

World
Cancer
Research Fund



American
Institute for
Cancer Research

CONTINUOUS UPDATE PROJECT

COLORECTAL CANCER REPORT 2010 SUMMARY

*Food, Nutrition, Physical Activity, and the
Prevention of Colorectal Cancer*

May 2011

WORLD CANCER RESEARCH FUND GLOBAL NETWORK

OUR VISION

We help people make choices that reduce their chances of developing cancer

OUR HERITAGE

We were the first cancer charity

To create awareness of the relationship between diet and cancer risk

To focus funding on research into diet and cancer prevention

To consolidate and interpret global research to create a practical message on cancer prevention

OUR MISSION

Today the World Cancer Research Fund global network continues

Funding research on the relationship of nutrition, physical activity and weight management to cancer risk

Interpreting the accumulated scientific literature in the field

Educating people about choices they can make to reduce their chances of developing cancer

The World Cancer Research Fund global network consists of World Cancer Research Fund International (WCRF International) an umbrella association and the following charitable organisations: the American Institute for Cancer Research (AICR); World Cancer Research Fund UK (WCRF UK); Wereld Kanker Onderzoek Fonds (WCRF NL); World Cancer Research Fund Hong Kong (WCRF HK); and Fonds Mondial de Recherche contre le Cancer (FMRC/WCRF FR).

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This summary provides an updated version of section 7.9 Colon and rectum from the Second Expert Report: *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective*. This section has been updated based upon Panel discussions between November 2010 and January 2011 on the 2010 Continuous Update Project Colorectal Cancer Report, prepared by the research team at Imperial College London, UK (see acknowledgements). The Report included research papers published until December 2009 for all exposures except for fruits, vegetables, red and processed meat, vitamin D, alcohol and height papers published until May/June 2010 were included. For further details please see the full 2010 Continuous Update Project Colorectal Cancer Report and the Second Expert Report [www.dietandcancerreport.org/er].

To keep the evidence current and updated into the future, WCRF/AICR is undertaking the Continuous Update Project (CUP), in collaboration with Imperial College London. The project is an ongoing review of food, nutrition and physical activity, and cancer research. The CUP builds upon the foundations of the WCRF/AICR Second Expert Report (SER) (1).

The Continuous Update Project provides a comprehensive and up-to-date depiction of scientific developments on the relationship between diet, physical activity, obesity and cancer. It also provides an impartial analysis and interpretation of the data as a basis for reviewing and where necessary revising WCRF/AICR's Recommendations for Cancer Prevention based on the Second Expert Report.

In the same way that the Second Expert Report was informed by a process of systematic literature reviews (SLRs), the Continuous Update Project systematically reviews the science. WCRF/AICR has convened a panel of experts (the Continuous Update Project Panel (see acknowledgements)) consisting of leading scientists in the field of food, nutrition, physical activity, obesity and cancer who consider the updated evidence from systematic literature reviews and draw conclusions.

Once all the cancers have been updated in the CUP database in 2015, the Panel will formally review the WCRF/AICR Recommendations for Cancer Prevention, and any changes will be communicated through the WCRF global network scientific, education and communications programmes in 2017. From 2015 the CUP database will be continuously updated with new evidence for all the cancer sites. Prior to 2017 the Panel will revise one or more Recommendations only if they agree there is strong evidence for a change.

The updates to the SLRs are being conducted by a team of scientists at Imperial College London in liaison with the original SLR centres.

Instead of periodically repeating the extensive task of conducting multiple systematic literature reviews that cover a long period of time, the continuous review process is based on a live system of scientific data. The database is updated on an ongoing basis from which, at any point in time, the most current review of scientific data (including and meta-analyses where appropriate) can be performed.

Periodically WCRF/AICR will produce reports, peer reviewed by scientists, which will outline the scientific developments in the field of diet, physical activity, obesity and cancer.

New information in this summary

Section 1. Updated with recent incidence, mortality and survival data.

Section 3. Updated section on other specific causes

Section 5. A new section briefly describing the methodology of the Continuous Update Project.

Section 6. Evidence has been updated based on the 2010 Continuous Update Project Colorectal Cancer Report and considered by the Continuous Update Project Panel.

Section 7. A comparison with the Second Expert Report.

Section 8. Updated summary of conclusions

Abbreviations

CUP – Continuous Update Project

SER – Second Expert Report '*Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*'

SLR – Systematic literature review conducted for the Second Expert Report

Second Expert Report Matrix

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 | |

- Physical activity of all types: occupational, household, transport, and recreational.
- 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.
- The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.
- Although red and processed meats contain iron, the general category of 'foods containing iron' comprises many other foods, including those of plant origin.
- The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.
- 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.
- 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).
- 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).
- Judgements on vegetables and fruits do not include those preserved by salting and/or pickling.
- 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.
- 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.
- The evidence is derived from studies using supplements at a dose of 1200 mg/day.
- Found mostly in fortified foods and animal foods.
- The evidence is derived from studies using supplements at a dose of 200 µg/day. Selenium is toxic at high doses.
- '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.



Chapter references in the matrices relate to the Second Expert Report

Cancers of the colon and rectum are the third most common type worldwide. Around 1.2 million cases were recorded in 2008, accounting for around 10 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 (2).

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 colon cancer is convincing. The evidence that consumption of foods containing dietary fibre protects against colorectal cancer is convincing. The evidence that red meat, processed meat, ethanol from alcoholic drinks (by men, and probably by women), as well as 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. Consumption of garlic, milk, and calcium, probably protect against this cancer.

The evidence that non-starchy vegetables, fruits and foods containing vitamin D 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 is limited. Evidence for foods containing folate, fish, and selenium and foods containing it is less consistent and no conclusion could be drawn.

See chapter 8 of the Second Expert Report 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 physical activity protects against colon cancer and foods containing dietary fibre protect against colorectal cancer. The evidence also shows that consumption of red meat and processed meat, ethanol from alcoholic drinks (by men and probably by women), as well as body fatness and abdominal fatness, the factors that lead to greater adult attained height, or its consequences. Consumption of garlic, milk, and calcium probably protect against this cancer.

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.(3) 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.

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.(4) Colorectal cancer is mainly 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 30 or more 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 and parts of Asia(2). In the USA, rates are higher among African-American people than white people(5). This disease is slightly more common in men than in women, by seven to five(2).

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 ranges from around 60 per cent in North America, Japan, Australia and some Western European countries to 40 per cent or less in Algeria, Brazil and other European countries(2). This cancer accounts for around 10 per cent of all cancer incidence, and around 8 per cent of all cancer deaths. See box 1.

Box 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.

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)(6).

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 Hereditary non-polyposis colorectal cancer (HNPCC) (7) (also see 7.5.2, Second Expert Report). A further 20 per cent of cases occur in people who have a family history of colorectal cancer(7). 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(8).

On average, people develop HNPCC in their mid-40s(8); 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 sporadic colorectal cancer, although they are likely to be linked — the ‘gatekeeper’ and the ‘caretaker’ pathways(9). The gatekeeper pathway is involved in 85 per cent of sporadic colorectal cancers, and is the one associated with FAP(8). 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.(8) Several tumour-suppressor genes are mutated in this pathway(10) (Also see box 2.2. chapter 2, Second Expert Report).

3. Other established causes

3.1 General

This section lists factors outside the scope of this Summary, identified as established causes of cancer by the World Health Organization International Agency for Research on Cancer, and other authoritative bodies. These factors are listed in Chapter 2.4 of the SER: 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 Summary. 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 summary 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.

3.2 Specific

Other diseases. Inflammatory bowel disease (Crohn’s disease and ulcerative colitis) increases 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(11, 12).

Tobacco use. There is a 38% increased risk of colorectal cancer for an increase of 40 cigarette per day(13). There is now sufficient evidence that tobacco smoking is a cause of colorectal cancer(14).

4. Interpretation of the evidence specific to colorectal cancer

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 of the SER.

‘Relative risk’ is used in this Summary to denote ratio measures of effect, including ‘risk ratios’, ‘rate ratios’, ‘hazard ratios’, and ‘odds ratios’.

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.

5. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report much of the methodology following for the Continuous Update Project remains unchanged from that used previously. Based upon the experience of conducting the systematic literature reviews for the Second Expert Report some modifications to the methodology were made. The literature search was restricted to Medline and included only randomised controlled trials, cohort and case-control studies. The 2010 Continuous Update Project Colorectal Cancer Report included studies published up to December 2009 for all exposures except for fruits, vegetables, red and processed meat, vitamin D, alcohol and height papers published until May/June 2010 were included. Publications in foreign languages were not included.

Due to the large number of cohort studies, analysis and interpretation of case-control studies was not included in the Continuous Update Project Report. Meta-analyses and forest plots of highest versus lowest categories were prepared for colorectal cancer incidence. Studies with mortality endpoints previously included in analyses were removed. Studies reporting mean difference as a measure of association are not included in the Continuous Update Project Report as relative risks estimated from the mean differences are not adjusted for possible confounders, and thus not comparable to adjusted relative risks from other studies. (For more information on methodology see the 2010 Continuous Update Project Colorectal Cancer Report).

6. Evidence and judgements

The updated search identified 263 new articles from cohort studies and randomised controlled trials. Fuller summaries of the experimental and mechanistic evidence can be found in chapters 4-6 of the SER. For red and processed meat an updated narrative review of mechanisms was conducted by Denis Corpet (see acknowledgements) and has been added to the 2010 CUP Colorectal Cancer Report (see section 2.5.1.1). A summary is included under red and processed meat.

The CUP Panel's conclusions will be reviewed again after 2015, when the CUP database is up-to-date, in preparation for the review of the 10 Recommendations for Cancer Prevention in 2017. This summary includes the conclusions of the SER, with an updated description of the evidence and revised conclusions.

For information on the criteria for grading the evidence see box 3.8 of the SER. References to studies added as part of the CUP have been included in the following sections; for details on references to other studies see the SER. Summary estimates from dose-response meta-analyses were regarded as non-significant if the 95% confidence interval included 1.0.

6.1 Foods containing dietary fibre

(Also see CUP Colorectal cancer report 2010: section 5.1.2 Non-starch polysaccharides/dietary fibre)

The CUP identified 12 new papers from cohort studies(15-26) that investigated total dietary fibre, fibre from specific sources (cereal, fruit, vegetables and legumes) or wholegrains. For colorectal cancer a total of 18 cohort studies investigated dietary fibre, and 10 cohort studies investigated sources of fibre or wholegrains. The respective numbers for colon cancer were 12 and four, and for rectal cancer were 10 and zero.

Overall the CUP found that 13 of 18 studies for colorectal cancer showed decreased risk with increased intake of total dietary fibre.

CUP meta-analyses (per 10g/d) showed a 10 per cent decreased risk for colorectal cancer and 11 per cent for colon cancer (see CUP figures 125 and 130). The SER meta-analyses (per 10g/d) showed a 10 per cent decreased risk for colorectal cancer and 8 per cent for colon cancer (see SER figure 4.1.2 and SLR figure 5.5.9). The CUP meta-analyses included more studies than the SER (15 vs. 8) and showed less heterogeneity ($I^2 = 4$ vs. 57 per cent) for colorectal cancer. The CUP and SER summary estimates for the meta-analyses for rectal cancer were in the direction of decreased risk but did not reach conventional levels of statistical significance (see CUP figure 135 and SER figure 5.5.12).

CUP meta-analyses (per 10g/d) showed a 12 per cent decreased risk for men and an 8 per cent decreased risk for women for colorectal cancer (see CUP figure 126). Adjustment for folate intake had little effect on the summary estimates (7 per cent decreased risk for not adjusted and 11 per cent decreased risk for adjusted (see CUP figure 128)).

CUP meta-analyses for sources of fibre and colorectal cancer showed a 10 per cent decreased risk for cereal fibre, summary estimates for other sources of fibre were in the direction of decreased risk but did not reach statistical significance (see CUP figures 144, 147, 154, 161). For wholegrains there was a 21 per cent decreased risk per 3 servings per day for colorectal cancer and 16 per cent decreased risk for colon cancer (see CUP figures 2 and 5).

A published pooled analysis of 8100 colorectal cancer cases among 730 000

participants, followed up for 6–20 years, showed a non-significant decreased risk for the groups that consumed the most dietary fibre(27). 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. The gut flora from a wide range of dietary carbohydrates and mucins that reach the colon produces fermentation products, especially short-chain fatty acids. 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.

There is substantial consistent evidence from cohort studies, together with a clear dose-response relationship, supported by evidence for plausible mechanisms. The effect is apparent in men and women.

Foods containing dietary fibre were considered probably to protect against colorectal cancer by the SER Panel. The CUP Panel agreed that the evidence for a protective effect from foods containing dietary fibre had strengthened and could be upgraded to convincing.

6.2 Non-starchy vegetables and fruits

(Also see CUP Colorectal cancer report 2010: section 2.2 Fruit and non-starchy vegetables)

The CUP identified five new papers from cohort studies(16, 28-31) that investigated non-starchy vegetables and fruits combined. The total number of studies for colorectal, colon and rectal cancers were seven, 11 and nine respectively.

Overall the CUP found that six of seven studies on colorectal cancer, as well as eight of 11 for colon and five of nine for rectal cancers, reported decreased risk with increased intake.

The summary estimates from meta-analyses from both the CUP (see figures 11, 15 and 19) and the SER (see SLR figures 5.2.5, 5.2.8, 5.2.11) did not reach conventional levels of statistical significance, though were in the direction of decreased risk.

A published pooled analysis of 5838 colon cancer cases among 756 217 participants from 14 cohort studies, followed up for 6 to 20 years, showed a non-significant decreased risk for the groups that consumed the most non-starchy vegetables and fruits(32).

6.2.1 Non-starchy vegetables

(Also see CUP Colorectal cancer report 2010: section 2.2.1 Non-starchy vegetables)

The CUP identified six new papers from cohort studies (16, 24, 28, 29, 31, 33) that investigated non-starchy vegetables. The total number of studies for colorectal, colon and rectal cancers were 12, 11 and eight respectively.

Overall the CUP found that nine of 12 studies for colorectal cancer reported decreased risk with increased intake.

CUP summary estimates from the meta-analyses (per 100g/d) showed a 2 per cent decreased risk for colorectal cancer (see CUP figure 23) and were in the direction of decreased risk for colon cancer but did not reach statistical significance (see CUP figure 27). The SER summary estimates from meta-analyses (per 2 servings per day) were 1.00 for colorectal cancer and in the direction of decreased risk for colon and rectal cancers, but did not reach statistical significance (see SLR figures 5.2.24, 5.2.27 and 5.2.30).

CUP summary estimates from meta-analyses (per 100g/d) showed a 4 per cent decreased risk for men and were in the direction of decreased risk but did not reach statistical significance for colorectal cancer (see CUP figure 24).

A published pooled analysis of 5838 colon cancer cases among 756 217 participants for 14 cohort studies, followed up for 6-20 years, showed a non-significant decreased risk for the groups that consumed the most non-starchy vegetables(32). A published meta-analysis of highest versus lowest intakes of non-starchy vegetables of 7916 cases from 16 studies showed a non-significant increased risk for colorectal cancer and a non-significant decreased risk for colon and rectal cancers(34).

This is a wide and disparate food category, and many different plant food constituents could feasibly 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. Antioxidants, one of the multiple potential mechanisms, 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 a substantial amount of evidence for non-starchy vegetables, but it is inconsistent.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; the evidence that non-starchy vegetables protect against colorectal cancer is limited.

6.2.1.1 Garlic

(Also see chapter 4.2.5.1.2. of the SER)

No new cohort studies were identified as part of the CUP. Two cohort studies and six case-control studies identified as part of the SER 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.

As there was no new evidence the SER Panel's conclusion remains the same. Garlic probably protects against colorectal cancer.

6.2.2 Fruits

(Also see CUP Colorectal cancer report 2010: section 2.2.2 Fruits)

The CUP identified seven new papers from cohort studies(16, 24, 28, 29, 31, 33, 35) that investigated fruits. The total number of studies for colorectal, colon and rectal cancers were 13, 11 and seven respectively.

Overall the CUP showed that nine of 13 studies for colorectal cancer reported decreased risk with increased intake.

CUP summary estimates from meta-analyses (per 100g/d) showed a 3 per cent decreased risk for colorectal cancer (see CUP figure 35) and were in the direction of decreased risk for colon and rectal cancers, but did not reach statistical significance (see CUP figures 39 and 43). The SER summary estimates from meta-analyses (per 2 servings per day) showed results in the direction of decreased risk for colorectal, colon and rectal cancers, but did not reach statistical significance (see SLR figures 5.2.86, 5.2.89 and 5.2.92).

CUP meta-analyses (per 100g/d) showed a 4 per cent decreased risk for men and a non-significant decreased risk for women for colorectal cancer (see CUP figure 36). However for colon cancer there was a 7 per cent decreased risk for women and a non-significant increased risk for men (see CUP figure 40).

A published pooled analysis of 5838 colon cancer cases among 756 217 participants from 14 cohort studies, followed up for 6-20 years, showed a non-significant decreased risk for the groups that consumed the most fruits(32). A published meta-analysis of highest versus lowest intakes of fruits for 7803 cases from 15 studies showed a non-significant increased risk for colorectal and colon cancers and a significant decreased risk (22 per cent) for rectal cancers(34).

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(36). 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 for fruits, but it is inconsistent.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; the evidence that fruits protect against colorectal cancer is limited.

6.3 Foods containing folate

(Also see CUP Colorectal cancer report 2010: section 5.5.3 Dietary and serum folate)

The CUP identified 16 new papers from cohort studies(24, 37-51) that investigated dietary and/or serum/plasma folate. For colorectal cancer a total of eight cohort studies investigated dietary folate and eight cohort studies investigated serum/plasma folate. The respective numbers for colon cancer were six and two and for rectal cancer were four and three.

Overall the CUP showed that about half of studies showed decreased risk with increased dietary intake or increased serum/plasma levels.

CUP summary estimates from meta-analyses for dietary folate were in the direction of decreased risk for colorectal and colon cancers and in the direction of increased risk for rectal cancer, but did not reach statistical significance (see CUP figures 233, 237 and 241). The SER meta-analysis for dietary folate (per 100mcg/d) showed a 16 per cent decreased risk for colorectal cancer (see SER figure 4.2.34).

CUP summary estimates from meta-analyses for serum/plasma folate (per 2ng/ml) were in the direction of decreased risk for colorectal, colon and rectal cancers, but did not reach statistical significance (see CUP figures 244, 248 and 251). The two studies reporting on serum/plasma folate identified for the SER showed results in the direction of decreased risk, but no meta-analysis was conducted.

A published pooled analysis of 5720 colon cancer cases among 725 134 participants from 13 cohort studies, followed up for 7 to 20 years, showed non-significant decreased risk for the groups with the highest folate intake as well as when the analysis was conducted per 100mcg/d(52).

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 SER). In addition, folate intake is also strongly correlated with intake of

dietary fibre, which probably protects against colorectal cancer (see 6.1).

The evidence from cohort studies is plentiful; however the results are inconsistent for dietary, total and serum/plasma folate.

The SER Panel considered that there was limited evidence suggesting that foods containing folate protect against colorectal cancer. The CUP Panel agreed that the updated evidence showed inconsistency and was too limited to draw a conclusion.

6.4 Foods containing selenium

(Also see section 4.2.5.8 Foods containing selenium of the SER).

The CUP identified one new paper on dietary selenium(24) and one new paper on toenail selenium(53) both from cohort studies.

Fifteen case-control studies investigating dietary selenium were identified as part of the SER, all of which showed decreased risk with increased intake. Meta-analysis (10ug/dl) of case-control data showed a 14 per cent decreased risk with increased serum selenium levels for colorectal cancer (see SLR figure 5.5.192a). No cohort studies were identified.

New evidence for case-control studies was not reviewed for the CUP. One of the new cohort studies showed non-significant increased risk for dietary selenium and colorectal cancer and the other showed non-significant increased risk for toenail selenium and colon and rectal cancers.

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.

The evidence from cohort studies is sparse and does not support the decreased risk for dietary selenium observed in the case-control studies reviewed for the SER.

The SER Panel considered that there was limited evidence suggesting that foods containing selenium protect against colorectal cancer. The CUP Panel agreed that the updated evidence for cohort studies was not consistent with the previous evidence and was too limited to draw a conclusion.

6.5 Red and processed meat

(Also see CUP Colorectal cancer report 2010: section 2.5.1 Red and processed meat).

The CUP identified six new papers from cohort studies(54-59) that investigated combined intake of red and processed meat. The total number of studies identified for colorectal, colon and rectal cancers was 10, eight and six respectively.

Overall the CUP found that nine of 10 studies on colorectal cancer showed increased risk with higher intake.

CUP meta-analyses (per 100g/d) for colorectal, colon and rectal cancers showed 16, 21 and 31 per cent increased risk respectively (see CUP figures 47, 51 and 55). The SER meta-analyses (per 100g/d) that showed a 37 per cent increased risk for colon cancer (SLR figure 5.2.123).

A published meta-analysis of highest versus lowest intakes of red and processed meat of 13 407 cases from 33 risk estimates showed a significant increased risk (21 per cent for colorectal cancer(34). A published dose response meta-analysis of 7367 cases from 14 studies showed a 28 per cent increased risk per 120g/day increase in red and processed meat(60).

6.5.1 Red meat

(Also see CUP Colorectal cancer report 2010: section 2.5.1.3 Red meat)

The CUP identified six new papers from cohort studies (24, 30, 58, 59, 61, 62) that investigated red meat. The total number of studies identified for colorectal, colon and rectal cancers was 12, 10 and seven respectively.

Overall the CUP found that nine of 12 studies for colorectal cancer showed increased risk with higher intake.

CUP meta-analysis (per 100g/d) showed a 17 per cent increased risk for colorectal cancer (see CUP figure 70). Summary estimates from CUP meta-analysis were in the direction of increased risk for colon and rectal cancers, but did not reach statistical significance. The SER meta-analysis (per time per day) that showed a 43 per cent increased risk for colorectal cancer (see SER figure 4.3.2). The CUP meta-analysis showed less heterogeneity ($I^2 = 0$ vs. 58 per cent) for colorectal cancer than those in the SER.

There are several potential underlying mechanisms for a positive association of red meat consumption with colorectal cancer. Red meat contains haem, which promotes the formation of potentially carcinogenic *N*-nitroso compounds as well as cytotoxic alkenals forms from fat peroxidation. Red meat cooked at high temperatures, results in the production of heterocyclic amines and polycyclic aromatic hydrocarbons that can cause colon cancer in people with a genetic predisposition (see CUP Colorectal cancer report 2010: section 2.5.1.1).

A substantial amount of data from cohort studies showed a dose-response relationship, supported by evidence for plausible mechanisms operating in humans.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; red meat is a convincing cause of colorectal cancer.

6.5.2 Processed meat

(Also see CUP Colorectal cancer report 2010: section 2.5.1.2 Processed meat)

The CUP identified 11 new papers from cohort studies(24, 39, 54, 56, 58, 59, 61-65) that investigated processed meat. The total number of studies identified for colorectal, colon and rectal cancers were 13, 11 and 10 respectively.

Overall the CUP found that 10 of 13 studies for colorectal cancer showed increased risk with higher intake.

CUP meta-analysis (per 50g/d) showed an 18 per cent increased risk for colorectal cancer and a 24 per cent increased risk for colon cancer (CUP figures 58 and 62). The summary estimate from the CUP meta-analysis for rectal cancer was in the direction of increased risk but did not reach statistical significance (CUP figure 66). The SER meta-analysis (per 50g/d) showed a 21 per cent increased risk for colorectal cancer (see SER figure 4.3.6).

CUP meta-analyses (per 50g/d) showed a 38 per cent increased risk for women and a 64 per cent increased risk for men for colon cancer, though the result for men did not reach statistical significance (see CUP figure 63).

Heterogeneity was low and explained by the disparity in category definitions between studies, as well as by improved adjustment for confounders in recent studies.

A published meta-analysis of highest versus lowest intakes of processed meat of 13471 cases from 30 risk estimates showed a 19 per cent increased risk for colorectal cancer(34). A published dose-response meta-analysis of from 10 studies showed a 10 per cent increased risk of colorectal cancer for each 30g/d of processed meat consumed. The same study showed an increased risk of 16 per cent for 20 studies in a meta-analyses of highest versus lowest intakes of processed meat(66).

There are several potential underlying mechanisms for a positive association of red meat consumption with colorectal cancer. Red meat contains haem, which promotes the formation of potentially carcinogenic *N*-nitroso compounds as well as cytotoxic alkenals formed from fat peroxidation. The formation of *N*-nitroso compounds is particularly important when nitrate or nitrite is added as a preservative. Red meat cooked at high temperatures, results in the production of heterocyclic amines and polycyclic aromatic hydrocarbons that can cause colon cancer in people with a genetic predisposition (see CUP Colorectal cancer report 2010: section 2.5.1.1).

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.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; processed meat is a convincing cause of colorectal cancer.

6.6 Fish

(Also see CUP Colorectal cancer report 2010: section 2.5.2 Fish).

The CUP identified 12 new papers from cohort studies (24, 30, 39, 54, 65, 68-74) that investigated fish. The total number of studies identified for colorectal, colon and rectal cancers was 14, 12 and nine respectively.

Overall the CUP found about half of studies reported decreased risk with higher intake.

CUP summary estimates from meta-analyses (per 100g/d) were in the direction of decreased risk for colorectal, colon and rectal cancers, but did not reach statistical significance (see CUP figures 82, 87 and 93). The SER summary estimates for meta-analyses (per time per week) showed a 6 per cent decreased risk for colon cancer and were in the direction of decreased risk for colorectal cancer, but did not reach statistical significance (see SLR figures 5.2.191 and 5.2.192).

CUP summary estimates from meta-analyses of studies that adjusted for meat intake did not reach statistical significance but were in the direction of decreased risk for colorectal cancer and increased risk for colon and rectal cancers, while meta-analyses for studies that did not adjust for meat intake showed a 22 per cent decreased risk per 100g/d for colorectal cancer. Meta-analyses of studies that did not adjust for meat intake for colon and rectal were also statistically significant (10 and 36 per cent decreased risk respectively) (see CUP figures 85, 92 and 97).

Heterogeneity may be partly explained by varying definitions of fish in different studies to include fresh and/or salted and dried fish.

It is biologically plausible that long-chain n-3 polyunsaturated fatty acids (PUFAs) found in fish protect against cancer (see chapter 2.4.1.3 SER). Fish oils reduce tumours in animal studies. (75) 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. (76) Alternative suggestions include the relatively high selenium or vitamin D content of fish.

A substantial amount of data from cohort studies is available but the results are inconsistent.

The SER Panel considered that there was limited evidence suggesting that fish protects against colorectal cancer. The CUP Panel agreed that the updated evidence showed inconsistency and was too limited to draw a conclusion.

6.7 Vitamin D

(Also see CUP Colorectal cancer report 2010: section 5.5.10 Dietary vitamin D).

The CUP identified six new papers from cohort studies (16, 24, 77-80) that investigated dietary vitamin D intake. The total number of studies investigating dietary vitamin D for colorectal, colon and rectal cancers was 11, six and six respectively. The CUP identified six new papers from cohort studies (79, 81-85) that investigated plasma or serum vitamin D. The total number of studies for colorectal, colon and rectal cancers was six, six and five respectively.

Overall the CUP found six of 11 studies of intake, and five of six of the studies of plasma or serum vitamin D on colorectal cancer, showed decreased risk as measures of intake or status increased.

CUP summary estimates from meta-analyses for dietary vitamin D (per 100IU/d) showed a 5 per cent decreased risk for colorectal cancer and were in the direction of decreased risk for colon and rectal cancers, but did not reach statistical significance (see CUP figures 264, 267 and 270). The SER summary estimates from SER meta-analyses (per 100IU/d) showed a 23 per cent decreased risk for rectal cancer and were in the direction of decreased risk for colorectal and colon cancers, but did not reach statistical significance (see SLR figures 5.5.98, 5.5.99 and 5.5.100).

The CUP meta-analyses (per 100IU/l) for 25 hydroxyvitamin D showed a 4 per cent decreased risk for colorectal cancer and a 5 per cent decreased risk for colon cancer (see CUP figures 283 and 286). The summary estimate for the CUP meta-analysis for rectal cancer was in the direction of decreased risk for rectal cancer but did not reach statistical significance. (see CUP figure 289). There were no meta-analyses for serum/plasma for the SER.

A published meta-analysis of highest versus lowest comparison of dietary vitamin D for 2813 cases from 10 cohort studies showed a non-significant decreased risk for colorectal/colon cancers, and for 5 studies a non-significant decreased risk for rectal cancer (86).

The effects of vitamin D and calcium are strongly interrelated because both restrain cellular proliferation, 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.

There is plentiful evidence from cohort studies, but it is inconsistent. There is sparse information on vitamin D supplements from cohort studies and randomised controlled trials.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; the evidence suggesting that vitamin D or foods containing it protect against colorectal cancer is limited.

6.8 Foods containing iron

(Also see CUP Colorectal cancer report 2010: section 5.6.2 Dietary iron)

The CUP identified five new papers from cohort studies (57, 59, 63, 87, 88) that investigated haem iron intake. The total number of studies for colorectal, colon and rectal cancers was three, five and three respectively.

Overall the CUP found all three studies on colorectal cancer showed increased risk with increased intake.

CUP summary estimates from meta-analyses (per 1 mg/d) for haem iron were in the direction of increased risk for colorectal, colon and rectal cancers, but did not reach statistical significance (see CUP figures 297, 300 and 304). There were no meta-analyses for the SER and most studies reported on total iron intake rather than haem iron.

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.⁽⁸⁹⁾ Iron overload also activates oxidative responsive transcription factors, pro-inflammatory cytokines and iron-induced hypoxia signalling. ⁽⁹⁰⁾ Also see box 4.3.3 SER.

There is a limited amount of evidence from cohort studies with some inconsistency.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; the evidence suggesting that foods containing iron are in general a cause of colorectal cancer is limited. (Also see section 6.5 for evidence specifically on red and processed meat, which are classified as convincing causes of colorectal cancer).

6.9 Milk

(Also see CUP Colorectal cancer report 2010: section 2.7.1 Milk)

The CUP identified six new papers from cohort studies (30, 65, 78, 91-93) that investigated milk. Ten new papers from cohort studies investigated dietary calcium. The number of studies investigating milk and colorectal, colon and rectal cancers was 10, seven and four respectively and for dietary calcium was 17, 11 and 10.

Overall the CUP found that 8 of 10 cohort studies for colorectal cancer showed decreased risk with increased milk intake.

CUP summary estimates for meta-analyses (per 200g/d) showed a 9 per cent decreased risk for colorectal cancer and were in the direction of decreased risk for colon and rectal cancers, but did not reach statistical significance (see CUP figures 109, 113, 117). The SER summary estimate for the meta-analysis (per serving per day) was in the direction of decreased risk for colorectal cancer, but did not reach statistical significance (see SER figure 4.4.1).

Overall the CUP found that 16 of 17 cohort studies reported decreased risk with increasing dietary calcium intake.

CUP meta-analyses for dietary calcium (per 200mg/d) showed a 6 per cent decreased risk for colorectal cancer and a 7 per cent decreased risk for colon cancer. The summary estimate for the CUP meta-analysis for rectal cancer was in the direction of decreased risk for rectal cancer, but did not reach statistical significance (see CUP figures 318, 322 and 326). The SER summary estimates for the meta-analyses (per 200mg/d) showed a 5 per cent decreased risk for colon cancer and were in the direction of decreased risk for colorectal and rectal cancers, but did not reach statistical significance (see SER figure 4.43 and SLR figures 5.5.147 and 5.5.155).

CUP meta-analyses (per 200mg/d) for colorectal cancer showed a 7 per cent decreased for both men and women when analysed separately (see CUP figure 319).

A published meta-analysis of highest versus lowest comparison of milk intake for 2813 cases from 14 cohort studies showed a 10 per cent decreased risk for colorectal/colon cancer and a non-significant decreased risk for rectal cancer (86). A published pooled analysis of 4992 cases among 534 536 participants, followed up for 6 to 16 years 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 (94).

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 restrains cellular proliferation and promotes differentiation and apoptosis in normal and tumour colorectal cells.(95) Milk includes many other 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 marker. There is evidence for plausible mechanisms.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; there is evidence for plausible mechanisms. Milk probably protects against colorectal cancer.

6.10 Cheese

(Also see SER: section 4.4.5.1.2)

The CUP identified one new paper from a cohort study (91) that investigated cheese intake. The total number of studies for colorectal, colon and rectal cancers was 9, four and two respectively.

Overall the CUP found that eight of nine cohort studies showed increased risk with increased intake.

No meta-analyses were conducted for the CUP. The summary estimate for the SER meta-analysis was in the direction of increased risk, but did not reach statistical

significance (see SLR figure 5.2.7.1).

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.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; the evidence suggesting that cheese is a cause of colorectal cancer is limited.

6.11 Foods containing animal fats

(Also see SER: section 4.5.5.2 Foods containing animal fats)

The CUP identified two new papers from cohort studies(24, 54) that investigated animal fat intake. Three studies investigated colorectal cancer and four studies investigated colon cancer.

Overall the CUP found that all three studies on colorectal showed increased risk with increased intake but there is potential for residual confounding.

No meta-analyses were conducted for the CUP. The summary estimate from the SER meta-analysis was in the direction of increased risk, but did not reach statistical significance (see SLR figure 5.5.36).

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. (96)

There is a limited amount of fairly consistent evidence.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; the evidence suggesting that consumption of foods containing animal fats is a cause of colorectal cancer is limited.

6.12 Foods containing sugars

(Also see SER: section 4.6.5.1 Sugars)

The CUP identified two new papers from cohort studies (23, 97) that investigated sugar intake. Three studies investigated colorectal cancer and four studies investigated colon cancer.

A total of two studies investigated sugars as foods and six studies investigated sugars as nutrients, defined as total sugar, sucrose, or fructose. Four of the 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 SER).

The evidence is sparse and inconsistent.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; the evidence suggesting that consumption of foods containing sugar is a cause of colorectal cancer is limited.

6.13 Alcoholic drinks

(Also see CUP Colorectal cancer report 2010: section 5.4 Alcohol as ethanol)

The CUP identified 15 new papers from cohort studies(35, 42, 43, 98-109) that investigated alcohol as ethanol. The number of studies investigating alcohol as ethanol and colorectal, colon and rectal cancers was eight, 12 and 11 respectively

Overall the CUP found that all cohort studies investigating alcohol as ethanol showed increased risk with increased intake for colorectal and colon cancers.

CUP meta-analyses (per 10g/d) showed a 10 per cent increased risk for colorectal and rectal cancers and an 8 per cent increased risk for colon cancer (see CUP figures 208, 212 and 217). The SER meta-analysis (per 10g/d) showed a 9 per cent increased risk per 10 g ethanol/day for colon cancer and a 6 per cent increased risk for rectal cancer (see SER figures 4.8.10 and 4.8.12, and SLR figure 5.5.54).

CUP meta-analyses showed a greater effect in men than women for colorectal and colon cancers (see CUP figures 209 and 213) with the results for colorectal cancer showing an 11 per cent increased risk in men compared with 7 per cent for women.

A published pooled analysis of more than 4600 colorectal cancer cases among more than 475 000 participants, followed up for 6 to 16 years, showed a 41 per cent increased risk for the groups that drank the most alcohol (110).

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.

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. For colorectal and colon cancer the effect appears stronger in men than in women.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; ethanol from alcoholic drinks is a cause of colorectal cancer in men is convincing; and it is probably a cause in women.

6.14 Calcium

(Also see CUP Colorectal cancer report 2010: section 5.6.3 Supplemental calcium)

The CUP identified three new papers from cohort studies (78, 111, 112) that investigated calcium supplements. In total seven studies investigated calcium supplements and colorectal cancer.

Overall the CUP found that all but one study reported decreased risk with calcium supplementation. No meta-analyses were conducted for the CUP or the SER.

A published meta-analysis showed a 24 per cent decreased risk with use of calcium supplements for colorectal/colon cancer (86). A pooled analysis of 4992 cases among 534 536 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) (94). 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.

Calcium from diet is an important nutrient; intracellular calcium is a pervasive second messenger acting on many cellular functions including cell growth. Calcium restrains cellular proliferation and promotes differentiation and apoptosis in normal and tumour colorectal cells(95).

There is generally consistent evidence on dietary calcium, total calcium (dietary and supplemental) and calcium supplements from cohort studies. The effect was apparent in men and women. There is evidence for plausible mechanisms.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; calcium probably protects against colorectal cancer.

6.15 Selenium

(Also see CUP Colorectal cancer report 2010: section 5.6.4 Selenium from supplement)

One randomised controlled trial and one cohort study investigating selenium supplements were identified for the SER. The trial showed a statistically significant

decreased risk with a daily supplement of 200 ug of selenium. This was a relatively small study (1321 participants; eight 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. A further trial was identified as part of the CUP, this trial had 123 cases after a 5 year follow-up and reported a non-significant increased risk in participants taking 200ug/d (113).

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 and inconsistent.

The SER Panel considered that there was limited evidence suggesting that selenium protects against colorectal cancer. The CUP Panel agreed that the updated evidence showed inconsistency and was too limited to draw a conclusion.

6.16 Physical activity

(Also see CUP Colorectal cancer report 2010: chapter 6. Physical activity)

The CUP identified 15 new papers from cohort studies(16, 30, 114-126) that investigated total, recreational or occupational physical activity. The number of studies investigating total physical activity and colorectal, colon and rectal cancers was five, 10 and eight respectively. The corresponding numbers for recreational activity cancer was nine, 16 and 13 and for occupational activity were seven for colon and seven for rectal cancers.

Overall the CUP found that eight of 10 studies on colon cancer reported decreased risk with increased total physical activity. Many studies were unsuitable for meta-analysis due to the disparate measures used to assess physical activity.

CUP meta-analyses (per 5 MET hr/d) showed for total physical activity a 3 per cent decreased risk for colorectal cancer and an 8 per cent decreased risk for colon cancer (see CUP figures 347 and 350). For recreational activity summary estimates from CUP meta-analyses (per 5 MET-hrs per week) were in the direction of decreased risk for colorectal and colon cancers, but did not reach statistical significance; whereas CUP meta-analyses per 30 mins/d showed an 11 per cent decreased risk for colorectal and 12 per cent decreased risk for colon cancer (see CUP figures 366 and 368). The data also suggested that the effect was reduced or removed for rectal cancer (see CUP figures 354, 366 and 368). The SER summary estimate from the meta-analysis for recreational activity (per MET hr/week) showed a 6 per cent decreased risk for colorectal cancer (see SLR figure 5.6.22b).

A published meta-analysis of highest versus lowest comparisons of leisure time physical activity and colon cancer showed a 20 per cent decrease risk in men (10

studies) and 14 per cent decreased risk in women (9 studies) for colon cancer. Non-significant increased risk was found for rectal cancer (127).

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), and so have a beneficial effect on body fatness. In addition, physical activity may protect against colon cancer by decreasing inflammation, reducing insulin levels and reduced insulin resistance.

There is abundant epidemiological evidence from prospective studies showing a lower risk of colorectal cancer with higher overall levels of physical activity, and there is evidence of a dose-response effect. The effect is strong for colon cancer; however there is no evidence of an effect for rectal cancer. The effect is strong and consistent in men, but less strong in women. There is plausible evidence for mechanisms operating in humans.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; the evidence that higher levels of physical activity, within the range studied, protect against colon cancer is convincing.

6.17 Body fatness

(Also see CUP Colorectal cancer report 2010: section 8.1.1 BMI)

The CUP identified 22 new papers from cohort studies (16, 30, 35, 108, 114, 123, 125, 128-142) investigated as measured by body mass index. The number of studies investigating body fatness and colorectal, colon and rectal cancers was 29, 36 and 27 respectively.

Overall the CUP found that 25 of the 29 cohort studies showed increased risk with increased body fatness.

CUP meta-analyses (per kg/m^2) showed for colorectal, colon and rectal cancers increased risks of 2, 3 and 1 per cent for colorectal, colon and rectal cancers respectively (see CUP figures 383, 391 and 399). CUP meta-analyses tended to show a larger effect in men than women (4 vs. 2 per cent for colon cancer) (see CUP figures 384, 392, 393, 400 and 401). The effect was stronger for USA and Asia than Europe (4 vs. 3 per cent for colon cancer) (see CUP figures 383 and 391). Heterogeneity is explained partly by sexual and geographical differences, and also by cancer site. Meta-analysis for the SER showed a 3 per cent increased risk per kg/m^2 for colorectal cancer (SER figure 6.1.6).

Two published dose-response meta-analyses (per 5kg/m^2) with a large number of cases (over 20,000 for colon cancer for both men and women separately) showed a 24 per cent increased risk for men and 9 per cent increased risk for women (20 975 cases from 19 studies) for colon cancer, and 9 per cent increased risk for men (14 894 cases from 18 studies) and non-significant increased risk for women (9052 cases from 14 studies) for rectal cancer (143, 144).

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 from SER.

There is abundant and consistent epidemiological evidence with a clear dose-response relationship, and evidence for plausible mechanisms that operate in humans.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; the evidence that greater body fatness is a cause of colorectal cancer is convincing.

6.18 Abdominal fatness

(Also see CUP Colorectal cancer report 2010: sections 8.2.1 Waist circumference and 8.2.3 Waist to hip ratio)

The CUP identified eight new papers from cohort studies (16, 30, 114, 129, 130, 136, 137, 140) that investigated waist circumference and/or waist to hip ratio. The number of studies investigating waist circumference and colorectal, colon and rectal cancers was five, eight and four respectively. The corresponding numbers for waist to hip ratio was nine, 16 and 13.

Overall the CUP found that all cohort studies showed increased risk with either increased waist circumference or increased waist to hip ratio.

CUP meta-analyses for waist circumference (per inch for studies that did not adjust for BMI) showed increased risks of 3, 5 and 3 per cent for colorectal, colon and rectal cancers (see CUP figures 416, 419 and 426). Meta-analyses for studies that adjusted for BMI also found increased risk for colorectal and colon cancer though the summary estimate was attenuated (see CUP figures 417, 420 and 427). The meta-analyses for waist circumference showed a 6 per cent increased risk for men and a 3 per cent increased risk for women for colon cancer (see CUP figure 421). CUP meta-analyses for waist to hip ratio showed a 17, 27 and 20 per cent increased risk for colorectal, colon and rectal cancers (see CUP figure 431). SER meta-analyses showed a 5 per cent increased risk per inch of waist circumference, and a 30 per cent increased risk per 0.1 increment of waist to hip ratio for colon cancer (see SER figures 6.1.22 and 6.1.23).

The general mechanisms through which abdominal fatness could plausibly influence cancer risk are outlined in the SER (see 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 of the SER. 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 evidence from cohort studies with a clear dose-response relationship and robust evidence for mechanisms that operate in

humans.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; the evidence that abdominal fatness is a cause of colorectal cancer is convincing.

6.19 Adult attained height

(Also see CUP Colorectal cancer report 2010: section 8.3.1. Height)

The CUP identified 11 new papers from cohort studies (16, 125, 135-137, 139, 142, 145-148) that investigated adult attained height. The total number of studies for colorectal, colon and rectal cancers was eight, 13 and 11 respectively.

Overall the CUP found that six of the eight cohort studies for colorectal cancer showed increased risk with increased height.

CUP meta-analyses (per 5cm) showed a 5 and 9 per cent increased risk for colorectal and colon cancers (see CUP figures 438 and 442). The summary estimate for the meta-analysis for rectal cancer was in the direction of increased risk, but did not reach statistical significance (see CUP figure 446). For both colorectal and colon cancers the increased risk was observed in both men and women; however for rectal cancer it was only statistically significant in men (see CUP figures 439, 443 and 447). The SER Meta-analysis showed a 9 per cent increased risk per 5 cm of height for colorectal cancer (see SER figure 6.2.1).

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 the SER see 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 epidemiological evidence from cohort studies, which is consistent, and there is a clear dose-response relationship, with evidence for plausible mechanisms operating in humans.

The CUP Panel agreed that the recent evidence was consistent with the conclusion of the SER; 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.

6.20 Other exposures

Glycaemic index and load were evaluated. However, the data were too inconsistent to draw conclusions.

7. Comparison with the Second Expert Report

Overall the evidence from the additional cohort studies identified in the Continuous Update Project was consistent with those reviewed as part of the Second Expert Report for exposures graded convincing or probable. The evidence for a protective effect from foods containing dietary fibre has strengthened. The updated evidence for some exposures (foods containing folate, fish, and foods and supplements containing selenium) where there was limited evidence of a protective effect was more inconsistent. Much of the new evidence related to foods containing dietary fibre, foods containing folate, processed meat, fish, dietary calcium, alcoholic drinks, physical activity, body fatness and adult attained height.

8. Conclusions

The CUP Panel will review the evidence relating to colorectal cancer again after 2015 once the CUP database is being continuously updated for all cancers. The Recommendation for Cancer Prevention will be reviewed in 2017 when the Panel have reviewed the conclusions for the other cancers.

The Continuous Update Project Panel concludes:

The evidence that physical activity protects against colon cancer is convincing. The evidence that consumption of foods containing dietary fibre protects against colorectal cancer is convincing.

The evidence that consumption of red meat, processed meat, ethanol from 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.

Consumption of garlic, milk, and calcium, probably protect against this cancer.

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

Evidence for foods containing folate, fish, and selenium and foods containing it, is less consistent and was too limited to draw a conclusion.

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