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.