus infection, liver cancer risk, and consumption of alcoholic drinks.[132] There is no vaccine against hepatitis C. It is mostly spread by blood.

The early stages of liver cancer do not usually produce symptoms, so the disease is generally advanced when it is diagnosed. Survival rates are poor: at 5 years, approximately 5 per cent.[124] This cancer accounts for almost 6 per cent of all cancer incidence, but around 9 per cent of all cancer deaths.[2] Also see box 7.1.1.

7.8.2 Pathogenesis

Liver cancer generally follows cirrhosis, so any cause of cirrhosis — either viral (see box 7.8.1) or chemical — is likely to increase cancer risk. Approximately 80 per cent of hepatocellular carcinoma cases develop in cirrhotic livers.[123]

As for cancers at most sites, accumulated sequential changes (see chapter 2.5), specifically in mature hepatocytes, lead to the development of dysplastic nodules; over the course of around 5 years, 30 per cent may develop into tumours.[125] Hepatocellular carcinoma cells show numerous genetic changes, perhaps accumulated during cellular proliferation, which is part of the normal liver repair process.[126] The hepatitis B virus-related type (see box 7.8.1) appears to be more genetically unstable than others.[127 128]

The liver is a common site for metastasis of tumours originating in other organs.

7.8.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Other diseases. Cirrhosis of the liver increases the risk of, and so can be seen as a cause of, liver cancer.

Infection and infestation. Chronic viral hepatitis is a cause of liver cancer (see box 7.8.1).[130] Infestation with liver flukes is a cause of cholangiocarcinoma.

Medication. Oral contraceptives containing high doses of oestrogen and progesterone may be a cause of this cancer.[90 133]

7.8.4 Interpretation of the evidence

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

7.8.4.2 Specific

Considerations specific to cancer of the liver include:

Classification. Most of the data is on hepatocellular carcinoma, the most well characterised (and most common) form of liver cancer. However, different outcomes are reported for unspecified primary liver cancer, compared with hepatocellular carcinoma or cholangiocarcinoma. This suggests different causation and so may therefore be a cause of heterogeneity.

Confounding. Hepatitis B and C viruses are possible confounders or effect modifiers; high-quality studies adjust for them. Not all studies do so.

Measurement. Owing to low survival rates, both incidence and mortality can be assessed. Low survival times and rates decrease the reliability of case-control studies, which often rely on proxy reporting.

7.8.5 Evidence and judgements

In total, 273 publications were included in the SLR for liver cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.8.5.1 Fruits

(Also see chapter 4.2.5.2.)

One cohort study and five case-control studies investigated fruits. The cohort study and most of the case-control stud-

ies showed decreased risk with increased fruit intake. No studies showed statistically significant increased risk.

Fruits are sources of vitamin C and other antioxidants, such as carotenoids, phenols, and flavonoids, as well as other potentially bioactive phytochemicals. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage.

In addition, flavonoids found in fruit directly inhibit the expression of a cytochrome P450 enzyme, which helps to metabolise toxins and has been associated with increased risk of lung cancer, primarily in smokers.[68] It is difficult to unravel the relative importance of each constituent and is likely that a protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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[134] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.8.5.2 Aflatoxins

(Also see chapter 4.1.5.4.)

Five cohort studies and seven case-control studies investigated biomarkers of exposure to aflatoxins. All of the cohort studies and most of the case-control studies showed increased risk with elevated measures of exposure. Most cohort studies showed significant dose-response relationships, although the variety of measures used prevented meta-analysis. Effect estimates ranged from a three- to sevenfold increased risk for the highest measures of exposure.

There is strong mechanistic evidence through the metabolic product of aflatoxin B1, which is known to be genotoxic and is formed in the liver. It directly damages DNA, forming adducts. The activity of GST enzymes can result in lower levels of adducts with varying efficiency between genotypes. There is clear and consistent evidence that GST-positive genotypes protect against the increased risk of liver cancer from hepatitis infection combined with aflatoxin exposure. This supports a causal role for aflatoxin B1 in hepatocellular carcinoma.

The evidence is ample and consistent and is supported by strong evidence for mechanisms operating in humans. A dose-response relationship 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.

7.8.5.3 Alcoholic drinks

(Also see chapter 4.8.5.1.)

A total of 15 cohort studies and 33 case-control studies investigated alcoholic drinks, and 14 cohort studies and 21 case-control studies investigated total ethanol intake. Most studies showed increased risk with increased alcohol intake, with none reporting statistically significant decreased risk. Meta-analysis of cohort data showed a 10 per cent increased risk per 10 g ethanol/day. Meta-analysis of case-control data showed an 18 per cent increased risk per drink/week, or a 17 per cent increased risk per 10 g ethanol/day (figures 4.8.18–4.8.19).

Heterogeneity in case-control studies may be explained by alcoholic behaviour, by proxy reporting, or by failure to adjust for hepatitis virus status. Several studies used participants judged to be at high risk of developing liver cancer (people who already had liver cirrhosis). These results are particularly difficult to interpret as cirrhosis status affects drinking behaviour. Also, the cancer disease path may be different in people with cirrhosis.

It is biologically highly plausible that alcoholic drinks are a cause of liver cancer. Reactive metabolites of alcohol such as acetaldehyde can be carcinogenic. DNA mutations may be less efficiently repaired in the presence of alcohol. Alcohol may also function as a solvent, enhancing penetration of other carcinogenic molecules into cells. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation, and the generation of free radical oxygen species. Lastly, heavy consumers of alcohol may have diets low in essential nutrients, making tissues susceptible to carcinogenesis. 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. Alcohol consumption, even at moderate levels, is associated with increases in levels of circulating hepatitis C virus RNA in carriers of this infection. This infection is highly prevalent among alcoholics with chronic liver disease, and appears to accelerate the course of alcoholic liver disease.

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, which 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[135] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.8.5.4 Body fatness

(Also see chapter 6.1.3.1).

Six cohort studies and two case-control studies investigated body fatness, as measured by BMI, or obesity. All cohort studies showed increased risk with increased body fatness, except in one subgroup of African-American men. There was substantial heterogeneity and none of the studies adjusted for hepatitis virus status. The two case-control studies provided no clear evidence of any effect.

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (see box 2.4). It stim-

ulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers (see chapter 2.4.1.3).

The epidemiological evidence shows some inconsistencies and the mechanistic evidence is speculative. There is limited evidence suggesting that greater body fatness is a cause of liver cancer.

The Panel is aware that since the conclusion of the SLR, two cohort studies[58 136] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.8.5.5 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) and their products; non-starchy vegetables; peanuts; fish; salted fish; water source; coffee; and tea.

In cases of cereals (grains) and peanuts, there are data connecting these foods to liver cancer, but *the Panel judges* that any causative factor is likely to be aflatoxins.

7.8.6 Comparison with previous report

7.8.6.1 General

See 7.1.6.1, and box 3.8 in chapter 3.

7.8.6.2 Specific

Since publication of the previous report, the evidence that aflatoxin contamination of food is a cause of liver cancer is stronger and now justifies a judgement of 'convincing'.

7.8.7 Conclusions

The Panel concludes:

The evidence is convincing that aflatoxins, which contaminate mostly cereals (grains) and pulses (legumes), usually as a result of long storage in hot, wet conditions, are a cause of liver cancer.

Alcoholic drinks are probably a cause of liver cancer.

There is limited evidence suggesting that fruits are protective, and that body fatness is a cause of this cancer.

7.9 Colon and rectum

Cancers of the colon and rectum are the third most common type worldwide. Around 1 million cases were recorded in 2002, accounting for around 9 per cent overall. Rates of this cancer increase with industrialisation and urbanisation. It has been much more common in high-income countries but is now increasing in middle- and low-income countries. It remains relatively uncommon in Africa and much of Asia. It is somewhat more common in men than in women. It is fatal in just under half of all cases and is the fourth most common cause of death from cancer.

Overall, *the Panel judges* that food and nutrition have a highly important role in the prevention and causation of cancers of the colon and rectum (here termed colorectum).

***The Panel judges* as follows:**

The evidence that physical activity protects against colorectal cancer is convincing, although the evidence is stronger for colon than for rectum. The evidence that red meat, processed meat, substantial consumption of alcoholic drinks (in men), body fatness and abdominal fatness, and the factors that lead to greater adult attained height, or its consequences, are causes of colorectal cancer is convincing. Substantial consumption of alcoholic drinks is probably a cause of this cancer in women. Foods containing dietary fibre, and garlic, milk, and calcium probably protect against this cancer.

There is limited evidence suggesting that non-starchy vegetables, fruits, foods containing folate, fish, foods containing vitamin D, and selenium and foods containing it protect against colorectal cancer, and that foods containing iron, cheese, foods containing animal fats, and foods containing sugars are causes of this cancer.

See chapter 8 for evidence and judgements on factors that modify the risk of body fatness and abdominal fatness, including physical activity and sedentary ways of life, the energy density of foods and drinks, and breastfeeding.

It has been estimated that this cancer is mostly preventable by appropriate diets and associated factors.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable",shows that physical activity protects against colorectal cancer. The evidence also shows that red meat and processed meat, substantial consumption of alcoholic drinks (by men and probably by women), body fatness and abdominal fatness, and the factors that lead to greater adult attained height, or its consequences, are causes of this cancer. Foods containing dietary fibre, and also garlic, milk, and calcium, probably protect against this cancer.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCERS OF THE COLON AND THE RECTUM

In the judgement of the Panel, the factors listed below modify the risk of cancers of the colon and the rectum. Judgements are graded according to the strength of the evidence.

	DECREASES RISK	INCREASES RISK
Convincing	**Physical activity[1 2]**	**Red meat[3 4]** **Processed meat[4 5]** **Alcoholic drinks (men)[6]** **Body fatness** **Abdominal fatness** **Adult attained height[7]**
Probable	**Foods containing dietary fibre[8]** **Garlic[9]** **Milk[10 11]** **Calcium[12]**	**Alcoholic drinks (women)[6]**
Limited — suggestive	Non-starchy vegetables[9] Fruits[9] Foods containing folate[8] Foods containing selenium[8] Fish Foods containing vitamin D[8 13] Selenium[14]	Foods containing iron[4 8] Cheese[10] Foods containing animal fats[8] Foods containing sugars[15]
Limited — no conclusion	Cereals (grains) and their products; potatoes; poultry; shellfish and other seafood; other dairy products; total fat; fatty acid composition; cholesterol; sugar (sucrose); coffee; tea; caffeine; total carbohydrate; starch; vitamin A; retinol; vitamin C; vitamin E; multivitamins; non-dairy sources of calcium; methionine; beta-carotene; alpha-carotene; lycopene; meal frequency; energy intake	
Substantial effect on risk unlikely	None identified	

1 Physical activity of all types: occupational, household, transport, and recreational.
2 Much of the evidence reviewed grouped colon cancer and rectal cancer together as 'colorectal' cancer. *The Panel judges* that the evidence is stronger for colon than for rectum.
3 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
4 Although red and processed meats contain iron, the general category of 'foods containing iron' comprises many other foods, including those of plant origin.
5 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
6 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.
7 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).
8 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 box 4.1.2 and chapter 4.2).
9 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
10 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.
11 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.
12 The evidence is derived from studies using supplements at a dose of 1200 mg/day.
13 Found mostly in fortified foods and animal foods.
14 The evidence is derived from studies using supplements at a dose of 200 µg/day. Selenium is toxic at high doses.
15 '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 milks.

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.

The colon is the lower part of the intestinal tract. It extends from the caecum to the rectum. In the colon, water and salts are absorbed from undigested foods, and muscles move the waste products towards the rectum. The colon contains a vast population of many types of bacteria, which have potentially important functions. These include the fermentation of unabsorbed carbohydrate (non-starch polysaccharides and resistant starch) to release energy and short chain fatty acids that influence the health of the colonic mucosa. It may also be infected with harmful types of bacteria. The colon is lined with mucous membranes, and also contains lymphoid cells that form part of the body's immune defences.

Approximately 95 per cent of colorectal cancers are adenocarcinomas. Other types of cancer that can occur here

include mucinous carcinomas and adenosquamous carcinomas.[4] Adenocarcinomas are covered here. A systematic review of colorectal adenomas was conducted to understand the contribution of food, nutrition, and physical activity to the pathogenesis of colorectal cancer, and contributed to interpretation of the underlying mechanisms.

7.9.1 Trends, incidence, and survival

There is no clear trend in global age-adjusted rates of colorectal cancer. There has, however, been a rapid increase in rates in high-income countries that have recently made the transition from a relatively low-income economy, such as Japan, Singapore, and eastern European countries. Rates have at least doubled in many of these countries since the mid-1970s.[137] Colorectal cancer is mainly a disease of high-income countries, where overall rates are nearly four times higher than in middle- to low-income countries. Around the world, age-adjusted incidence rates range from more than 40 per 100 000 people in North America, parts of Europe, Australia, New Zealand, and Japan to less than 5 per 100 000 in much of Africa, Central America, and parts of Asia.[2] In the USA, rates are higher among African-American people than in white people.[3] This disease is slightly more common in men than in women, by seven to five. Risk increases with age until old age, when it levels off.[6]

Colorectal cancer often produces symptoms at an early enough stage to make it treatable, meaning that survival rates are relatively high. In addition, regular screening is common in some countries such as the USA. The 5-year overall survival rate averages 50 per cent, with 55 per cent in high-income countries and 39 per cent in middle- to low-income countries.[124] This cancer accounts for somewhat over 9 per cent of all cancer incidence, but around 8 per cent of all cancer deaths. Also see box 7.1.1.

7.9.2 Pathogenesis

Carcinogens ingested as part of, or with, foods and drinks can interact directly with the cells that line the colon and rectum if they are not metabolised or absorbed in the small intestine. Colorectal cancer can also develop from a background of inflammatory bowel disease (ulcerative colitis or Crohn's disease).[138]

Between 5 and 10 per cent of colorectal cancers are a consequence of recognised hereditary conditions. The two major ones are familial adenomatous polyposis (FAP) and HNPCC[139] (also see 7.5.2). A further 20 per cent of cases occur in people who have a family history of colorectal cancer.[139] People with FAP develop a large number of adenomas at a relatively young age; if left untreated, nearly all will develop colorectal cancer by the time they reach 40.[140]

On average, people develop HNPCC in their mid-40s[140]; having this form of the disease increases the risk of a number of other gastrointestinal cancers. HNPCC involves mutations in DNA repair genes, a recognised step in the development of many colorectal cancers.

There are two characterised pathways to colorectal cancer, although they are likely to be linked — the 'gatekeeper' and the 'caretaker' pathways.[141] The gatekeeper pathway is involved in 85 per cent of sporadic colorectal cancers, and is the one associated with FAP.[140] It involves the disruption of genes that regulate growth, and for colorectal cancer, the key one is the tumour-suppressor gene APC. The caretaker pathway is characterised by disruption to genes that maintain genetic stability. It leads to 15 per cent of sporadic cancers, and is involved in the development of HNPCC.[140] Several tumour-suppressor genes are mutated in this pathway[142] (also see box 2.2 in chapter 2).

7.9.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Other diseases. Inflammatory bowel disease (Crohn's disease and ulcerative colitis) increase the risk of, and so may be seen as a cause of, colon cancer.

Medication. Non-steroidal anti-inflammatory drugs such as aspirin and hormone replacement therapy in postmenopausal women have been shown to decrease colon cancer risk.[143 144]

7.9.4 Interpretation of the evidence

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

7.9.4.2 Specific

Considerations specific to colorectal cancer include:

Classification. Cancers in different parts of the colon and in the rectum could have different pathogeneses and different causal agents.

7.9.5 Evidence and judgements

In total, 752 publications were included in the SLR for cancers of the colon and rectum. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.9.5.1 Foods containing dietary fibre

(Also see chapter 4.1.5.3.)

Sixteen cohort studies and 91 case-control studies investigated dietary fibre. Most studies showed decreased risk with

increased intake. Meta-analysis of cohort data showed a 10 per cent decreased risk per 10 g/day (see figure 4.1.1). Heterogeneity may be caused by variation in the definition of dietary fibre between studies. A pooled analysis of 8100 colorectal cancer cases among 730 000 participants, followed up for 6–20 yeas, showed a non-significant decreased risk for the groups that consumed the most dietary fibre. Data come predominantly from dietary sources, not supplements; therefore no effect can be attributed specifically to fibre, which is interpreted simply as a marker of consumption of foods containing it, although specific mechanisms have been identified.

Fibre exerts several effects in the gastrointestinal tract, but the precise mechanisms for its probable protective role are still not clearly understood. Fibre dilutes faecal content, decreases transit time, and increases stool weight. Fermentation products, especially short-chain fatty acids, are produced by the gut flora from a wide range of dietary carbohydrates and mucins that reach the colon. Short-chain fatty acids, such as butyrate, induce apoptosis, cell cycle arrest, and differentiation in experimental studies. Fibre intake is also strongly correlated with intake of folate, though adjusting for this often does not affect the risk reduction attributed to fibre.

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, seven cohort studies[145-151] and one case-control study[152] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.2 Non-starchy vegetables

(Also see chapter 4.2.5.1.)

Seventeen cohort studies and 71 case-control studies investigated non-starchy vegetables. Although meta-analysis of cohort data produced no evidence of an association, a comparison of the groups with the highest intakes against those with the lowest was suggestive of an association.

This is a wide and disparate category, and many different plant food constituents are represented that could contribute to a protective effect of non-starchy vegetables. These include dietary fibre, carotenoids, folate, selenium, glucosinolates, dithiolthiones, indoles, coumarins, ascorbate, chlorophyll, flavonoids, allylsulphides, flavonoids, and phytoestrogens, some of which are potentially antioxidants. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. It is difficult to unravel the relative importance of each constituent and it is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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[17 152 154] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.3 Garlic

(Also see chapter 4.2.5.1.2.)

Two cohort studies and six case-control studies investigated garlic. All studies reported decreased risk with increased intake, with none reporting contrary results. Most studies did not reach statistical significance, and meta-analysis was not possible.

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 laboratory experiments.

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[17] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.4 Fruits

(Also see chapter 4.2.5.2.)

Twenty cohort studies and 57 case-control studies investigated fruits. More than half of the cohort studies showed decreased risk with increased intake. Meta-analysis of cohort data produced no clear evidence of an overall association. However, stratification by sex did show a statistically significant decreased risk with increased intake among women, but not men.

This difference could be hormone-related, speculating a connection with the protective effects observed in postmenopausal women provided by hormone replacement therapy. Another possibility is that this could be artefactual: men may have not reported their diets as accurately as women.

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

Fruits are sources of vitamin C and other antioxidants, such as carotenoids, phenols, and flavonoids, as well as other potentially bioactive phytochemicals. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. In addition, flavonoids found in fruit directly inhibit the expression of a cytochrome P450 enzyme, which helps to metabolise toxins and has been associated with increased risk of lung cancer, primarily in smokers.[68] It is difficult to unravel the relative importance of each constituent and it is likely that a protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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[147 153 155] and five case control studies[152 154 156-158] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.5 Foods containing folate

(Also see chapter 4.2.5.4.)

Nine cohort studies investigated dietary folate and two cohort studies investigated serum folate. Most studies showed decreased risk with increased intake. Meta-analysis of cohort data produced evidence of decreased risk with a clear dose-response relationship. Both studies that investigated serum folate levels, which may be a more accurate and precise measure than dietary estimates, showed decreased risk for colon cancer, but not rectal cancer; this was statistically significant in one study. Data come predominantly from dietary sources, not supplements; therefore no effect can be attributed specifically to folate, which is interpreted simply as a marker of consumption of foods containing it.

Folate plays an important role in the synthesis, repair, and methylation of DNA. Abnormal DNA methylation has been linked to aberrant gene expression and also to cancers at several sites. Folate may also reduce HPV proliferation in cells (also see box 7.13.1). In addition, folate intake is also strongly correlated with intake of dietary fibre, which probably protects against colorectal cancer (see 7.9.5.1).

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[159-163] and two case control studies[152 164] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.6 Foods containing selenium

(Also see chapter 4.2.5.8.)

Fifteen case-control studies investigated dietary selenium, all of which showed decreased risk with increased intake. Meta-analysis of case-control data produced evidence of decreased risk with increased serum selenium levels, showing a clear dose-response relationship.

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. Four are glutathione peroxidases, which protect against oxidative damage to biomolecules such as lipids, lipoproteins, and DNA. Three are thioredoxin reductases, which regenerate oxidised ascorbic acid to its active antioxidant form, among other functions.

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.

7.9.5.7 Red meat

(Also see chapter 4.3.5.1.1.)

Sixteen cohort and 71 case-control studies investigated red meat. Nearly all cohort studies showed increased risk with higher intake. Meta-analysis of cohort data showed a 43 per cent increased risk per time consumed/week (figure 4.3.2) or a 15 per cent increased risk per 50 g/day (figure 4.3.3). Heterogeneity could not be fully explained but some studies could have included processed meats in the 'red meat' category.

There are several potential underlying mechanisms for a positive association of red meat consumption with colorectal cancer, including the generation of potentially carcinogenic *N*-nitroso compounds (see box 4.3.2). Some meats are also cooked at high temperatures, resulting in the production of heterocyclic amines and polycyclic aromatic hydrocarbons (see box 4.3.4). Red meat contains haem iron. Free iron can lead to the production of free radicals (see box 4.3.3).

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[165-173] and four case-control studies[154 156 157 174] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.8 Processed meat

(Also see chapter 4.3.5.1.2.)

Fourteen cohort studies and 44 case-control studies investigated processed meat. Nearly all cohort studies showed increased risk with higher intake. Meta-analysis of cohort data showed a 21 per cent increased risk per 50 g/day (figure 4.3.6). Heterogeneity was low and explained by the disparity in category definitions between studies, as well as by improved adjustment for confounders in recent studies.

Nitrates are both produced endogenously in gastric acid and added as preservatives to processed meats. They may contribute to *N*-nitroso compound production and exposure. These compounds are suspected mutagens and carcinogens (see box 4.3.2).[55] Many processed meats also contain high levels of salt and nitrite. Meats cooked at high temperatures can contain heterocyclic amines and polycyclic aromatic hydrocarbons (see 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 (see box 4.3.3).

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[153 165-169 171 173 175] and two case-control studies[154 157] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.9 Fish

(Also see chapter 4.3.5.3.)

Nineteen cohort studies and 55 case-control studies investigated fish. Most cohort studies showed decreased risk with higher intake. Meta-analysis showed a non-significant decreased risk. Heterogeneity may be partially explained by varying definitions of fish in different studies to include fresh and/or salted and dried fish. Also, high fish intake may be associated with low meat intake, which is a potential confounder that has not been adjusted for.

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

It is biologically plausible that long-chain fish n-3 polyunsaturated fatty acids (PUFAs) protect against cancer (see chapter 2.4.1.3). Fish oils reduce tumours in animal studies.[176] Likely mechanisms are thought to include their role in reduction of n-6 PUFA-derived eicosanoid biosynthesis (eicosanoids influence inflammation) and direct inhibition of cyclo-oxygenase-2, also implicated in the cancer process This mechanism, though plausible, is not well supported.[177] 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[147 165 167-169 171 178] and two case-control studies[152 154] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.10 Foods containing vitamin D

(Also see chapter 4.3.5.5.)

Eleven cohort studies and 17 case-control studies investigated total vitamin D and/or dietary vitamin D. Four cohort studies investigated plasma or serum vitamin D. Most of the studies of intake, and all of the studies of plasma or serum vitamin D, showed decreased risk as measures of intake increased.

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 were limited by the fact that levels of the biologically active form are not only dependent on diet but also on supplements, and ultraviolet (UV) exposure of the skin.

The evidence on vitamin D was inconsistent. There is limited evidence suggesting that foods containing vitamin D or vitamin D status protect against colorectal cancer.

The Panel is aware that since the conclusion of the SLR, two case-control studies[152 179] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.11 Foods containing iron

(Also see chapter 4.3.5.6.)

Four cohort studies and 23 case-control studies investigated iron intake. All cohort studies showed increased risk with increased intake, which was statistically significant in two.

It is biologically plausible that iron increases colorectal cancer risk due to its catalytic activity on the formation of reactive oxygen species. However, this role has not been confirmed in animal studies. Another hypothesis relates to dietary haem, which can induce colonic cytotoxicity and hyperproliferation.[180] Iron overload also activates oxidative responsive transcription factors, pro-inflammatory cytokines and iron-induced hypoxia signalling.[181] Also see box 4.3.3.

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 for evidence specifically 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[175 182] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.12 Milk

(Also see chapter 4.4.5.1.2.)

Thirteen cohort studies and 36 case-control studies investigated milk; 15 cohort studies and 58 case-control studies investigated dietary calcium. Most cohort studies showed decreased risk with increased intake. A pooled analysis of 10 cohort studies (nearly 5000 colorectal cancer cases among more than 530 000 participants) showed a 15 per cent decreased risk for the groups that drank the most milk, and a 14 per cent decreased risk for the groups with the highest dietary calcium intakes.[183]

Most of the evidence used here comes from Western countries, where dietary calcium intake can be taken as a marker for dairy consumption.

Any effect of milk in reducing colorectal cancer risk is likely to be mediated at least in part by calcium, which has direct growth-restraining and differentiation- and apoptosis-inducing actions on normal and tumour colorectal cells.[184] Milk includes many bioactive constituents, which may also play a role.

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[185-188] and three case-control studies[154 158 189] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.13 Cheese

(Also see chapter 4.4.5.1.2.)

Eleven cohort studies and 25 case-control studies investigated cheese. Most cohort studies showed increased risk with increased intake. Meta-analysis showed a non-significant increased risk.

The potential mechanisms for the association of cheese with cancers of the colon and rectum are unclear. Saturated fatty acids can induce expression of inflammatory mediators and stimulate increased insulin production.

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[185-188] and one case-control study[189] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.14 Foods containing animal fats

(Also see chapter 4.5.5.2.)

Five cohort studies investigated animal fats. Most studies showed increased risk with increased intake but there is potential for residual confounding. Meta-analysis of cohort data showed a non-significant increased risk.

Diets high in fat lead to increased levels of bile acids in the colon. Bile acids are metabolised by the bacterial flora to deoxycholic acid, which can promote cancer in rodents. The conversion of bile acids to secondary bile acids such as deoxycholic acid is decreased by the lower pH induced by short-chain fatty acids produced in diets high in non-starch polysaccharides. Also, deoxycholic acid is less soluble at a lower pH, which may limit its adverse effects.[190]

There is a limited amount of fairly consistent evidence suggesting that consumption of foods containing animal fats is a cause of colorectal cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[167] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.15 Foods containing sugars

(Also see chapter 4.6.5.1.)

A total of one cohort study and seven case-control studies investigated sugars as foods. Seven cohort studies and 16 case-control studies investigated sugars as nutrients, defined as total sugar, sucrose, or fructose. Most studies showed increased risk with increased total sugars, sucrose, or fructose intake. Data were particularly suggestive for fructose.

In most, though not all, animal experiments, sucrose and fructose are associated with increased colonic proliferation and aberrant crypt foci, which are precursors of colon cancers (see chapter 2).

The evidence is sparse and inconsistent. There is limited evidence suggesting that foods containing sugars are a cause of colorectal cancer.

7.9.5.16 Alcoholic drinks

(Also see chapter 4.8.5.1.)

Twenty-four cohort studies investigated alcoholic drinks; 13 cohort studies and 41 case-control studies investigated ethanol intake. Nearly all cohort studies showed increased risk with increased intake, with none reporting statistically significant contrary results. Meta-analysis of cohort data showed a 9 per cent increased risk per 10 g ethanol/day (figure 4.8.10). A pooled analysis of more than 4600 colorectal cancer cases among more than 475 000 participants, followed up for 6–16 years, showed a 41 per cent increased risk for the groups that drank the most alcohol.[191] There was some suggestion of sexual dimorphism, with a possibly greater effect in men than in women. This more elevated risk may be because of the generally higher consumption of alcohol among men. Also, men and women may prefer different types of alcoholic drinks, there may be hormone-related differences in alcohol metabolism, or susceptibility to alcohol may exist. Data also suggested a 'J'-shaped dose-response relationship, with low intake being associated with lower risk compared with no intake.

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

Reactive metabolites of alcohol such as acetaldehyde can be carcinogenic. There is also an interaction with smoking. 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. Additionally, the effects of alcohol may be mediated through the production of prostaglandins, lipid peroxidation, and the generation of free radical oxygen species. Lastly, high consumers of alcohol may have diets low in essential nutrients, making tissues susceptible to carcinogenesis.

There is ample and generally consistent evidence from cohort studies. A dose-response relationship is apparent. There is evidence for plausible mechanisms. The evidence that consumption of more than about 30 g per day of ethanol from alcoholic drinks is a cause of colorectal cancer in men is convincing; and it is probably a cause in women.

The Panel is aware that since the conclusion of the SLR, four cohort studies[159 192-194] and four case-control studies[154 195-197] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.17 Calcium

(Also see chapter 4.10.6.4.4.)

Seven cohort studies investigated calcium supplements. All but one reported decreased risk with calcium supplementation. A pooled analysis of 10 cohort studies (nearly 5000 colorectal cancer cases among more than 530 000 participants, followed up for 6–16 years) showed a 22 per cent decreased risk for the groups with the highest calcium intakes (dietary and supplemental sources).[183] In addition, two randomised controlled trials and four cohort studies investigated calcium supplements and the risk of adenomas. Both trials and

most of the cohort studies showed decreased risk with supplementation.

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

Calcium from diet is an important nutrient; intracellular calcium is a pervasive second messenger acting on many cellular functions including cell growth. Calcium has direct growth-restraining and differentiation- and apoptosis-inducing actions on normal and tumour colorectal cells.[184]

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.

7.9.5.18 Selenium

(Also see chapter 4.10.6.4.5.)

One randomised controlled trial and one cohort study investigated selenium supplements. The trial showed a statistically significant decreased risk with a daily supplement of 200 g of selenium. This was a relatively small study (1321 participants; 8 cases in the supplement group and 19 in the control group) and colorectal cancer was a secondary outcome. The cohort study showed non-significant decreased risk.

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. Four are glutathione peroxidases, which protect against oxidative damage to biomolecules such as lipids, lipoproteins, and DNA. Three are thioredoxin reductases and, among other functions, these regenerate oxidised ascorbic acid to its active antioxidant form.

The evidence is sparse. There is limited evidence to suggest that selenium protects against colorectal cancer.

7.9.5.19 Physical activity

(Also see chapter 5.4.1.)

Eleven cohort studies investigated total physical activity; 12 cohort studies investigated occupational physical activity; and 24 cohort studies investigated recreational activity. Most studies reported an association between increased physical activity and decreased cancer risk. Most studies were unsuitable for meta-analysis due to the disparate measures used to assess physical activity. The data also suggested that the effect was reduced or removed for rectal cancer. The evidence, overall, was broad and consistent. A published meta-analysis of 19 cohort studies reported a statistically significant decreased risk for physical activity for colon cancer, but not for rectal cancer.

Sustained moderate physical activity raises the metabolic rate and increases maximal oxygen uptake. In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity (the amount of work that it can perform), as well as reducing blood pressure and insulin resistance. In addition, physical activity increases gut motility.

There is abundant epidemiological evidence from prospective studies showing lower risk of colorectal cancer with higher overall levels of physical activity, as well as with greater frequency and intensity, and there is evidence of a dose-response effect. There is little heterogeneity, except that the effect is not as clear for rectal cancer as it is for colon cancer. There is plausible evidence for mechanisms operating in humans. The evidence that higher levels of physical activity, within the range studied, protect against colon cancer is convincing.

The Panel is aware that since the conclusion of the SLR, four cohort[198-201] and four case-control studies[154 202-204] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.20 Body fatness

(Also see chapter 6.1.3.1.)

Sixty cohort studies and 86 case-control studies investigated body fatness, as measured by BMI. Most of the cohort studies showed increased risk with increased body fatness. Meta-analysis of cohort data showed a 15 per cent increased risk per 5 kg/m^2 (figure 6.1.6). Heterogeneity is explained partially by sexual and geographical differences, and also by cancer site. When stratified according to cancer site, data are more consistent and suggest a larger increased risk for colon cancer (figure 6.1.7) than for rectal cancer (figure 6.1.8).

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

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis. It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers. Also see chapter 6.1.3 and box 2.4.

There is abundant and consistent epidemiological evidence with a clear dose-response relationship, and evidence for plausible mechanisms that operate in humans. The evidence that greater body fatness is a cause of colorectal cancer is convincing.

The Panel is aware that since the conclusion of the SLR, 15 cohort[58 59 151 205-215] and 2 case-control studies[216-218] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.21 Abdominal fatness

(Also see chapter 6.1.3.2.)

Seven cohort studies and two case-control studies investigated waist circumference; six cohort studies and four case-control studies investigated waist to hip ratio. All cohort studies showed increased risk with either increased waist circumference or increased waist to hip ratio. Meta-analysis was possible on four cohort studies measuring waist circumference and five cohort studies measuring waist to hip ratio. This showed a 5 per cent increased risk per inch of waist cir-

cumference, or a 30 per cent increased risk per 0.1 increment of waist to hip ratio (figures 6.1.22 and 6.1.23).

The general mechanisms through which abdominal fatness could plausibly influence cancer risk are outlined in chapter 6.1.3 (for more detail see box 2.4). The hormonal and other biological effects of being overweight or obese are outlined in chapter 8. Many of these, such as increased circulating oestrogens and decreased insulin sensitivity, are associated with abdominal fatness independently of overall body fatness.

There is ample consistent epidemiological evidence with a clear dose-response relationship and robust evidence for mechanisms that operate in humans. The evidence that abdominal fatness is a cause of colorectal cancer is convincing.

The Panel is aware that since the conclusion of the SLR, three cohort studies[146 205 209] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.22 Adult attained height

(Also see chapter 6.2.3.1.)

Twenty-one cohort studies and 16 case-control studies investigated adult attained height. Most cohort studies showed increased risk with increased height. Meta-analysis of cohort data showed a 9 per cent increased risk per 5 cm of height (figure 6.2.1).

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

The general mechanisms through which the factors that lead to greater adult attained height, or its consequences, could plausibly influence cancer risk are outlined in chapter 6.2.1.3 (for more detail see box 2.4). Many of these, such as early-life nutrition, altered hormone profiles, and the rate of sexual maturation, could plausibly increase cancer risk.

There is ample prospective epidemiological evidence, which is consistent, and there is a clear dose-response relationship, with evidence for plausible mechanisms operating in humans. The evidence that the factors that lead to greater adult attained height, or its consequences, are a cause of colorectal cancer is convincing. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

The Panel is aware that since the conclusion of the SLR, four cohort studies[146 151 206 207 209] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.9.5.23 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) or their products; potatoes; poultry; shellfish and other seafood; dairy products other than cheese or milk; non-dairy sources of calcium; coffee; caffeine; tea; total carbohydrate; starch; sugar; total fat; fatty acid composition; cholesterol; vitamin A; retinol; beta-carotene; alpha-carotene; lycopene; vitamin C; vitamin E; methionine; multivitamins; meal frequency; and energy intake.

7.9.6 Comparison with previous report

7.9.6.1 General

See 7.1.6.1, and box 3.8 in chapter 3.

7.9.6.2 Specific

The previous report judged the evidence that vegetables protect against colorectal cancer to be convincing. The results of cohort studies since then have generally not been supportive of this judgement.

Evidence that red meat and, in particular, processed meat are causes of colorectal cancer is now stronger.

The previous report noted the evidence showing that greater adult height was a possible cause of colorectal cancer. The evidence now is stronger, as is that for body fatness and for abdominal fatness. The previous report found that frequent meals or snacks possibly increased the risk of colorectal cancer; this was not found here.

The evidence that dietary fibre protects against colorectal cancer is here judged to be stronger than it was previously. Evidence that garlic, milk, and calcium supplements are probably protective was not found previously.

7.9.7 Conclusions

The Panel concludes:

The evidence that physical activity protects against colorectal cancer is convincing, although the evidence is stronger for colon than for rectum.

The evidence that red meat, processed meat, substantial consumption (more than about 30 g per day ethanol) of alcoholic drinks (by men, and probably by women), body fatness and abdominal fatness, and the factors that lead to greater adult attained height, or its consequences, are causes of colorectal cancer is convincing.

Foods containing dietary fibre, as well as garlic, milk, and calcium, probably protect against this cancer.

There is limited evidence suggesting that non-starchy vegetables, fruits, foods containing folate, as well as fish, foods containing vitamin D, and also selenium and foods containing it, protect against colorectal cancer, and that foods containing iron, and also cheese, foods containing animal fats, and foods containing sugars are causes of this cancer.

7.10 Breast

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE BREAST (PREMENOPAUSE)

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

	DECREASES RISK	INCREASES RISK
Convincing	**Lactation**	**Alcoholic drinks**
Probable	**Body fatness**	**Adult attained height[1]** **Greater birth weight**
Limited — suggestive	Physical activity[2]	
Limited — no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; vegetables; fruits; pulses (legumes); soya and soya products; meat; poultry; fish; eggs; milk and dairy products; fats and oils; total fat; vegetable fat; fatty acid composition, *trans*-fatty acids; cholesterol; sugar (sucrose); other sugars; sugary foods and drinks; coffee; tea; carbohydrate; starch; glycaemic index; protein; vitamin A; riboflavin; vitamin B6; folate; vitamin B12; vitamin C; vitamin D; vitamin E; calcium; iron; selenium; carotenoids; isoflavones; dichlorodiphenyldichloroethylene; dichlorodiphenyltrichloroethane; dieldrin; hexachlorobenzene; hexachlorocyclohexane; *trans*-nonachlor; polychlorinated biphenyls; dietary patterns; culturally defined diets; adult weight gain; energy intake; being breastfed	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).
2 Physical activity of all types: occupational, household, transport, and recreational.

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.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE BREAST (POSTMENOPAUSE)

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

	DECREASES RISK	INCREASES RISK
Convincing	**Lactation**	**Alcoholic drinks** **Body fatness** **Adult attained height[1]**
Probable	**Physical activity[2]**	**Abdominal fatness** **Adult weight gain**
Limited — suggestive		Total fat
Limited — no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; vegetables and fruits; pulses (legumes); soya and soya products; meat; poultry; fish; eggs; milk and dairy products; fats and oils; vegetable fat; fatty acid composition; cholesterol; sugar (sucrose); sugary foods and drinks; coffee; tea; carbohydrate; starch; glycaemic index; protein; vitamin A; riboflavin; vitamin B6; folate; vitamin B12; vitamin C; vitamin D; vitamin E; calcium; iron; selenium; carotenoids; isoflavones; dichlorodiphenyldichloroethylene; dichlorodiphenyltrichloroethane; dieldrin; hexachlorobenzene; hexachlorocyclohexane; *trans*-nonachlor; polychlorinated biphenyls; dietary patterns; culturally defined diets; birth weight; birth length; energy intake; being breastfed	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).
2 Physical activity of all types: occupational, household, transport, and recreational.

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.

Cancer of the breast is the most common cancer in women worldwide. Around 1.15 million cases were recorded in 2002, accounting for around 23 per cent of all cancers in women (11 per cent overall).

Observed rates of this cancer increase with industrialisation and urbanisation, and also with facilities for early detection. It remains much more common in high-income countries but is now increasing rapidly in middle- and low-income countries, including within Africa, much of Asia, and Latin America. Breast cancer is fatal in under half of all cases and is the leading cause of death from cancer in women (fifth overall), accounting for 14 per cent of all cancer deaths worldwide.

Breast cancer is hormone related, and the factors that modify the risk of this cancer when diagnosed premenopausally and when diagnosed (much more commonly) postmenopausally are not the same.

Overall, *the Panel is impressed* by the pattern of evidence showing the importance of early life events, including food and nutrition, as well as factors that affect hormone status, in modification of the risk of breast cancer.

The Panel judges as follows:

The evidence that lactation protects against breast cancer at all ages is convincing.

Physical activity probably protects against breast cancer postmenopause, and there is limited evidence suggesting that it protects against this cancer diagnosed premenopause. The evidence that alcoholic drinks are a cause of breast cancer at all ages is convincing. The evidence that the factors that lead to greater adult attained height, or its consequences, are a cause of postmenopausal breast cancer is convincing, and these are probably also a cause of breast cancer diagnosed premenopause.

The factors that lead to greater birth weight, or its consequences, are probably a cause of breast cancer diagnosed premenopause. Adult weight gain is probably a cause of postmenopausal breast cancer. The evidence that body fatness is a cause of postmenopausal breast cancer is convincing, and abdominal body fatness is probably also a cause. On the other hand, body fatness probably protects against breast cancer diagnosed premenopause. There is limited evidence suggesting that total dietary fat is a cause of postmenopausal breast cancer.

Life events that protect against breast cancer include late menarche, early pregnancy, bearing children, and early menopause, all of which have the effect of reducing the number of menstrual cycles, and therefore lifetime exposure to oestrogen. The reverse also applies.

See chapter 8 for evidence and judgements on factors that modify the risk of body fatness and abdominal fatness, including physical activity and sedentary ways of life, the energy density of foods and drinks, and breastfeeding.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that lactation protects against breast cancer; that alcoholic drinks are a cause of this cancer; that the factors that lead to greater adult attained height, or its consequences, are a cause of postmenopausal and probably also premenopausal breast cancer; that factors that lead to greater birth weight, or its consequences, are probably a cause of premenopausal breast cancer; and that abdominal body fatness and adult weight gain are probably a cause of postmenopausal breast cancer. Body fatness is a cause of postmenopausal breast cancer but probably protects against premenopausal breast cancer.

Breast tissue comprises mainly fat, glandular tissue (arranged in lobes), ducts, and connective tissue. Breast tissue develops in response to hormones such as oestrogens, progesterone, insulin, and growth factors. The main periods of development are during puberty, pregnancy, and lactation. The glandular tissue atrophies after menopause.

Breast cancers are almost all carcinomas of the epithelial cells lining the ducts (the channels in the breast that carry milk to the nipple).[219] Premenopausal and postmenopausal breast cancers are considered separately in this Report. Although rare, breast cancer can occur in men, but it is not included here.

7.10.1 Trends, incidence, and survival

Age-adjusted rates of breast cancer in women are increasing in most countries, particularly in areas where the incidence had previously been low, such as Japan, China, and southern and eastern Europe.[124 137]

This is predominantly a disease of high-income countries, where overall rates are nearly three times higher than in middle- to low-income countries. Around the world, age-adjusted incidence rates range from 75–100 per 100 000 women in North America, northern Europe, and Australia, to less than 20 per 100 000 in parts of Africa and Asia.[2] In the USA, rates are higher among white women than those from other ethnic groups, although mortality is highest in black women.[3]

Overall risk doubles each decade until the menopause, when the increase slows down or remains stable. However, breast cancer is more common after the menopause. Studies of women who migrate from areas of low risk to areas of high risk show that rates of breast cancer in migrants assume the rate in the host country within one or two generations. This shows that environmental factors are important in the progression of the disease.[220]

Breast cancers can often be detected at a relatively early stage. In countries that provide or advocate screening, most of these cancers are diagnosed when the disease is still at a localised stage.[221] Survival rates range from more than 90 to less than 50 per cent, depending on the characteristics of the tumour, its size and spread, and the availability of treatment.[4] Average 5-year survival rates are higher in high-income countries: around 73 per cent, compared with 57 per cent in middle- to low-income countries. Breast cancer accounts for nearly 23 per cent of all cancer incidence in women and 14 per cent of all cancer deaths (all sites except for skin (non-melanoma) and in women only). Also see box 7.1.1.

7.10.2 Pathogenesis

Breast tissue, as well as hormones and hormone-receptor status, varies at different stages of life. It is therefore possible that individual risk factors will have different effects at different life stages (see 7.10.5). Early menarche, late menopause, not bearing children, and late (over 30) first pregnancy all increase breast cancer risk.[220 222] The age when breasts develop, and menopause, are both influenced by nutrition, with overnutrition leading to early puberty and late menopause; undernutrition delays puberty and advances menopause (see chapter 6.2).

Hormones play an important role in breast cancer progression because they modulate the structure and growth of epithelial tumour cells.[4] Different cancers vary in hormone sensitivity. Many breast cancers also produce hormones, such as growth factors, that act locally, and these can both stimulate and inhibit the tumour's growth.[223 224]

Between 4 and 9 per cent of breast cancer cases are hereditary, and are usually caused by inherited mutations in either the BRCA1 or BRCA2 gene.[225 226] In addition, growth factor receptor genes, as well as some oncogenes, are overexpressed in many breast cancers[4] (see box 2.2).

7.10.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Life events. As stated above, lifetime exposure to oestrogen, influenced by early menarche, late natural menopause, not bearing children, and late (over 30) first pregnancy all increase the risk of, and may be seen as causes of, breast cancer.[220 222] The reverse also applies: late menarche, early menopause, bearing children, and early pregnancy all reduce the risk of, and may be seen as protective against, breast cancer. Age of breast development and menopause are influenced by nutrition, with high-energy diets promoting earlier puberty and late menopause, and low-energy diets delaying puberty and advancing menopause.

Radiation. Ionising radiation exposure from medical treatment such as X-rays, particularly during puberty, increases risk, even at low doses.[227]

Medication. Hormone replacement therapy is a cause of breast cancer. The increased risk appears to disappear a few years after cessation.[144] Oral contraceptives containing both oestrogen and progesterone cause a small, transient, increased risk of breast cancer; the increased risk disappears after cessation.[133]

7.10.4 Interpretation of the evidence

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

7.10.4.2 Specific

Considerations specific to breast cancer include:

Patterns. The preponderance of data from high-income countries is a special issue with breast cancer. Breast cancer is hormone related, and factors that modify risk have different effects on cancers diagnosed pre- and postmenopause.

Classification. Because of the importance of menopause as an effect modifier, studies should stratify for menopause status. Many do not.

Confounding. Hormone replacement therapy is an important possible confounder in postmenopausal breast cancer. A few studies also reported results separately for different hormone receptor profiles within cancers. High-quality studies adjust for age, number of reproductive cycles, age at which children were born, and the taking of hormone-based medications.

7.10.5 Evidence and judgements

In total, 873 publications were included in the SLR for breast cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.10.5.1 Alcoholic drinks

(Also see chapter 4.8.5.1.)

A total of 11 cohort studies, 31 case-control studies, and 2 ecological studies investigated alcoholic drinks; 25 cohort studies, 29 case-control studies, and 4 ecological studies investigated ethanol intake and all-age breast cancer. Further studies investigated the relationship with alcoholic drinks in either pre- or postmenopausal breast cancer. Most studies showed increased risk with increased intake. Meta-analysis of cohort data showed a 10 per cent increased risk per 10 g ethanol/day; meta-analysis of case-control data showed a 5 per cent increased risk per 5 drinks/week, and a 6 per cent increased risk per 10 g ethanol/day (figures 4.8.13, 4.8.15, and 4.8.16). Menopausal status did not significantly alter the association. Two pooled analyses also showed statistically significant increased risks of 9 and 7 per cent per 10 g ethanol/day. The first was based on 6 cohort studies with more than 320 000 participants, followed up for up to 11 years, with more than 4300 breast cancer cases. The other analysed 53 case-control studies, with more than 58 000 cases and more than 95 000 controls.[228 229]

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. High consumers of alcohol may have diets deficient in essential nutrients, making tissues susceptible to carcinogenesis. In addition, most experimental studies in animals have shown that alcohol intake is associated with increased breast cancer risk. Alcohol interferes with oestrogen metabolism and action in multiple ways, influencing hormone levels and oestrogen receptors.

There is an interaction between folate and alcohol affecting breast cancer risk: increased folate status partially mitigates the risk from increased alcohol consumption.[230]

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[231] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.10.5.2 Lactation

(Also see chapter 6.3.3.)

One cohort study and 37 case-control studies investigated ever having breastfed as compared to never having breastfed; and 5 cohort studies and 55 case-control studies investigated the total duration of lactation. The single cohort study and most case-control studies showed decreased risk (age unspecified) with ever having breastfed compared with never. Most studies showed decreased risk with increasing duration of breastfeeding. Meta-analysis of case-control data showed a 3 per cent decreased risk per 5 months of total breastfeeding (figure 6.3.1); meta-analysis of cohort data showed a non-significant decreased risk. Pooled analysis from 47 epidemiological studies in 30 countries (more than 50 000 controls and nearly 97 000 breast cancer cases) showed a statistically significant decreased risk of breast cancer of 4.3 per cent for each 12 months of breastfeeding. Menopause status was not an effect modifier.[228 386]

Lactation is associated with increased differentiation of breast cells and with lower exposure to endogenous sex hormones during amenorrhea accompanying lactation. In addition, the strong exfoliation of breast tissue during lactation, and the massive epithelial apoptosis at the end of lactation, could decrease risk by elimination of cells with potential DNA damage.

There is abundant epidemiological evidence from both prospective and case-control studies, which is consistent and shows a dose-response relationship. There is robust evidence for plausible mechanisms that operate in humans. The evidence that lactation protects against both premenopausal and postmenopausal breast cancer is convincing.

7.10.5.3 Physical activity

(Also see chapter 5.4.2.)

Six cohort studies and 8 case-control studies investigated total physical activity; 5 cohort studies and 7 case-control studies investigated occupational activity; and 14 cohort studies and 11 case-control studies investigated recreational activity.

Menopause age unspecified

Most studies showed decreased risk with increased physical activity. Meta-analysis of case-control data showed a 10 per cent decreased risk per 7 MET-hours recreational activity/week (figure 5.4.5).

Premenopause

Data were inconsistent for most categories, but data on occupational activity were suggestive of decreased risk.

Postmenopause

Nearly all of the cohort studies and most case-control studies showed decreased risk with increased physical activity. Meta-analysis of cohort data showed a 3 per cent decreased risk per 7 MET-hours recreational activity/week (figure 5.4.6).

Sustained moderate physical activity raises the metabolic rate and increases maximal oxygen uptake. In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity (the amount of work that it can perform), as well as reducing blood pressure and insulin resistance. In addition, it decreases levels of oestrogens and androgens in postmenopausal women. Some trials have also shown decreases in circulating oestrogens, increased menstrual cycle length, and decreased ovulation in premenopausal women with a high level of physical activity.

Premenopause: There is ample evidence from prospective studies, but it is inconsistent. There is limited evidence suggesting that physical activity protects against premenopausal breast cancer.

Postmenopause: There is ample evidence from prospective studies showing lower risk of postmenopausal breast cancer with higher levels of physical activity, with a dose-response relationship, although there is some heterogeneity. There is little evidence on frequency, duration, or intensity of activity. There is robust evidence for mechanisms operating in humans. Physical activity probably protects against postmenopausal breast cancer.

The Panel is aware that since the conclusion of the SLR, one case-control study[232] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.10.5.4 Body fatness

(Also see chapter 6.1.3.1.)

Forty-three cohort studies, more than 100 case-control studies, and 2 ecological studies investigated body fatness, as measured by BMI. When grouped for all ages, data were inconsistent. However, a consistent effect emerged when they were stratified according to menopausal status. Most studies showed a decreased risk for premenopausal breast cancer and an increased risk for postmenopausal breast cancer with increased body fatness. For cancer diagnosed premenopause, meta-analysis of cohort data showed a 15 per cent decreased risk per 5 kg/m^2; meta-analysis of case-control data showed a 15 per cent increased risk per 5 kg/m^2. For cancer diagnosed postmenopause, meta-analysis of cohort data showed an 8 per cent increased risk per 5 kg/m^2; meta-analysis of case-control data showed a 13 per cent increased risk per 5 kg/m^2 (figures 6.1.11–6.1.16).

Two pooled analyses showed statistically significant increased risk for postmenopausal cancer. One of these also showed a statistically significant decreased risk for premenopausal breast cancer. One pooled analysis was based on 7 cohort studies with more than 337 000 participants, followed up for up to 11 years, with more than 4300 breast cancer cases. It showed a 14 per cent decreased risk per 5 kg/m^2 for cancer diagnosed premenopause and a 9 per cent increased risk per 5 kg/m^2 for cancer diagnosed postmenopause. The other pooled analysis, based on 53 case-control studies with more than 58 000 cases and more than 95 000 controls, showed a 19 per cent increased risk per 5 kg/m^2 for postmenopausal breast cancer.[233 234]

Body fatness directly affects levels of many circulating hor-

mones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (see box 2.4). It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers (see chapter 2.4.1.3). Adjusting for serum levels of oestradiol diminishes or destroys the association with BMI, suggesting that hormones are a predominant mechanism.[235]

There is no single well established mechanism through which body fatness could prevent premenopausal breast cancer. According to the oestrogen plus progesterone theory, overweight premenopausal women would be protected because they would be more frequently anovulatory, and therefore less exposed to endogenous progesterone. However, this theory is not well supported by recent studies, which suggest that natural progesterone could be protective.[236] Normal levels of natural progesterone are likely to be protective, and well nourished, or perhaps overnourished women, who may become slightly overweight in adulthood, may be protected by their natural fertile condition. Another possible mechanism is that the increased adipose tissue-derived oestrogen levels in overweight children could induce early breast differentiation and eliminate some targets for malignant transformation.[237] Anovulation and abnormal hormone profiles are commonly associated with obesity.[238] The age-specific pattern of association of breast cancer with BMI, therefore, is largely explained by its relationship with endogenous sex hormone levels.

Breast cancer diagnosed postmenopause is much more common. Therefore, throughout life, a decreased risk of premenopausal breast cancer would be expected to be outweighed by an increased risk of postmenopausal breast cancer.

Premenopause: There is a substantial amount of consistent epidemiological evidence with a dose-response relationship, but the mechanistic evidence is speculative. Greater body fatness probably protects against premenopausal breast cancer.

Postmenopause: There is abundant and consistent epidemiological evidence and a clear dose-response relationship with robust evidence for mechanisms operating in humans. The evidence that greater body fatness is a cause of postmenopausal breast cancer is convincing.

The Panel is aware that since the conclusion of the SLR, one cohort[239] and one case-control study[240] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.10.5.5 Adult attained height

(Also see chapter 6.2.3.1.)

Thirty-three cohort studies, 56 case-control studies, and 3 ecological studies investigated adult attained height.

Age unspecified

Twenty cohort studies and 29 case-control studies investigated adult attained height and breast cancer at all ages, or unspecified menopausal status. Most of the studies showed increased risk. Meta-analysis of cohort data showed a 9 per cent increased risk per 5 cm of height; meta-analysis of case-control data showed a 3 per cent increased risk per 5 cm of height (figure 6.2.2).

Premenopause

Seventeen cohort studies and 38 case-control studies investigated adult attained height and premenopausal breast cancer. Most of the studies showed increased risk. Meta-analysis of cohort data showed a 9 per cent increased risk per 5 cm of height; meta-analysis of case-control data showed a 4 per cent increased risk per 5 cm of height (figure 6.2.4). A pooled analysis of 7 cohort studies (more than 337 000 participants, followed up for up to 11 years, with more than 4300 breast cancer cases) showed a non-significant increased risk with greater adult attained height.[234]

There are fewer data for premenopausal than for postmenopausal breast cancer. The epidemiological evidence is generally consistent, with a dose-response relationship and evidence for plausible mechanisms. The factors that lead to greater adult attained height, or its consequences, are probably a cause of premenopausal breast cancer. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

Postmenopause

Twenty-two cohort studies and 34 case-control studies investigated adult attained height and postmenopausal breast cancer. Nearly all of the cohort studies and most of the case-control studies showed increased risk, with no studies showing statistically significant contrary results. Meta-analysis of cohort data showed an 11 per cent increased risk per 5 cm of height; meta-analysis of case-control data showed a 2 per cent increased risk per 5 cm of height (figure 6.2.3). A pooled analysis of 7 cohort studies (more than 337 000 participants, followed up for up to 11 years, with more than 4300 breast cancer cases) showed a statistically significant 7 per cent increased risk per 5 cm of height.[234] The ecological studies provided supporting data.

The general mechanisms through which the factors that lead to greater adult attained height, or its consequences, could plausibly influence cancer risk are outlined in chapter 6.2.1.3 (for more detail see box 2.4). Many of these, such as early-life nutrition, altered hormone profiles, and the rate of sexual maturation, could plausibly increase cancer risk.

There is abundant prospective epidemiological evidence, which is generally consistent, with a clear dose-response relationship, and evidence for plausible mechanisms operating in humans. The evidence that the factors that lead to greater adult attained height, or its consequences, are a cause of postmenopausal breast cancer is convincing. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

The Panel is aware that since the conclusion of the SLR, one cohort study[241] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.10.5.6 Abdominal fatness (postmenopause)

(Also see chapter 6.1.3.2.)

Eight cohort studies and three case-control studies investigated waist circumference and postmenopausal breast cancer; eight cohort studies and eight case-control studies investigated waist to hip ratio. All of the waist-circumference studies and most of those on waist to hip ratio showed increased risk with increased measures of abdominal fatness. Meta-analysis of cohort data showed a 19 per cent increased risk per 0.1 increment in waist to hip ratio (figure 6.1.24).

The general mechanisms through which abdominal fatness could plausibly cause cancer are outlined in chapter 6.1.3 (for more detail see box 2.4). The hormonal and other biological effects of being overweight or obese are outlined in chapter 8. Many of these, such as increased levels of circulating oestrogens and decreased insulin sensitivity, are associated with abdominal fatness independently of overall body fatness.

There is a substantial amount of epidemiological evidence but some inconsistency. There is robust evidence for mechanisms that operate in humans. Abdominal fatness is a probable cause of postmenopausal breast cancer.

7.10.5.7 Adult weight gain (postmenopause)

(Also see chapter 6.1.3.3.)

Seven cohort studies and 17 case-control studies investigated adult weight gain and postmenopausal breast cancer. Nearly all of the studies showed increased risk with increased weight gain in adulthood. Meta-analysis of case-control data showed a 5 per cent increased risk per 5 kg gained (figure 6.1.26). Heterogeneity may be explained by failure to separate postmenopausal participants taking hormone replacement therapy.

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (see chapter 2.7.1.3). It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers.

There is ample, consistent epidemiological evidence from both cohort and case-control studies. A dose-response relationship was apparent from case-control and cohort studies. Adult weight gain is a probable cause of postmenopausal breast cancer.

7.10.5.8 Greater birth weight (premenopause)

(Also see chapter 6.2.3.2.)

Six cohort studies and four case-control studies investigated birth weight. All cohort studies and most case-control studies showed increased risk with greater birth weight, with none reporting statistically significant contrary results. Meta-analysis of cohort data showed an 8 per cent increased risk per kg (figure 6.2.8).

The general mechanisms through which the factors that lead to greater birth weight, or its consequences, could plausibly influence cancer risk are outlined in chapter 6.2.1.1. Many of these, such as long-term programming of hormonal systems, could plausibly increase cancer risk. Greater birth weight raises circulating maternal oestrogen levels and may increase insulin-like growth factor (IGF)-1 activity; low birth weight raises both fetal and maternal levels of IGF-1 binding protein. The action of both oestrogens and IGF-1 are thought to be important in fetal growth and mammary gland development, and play a central, synergistic role in the initiation and promotion of breast cancer.[242] Animal experiments also provide evidence that exposure to oestrogens during fetal and early postnatal development can increase the risk of mammary cancers.[243]

There is general consistency amongst the relatively few epidemiological studies, with some evidence for a dose-response relationship. The mechanistic evidence is speculative. The factors that lead to greater birth weight, or its consequences, are probably a cause of premenopausal breast cancer.

The Panel is aware that since the conclusion of the SLR, one cohort study[239] and one case-control study[244] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.10.5.9 Total fat (postmenopause)

(Also see chapter 4.5.5.1.)

Nine cohort studies and 16 case-control studies investigated total fat intake and postmenopausal breast cancer. Most studies showed increased risk with increased intake. Meta-analysis of cohort data showed a non-significant increased risk; meta-analysis of case-control data showed a statistically significant increased risk. A pooled analysis (more than 350 000 participants and more than 7300 breast cancer cases) showed an overall non-significant decreased risk with increased fat intake. Menopausal status did not significantly alter the result.[245]

Higher endogenous oestrogen levels after menopause are a known cause of breast cancer.[235 246] Dietary fat may also increase endogenous oestrogen production.[247]

Evidence from prospective epidemiological studies of different types on the whole shows inconsistent effects, 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.

7.10.5.10 Other exposures

For premenopausal breast cancer, other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals

(grains) and their products; potatoes; vegetables; fruits; pulses (legumes); soya and soya products; meat; poultry; fish; eggs; fats and oils; vegetable fat; sugar; sugary foods and drinks; milk and dairy products; coffee; tea; carbohydrate; starch; dietary fibre; sugars; total fat; fatty acid composition; *trans*-fatty acids; cholesterol; protein; vitamin A; carotenoids; folate; riboflavin; vitamin B6; cobalamin; vitamin C; vitamin D; vitamin E; iron; calcium; selenium; isoflavones; dieldrin; *trans*-nonachlor; dichlorodiphenyltrichloroethane; dichlorodiphenyldichloroethylene; polychlorinated biphenyls; hexachlorocyclohexane; hexachlorobenzene; energy intake; adult weight gain; adult attained height; dietary patterns; culturally defined diets; glycaemic index; and being breastfed.

For postmenopausal breast cancer other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) and their products; potatoes; vegetables and fruits; pulses; soya and soya products; meat; poultry; fish; eggs; fats and oils; sugar; sugary drinks and foods; milk and dairy products; coffee; tea; carbohydrate; starch; dietary fibre; vegetable fat; fatty acid composition; cholesterol; protein; vitamin A and carotenoids; riboflavin; vitamin B6; vitamin B12; folate; vitamin C; vitamin D; vitamin E; isoflavones; iron; calcium; selenium; dieldrin; *trans*-nonachlor; dichlorodiphenyltrichloroethane; dichlorodiphenyldichloroethylene; polychlorinated biphenyls; hexachlorocyclohexane; hexachlorobenzene; energy intake; birth length; culturally defined diets; dietary patterns; glycaemic index; being breastfed; and birth weight.

There is considerable speculation around a biologically plausible interaction of soya and soya products with breast cancer development, due to their high phytoestrogen content. Data on pulses (legumes) were sparse and inconsistent, and there were insufficient studies available on soya consumption to allow a conclusion to be reached.

7.10.6 Comparison with previous report

7.10.6.1 General

See 7.1.6.1, and box 3.8.

7.10.6.2 Specific

One of the most striking differences between the two reports is the finding here on lactation. The previous report mentioned studies indicating that breastfeeding may protect against breast cancer, but it did not review or judge this evidence.

The previous report found that high body mass probably increases the risk for breast cancer diagnosed after the menopause, while this Report found the evidence for body fatness to be convincing. While the previous report made no judgement on high body mass and premenopausal breast cancer, this Report found that greater body fatness probably decreases the risk. The previous report judged the evidence to be convincing that rapid growth, together with greater adult height, are causes of breast cancer. This Report does not make a judgement on rates of growth. The previous report did not make judgments on birth weight.

The previous report judged it probable that vegetables and fruits decrease breast cancer risk. Cohort findings since then have been equivocal.

7.10.7 Conclusions

The Panel concludes:

The evidence that lactation protects against breast cancer at all ages therafter is convincing. Physical activity probably protects against postmenopausal breast cancer, and there is limited evidence suggesting that it protects against premenopausal breast cancer. The evidence that alcoholic drinks are a cause of breast cancer at all ages is convincing. The evidence that the factors that lead to greater attained adult height or its consequences are a cause of postmenopausal breast cancer is convincing; these are probably a cause of premenopausal breast cancer.

The factors that lead to greater birth weight or its consequences are probably a cause of breast cancer diagnosed premenopause. Adult weight gain is probably a cause of postmenopausal breast cancer. The evidence that body fatness is a cause of postmenopausal breast cancer is convincing, and abdominal body fatness is probably a cause of this cancer. On the other hand, body fatness probably protects against breast cancer diagnosed premenopause. There is limited evidence suggesting that total dietary fat is a cause of postmenopausal breast cancer.

7.11 Ovary

Ovarian cancer is the seventh most common cancer in women (and the 16th most common cancer overall) worldwide. Around 200 000 cases were recorded in 2002, accounting for around 4 per cent of all new cases of cancer in women (2 per cent overall). It is most frequent in high-income countries. This cancer is usually fatal, and is the seventh most common cause of cancer death in women worldwide (15th overall).

***The Panel judges* as follows:**

The factors that lead to greater adult attained height, or its consequences, are probably a cause of cancer of the ovary. There is limited evidence suggesting that non-starchy vegetables, and also lactation, protect against this cancer.

Life events that protect against ovarian cancer include late menarche, bearing children, and early menopause, all of which have the effect of reducing the number of menstrual cycles, and therefore lifetime exposure to oestrogen.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that the factors that lead to greater adult attained height, or its consequences, are probably a cause of cancer of the ovary.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE OVARY

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		**Adult attained height[1]**
Limited — suggestive	Non-starchy vegetables[2] Lactation	
Limited — no conclusion	Dietary fibre; fruits; pulses (legumes); meat; poultry; fish; eggs; milk and dairy products; total fat; cholesterol; coffee; tea; alcohol; carbohydrate; lactose; protein; vitamin A; folate; vitamin C; vitamin E; recreational activity; body fatness; abdominal fatness; weight change; energy intake	
Substantial effect on risk unlikely	None identified	

1 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).
2 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.

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.

The ovaries are the sites of egg production in women. They are also the main source of the hormones oestrogen and progesterone.

There are three types of ovarian tissue that can produce cancers: epithelial cells, which cover the ovary; stromal cells, which produce hormones; and germ cells, which become eggs. Many different types of ovarian cancers can occur. About 85–90 per cent of ovarian cancers are carcinomas,[4] the type included here.

7.11.1 Trends, incidence, and survival

There is no clear global trend in ovarian cancer incidence. Rates appear to be high in high-income countries, and rising in countries undergoing economic transition.[137] For instance in Japan, there was a fourfold increase in the age-adjusted mortality rate (from 0.9 to 3.6 per 100 000 women) between 1950 and 1997.[248]

Ovarian cancer rates are nearly three times higher in high- than in middle- to low-income countries. Around the world, age-adjusted incidence rates range from more than 10 per 100 000 women in Europe and North America, to less than 5 per 100 000 in parts of Africa and Asia. But rates are relatively high elsewhere in Asia, for example in Singapore and the Philippines.[2] In the USA, rates are higher among white women than in those from other ethnic groups; rates are also higher in Jewish women of Ashkenazi descent.[3 249]

Risk increases with age, although the rate of increase slows after the menopause, with most ovarian cancers occurring after menopause. Only 10–15 per cent of cases occur before the menopause, although germ cell cancers peak in women aged between 15 and 35.[4]

Ovarian cancer often has no symptoms at the early stages, so the disease is generally advanced when it is diagnosed. The 5-year survival rate ranges from approximately 30 to 50 per cent.[3 6] This cancer accounts for about 7 per cent of all cancer incidence and 4 per cent of cancer deaths in women worldwide. Also see box 7.1.1.

7.11.2 Pathogenesis

The pathogenesis of this disease is not well characterised, although various mechanisms have been suggested. Over many cycles of ovulation, the ovarian surface epithelium undergoes repeated disruption and repair. The epithelial cells

are stimulated to proliferate, which increases the probability of spontaneous mutations. Alternatively, following ovulation, these cells may become trapped within the connective tissue surrounding the ovary, which can lead to the formation of inclusion cysts. If this happens, the epithelial cells are subjected to a unique pro-inflammatory microenvironment, which may increase the rate of DNA damage.

Most ovarian cancers occur spontaneously, although 5–10 per cent of cases develop due to a genetic predisposition.[104] The latter, involving dysfunctional BRCA1 or BRCA2 genes (see chapter 2.4.1.1), produces high-grade carcinomas, with a poorer prognosis.[250]

7.11.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Life events. The risk of ovarian cancer is affected by the number of menstrual cycles during a woman's lifetime. Not bearing children increases the risk of, and may be seen as a cause of, ovarian cancer. The reverse also applies: bearing children reduces the risk of, and may be seen as protective against, ovarian cancer.[251-253] There is also substantial evidence that, as with breast cancer, early menarche and late natural menopause increase the risk of, and may be seen as causes of, ovarian cancer. The reverse also applies: late menarche and early menopause reduce the risk of, and may be seen as protective against, ovarian cancer.[251-253]

Medication. Oral contraceptives protect against this cancer.[133]

7.11.4 Interpretation of the evidence

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

7.11.4.2 Specific

Considerations specific to cancer of the ovary include:

Patterns. Because ovarian cancer is hormone related, factors that modify risk might have different effects at different times of life. If so, this might partly explain heterogeneous results.

Confounding. High-quality studies adjust for age, number of reproductive cycles, age at which children were born, and the taking of hormone-based medications.

Classification. There are different histological subtypes of ovarian cancer, which may have independent risk factors and disease progression patterns. Most studies combine these subtypes.

7.11.5 Evidence and judgements

In total, 187 publications were included in the SLR for ovarian cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.11.5.1 Non-starchy vegetables

(Also see chapter 4.2.5.1.)

A total of five cohort studies, eight case-control studies, and two ecological studies investigated non-starchy vegetables; three cohort studies and two case-control studies investigated green, leafy vegetables. All showed decreased risk with increased intake, with none reporting contrary results. Meta-analysis of cohort data showed a statistically significant decreased risk for non-starchy vegetables, with a clear dose-response relationship. A pooled analysis of 12 cohort studies (more than 560 000 participants, followed up for 7–22 years, with more than 2100 ovarian cancer cases) showed a non-significant decreased risk for the highest intake group of non-starchy vegetables.[254]

This is a wide and disparate category, and many different plant food constituents are represented that could contribute to a protective effect of non-starchy vegetables. These include dietary fibre, carotenoids, folate, selenium, glucosinolates, dithiolthiones, indoles, coumarins, ascorbate, chlorophyll, flavonoids, allylsulphides, flavonoids, and phytoestrogens, some of which are potentially antioxidants. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage. It is difficult to unravel the relative importance of each constituent and it is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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[17] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.11.5.2 Adult attained height

(Also see chapter 6.2.3.1.)

Seven cohort studies, nine case-control studies, and two ecological studies investigated adult attained height. All cohort studies and most other studies showed increased risk with greater adult attained height. Meta-analysis of cohort data showed an 8 per cent increased risk per 5 cm of height (figure 6.2.7); meta-analysis of case-control data showed no statistically significant relationship. Heterogeneity in the latter was derived almost entirely from one study.

The general mechanisms through which the factors that lead to greater adult attained height, or its consequences, could plausibly influence cancer risk are outlined in chapter 6.2.1.3 (see box 2.4). Many of these, such as early-life

nutrition, altered hormone profiles, and the rate of sexual maturation, could plausibly increase cancer risk.

There is some inconsistency, but the better quality epidemiological data show a clearer effect, with a dose-response relationship. There is evidence for plausible mechanisms operating in humans. The factors that lead to greater adult attained height, or its consequences, are probably a cause of ovarian cancer. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

The Panel is aware that since the conclusion of the SLR, one cohort study[255] and one case-control study[256] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.11.5.3 Lactation

(Also see chapter 6.3.3.)

One cohort study and 10 case-control studies investigated lactation, most of which showed an association with reduced risk. Meta-analysis of case-control data showed statistically significant decreased risk with increased accumulated lifetime duration of breastfeeding, with a clear dose-response relationship. Substantial heterogeneity is partially explained by variation in the assessment of breastfeeding when, for example, exclusivity of breastfeeding is not always assessed.

Lactation delays the return of menstruation and ovulation after childbirth. The general mechanisms through which lactation could plausibly protect against cancer are outlined in chapter 6.3.3. There is evidence that the reduced number of menstrual cycles associated with breastfeeding protect against some cancers.

There are sparse prospective epidemiological data, though some evidence for a dose-response relationship. The mechanistic evidence is speculative. There is limited evidence suggesting that lactation protects against ovarian cancer.

The Panel is aware that since the conclusion of the SLR, one case-control study[257] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.11.5.4 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: pulses (legumes); fruits; meat; poultry; fish; eggs; milk and dairy products; coffee; tea; alcohol; carbohydrate; dietary fibre; lactose; total fat; cholesterol; protein; vitamin A; folate; vitamin C; vitamin E; recreational activity; energy intake; body fatness; weight change; and abdominal fatness.

7.11.6 Comparison with previous report

7.11.6.1 General

See 7.1.6.1, and box 3.8 in chapter 3.

7.11.6.2 Specific

The finding here on adult attained height is new.

7.11.7 Conclusions

The Panel concludes:

The factors that lead to greater adult attained height, or its consequences, are probably a cause of cancer of the ovary.

There is limited evidence suggesting that non-starchy vegetables, and also lactation, protect against this cancer.

7.12 Endometrium

Endometrial cancer is the eighth most common cancer in women (and the 17th most common cancer overall) worldwide. Around 200 000 cases were recorded in 2002, accounting for around 4 per cent of all new cases of cancer in women (2 per cent overall). It is most frequent in high-income countries. Around three quarters of women with this cancer survive for 5 years. It is the 13th most common cause of cancer death in women worldwide (21st overall).

Overall, *the Panel is impressed* by the pattern of evidence showing the importance of physical activity and body fatness, as well as factors that affect hormone status, in modification of the risk of endometrial cancer.

***The Panel judges* as follows:**
The evidence that body fatness is a cause of cancer of the endometrium is convincing; abdominal fatness is probably a cause. Physical activity probably protects against this cancer. There is limited evidence suggesting that non-starchy vegetables protect against endometrial cancer, and that red meat, and also the factors that lead to greater adult attained height, or its consequences, are causes of this cancer.

Life events that protect against endometrial cancer include bearing children and early menopause, which have the effect of reducing the number of menstrual cycles and therefore lifetime exposure to oestrogens. The reverse also applies.

See chapter 8 for evidence and judgements on factors that modify the risk of body fatness and abdominal fatness, including physical activity and sedentary ways of life, the energy density of foods and drinks, and breastfeeding.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that body fatness and probably abdominal fatness are causes of endometrial cancer, and that physical activity is protective.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE ENDOMETRIUM

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

	DECREASES RISK	INCREASES RISK
Convincing		**Body fatness**
Probable	**Physical activity**[1]	**Abdominal fatness**
Limited — suggestive	Non-starchy vegetables[2]	Red meat[3] Adult attained height[4]
Limited — no conclusion	Cereals (grains) and their products; dietary fibre; fruits; pulses (legumes); soya and soya products; poultry; fish; eggs; milk and dairy products; total fat; animal fats; saturated fatty acids; cholesterol; coffee; alcohol; carbohydrates; protein; retinol; vitamin C; vitamin E; beta-carotene; lactation; energy intake	
Substantial effect on risk unlikely	None identified	

1 Physical activity of all types: occupational, household, transport, and recreational.
2 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
3 The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
4 Adult attained height is unlikely directly to modify the risk of cancer. It is a marker for genetic, environmental, hormonal, and also nutritional factors affecting growth during the period from preconception to completion of linear growth (see chapter 6.2.1.3).

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.

The endometrium is the lining of the uterus. It is subject to a process of cyclical change during the fertile years of a woman's life.

The majority of cancers that occur in the body of the womb are endometrial cancers, mostly adenocarcinomas,[4] the type included here.

7.12.1 Trends, incidence, and survival

Age-adjusted rates of endometrial cancer are increasing in countries undergoing transition from low- to high-income economies, although there is no clear, overall trend in high-income countries.

This is mainly a disease of high-income countries, where overall rates are nearly five times higher than in middle- to low-income countries. Around the world, age-adjusted incidence rates range from more than 15 per 100 000 women in North America and parts of Europe to less than 5 per 100 000 in most of Africa and Asia. In the USA, rates are higher in white women than among those from other ethnic groups, although mortality rates are higher in black women.[3 258] Risk increases with age, with most diagnoses made postmenopause.

Endometrial cancer often produces symptoms at relatively early stages, so the disease is generally diagnosed early. At around 73 per cent, the overall 5-year survival rate is relatively high, although it is lower in middle- than in high-income countries (67 compared with 82 per cent).[124 259] Endometrial cancer accounts for almost 2 per cent of all cancer incidence (around 4 per cent in women), but just under 1 per cent of all cancer deaths (nearly 2 per cent in women). Also see box 7.1.1.

7.12.2 Pathogenesis

Type 1 endometrial tumours are oestrogen driven, account for around 80 per cent of endometrial cancers, and have a favourable prognosis.[260] They follow a clear development pathway, starting with endometrial hyperplasia (an increase in the number of cells), and are relatively well differentiated. Type 2 tumours are less common, accounting for around 10 per cent of endometrial cancers. Most are associated with endometrial atrophy (wasting), tend to metastasise, and have a less favourable prognosis.

Up to 70 per cent of endometrial cancers are reported in women who have no recognised risk factors — such as those that might disrupt endocrine (hormone) processes.[4] Some studies have shown that polycystic ovary syndrome and insulin sensitivity, which are both components of metabolic syndrome, may play a role in the pathogenesis of endometrial cancer, perhaps through hormonal disruption.[261]

The tumour-suppressor gene PTEN is also involved in the development of endometrial cancers.[260] Also see also box 2.2.

7.12.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Life events. Not bearing children increases the risk of, and may be seen as a cause of, endometrial cancer.[262] The reverse also applies: bearing children reduces the risk of, and may be seen as protective against, endometrial cancer.[258-261] There is also substantial evidence that, as with breast and ovarian cancer, late natural menopause increases the risk of, and may be seen as a cause of, endometrial cancer. The reverse also applies: early menopause reduces the risk of, and may be seen as protective against, this cancer.[133]

Medication. Oral contraceptives protect against this cancer.[133] Oestrogen-only hormone replacement therapy is a cause of this cancer,[144] as is tamoxifen.

7.12.4 Interpretation of the evidence

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

7.12.4.2 Specific

Considerations specific to cancer of the endometrium include:

Patterns. Because endometrial cancer is hormone related, factors that modify risk might have different effects at different times of life.

Confounding. High-quality cohort studies eliminate women who have had hysterectomies from 'at-risk' populations. High-quality case-control studies assess the levels of hysterectomies in control groups.

7.12.5 Evidence and judgements

In total, 282 publications were included in the SLR for endometrial cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.12.5.1 Non-starchy vegetables

(Also see chapter 4.2.5.1.)

Ten case-control studies investigated non-starchy vegetables, and seven case-control studies investigated cruciferous vegetables. Most studies showed decreased risk with increased intake. Meta-analysis of case-control data produced evidence of decreased risk with non-starchy or cruciferous vegetable intake, with a clear dose-response relationship. There were no cohort data.

This is a wide and disparate category, and many different plant food constituents are represented that could contribute to a protective effect of non-starchy vegetables. These include dietary fibre, carotenoids, folate, selenium, glucosinolates, dithiolthiones, indoles, coumarins, ascorbate, chlorophyll, flavonoids, allylsulphides, flavonoids, and phytoestrogens, some of which are potentially antioxidants. Antioxidants trap free radicals and reactive oxygen molecules, protecting against oxidation damage.

It is difficult to unravel the relative importance of each constituent and it is likely that any protective effect may result from a combination of influences on several pathways involved in carcinogenesis.

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

7.12.5.2 Red meat

(Also see chapter 4.3.5.1.1.)

One cohort study and seven case-control studies investigated red meat. Most studies showed increased risk with higher intake. Meta-analysis of case-control data produced evidence of increased risk with higher intake, with a clear dose-response relationship.

There are several potential underlying mechanisms for a positive association of red meat consumption with endometrial cancer, including the generation of potentially carcinogenic *N*-nitroso compounds (see box 4.3.2).

Some meats are also cooked at high temperatures, resulting in the production of heterocyclic amines and polycyclic aromatic hydrocarbons (see box 4.3.4). Red meat contains haem iron. Free iron can lead to the production of free radicals (see box 4.3.3).

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[263] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.12.5.3 Physical activity

(Also see chapter 5.4.3.)

Two cohort studies and 4 case-control studies investigated total physical activity; 3 cohort studies and 10 case-control studies investigated occupational activity; and 4 cohort studies and 10 case-control studies investigated recreational activity. Nearly all of the cohort studies and most of the other studies showed decreased risk with increased physical activity. Although meta-analysis was not possible due to the wide variety in measures used, comparisons of high with low activity levels showed a consistent association with decreased risk (figures 5.4.8 and 5.4.9).

Sustained moderate physical activity raises the metabolic rate and increases maximal oxygen uptake. In the long term, regular periods of such activity increase the body's metabolic efficiency and capacity (the amount of work that it can perform), as well as reducing blood pressure and insulin resistance. In addition, physical activity has been found to affect serum levels of oestradiol, oestrone, and androgens in postmenopausal women, even after adjusting for BMI. More generally, effects on oestrogen metabolism may operate directly, or through decreasing body fat stores. Physical activity is also known to have favourable effects on insulin resistance, which may also result in decreased risk of endometrial cancer. Physical activity also results in decreased risk of diabetes and high blood pressure, which are risk factors for endometrial cancer.

There is generally consistent evidence, mostly from case-control studies, showing lower risk of cancer of the endometrium with higher levels of physical activity. There is evidence for mechanisms operating in humans. Physical activity probably protects against cancer of the endometrium.

7.12.5.4 Body fatness

(Also see chapter 6.1.3.1.)

Twenty-three cohort studies, 41 case-control studies and 2 cross-sectional studies investigated body fatness, as measured by BMI. Three cohort studies and six case-control studies investigated BMI as a young adult. Nearly all of the studies showed increased risk with increased body fatness, more than half of which were statistically significant. Meta-analysis of cohort data showed an overall 52 per cent increased risk per 5 kg/m^2, or a 31 per cent increased risk per 5 kg/m^2 as a young adult; meta-analysis of case-control data showed an overall 56 per cent increased risk per 5 kg/m^2, with a non-significant increased risk for BMI as a young adult (figures 6.1.17 and 6.1.18). Heterogeneity existed in the size, but not direction, of the effect.

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (see box 2.4). It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers (see chapter 2.4.1.3).

There is abundant, consistent epidemiological evidence with a clear dose-response relationship, and robust evidence for mechanisms operating in humans. The evidence that greater body fatness is a cause of endometrial cancer is convincing.

The Panel is aware that since the conclusion of the SLR, one cohort study[215] and one case-control study[264] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.12.5.5 Abdominal fatness

(Also see chapter 6.1.3.2.)

One cohort study and four case-control studies investigated waist circumference; one cohort study and six case-control studies investigated waist to hip ratio. Both cohort studies and most case-control studies showed statistically significant increased risk with increased abdominal fatness. Meta-analysis of case-control data showed a non-significant increased risk.

The general mechanisms through which abdominal fatness could plausibly cause cancer are outlined in chapter 6.1.3 (for more detail see box 2.4). The hormonal and other biological effects of being overweight or obese are outlined in chapter 8. Many of these, such as increased circulating oestrogens and decreased insulin sensitivity, are associated with abdominal fatness independently of overall body fatness.

There is a substantial amount of generally consistent epidemiological evidence, but limited prospective data. There is evidence for plausible mechanisms. Greater abdominal fatness is a probable cause of endometrial cancer.

7.12.5.6 Adult attained height

(Also see chapter 6.2.3.1.)

Ten cohort studies, 16 case-control studies and 1 ecological study investigated adult attained height. Most studies showed increased risk with greater adult attained height. Meta-analysis of cohort and case-control data showed non-significant increased risk.

The general mechanisms through which the factors that lead to greater adult attained height, or its consequences, could plausibly influence cancer risk are outlined in chapter 6.2.1.3 (for more detail see box 2.4). Many of these, such as early-life nutrition, altered hormone profiles, and the rate of sexual maturation, could plausibly increase cancer risk.

Although there is generally consistent evidence for prospective epidemiological data, there is some inconsistency in the evidence between cohort and

case-control studies, and the mechanistic evidence is speculative. There is limited evidence that greater adult attained height, or the factors that lead to it, are a cause of endometrial cancer. The causal factor is unlikely to be tallness itself, but factors that promote linear growth in childhood.

7.12.5.7 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) and their products; fruits; pulses (legumes); tofu and soya; poultry; fish; eggs; milk and dairy products; coffee; alcohol; carbohydrates; dietary fibre; total fat; animal fats; saturated fatty acids; cholesterol; protein; retinol; beta-carotene; vitamin C; vitamin E; energy intake; and lactation.

7.12.6 Comparison with previous report

7.12.6.1 General

See 7.1.6.1, and box 3.8 in chapter 3.

7.12.6.2 Specific

The finding here on physical activity is new. The evidence on body fatness and on abdominal fatness (not considered separately in the previous report's matrices) has strengthened.

7.12.7 Conclusions

The Panel concludes:
The evidence that body fatness is a cause of cancer of the endometrium is convincing; abdominal fatness is probably also a cause.

Physical activity probably protects against this cancer.

There is limited evidence suggesting that non-starchy vegetables protect against endometrial cancer, and that red meat, and also the factors that lead to greater adult attained height, or its consequences, are causes of this cancer.

7.13 Cervix

Cervical cancer is the second most common cancer in women worldwide. Around half a million cases were recorded in 2002, accounting for around 10 per cent of all new cases of cancer in women (5 per cent overall). It is most common in Africa, some parts of Asia including India, and in Latin America. It is most common in relatively young women. Five-year survival rates are around 50 per cent. It is the third most common cause of cancer death in women.

Overall, *the Panel notes* that food and nutrition and associated factors are not significant factors in modification of the risk of cancer of the cervix, although general nutritional status may affect a woman's vulnerability to infection.

Life events that protect against cervical cancer include having relatively few sexual partners. The reverse also applies. Infection with HPV is a necessary cause of this cancer, and smoking tobacco increases risk.

***The Panel judges* as follows:**
There is limited evidence suggesting that carrots protect against cervical cancer.

In final summary, there is no strong evidence, corresponding to judgements of "convincing" and "probable", to conclude that any aspect of food, nutrition, and physical activity modifies the risk of cervical cancer.

The cervix is the neck of the womb. The part of the cervix inside the cervical canal is called the endocervix. The part on the outside is the ectocervix. Most cervical cancers start where these two parts meet. There are two main types, squamous cell carcinoma and adenocarcinoma. Occasionally, mixed carcinomas, with features of both types, occur. Approximately 80 per cent of cervical cancers are squamous cell carcinomas, with most of the rest being adenocarcinomas.[265] Both types of cervical cancer are covered in this Report.

7.13.1 Trends, incidence, and survival

Age-adjusted rates of cervical cancer are decreasing, particularly in high- and middle-income countries, although there are insufficient data to derive trends in low-income countries. In high-income countries, the incidence of adenocarcinomas has increased since the 1970s, both absolutely and relative to squamous cell carcinomas. The prevalence appears to be increasing disproportionately in young women.[266]

Cervical cancer is predominantly a disease of low-income countries, with overall rates nearly twice as high in middle- to low- as in high-income countries. Around the world, age-adjusted incidence rates range from more than 40 per 100 000 women in parts of Africa, South America, and Melanesia, to less than 10 per 100 000 in North America and parts of Asia. However, rates are relatively high elsewhere

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE CERVIX

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		
Limited — suggestive	Carrots[1]	
Limited — no conclusion	Non-starchy vegetables; fruits; milk; retinol; vitamin E; alcoholism[2]; body fatness; adult attained height.	
Substantial effect on risk unlikely	None identified	

1 Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
2 Although data suggest that alcoholism is related to increased risk, *the Panel concludes* that this is likely to be due to factors other than alcohol intake 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.

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in Asia, for example in India and Bangladesh. In the USA, rates are higher among both African-American and Hispanic-American women than in white women. The incidence of many cancers rises with age, but cervical cancer peaks in younger women, between the ages of 30 and 45.[6] However, mortality does not follow the same pattern, and rises with age. Most women in high-income countries, and to varying degrees in other countries, have access to preventive screening programmes that are designed to detect precancerous lesions. If these are identified and removed, the incidence of this cancer is reduced. After a screening programme was implemented in the UK in 1988, cervical cancer incidence (age-standardised rate) has fallen by nearly 60 per cent.[6] It is generally well accepted that better access to cervical screening programmes worldwide would decrease both the incidence and mortality rates for this cancer.[267] More recently vaccination against HPV has become a preventive option.

The overall 5-year survival rate is approximately 50 per cent: 61 per cent in high-income countries compared with 41 per cent in middle- to low-income countries.[124] This cancer accounts for somewhat over 4 per cent of all cancer incidence (around 10 per cent in women) but only around 4 per cent of all cancer deaths (just over 9 per cent in women). Also see box 7.1.1.

7.13.2 Pathogenesis

Virtually all cervical cancers are associated with HPV infection (see box 7.13.1), and a woman's nutrition status may influence her susceptibility to this infection.[268] However, the majority of women with HPV do not develop cervical cancer. Therefore, HPV infection is a necessary but not a sufficient cause of cervical cancer. Women become susceptible to developing cervical cancer following HPV infection, but other environmental factors are required for the cancer to develop.

These factors may include toxins such as polycyclic aromatic hydrocarbons (see box 4.3.4) from tobacco smoke, food, or other environmental sources, which have been found in the mucus lining the cervix.[269]

Box 7.13.1 Human papilloma viruses

Human papilloma viruses (HPVs) are common. They infect squamous epithelia and generate warts. They are passed by direct contact; genital HPV infections are sexually transmitted. HPV infection rates are higher in women who have had a higher number of sexual partners (particularly male partners); do not use barrier methods of contraception; and who started having sex at a younger age.

There are more than 100 types of HPV. All can interfere with host-cell machinery that prevents cells from growing and replicating excessively, which are some of the cellular mechanisms that help protect the body against cancer development. Low-risk HPVs cause genital warts; high-risk HPVs cause squamous intra-epithelial lesions that can progress to invasive squamous cell carcinoma. The majority of human cervical cancers are associated with high-risk HPV infections. Four subtypes of this virus account for 80 per cent of all cervical cancer.

HPV infection tends to remain dormant, and with repeated infection, the HPV genome becomes integrated within the host cell genome and some cells may become cancerous.

Most HPV infections do not become persistent, and most persistent HPV infections do not lead to cancer. However, HPV infection is demonstrably present in 99 per cent of women with cervical cancer, and may be present but undetected in the remainder. HPV is a necessary while not sufficient cause of cervical cancer.

There are several stages at which foods or nutrition status could influence progression. Dietary factors influence susceptibility to infection; infection can alter nutrition status; diet may affect the likelihood of infections becoming persistent; and dietary factors have been shown to alter DNA stability and repair. Unfortunately, there is a shortage of epidemiological evidence specific to HPV at each of these stages. There is some limited evidence that eating vegetables and fruits can protect against persistence.[268] There is also evidence that folate can reduce persistence and independently reduce the risk of precancerous lesions in high-risk-HPV infected women.[270-272]

7.13.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Life events. Early sexual experience and a relatively high number of sexual partners increase the risk and severity of HPV infection, and may be seen as indirect causes of cervical cancer.[220 222]

Tobacco use. Smoking tobacco makes a woman twice as likely to develop cervical cancer.[10] Tobacco by-products have been found in the cervical mucus of women who smoke. The effect of smoking is independent of that of viral infection.[10 273]

Infectious agents. HPV infection (see box 7.13.1) is a necessary but not sufficient cause of cervical cancer.[273 274]

Medication. Dethylstilboestrol (a synthetic oestrogen, now withdrawn) used by women during pregnancy is a cause of vaginal and cervical clear-cell adenocarcinoma in their daughters.[275]

7.13.4 Interpretation of the evidence

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

7.13.4.2 Specific

Considerations specific to cancer of the cervix include:

Confounding. High-quality studies adjust for HPV infection. Early studies that failed to adjust for HPV status have reduced validity.

7.13.5 Evidence and judgements

In total, 154 publications were included in the SLR for cervical cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.13.5.1 Carrots

(Also see chapter 4.2.5.1.3.)

Five case-control studies and one ecological study investigated carrots. All of the case-control studies showed decreased risk for the highest levels of intake compared with the lowest, statistically significant in three. The case-control studies all used hospital-based controls and none adjusted for HPV status. The single ecological study showed non-significant increased risk with high intake of carrots.

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 HPV persistence.[276]

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

7.13.5.2 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: non-starchy vegetables; fruits; milk; retinol; vitamin E; alcoholism; body fatness; and adult attained height.

Although data suggest that alcoholism is related to increased risk, *the Panel concludes* that this is likely to be due to factors other than alcohol intake itself.

7.13.5.3 Exposures as related to non-invasive cancer outcomes

The following exposures were evaluated. However, the data were either too sparse, too inconsistent, or the number of studies too few to allow conclusions to be reached: vitamin A (as beta-carotene, alpha-carotene, or retinol); folate; vitamin C; vitamin E; and lycopene.

7.13.6 Comparison with previous report

7.13.6.1 General

See 7.1.6.1, and box 3.8 in chapter 3.

7.13.6.2 Specific

The previous report found that vegetables and fruits, and carotenoids (not carrots specifically), and also vitamins C and E possibly protect against cervical cancer.

7.13.7 Conclusions

The Panel concludes:

There is limited evidence suggesting that carrots protect against cervical cancer. The evidence is too limited to conclude that any aspect of food, nutrition, and physical activity directly modifies the risk of this cancer.

7.14 Prostate

Prostate cancer is the second most common cancer in men (and the sixth most common cancer overall) worldwide. Around 680 000 cases were recorded in 2002, accounting for around 12 per cent of all new cases of cancer in men (6 per cent overall). It is most commonly diagnosed in high-income countries, where screening is common. Five-year survival rates are around 60 per cent. It is the sixth most common cause of cancer death in men worldwide.

Overall, *the Panel notes* the impressive recent evidence from cohort studies and trials demonstrating effects, or absence of effect, of specific foods and nutrients on prostate cancer.

***The Panel judges* as follows:**
Foods containing lycopene, as well as selenium or foods containing it, probably protect against prostate cancer. Foods containing calcium are a probable cause of this cancer. It is unlikely that beta-carotene (whether from foods or supplements) has a substantial effect on the risk of this cancer. There is limited evidence suggesting that pulses (legumes) including soya and soya products, foods containing vitamin E, and alpha-tocopherol supplements are protective; and that processed meat, and milk and dairy products are a cause of this cancer.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that foods containing lycopene, as well as selenium or foods containing it, probably protect against prostate cancer, and that foods containing calcium are a probable cause of this cancer. It is unlikely that beta-carotene (whether from foods or supplements) has a substantial effect on the risk of this cancer.

The prostate is a walnut-sized gland in men that surrounds the top of the urethra; it produces seminal fluid. Its growth and function are controlled by male hormones such as testosterone.

Almost all prostate cancers are adenocarcinomas,[4] the type included here.

7.14.1 Trends, incidence, and survival

Age-adjusted incidence rates of prostate cancer increased dramatically between 1988 and 1992.[137] This was largely because of the increased availability of screening for prostate-specific antigen (PSA) in men without symptoms of the disease. This test leads to the detection of many prostate cancers that are small and/or would otherwise remain unrecognised, and which may or may not develop further into higher stage disease (see 7.14.2). Rates were already increasing before the availability of PSA testing, and have continued to increase in middle-income countries where screening is still not widely available.[124] This suggests that prostate cancer is influenced

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE PROSTATE

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable	**Foods containing lycopene[1 2]** **Foods containing selenium[1]** **Selenium[3]**	**Diets high in calcium[4 5]**
Limited — suggestive	Pulses (legumes)[6] Foods containing vitamin E[1] Alpha-tocopherol[7]	Processed meat[8] Milk and dairy products[5]
Limited — no conclusion	Cereals (grains) and their products; dietary fibre; potatoes; non-starchy vegetables; fruits; meat; poultry; fish; eggs; total fat; plant oils; sugar (sucrose); sugary foods and drinks; coffee; tea; alcohol; carbohydrate; protein; vitamin A; retinol; thiamin; riboflavin; niacin; vitamin C; vitamin D; gamma-tocopherol; vitamin supplements; multivitamins; iron; phosphorus; zinc; other carotenoids; physical activity; energy expenditure; vegetarian diets; Seventh-day Adventist diets; body fatness; abdominal fatness; birth weight; energy intake	
Substantial effect on risk unlikely	Beta-carotene[1 9]	

1 Includes both foods naturally containing the constituent and foods which have the constituent added (see chapter 3.5.3).
2 Mostly contained in tomatoes and tomato products. Also fruits such as grapefruit, watermelon, guava, and apricot.
3 The evidence is derived from studies using supplements at a dose of 200 µg/day. Selenium is toxic at high doses.
4 Includes diets that naturally contain calcium and that contain foods fortified with calcium. See box 4.10.1.
5 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 countries with populations that have high calcium and dairy consumption.
6 Including soya and soya products.
7 The evidence is derived from studies using supplements at a dose of 50 mg/day.
8 The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
9 The evidence is derived from studies using supplements at doses of 20, 30, and 50 mg/day.

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.

by environmental factors. Although screening is increasingly popular in many high-income countries, its value, for example in reducing mortality, is controversial. There has been a decline in incidence and mortality in several high-income countries since the 1990s although rates remain higher than those recorded before screening became available. This trend may be due to elimination of early stage disease and improved treatment.[277]

Prostate cancer is mainly a disease of high-income countries, where overall rates are nearly six times higher than in middle- to low-income countries. Around the world, age-adjusted incidence rates range from more than 100 per 100 000 men in North America, parts of the Caribbean, and Oceania, to less than 10 per 100 000 in Melanesia and much of Asia.[2] This wide range is partly, but not entirely, attributable to the increased availability of screening in high-income countries. In the USA, rates are higher among African-American men than in white men.[3]

Risk increases with age, rising sharply after 40. In most high-income countries, incidence in men below 40 is typically less than 1 per 100 000, rising to more than 1000 per 100 000 in those aged 65 and over.[278]

Average survival for prostate cancer is relatively high worldwide, although markedly more so in high-income countries. The 5-year survival rate is approximately 60 per cent overall: 76 per cent in high-income countries compared with 45 per cent in middle- to low-income countries.[124] This cancer accounts for around 6 per cent of all cancer incidence (nearly 12 per cent in men) but around 3 per cent of all cancer deaths (almost 6 per cent in men; all sites except for non-melanoma skin). Also see box 7.1.1.

7.14.2 Pathogenesis

The disease usually develops slowly and dysplastic lesions may precede cancer by many years or even decades. Extrapolations from autopsy studies suggest that most men would have prostate cancer if they lived to be more than 100.[278] The number of prostate cancers found incidentally at autopsy, which had been asymptomatic and not a cause of death, suggests that small, localised prostate cancers can remain unrecognised for many years before progressing to a clinically significant form. Men are more likely to die with, rather than from, prostate cancer.[279 280]

The increased prostate cancer incidence in first-degree male relatives of women who have early onset breast cancer suggests a genetic predisposition.[281] Some studies propose that this may be linked to the BRCA genes.[282]

Growth factors, particularly IGF, as well as androgens have also been implicated in the development of prostate cancers. Serum levels of IGF-1 can be associated with prostate cancer independently of PSA levels.[283] High levels of testosterone promote cell differentiation, which could protect against the development of this cancer. Therefore, declining levels of this hormone in older age may contribute to the development of this cancer.[284]

7.14.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

There are no other established causes of prostate cancer.

7.14.4 Interpretation of the evidence

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

7.14.4.2 Specific

Considerations specific to cancer of the prostate include:

Confounding. Screening is associated with relatively high socioeconomic status and also with 'health-conscious' behaviour such as taking exercise or following dietary guidelines. High-quality studies adjust for these factors. Some case-control studies use cases that have been detected by screening. If so, it is important that control groups are also from a screened population.

7.14.5 Evidence and judgements

In total, 558 publications were included in the SLR for prostate cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.14.5.1 Pulses (legumes) including soya and soya products

(Also see chapter 4.2.5.10.)

A total of 3 cohort studies, 11 case-control studies, and 6 ecological studies investigated pulses (legumes); 4 cohort studies, 4 case-control studies, and 2 ecological studies investigated soya and soya products. Most studies showed decreased risk with increased intake. Meta-analysis of case-control data produced evidence of an association with legume intake, with a clear dose-response relationship.

Pulses (legumes), particularly soya foods, contain various compounds that may have anti-cancer effects. These compounds could plausibly influence oestrogen metabolism. 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.

7.14.5.2 Processed meat

(Also see chapter 4.3.5.1.2.)

Four cohort studies and six case-control studies investigated processed meat. All cohort studies reported increased risk with higher intake; and most case-control studies also showed this effect.

Nitrates are both produced endogenously in gastric acid and added as preservatives to processed meats (box 4.3.2). They may contribute to *N*-nitroso compound production and exposure. These compounds are suspected mutagens and carcinogens.[55]

Many processed meats also contain high levels of salt and nitrite. Meats cooked at high temperatures can contain 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).

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[285 286] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.14.5.3 Milk and dairy products

(Also see chapter 4.4.5.1.)

A total of 10 cohort studies, 13 case-control studies, and 2 ecological studies investigated milk and dairy foods; 16 cohort studies, 11 case-control studies, and 11 ecological studies investigated milk. Most of the studies showed increased risk with increased intake. Meta-analysis of cohort data produced evidence of a clear dose-response relationship between advanced/aggressive cancer risk with milk intake, and between all prostate cancer risk and milk and dairy products.

Most other meta-analyses show non-significant increased risk. Ecological studies consistently report a relationship in the direction of increased risk between milk or dairy consumption and prostate cancer.

High calcium intake downregulates the formation of 1,25-dihydroxy vitamin D3 from vitamin D, thereby increasing cell proliferation in the prostate.[287] Prostate cancer tumours in rats treated with 1,25-dihydroxy vitamin D3 were significantly smaller, and presented smaller numbers of lung metastases.[288] Also, consumption of milk increases blood levels of IGF-1, which has been associated with increased prostate cancer risk in some studies.[283 289]

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[290 291] and one case-control study[189] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.14.5.4 Diets high in calcium

(Also see chapter 4.4.5.2.)

Nine cohort studies, 12 case-control studies, and 2 ecological studies investigated dietary calcium. Most cohort studies showed increased risk with increased calcium intake; case-control studies were inconsistent. Meta-analysis of cohort data showed an increased risk of 27 per cent per g/day; meta-analysis of cohort data on advanced or aggressive prostate cancer showed an increased risk of 32 per cent per g/day. Meta-analyses of case-control data showed non-significant increased risk.

Calcium can be taken to be a marker for dairy intake in high-income populations. In areas outside the USA, Europe, and Oceania, dairy products are not as widely consumed, and the range of calcium intakes is smaller.

High calcium intake downregulates the formation of 1,25-dihydroxy vitamin D3 from vitamin D, thereby increasing cell proliferation in the prostate.[287] Prostate cancer tumours in rats treated with 1,25-dihydroxy vitamin D3 were significantly smaller and presented fewer lung metastases.[288]

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[290 291] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.14.5.5 Foods containing selenium

(Also see chapter 4.2.5.8.)

A total of 1 cohort study, 7 case-control studies, and 2 ecological studies investigated dietary selenium; 12 cohort studies and 4 case-control studies investigated serum or plasma selenium; and 3 cohort studies, 3 case-control studies, and 1 ecological study investigated levels in nails. Most studies, including all of those that reported separately on advanced/aggressive prostate cancer, showed decreased risk with increased intake. Meta-analysis of cohort data on advanced or aggressive prostate cancer showed a decreased risk of 13 per cent per 10 μg selenium/litre of serum or plasma (figure 4.2.37), or 20 per cent per 100 ng selenium per g of nail clippings. Meta-analyses of cohort data that included all prostate cancer diagnoses showed non-significant decreased risk. Case-control studies were inconsistent.

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. Four are glutathione peroxidases, which protect against oxidative damage to biomolecules such as lipids, lipoproteins, and DNA. Three are thioredoxin reductases; among other functions, these regenerate oxidised ascorbic acid to its active antioxidant form.

In addition, selenoproteins are involved in testosterone production, which is an important regulator of both normal and abnormal prostate growth.

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.

7.14.5.6 Foods containing lycopene

(Also see chapter 4.2.5.3.)

A total of 5 cohort studies, 9 case-control studies, and 3 ecological studies investigated tomatoes; 3 cohort studies and 14 case-control studies investigated dietary lycopene; and 6 cohort studies and 2 case-control studies investigated serum or plasma lycopene. Most of the studies showed decreased risk with increased intake. Studies of cumulative lycopene intake, or of tomato sauce products (from which lycopene is highly bioavailable), showed statistically significant decreased risk. Meta-analysis of cohort data on serum or plasma lycopene, which are likely to be more precise and accurate than dietary assessments, showed a 4 per cent decreased risk per 10 μg lycopene/litre.

Lycopene is best absorbed from vegetables and fruits that contain it after they are cooked and pureed. The best measures, that take the degree of absorption into account, are therefore from studies on tomato sauce or serum/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 unrecognised disease.

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

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[292 293] and one case-control study[294] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.14.5.7 Selenium

(Also see chapter 4.10.6.4.5.)

One randomised controlled trial and two cohort studies investigated selenium supplements. The randomised controlled trial was conducted in 974 men with a history of skin cancers, randomised to receive a daily supplement of 200 μg selenium or a placebo. Prostate cancer was not a prior stated outcome, and was assessed as a secondary endpoint. The trial showed a 63 per cent decreased risk from selenium supplementation. Both cohort studies showed non-significant decreased risk with selenium supplementation.

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. Four are glutathione peroxidases, which protect against oxidative damage to biomolecules such as lipids, lipoproteins, and DNA. Three are thioredoxin reductases; among other functions, these regenerate oxidised ascorbic acid to its active antioxidant form. 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.

7.14.5.8 Foods containing vitamin E

(Also see chapter 4.2.5.7.)

A total of 2 cohort studies, 13 case-control studies, and 1 ecological study investigated dietary vitamin E; and 4 cohort studies and 1 case-control study investigated serum vitamin E. Other groupings examined were serum or plasma alpha-tocopherol (8 cohort, 2 case-control) and serum gamma-tocopherol (6 cohort, 1 case-control). Most studies showed decreased risk with increased intake. Meta-analysis of cohort data on serum gamma-tocopherol produced evidence of an association with decreased risk, with a clear dose-response relationship.

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.

The evidence on vitamin E, 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[293 295] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.14.5.9 Beta-carotene

(Also see chapters 4.2.5.3 and 4.10.6.4.2.)

Six cohort studies and 21 case-control studies investigated dietary beta-carotene; 10 cohort studies and 5 case-control studies investigated serum or plasma beta-carotene; 3 randomised controlled trials and 2 cohort studies investigated beta-carotene supplements. Meta-analyses of 6 cohort studies and 15 case-control studies that investigated beta-carotene from food and 7 cohort studies that investigated serum or plasma beta-carotene produced evidence for there being no association with prostate cancer risk. One randomised controlled trial produced evidence of no association; the other two showed that it was unlikely that beta-carotene reduced incidence, but did not exclude an effect of increasing incidence.

There is strong evidence from good quality trials and from cohort studies, which consistently fail 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. It is unlikely that beta-carotene or foods containing it have a substantial effect on the risk of prostate cancer.

The Panel is aware that since the conclusion of the SLR, two cohort studies[293 295] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.14.5.10 Alpha-tocopherol (vitamin E)

(Also see chapter 4.10.6.4.3.)

One randomised controlled trial investigated alpha-tocopherol supplements and prostate cancer. The large randomised controlled trial of male smokers given daily supplements of 50 mg of alpha-tocopherol and 20 mg of beta-carotene showed a statistically significant 34 per cent decreased risk for alpha-tocopherol supplements. Prostate cancer was not a prior-stated outcome for this trial.

Vitamin E exists in eight different forms (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 cell proliferation, can directly activate certain enzymes, and exerts transcriptional control on several genes. Vitamin E may have a direct effect on prostate growth by decreasing cellular concentrations of testosterone, which could impair differentiation.

The evidence is sparse. There is limited evidence that alpha-tocopherol supplements protect against prostate cancer in smokers.

7.14.5.11 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: culturally defined diets (vegetarian, Seventh-day Adventist); cereals (grains) and their products; potatoes; fruit and (non-starchy) vegetables; poultry; meat; fish; eggs; all fats; plant oils; sugar; confectionery; dietary fibre; fat; protein; carbohydrate; coffee; tea; alcoholic drinks; vitamin supplements; multivitamins; vitamin A; retinol; carotenoids; thiamine; riboflavin; niacin; vitamin C; vitamin D; vitamin E from foods; iron; zinc; phosphorus; physical activity; energy intake; energy expenditure; body composition; size and shape; and birth weight.

7.14.6 Comparison with previous report

7.14.6.1 General

See 7.1.6.1, and box 3.8 in chapter 3.

7.14.6.2 Specific

The findings here on foods containing lycopene and/or calcium, and on selenium or foods containing it, are new, reflecting the recent intense research interest in prostate cancer, including randomised controlled supplementation trials.

7.14.7 Conclusions

The Panel concludes:

Foods containing lycopene, as well as selenium and foods containing it, probably protect against prostate cancer. Diets high in calcium are a probable cause of this cancer. It is unlikely that beta-carotene (whether from foods or supplements) has a substantial effect on the risk of this cancer. There is limited evidence suggesting that pulses (legumes) including soya and soya products, foods containing vitamin E, and alpha-tocopherol supplements are protective, and that processed meat, and milk and dairy products are a cause of this cancer.

7.15 Kidney

Cancer of the kidney is the 15th most common type worldwide. Around 200 000 cases were recorded in 2002, accounting for around 2 per cent of all cancers. Average overall survival rates are around 50 per cent at 5 years. It is the 16th most common cause of death from cancer.

Overall, *the Panel is impressed* by the pattern of evidence showing the importance of body fatness as a cause of cancer of the kidney.

***The Panel judges* as follows:**
The evidence that body fatness is a cause of this cancer is convincing. It is unlikely that coffee has a substantial effect, or that alcoholic drinks have an adverse effect, on the risk of this cancer. There is limited evidence suggesting that arsenic in drinking water is a cause of this cancer.

Smoking is a cause of cancer of the kidney.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable",shows that greater body fatness is a cause of kidney cancer; and that it is unlikely that coffee has a substantial effect, or alcoholic drinks an adverse effect, on the risk of this cancer.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE KIDNEY

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

	DECREASES RISK	INCREASES RISK
Convincing		**Body fatness**
Probable		
Limited — suggestive		Arsenic in drinking water[1]
Limited — no conclusion	Cereals (grains) and their products; vegetables; fruits; meat; poultry; fish; eggs; milk and dairy products; total fat; soft drinks; tea; alcoholic drinks (protective effect)[2]; carbohydrate; protein; vitamin A; retinol; vitamin C; vitamin E; beta-carotene; flavonol; Seventh-day Adventist diets; physical activity; body fatness at age 18–20; weight at age 18–20; birth weight; adult attained height; age at menarche; energy intake.	
Substantial effect on risk unlikely	Coffee; alcoholic drinks (adverse effect)[2]	

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 The evidence was sufficient to judge that alcoholic drinks were unlikely to have an *adverse* effect on the risk of kidney cancer; but 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.

The kidneys are at the back of the abdomen and outside the peritoneal cavity. They filter waste products and water from the blood, producing urine, which empties into the bladder through the ureter. They are also important endocrine organs concerned with salt and water metabolism, and convert vitamin D to its active form.

Renal cell carcinoma is the most common kidney cancer, accounting for approximately 85 per cent. The majority of these are adenocarcinomas,[4] the type included here. Kidney cancers also include transition cell carcinomas of the renal pelvis, sarcomas, and Wilms' tumour (nephroblastoma), a childhood cancer. This section refers mainly to renal cell carcinomas; some studies also examined transitional cell carcinomas.

7.15.1 Trends, incidence, and survival

Age-adjusted rates of kidney cancer are increasing worldwide. Rates have doubled in many high-income countries since the mid-1970s, with some of the largest increases in countries in eastern Europe, for example, that are undergoing profound economic transition.[137]

This is mainly a disease of high-income countries, where rates are nearly five times higher overall than in middle- to low-income countries. Around the world, age-adjusted incidence rates range from 10–20 per 100 000 people in North America, parts of Europe, and Australia to less than 2 per 100 000 in parts of Africa.[2] In the USA, rates are higher among African-American people than in white people. Globally, rates are higher in men than in women, by five to three.[3] Risk increases with age, with most diagnoses made in people between the ages of 60 and 80.[296]

Kidney cancer is diagnosed at an early stage in more than half of cases. The 5-year survival rate is about 95 per cent for early stage cancers, and about 20 per cent at the most advanced stages.[296] Overall, 5-year survival rates are more than 50 per cent in high-income countries, but lower in middle- to low-income countries.[3 6] This cancer accounts for almost 2 per cent of all cancer incidence, and somewhat over 1 per cent of all cancer deaths. Also see box 7.1.1.

7.15.2 Pathogenesis

Urine contains many waste products from food, drinks, and other environmental sources, and some of these are potential carcinogens, such as carcinogens from cigarette smoke, and may play a role in kidney cancer.

It is not clear whether benign renal adenomas are a precursor of renal cell carcinoma. They are similar histologically and are frequently distinguished predominantly by their size.

Most adult kidney cancers are sporadic renal cell carcino-

mas, which can be divided into two main types. The conventional (or clear cell) type accounts for 75 per cent; 12 per cent of cases are of the papillary form,[296] which are less likely to metastasise. In 60 per cent of conventional carcinoma cases, there is a mutation in the von Hippel–Lindau tumour suppressor gene (VHL) (see box 2.2).[297] VHL disease is also a cause of some familial kidney cancers.

7.15.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Tobacco use. Smoking is a cause of kidney cancer, increasing the risk approximately twofold.[10] The association is stronger for cancers of the renal pelvis.[298]

Medication. Analgesics containing phenacetin are a cause of cancer of the renal pelvis.[299] Dialysis is a cause of kidney cancer, perhaps through its role in the development of acquired renal cystic disease.[300 301]

7.15.4 Interpretation of the evidence

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

7.15.4.2 Specific

Considerations specific to cancer of the kidney include:

Classification. The subtype of kidney cancer may also be important. Papillary renal cell carcinomas may follow a different disease path from other renal cell carcinomas. Some studies also included transitional cell carcinomas or looked at both renal and urinary tract tumours.

Confounding. High-quality studies adjust for smoking.

7.15.5 Evidence and judgements

In total, 187 publications were included in the SLR for kidney cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.15.5.1 Arsenic in drinking water

(Also see chapter 4.7.5.1.1.)

Three cohort studies, one time-series study, and nine ecological studies investigated arsenic in drinking water. All studies showed increased risk for the highest intake levels compared with the lowest. Effect sizes, particularly from ecological studies in areas of high exposure levels, tend to be relatively large.

Arsenic is carcinogenic to humans and causes chromosomal abnormalities.[217] Arsenic biotransformation is thought to lead to a state of oxidative stress. 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. Arsenic can modify the urinary excretion of porphyrins in animals and humans.

The evidence is sparse. There is limited evidence suggesting that arsenic in drinking water is a cause of kidney cancer.

7.15.5.2 Coffee

(Also see chapter 4.7.5.4.)

Five cohort studies, 18 case-control studies, and 1 ecological study investigated coffee. None of the cohort studies and only 1 of the case-control studies reported a statistically significant association. Meta-analysis of case-control data produced evidence of no association.

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[302] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.15.5.3 Alcoholic drinks

(Also see chapter 4.8.5.1.)

A total of 3 cohort studies and 16 case-control studies investigated alcoholic drinks; 4 cohort and 5 case-control studies investigated ethanol intake. Studies showed no consistent direction of effect. Meta-analysis of cohort data on ethanol produced evidence of a dose-response relationship with decreased risk; cohort data on alcoholic drinks were heterogeneous. Meta-analyses of case-control data showed non-significant decreased risk.

It is unlikely that alcoholic drinks increase the risk of kidney cancer, though a protective effect cannot be excluded.

The Panel is aware that since the conclusion of the SLR, one cohort study[302] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.15.5.4 Body fatness

(Also see chapter 6.1.3.1.)

Seventeen cohort studies and 20 case-control studies investigated body fatness, as measured by BMI. Nearly all of them showed increased risk with increased body fatness, with none showing a statistically significant decreased risk. Meta-analysis of cohort data showed a 31 per cent increased risk

per 5 kg/m^2; meta-analysis of case-control data showed a 205 (adjusted for smoking) or 42 (unadjusted) per cent increased risk per 5 kg/m^2 (figures 6.1.19 and 6.1.20). There was little heterogeneity in the former two analyses; the heterogeneity in the latter could be partially explained by failure to adjust for smoking.

Body fatness directly affects levels of many circulating hormones, such as insulin, insulin-like growth factors, and oestrogens, creating an environment that encourages carcinogenesis and discourages apoptosis (box 2.4). It also stimulates the body's inflammatory response, which may contribute to the initiation and progression of several cancers (see chapter 2.4.1.3). In addition, laboratory studies point to a potential role for insulin and leptin in renal cell carcinoma.[303 304]

There is abundant and consistent epidemiological evidence with a dose-response relationship and evidence of plausible mechanisms. The evidence that greater body fatness is a cause of kidney cancer is convincing.

The Panel is aware that since the conclusion of the SLR, three cohort studies[58 213 305] and one case-control study[306] have been published. This new information does not change the Panel judgement. Also see box 3.8.

7.15.5.5 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) or their products; vegetables; fruits; meat; poultry; fish; eggs; milk and dairy products; soft drinks; tea; alcoholic drinks (protective effect); carbohydrate; total fat; protein; vitamin A; retinol; beta-carotene; vitamin C; vitamin E; flavonol; physical activity; energy intake; body fatness at age 18–20; weight at age 18–20; age at menarche; adult attained height; birth weight; and Seventh-day Adventist diets.

7.15.6 Comparison with previous report

7.15.6.1 General

See 7.1.6.1, and box 3.8.

7.15.6.2 Specific

The previous report judged that high body mass is probably a cause of kidney cancer. Since then the evidence for body fatness has become stronger.

7.15.7 Conclusions

The Panel concludes:

The evidence that body fatness is a cause of kidney cancer is convincing. It is unlikely that coffee has a substantial effect, or alcoholic drinks an adverse effect, on the risk of this cancer. There is limited evidence suggesting that arsenic in drinking water is a cause of this cancer.

7.16 Bladder

Cancer of the bladder is the 10th most common type worldwide. Around 350 000 cases were recorded in 2002, accounting for around 3 per cent of all cancers. It is most common in high-income countries. Rates are much higher in men than in women. Overall rates of this cancer are not changing much. Average overall survival rates vary depending on how soon the cancer is detected. It is the 11th most common cause of death from cancer.

Overall, *the Panel notes* the evidence that food, nutrition, and physical activity are not significant factors in the development of cancer of the bladder.

***The Panel judges* as follows:**

There is limited evidence suggesting that milk protects against bladder cancer; and that arsenic in drinking water is a cause.

Smoking tobacco and schistosomiasis are other causes of this cancer.

In final summary, the evidence is too limited to conclude that any aspect of food, nutrition, and physical activity directly modifies the risk of bladder cancer.

The bladder is a sac-like organ that is the reservoir for urine. The inside of the bladder is lined by transitional epithelial cells known as the urothelium.

The term 'urothelial cancers' includes predominantly transition cell carcinomas of the bladder and cancers of the upper part of the urinary tract. Transitional cell carcinoma is the most common form, accounting for more than 90 per cent of bladder cancers, the type mainly included here. Other types (in order of incidence) include squamous cell carcinomas, adenocarcinomas, and small cell cancers.[4]

7.16.1 Trends, incidence, and survival

There is no clear global trend in bladder cancer incidence. While rates increased in many countries during the 20th century, this rise has generally slowed since the mid-1980s or stopped.[137] However, there are exceptions, such as in Japan and countries in eastern Europe that are in economic transition.

Bladder cancer is predominantly a disease of high-income countries, where overall rates are slightly more than three times higher than in middle- to low-income countries. Around the world, age-adjusted incidence rates range from 20–30 per 100 000 men in southern and western Europe and North America to less than 1 per 100 000 in much of Middle Africa and Asia.[2] It is five times more common in men than in women, and risk increases with age. In northern Africa and parts of Asia, where schistosomiasis (a parasitic disease, also known as bilharzia) is prevalent, bladder cancer rates are high and squamous cell carcinomas of the bladder are

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE BLADDER

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		
Limited — suggestive	Milk[1]	Arsenic in drinking water[2]
Limited — no conclusion	Cereals (grains) and their products; vegetables; fruits; pulses (legumes); meat; poultry; fish; eggs; total fat; butter; dietetic foods; soft drinks; diet drinks; fruit juices; coffee; tea; caffeine; alcohol; chlorinated surface water; total fluid intake; sweeteners; frying; carbohydrate; protein; vitamin A; folate; vitamin C; vitamin E; multivitamin supplements; selenium; beta-carotene; alpha-carotene; lycopene; beta-cryptoxanthin; lutein; zeaxanthin; flavonoids; physical activity; body fatness; energy intake	
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 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.

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.

the most common type. In Egypt, it is the most common cancer among men and the third most common among women.[307] In the USA, rates are higher in white people than among other ethnic groups.[3]

Five-year survival rates vary according to the stage of the cancer when it is diagnosed. They range from 63 to 88 per cent in cases of superficial bladder carcinoma, and from 47 to 63 per cent in muscle-invasive bladder cancer.[4] However, recurrence rates for this cancer are relatively high.[308] This disease accounts for just over 3 per cent of all cancer incidence, and around 2 per cent of all cancer deaths. Also see box 7.1.1.

7.16.2 Pathogenesis

Dietary carcinogens, as well as those from tobacco smoke or other environmental sources, are often excreted in the urine, so the bladder lining is exposed to these toxins.

Urothelial cell carcinomas start as superficial bladder carcinomas. The majority have low rates of progression, although they can occur at multiple sites. Low-risk lesions may never progress, but they have a poor prognosis if they become invasive cancers.

The superficial lesion that carries the highest risk, carcinoma in situ, progresses to invasive cancer in more than 50 per cent of cases if it is not treated. These high-risk lesions are often found with multiple papillary tumours, but because they may involve different molecular changes, they are likely to have a different natural history to low-risk lesions.[308]

Squamous cell carcinoma may be caused by chronic inflammation, for instance from latent schistosomiasis, chronic infections, or long-term catheter use.

Mutations in the tumour-suppressor p53 gene, as well as abnormalities in chromosome 9, are common in invasive bladder cancer (see box 2.2). Inherited mutations of two other genes, GSTM1 (glutathione *S*-transferase null) and NAT2 (n-acetyltransferase; slow acetylation) also cause bladder cancer. NAT2 interacts with cigarette smoke, and may be responsible for 20–46 per cent of bladder cancers.[309]

7.16.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Tobacco use. Smoking is a major cause of bladder cancer. It is estimated that more than half of all cases in men and around a third in women are caused by smoking.[10 310]

Infection and infestation. Infestation with schistosomes (particularly *Schistosoma haematobium*) is a cause of bladder cancer, particularly squamous cell carcinomas.[311] This is estimated to be responsible for 10 per cent of bladder cancer cases in middle- and low-income countries, and 3 per cent of cases overall.[312]

Industrial chemicals. Occupational exposure to aromatic amines, such as 2-naphthylamine (used in dyes), also increases the risk of bladder cancer.[313]

7.16.4 Interpretation of the evidence

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

7.16.4.2 Specific

Considerations specific to cancer of the bladder include:

Confounding. High-quality studies adjust for smoking.

7.16.5 Evidence and judgements

In total, 349 publications were included in the SLR for bladder cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are to be found in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.16.5.1 Milk

(Also see chapter 4.4.5.1.1.)

Five cohort studies, 14 case-control studies, and 1 ecological study investigated milk. All of the cohort studies and half of the case-control studies showed decreased risk with increased intake of milk. Meta-analysis of cohort data produced evidence of an association with decreased risk, with a clear dose-response relationship. Meta-analysis of case-control data was inconclusive.

The possible effect of milk in reducing bladder cancer risk is likely to be mediated at least in part by calcium, which has direct growth-restraining and differentiation- and apoptosis-inducing actions on normal and tumour cells.[184] However, milk includes many bioactive constituents, which may also play a role.

The evidence is inconsistent and comes mainly from evidence on dietary calcium. There is limited evidence suggesting that milk protects against bladder cancer.

7.16.5.2 Arsenic in drinking water

(Also see chapter 4.7.5.1.1.)

Six cohort studies, 1 time-series study, 7 case-control studies, and 11 ecological studies investigated arsenic in drinking water. Most studies showed increased risk for groups with the highest intakes when compared with the lowest.

Soluble arsenic in drinking water induces lung cancers in experimental animal models.[71] In humans, arsenic is a chromosomal mutagen (an agent that induces mutations involving more than one gene, typically large deletions or rearrangements). It can also act as a synergistic co-mutagen. Arsenic exposure also causes chronic lung disease.[71] These mechanisms may also apply to bladder cancer. The Joint FAO/WHO Expert Committee on Food Additives has set a provisional tolerable weekly intake of 0.015 mg per kg body weight.[72]

The evidence is inconsistent. There is limited evidence suggesting that arsenic is a cause of bladder cancer.

7.16.5.3 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: cereals (grains) and their products; vegetables; fruits; pulses (legumes); meat; poultry; fish; eggs; butter; dietetic foods; soft drinks; diet drinks; fruit juices; coffee; caffeine; tea; alcohol; chlorinated surface water; sweeteners; frying; carbohydrate; total fat; protein; vitamin A; beta-carotene; alpha-carotene; lycopene; beta-cryptoxanthin; lutein; zeaxanthin; folate; vitamin C; vitamin E; selenium; multivitamin supplements; flavonoids; energy intake; physical activity; body fatness; and total fluid intake.

7.16.6 Comparison with previous report

7.16.6.1 General

See 7.1.6.1, and box 3.8.

7.16.6.2 Specific

The previous report judged that vegetables and fruits probably protect against bladder cancer. As with other sites, the evidence for these foods is now considered to be weaker, in this case, very much so. The previous finding that coffee (more than five cups per day) is a possible cause of bladder cancer was not found here.

7.16.7 Conclusions

The Panel concludes:

There is limited evidence suggesting that milk protects against bladder cancer and that arsenic in drinking water is a cause.

7.17 Skin

Cancer of the skin in its various forms is the most common type of cancer worldwide. Around 90 per cent of all skin cancers are non-melanoma. Around 4 million cases were recorded in 2002, but it is likely that many cases are not referred, and this cancer is not included in the rankings in this Report. Around 160 000 cases of melanoma skin cancer were recorded in 2002, accounting for around 1.5 per cent of all cancers. Skin cancers are more common in high-income countries and among light-skinned people. Overall rates of this cancer are increasing. Survival rates of melanoma are high and also depend on access to treatment. Five-year survival rates for non-melanoma skin cancer are more than 99 per cent. Melanoma is the 22nd most common cause of death from cancer.

Overall, *the Panel emphasises* that the main cause of skin cancer is over-exposure to radiation from sunlight.

***The Panel judges* as follows:**
Arsenic in drinking water is probably a cause of skin cancer. There is limited evidence suggesting that retinol protects against squamous cell carcinomas of the skin, and that selenium is a cause of skin cancer. It is unlikely that beta-carotene or foods containing it have a substantial effect on the risk of non-melanoma skin cancer.

In final summary, the strongest evidence, corresponding to judgements of "convincing" and "probable", shows that arsenic in drinking water is probably a cause of skin cancer. It is unlikely that beta-carotene or foods containing it have a substantial effect on the risk of non-melanoma skin cancer.

FOOD, NUTRITION, PHYSICAL ACTIVITY, AND CANCER OF THE SKIN

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

	DECREASES RISK	INCREASES RISK
Convincing		
Probable		**Arsenic in drinking water[1]**
Limited — suggestive	Retinol[2]	Selenium supplements[3]
Limited — no conclusion	Potatoes; non-starchy vegetables; fruits; fish; eggs; milk; total fat; cholesterol; coffee; tea; alcohol; protein; vitamin A; retinol (foods); folate; vitamin C; vitamin D; vitamin E; multivitamins; selenium; carotenoids; beta-carotene (melanoma); alpha-carotene; lycopene; physical activity; body fatness; energy intake	
Substantial effect on risk unlikely	Beta-carotene[4] (non-melanoma)	

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 The evidence is derived from studies using supplements at a dose of 25 000 international units/day. Applies only to squamous cell carcinoma.
3 The evidence is derived from studies using supplements at a dose of 200 µg/day.
4 The evidence is derived from studies using supplements at doses of 30, and 50 mg/day, and from 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.

The skin is the outer covering of the body. There are two main types of skin cancer: melanoma and non-melanoma. Non-melanoma is more common. The most common non-melanoma tumours are basal cell carcinoma and squamous cell carcinoma, which together account for 90 per cent of skin cancers.[4] Melanomas are nearly always pigmented and usually develop from pigmented lesions such as moles. Melanoma accounts for 4 per cent of skin cancers. Other skin cancers such as Kaposi's sarcoma and cutaneous lymphomas are not included here.

7.17.1 Trends, incidence, and survival

Age-adjusted rates of both melanoma and non-melanoma skin cancers are increasing. Rates have doubled since the mid-1950s in many high-income countries, particularly those that already had high rates. This trend is restricted to countries where a high proportion of the population is fair-skinned.[137] The incidence of non-melanoma skin cancer is also increasing.[4] It is estimated that there are more than a million new cases each year in the USA alone,[314] and in Australia the reported incidence is even higher.[315]

Skin cancer is mainly a disease of high-income countries, where overall melanoma rates are more than 10 times higher than in middle- to low-income countries. Age-adjusted incidence rates range from more than 30 per 100 000 people in Australia and New Zealand to less than 1 per 100 000 across much of Africa and Asia. Rates are relatively high (around 15 per 100 000) in North America, Israel, and many northern European countries.[2] In the USA, rates are higher in white people than among other ethnic groups.[3] Non-melanoma skin cancer is the most common cancer in the world, and correlates with lighter skin colour and accumulated sun exposure.[316]

Although both melanoma and non-melanoma skin cancer incidence increases with age, melanoma causes a disproportionate number of cancers in young and middle-aged people.[317] Melanomas are most common on exposed areas of the body, and are relatively rare on areas that are usually covered by clothing.

Despite the considerably higher incidence of non-melanoma skin cancer compared with melanoma (around 20 to 1 in the USA), this less common type accounts for 79 per cent of skin cancer deaths.[318] The 5-year survival rate is between 80 and 90 per cent in high-income countries, but just over half that in middle- to low-income countries.[124] This difference is partly due to a different, prevalent type of melanoma (acral melanoma, on the soles of the feet), which has a poorer prognosis. Melanoma accounts for somewhat over 1 per cent of all cancer incidence, but only around 0.5 per cent of all cancer deaths. Non-melanoma skin cancers are almost never fatal.[319] Also see box 7.1.1.

7.17.2 Pathogenesis

The skin changes with age and is affected by hormonal influences and exposure to the sun and wind. Skin pigmentation varies between individuals and its structure also differs, depending, for instance, on whether it covers the lips, the soles of the feet, or the eyelids. All of these aspects influence skin cancer risk. Both melanoma and non-melanoma skin cancers are thought to be caused largely by UV irradiation mainly from sunlight. There is a clear relationship between accumulated sun exposure and non-melanoma skin cancer, but melanoma is more common in office workers than in outdoor workers, suggesting that damage from episodic exposure and extreme occasional sun damage (blistering sunburn) may be more important.[4] The role of sun damage is supported by the association between measures of sun sensitivity and skin cancer incidence, which is higher in people who have freckles and skin that burns without tanning, more moles, blue eyes, and red hair.[320 321]

UV-damaged cells are usually removed by apoptosis (programmed cell death, see chapter 2.5.2) in a process involving the p53 protein. However, in non-melanoma skin cancer, the p53 tumour-suppressor gene is often damaged by UVB irradiation, so faulty cells are not removed from the skin. Both UVB and UVA irradiation also have direct and indirect effects on the cutaneous immune system, lowering the skin's cell-mediated immunity,[322] which is another factor that may influence carcinogenesis.

People who have a family history of melanoma may be predisposed to this type of skin cancer, although only one major inherited mutation has been found, and less than 2 per cent of melanomas are attributable to this inherited mutation.[323]

7.17.3 Other established causes

(Also see chapter 2.4 and 7.1.3.1.)

Radiation. Over-exposure to UV radiation (mainly from sunlight) is the chief cause of both non-melanoma and melanoma skin cancers.[324] In the case of melanoma, the main cause is episodic skin exposure involving severe sunburn, particularly in fair-skinned white people.[317]

Medication. Immune suppression in organ-transplant and AIDS patients is also associated with an increased risk of skin cancer (in addition to Kaposi's sarcomas).[325]

Infection and infestation. HPV can cause squamous cell carcinomas, especially in immune-compromised people.[325]

7.17.4 Interpretation of the evidence

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

7.17.4.2 Specific

Considerations specific to cancer of the skin include:

Classification. Melanoma and non-melanoma cancers may have different causes; this would explain heterogeneity in studies that do not distinguish between these two types of skin cancer. Non-melanoma skin cancer cases are commonly not recorded by cancer registries, and are therefore underestimated in many reports.

Confounding. High-quality studies adjust for sun exposure and distinguish between cancer types.

7.17.5 Evidence and judgements

In total, 167 publications were included in the SLR for skin cancer. Fuller summaries of the epidemiological, experimental, and mechanistic evidence are in Chapters 4–6.

The full SLR is contained on the CD included with this Report.

7.17.5.1 Arsenic in drinking water

(Also see chapter 4.7.5.1.1.)

Two cohort studies, 5 case-control studies, 1 cross-sectional study, and 11 ecological studies investigated arsenic in drinking water. Nearly all studies showed an association between increased arsenic and skin cancer. Two case-control studies used toenail and fingernail measurements, which are thought to be more reliable than dietary estimates. These studies both showed increased risk, which was statistically significant in one. The single cross-sectional study and all ecological studies showed increased risk, with several reporting relatively large and statistically significant effect estimates.

Soluble arsenic in drinking water induces lung cancers in experimental animal models.[71] In humans, arsenic is a chromosomal mutagen (an agent that induces mutations involving more than one gene, typically large deletions or rearrangements). It can also act as a synergistic co-mutagen. Arsenic exposure also causes chronic lung disease.[71] These mechanisms may also be applicable to skin cancer. The Joint FAO/WHO Expert Committee on Food Additives has set a provisional tol-

erable weekly intake of 0.015 mg per kg body weight.[72]

The evidence is consistent, from cohort, case-control, and ecological studies. There is robust mechanistic evidence. Arsenic in drinking water is a probable cause of skin cancer.

7.17.5.2 Retinol

(Also see chapter 4.10.6.4.1.)

Two randomised controlled trials investigated retinol supplements. Both trials included only participants at risk of developing non-melanoma skin cancer, and both gave results stratified according to this type. While neither trial reported a statistically significant association to basal cell carcinoma, one of the two studies did report a statistically significant relationship with decreased squamous cell carcinoma risk.

The mechanism of anti-tumour action of the retinoids is not completely understood, but retinol is known to bind to cell receptors with promotion of differentiation, alteration of membranes, and immunological adjuvant effects.[326]

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[327] has been published. This new information does not change the Panel judgement. Also see box 3.8.

7.17.5.3 Selenium supplements

(Also see chapter 4.10.6.4.5.)

One randomised controlled trial and one cohort study investigated selenium supplements. The trial showed a statistically significant increased risk of total non-melanoma skin cancer with daily supplementation of 200 μg selenium. Subgroup analysis indicated that this risk might differ according to cancer type, with a statistically significant increased risk for squamous cell carcinoma but not basal cell carcinoma. The single cohort study stated that there was no statistically significant association.

No plausible mechanisms for how selenium might increase risk of skin cancer have been suggested.

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.

7.17.5.4 Beta-carotene (non-melanoma)

(Also see chapters 4.2.5.3 and 4.10.6.4.2)

Four randomised controlled trials and one cohort study investigated beta-carotene supplements; two cohort studies and seven case-control studies investigated dietary beta-carotene; three cohort studies and one case-control study investigated beta-carotene from food and supplements combined; and eight cohort studies and three case-control studies investigated serum or plasma beta-carotene.

All three randomised controlled trials that investigated beta-carotene supplement interventions against placebo with respect to non-melanoma skin cancer reported results very close to null. Meta-analysis of the three trials produced evidence of no association. Two trials that investigated beta-carotene supplement interventions against placebo with respect to melanoma stated that there was no association with risk.

Meta-analysis of cohort data on plasma or serum beta-carotene and non-melanoma skin cancer, and cohort data that investigated the same exposure in melanoma, showed no clear association. No clear association was shown with dietary beta-carotene.

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

7.17.5.5 Other exposures

Other exposures were evaluated. However, the data were either of too low quality, too inconsistent, or the number of studies too few to allow conclusions to be reached. These were as follows: potatoes; non-starchy vegetables; fruits; fish; eggs; milk; coffee; tea; alcohol; foods containing selenium; total fat; cholesterol; protein; vitamin A; retinol (foods); beta-carotene (melanoma); alpha-carotene; carotenes; lycopene; folate; vitamin C; vitamin D; vitamin E; multivitamins; physical activity; energy intake; and body fatness.

7.17.6 Comparison with previous report

Skin cancers were not reviewed in the previous report.

7.17.7 Conclusions

The Panel concludes:

Arsenic in drinking water is probably a cause of skin cancer. There is limited evidence suggesting that retinol protects against squamous cell carcinomas of the skin and that selenium is a cause of skin cancer. It is unlikely that beta-carotene or foods containing it have a substantial effect on the risk of non-melanoma skin cancer. The main cause of skin cancer is over-exposure to UV radiation from sunlight.

7.18 Other cancers

***The Panel also considered* other cancers, not generally recognised to have a relationship to food, nutrition, and physical activity. These are cancers of the thyroid gland and testis, and cancers of the lymphoid and haemopoietic systems, the musculoskeletal system, and the nervous systems.**

Five narrative reviews were commissioned. This method was not systematic, and *the Panel decided* not to make any judgements regarding the causality of any associations in the text or matrices.

Some of the evidence that emerged may merit more thorough investigation and further studies.

***The Panel noted* as follows:**
Some of these cancers are known to have as established causes other diseases, tobacco use, radiation, infection, or industrial chemicals, or else not to have established causes. Some details are given in the following sections. From the reviews commissioned, some evidence emerges.

Thyroid cancer. Non-cruciferous, non-starchy vegetables and fish show an association with decreased risk. Body fatness and adult attained height show an association with increased risk.

Lymphoid and haemopoietic cancers. Vegetables and fruits are associated with decreased risk. Alcoholic drinks have an association with decreased risk. Meat, total fat, and body fatness are associated with increased risk. Milk and dairy products show an association with increased risk of non-Hodgkin's lymphoma.

Other cancers. The evidence on food, nutrition, physical activity, and cancers of the musculoskeletal and nervous systems is too limited to draw any conclusions.

7.18.1 Thyroid

Thyroid cancer is the 21st most common type worldwide. An estimated 141 000 cases occurred in 2002, accounting for just over 1 per cent overall. This cancer type is the 23rd most common cause of cancer death. It is more common in high-income countries, with rates more than twice those of middle- to low-income countries.

Thyroid cancer is not usually fatal, with a 5-year survival rate of approximately 70 per cent.[2] It is increasing in incidence worldwide, although this may be partly explained by changing diagnostic practices.[124 137]

Thyroid cancer rates peak between the ages of 25 and 55, then decline and rise again in the elderly. This cancer is more common in women than in men. Also see box 7.1.1.

Differentiated carcinomas account for 94 per cent of these cancers (80 per cent papillary and 14 per cent follicular carcinomas). Medullary carcinoma and the highly aggressive anaplastic carcinoma comprise the remainder.[4]

Exposure to ionising radiation, especially during childhood, is a cause of this cancer.[328]

7.18.1.1 Evidence

The evidence from the narrative review is summarised below.

7.18.1.1.1 Vegetables

One pooled analysis of 11 case-control studies (2241 cases and 3716 controls) investigated consumption of vegetables. It showed a statistically significant reduced incidence with higher intakes of vegetable other than cruciferous types. Cruciferous vegetables were not significantly associated with reduced incidence.

Vegetables contain many potentially protective substances, including several antioxidants, as well as phytochemicals with antiproliferative capabilities. They are also a rich source of folate, which plays an important role in the synthesis, repair, and methylation of DNA.

7.18.1.1.2 Fish

One pooled analysis of 13 case-control studies (2497 cases and 4337 controls) and 2 case-control studies investigated fish consumption. These were consistent in showing a significantly reduced incidence with increased consumption in areas of endemic iodine deficiency, but none in areas where iodine intakes are high.

Fish is known to be an important natural source of iodine in the diets of different populations, and therefore an association between fish intake and thyroid cancer risk may be mediated by iodine.

7.18.1.1.3 Body fatness

One pooled analysis of 12 case-control studies (cases: 2056 women and 417 men; controls: 3358 women and 965 men) and 1 cohort study investigated BMI or obesity. Obesity was associated with a statistically significant increased incidence in women, with a clear dose-response relationship. No association was observed in men (although this could have been influenced by the relatively small number of cases). The cohort study also showed a relationship with increased incidence.

Body size might affect iodine requirement and therefore, indirectly, influence thyroid cancer risk.

7.18.1.1.4 Adult attained height

One pooled analysis of 12 case-control studies (cases: 2056 women and 417 men; controls: 3358 women and 965 men) investigated adult attained height. Greater height was associated with a statistically significant increased incidence in both women and men, with a clear dose-response relationship. The effect was greater in men than in women.

Body size might affect iodine requirement and therefore, indirectly, influence thyroid cancer risk. The association with

height in both men and women may indicate a potential influence of some growth factor or hormone during childhood or adolescence, but the potential role of growth factors on thyroid carcinogenesis is still poorly defined.

7.18.1.2 Conclusions

Thyroid cancer was reviewed in the previous report. It judged that both iodine deficiency (probably) and iodine excess (possibly) were causes of this cancer, and also that vegetables and fruits were possibly protective.

The Panel concludes that the associations identified warrant more investigation into food, nutrition, and thyroid cancer.

7.18.2 Testis

Cancer of the testis is the 19th most common type in men. An estimated 49 000 cases occurred in 2002, accounting for around 0.5 per cent overall. This cancer is increasing worldwide, with rapid rises in many high-income countries and some transition countries.[124] Rates are more than five times higher than in middle- to low-income countries.

Cancer of the testis is usually not fatal where chemotherapy is available, with a 5-year survival rate of more than 90 per cent in high-income countries, but less than 60 per cent in middle- to low-income countries.[2 6] Also see box 7.1.1.

Most (95 per cent) testicular cancers are germ cell cancers, with seminomas being the other main subtype.[4]

The most well established risk factor for testicular cancer is the failure of one testis or both to descend into the normal position during fetal development.[4] Rates peak in young adulthood.

7.18.2.1 Evidence

The evidence from the narrative review is summarised below.

7.18.2.1.1 Milk and dairy products

Five case-control studies, one twin study, and four ecological studies investigated milk and dairy consumption. All ecological studies and two of the case-control studies showed statistically significant relationships between increased milk and dairy consumption and increased testicular cancer incidence.

None of the other studies reported statistically significant associations, although non-significant associations were heterogeneous.

There are no well established mechanisms through which milk could influence testicular cancer development. Milk and dairy products contain fat, protein, and calcium, all of which may have an effect on testicular cancer risk.

7.18.2.2 Conclusions

Cancer of the testis was not reviewed in the previous report.

The Panel concludes that the evidence does not warrant significant investigation into food, nutrition, and testicular cancer.

7.18.3 Lymphoid and haemopoietic system

Cancers of the lympho-haemopoietic system are predominantly lymphomas (Hodgkin's or non-Hodgkin's), leukaemias, and multiple myelomas. These cancers have different non-dietary causes and there is no reason to believe that they might be affected by food, nutrition, and physical activity in the same ways.

If taken together, this group of cancers would be the sixth most common type worldwide. An estimated 749 000 cases occurred in 2002, accounting for around 7 per cent overall. Approximately 48 per cent of these cancers were lymphomas (83 per cent non-Hodgkin's; 17 per cent Hodgkin's), and 40 per cent were leukaemias, with multiple myelomas accounting for the remaining 12 per cent.[2]

Non-Hodgkin's lymphoma is the 11th most common cause of cancer incidence. It is increasing in incidence worldwide.[124] Non-Hodgkin's lymphoma is most frequent in high-income countries, with rates more than twice those of middle- to low-income countries. It is usually fatal, with a 5-year survival rate of less than 35 per cent.[4] This is not a single cancer, but a wide group of cancers (such as Burkitt's lymphoma and diffuse large B-cell lymphoma), each with a distinct geographical distribution, development path, age profile, and prognosis.

Hodgkin's lymphoma is the 25th most common type. It is most frequent in high-income countries, where rates are more than twice those of middle- to low-income countries. It is not usually fatal, with a 5-year survival rate of approximately 75 per cent in high-income countries and less than 60 per cent in middle- to low-income countries.[2 4] This cancer occurs mainly in children, young adults, and the elderly (tending to occur at a younger age or in old age in middle- to low-income countries).[124]

Leukaemias are the 12th most common type and the 10th most common cause of cancer death. They are gradually increasing in incidence worldwide. They are most frequent in high-income countries, with rates more than twice those of middle- to low-income countries. Leukaemias are usually fatal, with a 5-year survival rate of approximately 40 per cent in high-income countries, and less than 20 per cent in middle- to low-income countries.[124] However, childhood leukaemias have a very high survival rate. This is not a single cancer, but a wide group of both acute and chronic leukaemias.

Multiple myeloma is the 24th most common type and the 19th most common cause of cancer death. It is gradually increasing in incidence worldwide, and is most frequent in high-income countries with rates more than three times higher than in middle- to low-income countries. It is usually fatal, with a 5-year survival rate of less than 50 per cent in high-income countries and less than 30 per cent in middle- to low-income countries.[2]

Infection with Epstein-Barr virus (see box 7.2.1) is a risk factor for developing Hodgkin's lymphoma.[329] HIV-1 infection, immune suppression (whatever the cause), and infection with Epstein-Barr and human T-cell leukaemia virus all increase the risk of developing non-Hodgkin's lymphoma.[330]

Tobacco use, infection with human T-cell leukaemia virus, radiation, and benzene are established causes of leukaemia.[10 67 328 331] Exposure to ionising radiation is a cause of multiple myeloma. Also see chapter 2.4.

7.18.3.1 Evidence

The evidence from the narrative review is summarised below.

7.18.3.1.1 Vegetables and fruits

One cohort study and six case-control studies investigated vegetables and fruits. The cohort study and five of the case-control studies showed statistically significant associations with increased vegetable and fruit intake and reduced incidence of lymphoid and haemopoietic cancers. However, the cohort study and two of the case-control studies reported on non-Hodgkin's lymphoma only. The sixth case-control study reported increased incidence with consumption of 'vegetables other than cruciferous, leafy, or yellow/orange'.

Vegetables and fruits contain many potentially protective substances, including several antioxidants, as well as phytochemicals with antiproliferative capabilities. They are also a rich source of folate, which plays an important role in the synthesis, repair, and methylation of DNA.

7.18.3.1.2 Milk and dairy products

One cohort study, nine case-control studies, and one ecological study investigated milk and dairy products, with most reporting on non-Hodgkin's lymphoma. The cohort study, the ecological study, and most of the case-control studies reported statistically significant associations between increased milk and dairy consumption and increased incidence.

There are no well established mechanisms by which milk could increase lymphoma incidence. Hypotheses include calcium restricting the bioavailability of vitamin D (this vitamin promotes differentiation and apoptosis and inhibits cancer cell growth in the laboratory). Alternatively, organochlorines (which are potential carcinogens) may accumulate in dairy fat. A final hypothesis is that bovine leukaemia virus might transmit through milk to humans, although there is no direct evidence for this.

7.18.3.1.3 Meat

One cohort study, seven case-control studies, and one ecological study investigated meat or red meat. The cohort study, the ecological study, and most of the case-control studies showed an association with increased incidence, with several reaching statistical significance. A review article came to the same conclusion.

There are no postulated mechanisms by which meat could increase the incidence of lymphoid and haemopoietic cancers.

7.18.3.1.4 Fish

Two cohort studies and seven case-control studies investigated fish and lymphoid and haematopoietic cancers. Most studies showed a non-significant relationship with reduced incidence. This reached statistical significance in two case-control studies that reported results separately for non-Hodgkin's lymphoma.

One animal study has shown that fish oils can inhibit the formation of lymphoid and haemopoietic cancers.

7.18.3.1.5 Fat

Two cohort studies and four case-control studies investigated fat consumption. All showed statistically significant relationships with increased incidence. One case-control study that reported separately on PUFAs described a significantly reduced incidence for that fatty acid type, while confirming a significant increased incidence for saturated fatty acids.

There are no postulated mechanisms by which fat could increase lymphoid and haemopoietic cancers.

7.18.3.1.6 Alcoholic drinks

One pooled analysis of case-control studies representing 15 175 participants, with 6492 non-Hodgkin's lymphoma cases, showed a statistically significant reduced incidence for this type, particularly Burkitt's lymphoma.

There are no postulated mechanisms by which alcohol could decrease the incidence of lymphoid and haemopoietic cancers.

7.18.3.1.7 Body fatness

Nine cohort studies and 11 case-control studies investigated BMI or obesity and non-Hodgkin's lymphoma, leukaemia, or multiple myeloma. In each case, most studies reported an association with increased incidence, with several reporting statistically significant relationships.

Obesity results in pathological states of inflammation and altered immune responses, both of which are factors that can influence lymphoid and haemopoietic cell function.

7.18.3.2 Conclusions

These cancers were not reviewed in the previous report.

The Panel concludes that more work into mechanisms that might underlie the associations identified is warranted. A more comprehensive and systematic review might also clarify the epidemiology. The different cancer types should be investigated separately unless there is reason to believe that they have common causes.

7.18.4 Musculoskeletal system

Cancers of the musculoskeletal system are a diverse group, including those of the bones, muscles, and related tissues, all around the body. These include liposarcomas, fibrosarcomas, osteosarcomas, and myosarcomas.

These cancers are all uncommon or rare, each accounting for less than 1 per cent — usually much less — of all cancers. There is no reason to think that they have causes in common.

The narrative review did not produce any findings.

Because these cancers are uncommon, any study investigating their possible links with food, nutrition, and physical activity would be unlikely to be fruitful. Because they are diverse, any investigation that grouped all of them together would also be unlikely to show consistent results.

7.18.4.1 Conclusions

These cancers were not reviewed in the previous report.

The Panel concludes that it is unlikely that any further investigation would be warranted.

7.18.5 Nervous system

Cancers of the brain and central nervous system are the 18th most common type worldwide. An estimated 189 000 cases occurred in 2002, accounting for around 2 per cent overall. These cancers are most frequent in high-income countries, with rates more than twice those of middle- to low-income countries. Brain tumours are relatively common among childhood cancers. They are the 13th most common cause of cancer death, and are usually fatal. The overall 5-year survival rate is less than 25 per cent, with higher rates for many brain tumours that occur during childhood, and in high- rather than in middle- to low-income countries.[2] Also see box 7.1.1.

Tumours of neural tissue account for approximately half of these cancers, with most of these being glioblastomas.[4] Meningiomas are the other major type of central nervous system tumour, with sellar tumours, cranial and spinal nerve tumours, central nervous system lymphomas, and other rare brain tumour types comprising the remainder.

The incidence of these cancers appears to be increasing worldwide, although the trend is not entirely clear.[124] The causes of brain and central nervous system cancers have not been well established.

The narrative review did not produce any findings.

Because these cancers are uncommon, any study investigating their possible links with food, nutrition, and physical activity would be unlikely to be fruitful. Because they are diverse, any investigation that grouped all of them together would also be unlikely to show consistent results.

7.18.5.1 Conclusions

These cancers were not reviewed in the previous report.

The Panel concludes that it is unlikely that any further investigation is warranted.