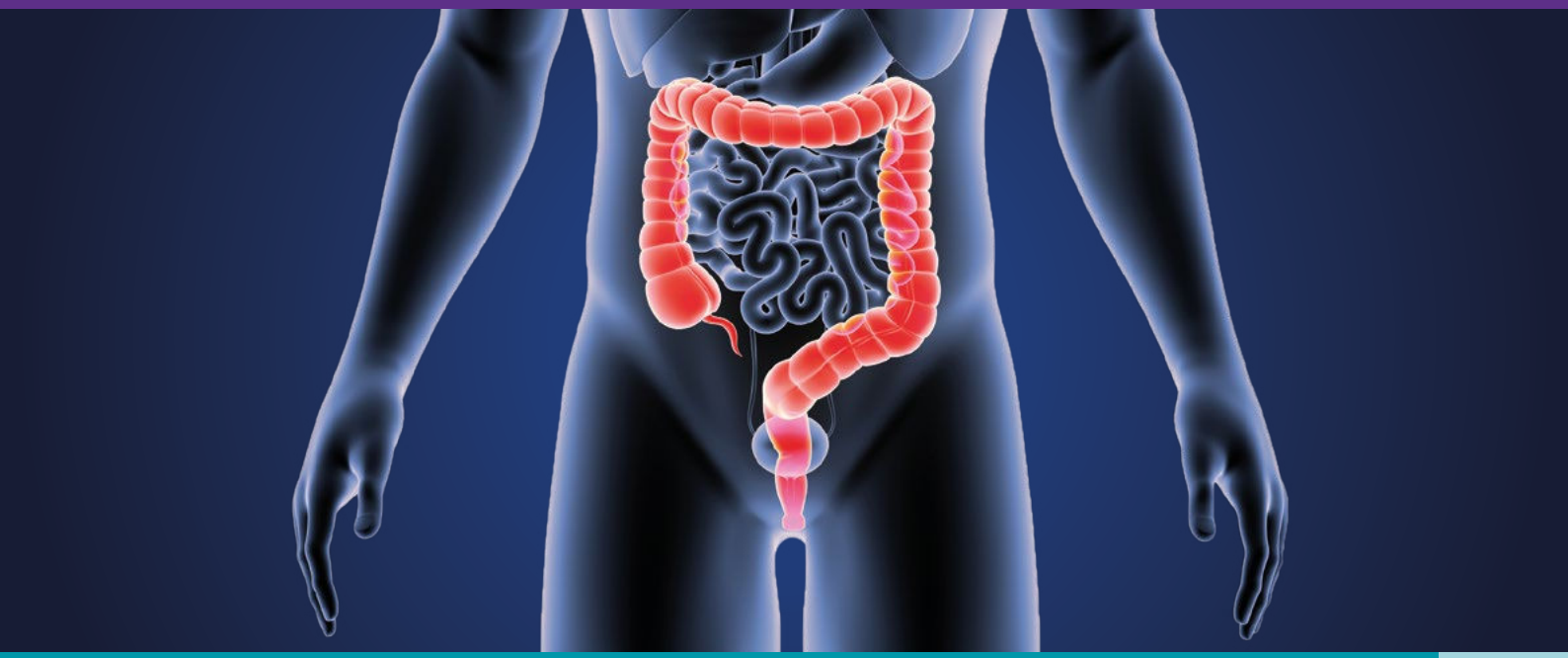
World Cancer Research Fund

American Institute for Cancer Research

CUP Continuous Update Project

Analysing research on cancer prevention and survival



# Diet, nutrition, physical activity and **colorectal cancer**

2017

Revised 2018

World Cancer Research Fund International

World Cancer Research Fund UK

Wereld Kanker Onderzoek Fonds

World Cancer Research Fund

世界癌症研究基金會

# Contents

# WORLD CANCER RESEARCH FUND NETWORK

## OUR VISION

We want to live in a world where no one develops a preventable cancer.

## OUR MISSION

We champion the latest and most authoritative scientific research from around the world on cancer prevention and survival through diet, weight and physical activity, so that we can help people make informed choices to reduce their cancer risk.

As a network, we influence policy at the highest level and are trusted advisors to governments and to other official bodies from around the world.

## OUR NETWORK

World Cancer Research Fund International is a not-for-profit organisation that leads and unifies a network of cancer charities with a global reach, dedicated to the prevention of cancer through diet, weight and physical activity.

The World Cancer Research Fund network of charities is based in Europe, the Americas and Asia, giving us a global voice to inform people about cancer prevention.

CUP Continuous Update Project

Analysing research on cancer prevention and survival

THIRD EXPERT REPORT

# OUR CONTINUOUS UPDATE PROJECT (CUP)

The Continuous Update Project (CUP) is the World Cancer Research Fund (WCRF) Network's ongoing programme to analyse cancer prevention and survival research related to diet, nutrition and physical activity from all over the world. Among experts worldwide it is a trusted, authoritative scientific resource which informs current guidelines and policy on cancer prevention and survival.

Scientific research from around the world is continually added to the CUP's unique database, which is held and systematically reviewed by a team at Imperial College London. An independent panel of experts carries out ongoing evaluations of this evidence, and their findings form the basis of the WCRF Network's Cancer Prevention Recommendations (**see inside back cover**).

Through this process, the CUP ensures that everyone, including policymakers, health professionals and members of the public, has access to the most up-to-date information on how to reduce the risk of developing cancer.

The launch of the WCRF Network's Third Expert Report, *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*, in 2018 brings together the very latest research from the CUP's review of the accumulated evidence on cancer prevention and survival related to diet, nutrition and physical activity. Diet, nutrition, physical activity and colorectal cancer is one of many parts that make up the CUP Third Expert Report: for a full list of contents, see **dietandcancerreport.org**.

The CUP is led and managed by World Cancer Research Fund International in partnership with the American Institute for Cancer Research, on behalf of World Cancer Research Fund UK, Wereld Kanker Onderzoek Fonds and World Cancer Research Fund HK.

# HOW TO CITE THIS REPORT

This part: World Cancer Research Fund/American Institute for Cancer Research. Continuous Update Project Expert Report 2018. Diet, nutrition, physical activity and colorectal cancer. Available at **dietandcancerreport.org**

The whole report: World Cancer Research Fund/American Institute for Cancer Research. *Diet, Nutrition, Physical Activity and Cancer: a Global Perspective*. Continuous Update Project Expert Report 2018. Available at **dietandcancerreport.org**

# KEY

References to other parts of the Third Expert Report are highlighted in purple.

# EXECUTIVE SUMMARY

## Background and context

Colorectal cancer is the third most common cancer worldwide. About 1.4 million new cases of colorectal cancer were recorded globally in 2012, accounting for 10 per cent of all new cases of cancer [2].

Colorectal cancer is the fourth most common cause of death from cancer, estimated to be responsible for almost 700,000 cancer deaths. Colorectal cancer survival depends on the stage at which it is diagnosed, with later-stage diagnosis having poorer survival. The five-year survival rate is 90 per cent for colorectal cancers diagnosed at an early stage compared with 13 per cent for those diagnosed at a late stage.

The highest estimated rates are in Australia and New Zealand, and the lowest in Western Africa. Patterns of colorectal cancer cases in men and women are similar globally [2].

Over the next 15 years, the number of cases of colorectal cancer is expected to increase by 60 per cent to more than 2.2 million. Globally it is one of the cancers whose incidence is increasing.

In this report from our Continuous Update Project (CUP) – the world's largest source of scientific research on cancer prevention and survivorship through diet, weight and physical activity – we analyse global research on how certain lifestyle factors affect the risk of developing colorectal cancer. This includes new studies as well as those included in our previous 2007 Second Expert Report, *Food, Nutrition, Physical Activity and the Prevention of Cancer: a Global Perspective* [1], and our 2011 CUP Colorectal Cancer Report [3].

In addition to the findings in this report, other established causes of colorectal cancer include the following:

**1. 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.

**2. Smoking:**

- There is an increased risk of colorectal cancer in people who smoke.

# How the research was conducted

The global scientific research on diet, weight, physical activity and the risk of colorectal cancer was systematically gathered and analysed, and then independently assessed by a panel of leading international scientists in order to draw conclusions about which of these factors increase or decrease the risk of developing colorectal cancer.

This new report includes all new relevant studies as well as studies included in our 2007 Second Expert Report [1] and in our 2011 Colorectal Cancer Report [3]. In total, this new report analyses 99 studies from around the world, comprising more than 29 million adults and over 247,000 cases of colorectal cancer. To ensure consistency, the methodology for the Continuous Update Project remains largely unchanged from that used for our 2007 Second Expert Report [1]. A summary of the mechanisms underpinning all the findings can be found in the Evidence and Judgements section of this report.

# Findings

## There is strong evidence that:

- **being physically active decreases the risk of colon cancer**
- **consuming wholegrains decreases the risk of colorectal cancer**
- **consuming foods containing dietary fibre decreases the risk of colorectal cancer**
- **consuming dairy products decreases the risk of colorectal cancer**
- **taking calcium supplements decreases the risk of colorectal cancer**
- **consuming red meat increases the risk of colorectal cancer**
- **consuming processed meat increases the risk of colorectal cancer**
- **consuming approximately two or more alcoholic drinks per day increases the risk of colorectal cancer**
- **being overweight or obese increases the risk of colorectal cancer**
- **being tall increases the risk of colorectal cancer**

## There is some evidence that:

- **consuming foods containing vitamin C might decrease the risk of colon cancer**
- **consuming fish might decrease the risk of colorectal cancer**
- **vitamin D might decrease the risk of colorectal cancer**
- **consuming multivitamin supplements might decrease the risk of colorectal cancer**
- **low consumption of non-starchy vegetables might increase the risk of colorectal cancer**
- **low consumption of fruit might increase the risk of colorectal cancer**
- **consumption of foods containing haem iron might increase the risk of colorectal cancer**

# Recommendations

Our Cancer Prevention Recommendations – for preventing cancer in general – include maintaining a healthy weight, being physically active and eating a healthy diet. They advise eating a healthy diet rather than relying on supplements to protect against cancer. The Cancer Prevention Recommendations are listed on the inside back cover of this report, with full details available in Recommendations and public health and policy implications.

### References


[1] World Cancer Research Fund/American Institute for Cancer Research. *Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective*. Washington DC: AICR, 2007. Available at **wcrf.org/about-the-report**

[2] Ferlay J, Soerjomataram I, Ervik M, *et al*. GLOBOCAN 2012 v1.2, Cancer Incidence and Mortality Worldwide: IARC CancerBase No. 11. 2015; available from **http://globocan.iarc.fr**

[3] World Cancer Research Fund/American Institute for Cancer Research. *Continuous Update Project* Report. *Food, Nutrition, Physical Activity, and the Prevention of Colorectal Cancer*. 2011

# 2017 DIET, NUTRITION, PHYSICAL ACTIVITY AND COLORECTAL CANCER

| | | DECREASES RISK | INCREASES RISK |
|---|---|---|---|
| **STRONG EVIDENCE** | **Convincing** | **Physical activity[1,2]** | **Processed meat[3]**<br>**Alcoholic drinks[4]**<br>**Body fatness[5]**<br>**Adult attained height[6]** |
| | **Probable** | **Wholegrains**<br>**Foods containing dietary fibre[7]**<br>**Dairy products[8]**<br>**Calcium supplements[9]** | **Red meat[10]** |
| **LIMITED EVIDENCE** | **Limited – suggestive** | Foods containing vitamin C[11]<br>Fish<br>Vitamin D[12]<br>Multivitamin supplements[13] | Low intakes of non-starchy vegetables[14]<br>Low intakes of fruits[14]<br>Foods containing haem iron[15] |
| | **Limited – no conclusion** | Cereals (grains) and their products; potatoes; animal fat; poultry; shellfish and other seafood; fatty acid composition; cholesterol; dietary n-3 fatty acid from fish; legumes; garlic; non-dairy sources of calcium; foods containing added sugars; sugar (sucrose); coffee; tea; caffeine; carbohydrate; total fat; starch; glycaemic load; glycaemic index; folate; vitamin A; vitamin B6; vitamin E; selenium; low fat; methionine; beta-carotene; alpha-carotene; lycopene; retinol; energy intake; meal frequency; dietary pattern | |
| **STRONG EVIDENCE** | **Substantial effect on risk unlikely** | | |

**1** Physical activity of all types: occupational, household, transport and recreational.

**2** The Panel judges that the evidence for colon cancer is convincing. No conclusion was drawn for rectal cancer.

**3** The term 'processed meat' refers to meats preserved by smoking, curing, or salting, or addition of chemical preservatives.

**4** Based on evidence for alcohol intakes above approximately 30 grams per day (about two drinks a day).

**5** Body fatness marked by body mass index (BMI), waist circumference or waist-hip ratio.

**6** Adult attained height is unlikely to directly influence the risk of cancer. It is a marker for genetic, environmental, hormonal and nutritional growth factors affecting growth during the period from preconception to completion of linear growth.

**7** Includes both foods naturally containing the constituent and foods that have the constituent added. Dietary fibre is contained in plant foods.

**8** Includes evidence from total dairy, milk, cheese and dietary calcium intakes.

**9** The evidence is derived from supplements at a dose >200 milligrams per day.

**10** The term 'red meat' refers to beef, pork, lamb, and goat from domesticated animals.

**11** The Panel judges that the evidence for colon cancer is limited. No conclusion was drawn for rectal cancer.

**12** Includes evidence from foods containing vitamin D, serum vitamin D, and supplemental vitamin D.

**13** Definitions and categorisation of multivitamin supplements are not standardised.

**14** Increased risk observed at low intakes (below 100 grams per day).

**15** Foods include red and processed meat, fish and poultry.

# 1. Summary of Panel judgements

Colorectal cancer is any cancer of the colon or rectum. In this report conclusions are drawn for colorectal cancer risk, except for physical activity and vitamin C, where the conclusions are for colon cancer risk only.

Overall, the Panel notes the strength of the evidence that foods containing wholegrains, foods containing dietary fibre, dairy products, and calcium supplements protect against colorectal cancer; that physical activity protects against colon cancer; and that processed meat, alcoholic drinks, greater body fatness, adult attained height and red meat are causes of colorectal cancer.

The Continuous Update Project (CUP) Panel judges as follows:

## Convincing evidence

**Physical activity: Physical activity convincingly protects against colon cancer.**

**Processed meat: Consumption of processed meat is a convincing cause of colorectal cancer.**

**Alcoholic drinks: Consumption of alcoholic drinks is a convincing cause of colorectal cancer. This is based on evidence for intakes above 30 grams per day (about two drinks a day).**

**Body fatness: Greater body fatness is a convincing cause of colorectal cancer.**

**Adult attained height: Developmental factors leading to greater linear growth (marked by adult attained height) are a convincing cause of colorectal cancer.**

## Probable evidence

**Wholegrains: Consumption of wholegrains probably protects against colorectal cancer.**

**Dietary fibre: Consumption of foods containing dietary fibre probably protects against colorectal cancer.**

**Dairy products: Consumption of dairy products probably protects against colorectal cancer.**

**Calcium supplements: Taking calcium supplements probably protects against colorectal cancer.**

**Red meat: Consumption of red meat is probably a cause of colorectal cancer.**

### Limited – suggestive evidence

**Foods containing vitamin C: The evidence suggesting that foods containing vitamin C decreases the risk of colon cancer is limited.**

**Fish: The evidence suggesting that consumption of fish decreases the risk of colorectal cancer is limited.**

**Vitamin D: The evidence suggesting that vitamin D decreases the risk of colorectal cancer is limited.**

**Multivitamin supplements: The evidence suggesting that taking multivitamin supplements decreases the risk of colorectal cancer is limited.**

**Non-starchy vegetables: The evidence suggesting that low consumption of non-starchy vegetables increases the risk of colorectal cancer is limited.**

**Fruits: The evidence suggesting that low consumption of fruit increases the risk of colorectal cancer is limited.**

**Foods containing haem iron: The evidence suggesting that consumption of foods containing haem iron increases the risk of colorectal cancer is limited.**

For a full description of the definitions of, and criteria for, the terminology of 'convincing', 'probable', 'limited – suggestive', 'limited – no conclusion' and 'substantial effect on risk unlikely', see the **Appendix** on page 106.

The Panel judgements for colorectal cancer are shown in the matrix on **page 8**.

# 2. Trends, incidence and survival

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. The colon is lined with mucous membranes and contains lymphoid cells that form part of the body's immune defences.

## Incidence and mortality

Worldwide, colorectal cancer is the third most commonly occurring cancer in men – approximately 746,000 cases (10 per cent of the total of all cancer cases) were diagnosed in 2012 (the latest year for which data are available) – and the second most commonly occurring cancer in women (614,000 cases, 9 per cent of the total of all cancer cases). There is wide geographical variation in incidence across the world and the geographical patterns are similar in men and women: incidence rates vary ten-fold in both sexes worldwide, the highest estimated rates being in Australia and New Zealand (age-standardised rate of 44.8 and 32.2 per 100,000 men and women, respectively), and the lowest in Western Africa (4.5 and 3.8 per 100,000 men and women respectively).

Annually colorectal cancer is the cause of approximately 694,000 deaths (9 per cent of all cancer deaths) across the globe. Colorectal cancer mortality is highest in countries characterised by higher indices of development and/or income. The highest estimated mortality rates in both sexes are seen in Central and Eastern Europe (20.3 per 100,000 for men, 11.7 per 100,000 for women), and the lowest in Western Africa, mostly due to lower incidence (3.5 and 3.0 per 100,000, for men and women respectively) [2].

## Trends

About two-thirds of colorectal cancer cases and about 60 per cent of colorectal cancer deaths occur in countries characterised by high or very high indices of development and/or income. Over the next 15 years, the global burden of colorectal cancer is expected to increase by 60 per cent to more than 2.2 million new cases and 1.1 million deaths [4]. Colorectal cancer is considered one of the clearest markers of epidemiological and nutritional transition, with incidence rates of this cancer – together with other cancers linked to Western lifestyles – increasing as previous high rates of infection-related cancers decline in countries that are undergoing rapid societal and economic changes [5-7]. Stabilising or decreasing trends – likely due to advances in screening and treatment – are seen in countries characterised by high indices of development and/or income, where rates remain among the highest in the world [4].

## Survival

As with many cancers, survival of colorectal cancer depends heavily on the stage at diagnosis. The higher proportion of advanced cancers in countries characterised by lower or middle indices of development and/or income may explain both the higher mortality-to-incidence ratios in these countries. In the United States, for example, colorectal cancer survival rates do not vary substantially by sex but depend on the stage of disease at diagnosis. Survival ranges from a 90 per cent five-year survival rate for cancers detected at the localised stage (40 per cent of cases), to 70 per cent for regionalised cancers (36 per cent of cases), to 13 per cent for people diagnosed with distant metastatic cancer (20 per cent of cases) [8]. For further information, see **Box 1**.

**Box 1: Cancer incidence and survival**

**The cancer incidence rates and figures given here 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 probably higher than the figures given here.**

**Most information on cancer survival is for the United States and Europe. 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 as well as well-established treatment facilities. Survival is often a function of the stage at which a cancer is detected, diagnosed and treated.**

# 3. Pathogenesis

Approximately 95 per cent of colorectal cancers are adenocarcinomas. Other types of cancer that can occur include mucinous carcinomas and adenosquamous carcinomas.

Carcinogens can interact directly with the cells that line the colon and rectum. Between five 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). A further 20 per cent of cases occur in people who have a family history of colorectal cancer. People with FAP have a mutation in the tumour-suppressor gene APC which regulates cell growth and 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 age 40. On average, people develop HNPCC in their mid-40s; having this form of the disease also increases the risk of a number of other gastrointestinal cancers. HNPCC involves mutations in DNA repair genes.

These two conditions also lead to sporadic colorectal cancer. The so-called 'gatekeeper' pathway involves the disruption of genes that regulate growth – principally APC, as in FAP – and is involved in 85 per cent of sporadic colorectal cancers [9]. The 'caretaker' pathway, which is characterised by disruption to genes that maintain genetic stability as in HNPCC, leads to 15 per cent of sporadic cancers [10].

# 4. Other established causes or protective factors

### Tobacco use

Smoking 40 cigarettes (two packs) per day increases risk of colorectal cancer by about 40 per cent and nearly doubles the risk of colorectal cancer death [11].

### Other diseases

Inflammatory bowel disease (Crohn's disease and ulcerative colitis) increases the risk of colon cancer.

### Medication

Long-term use (five years or more) of at least 75 mg per day of the non-steroidal anti-inflammatory drug aspirin can reduce the risk of colorectal cancer [12]. Hormone therapy in postmenopausal women decreases colorectal cancer risk [13].

# 5. Interpretation of the evidence

## 5.1 General

For general considerations that may affect interpretation of the evidence, see Judging the evidence.

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

## 5.2 Specific

Considerations specific to colorectal cancer include the following:

### Classification

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

# 6. Methodology

To ensure consistency with evidence collected and analysed for the Second Expert Report [1], the methodology for reviewing the epidemiological evidence in the Continuous Update Project (CUP) remains largely unchanged. However, based upon the experience of conducting the systematic literature reviews (SLRs) for the Second Expert Report, some modifications to the methodology were made. The updated literature search was restricted to Medline and included only randomised controlled trials, cohort and nested case-control studies. Due to their methodological limitations and because of the copious prospective data, case-control studies were not analysed in the CUP Colorectal SLR 2016.

In this update, dose-response meta-analyses were conducted for incidence (with the exception of an analysis on mortality for alcohol). Separate meta-analyses were also conducted for colon, rectal and other sub-types, for men and women, and by geographical location, where possible.

Studies reporting mean difference as a measure of association were not included in the CUP Colorectal SLR 2016, as relative risks estimated from mean differences are not adjusted for confounders and thus are not comparable with adjusted relative risks from other studies.

Non-linear meta-analysis was applied when the data suggested that the dose-response curve was non-linear, and when detecting a threshold or plateau of effect might be of interest. Details on the non-linear meta-analyses can be found in the CUP Colorectal SLR 2016.

The CUP Colorectal SLR 2016 included studies published up to 30 April 2015.
For more information on the methodology, see the full CUP Colorectal SLR 2016 at **wcrf.org/colorectal-cancer-slr.**

### 6.1 Mechanistic evidence

The mechanisms included in this report were produced by the International Agency for Research on Cancer and reviewed by CUP Panel members. A brief summary is given of possible mechanisms for physical activity, processed meat, alcoholic drinks, body fatness, adult attained height, foods containing dietary fibre, wholegrains, dairy products, calcium supplements, red meat, foods containing vitamin C, fish, vitamin D, multivitamin supplements, non-starchy vegetables (low intakes), fruits (low intake) and foods containing haem iron.

## 7. Evidence and judgements

The following sections summarise the evidence identified in the CUP Colorectal SLR 2016 and provide a comparison with the findings and the Panel's conclusions from the 2011 CUP Colorectal Cancer Report [3]. They also include a brief description of potential biological mechanisms for each exposure.

For information on the criteria for grading the epidemiological evidence, see the **Appendix** on page 106 in this report. References to studies added as part of the CUP have been included; for details of references to other studies from the Second Expert Report, see the CUP Colorectal SLR 2016.

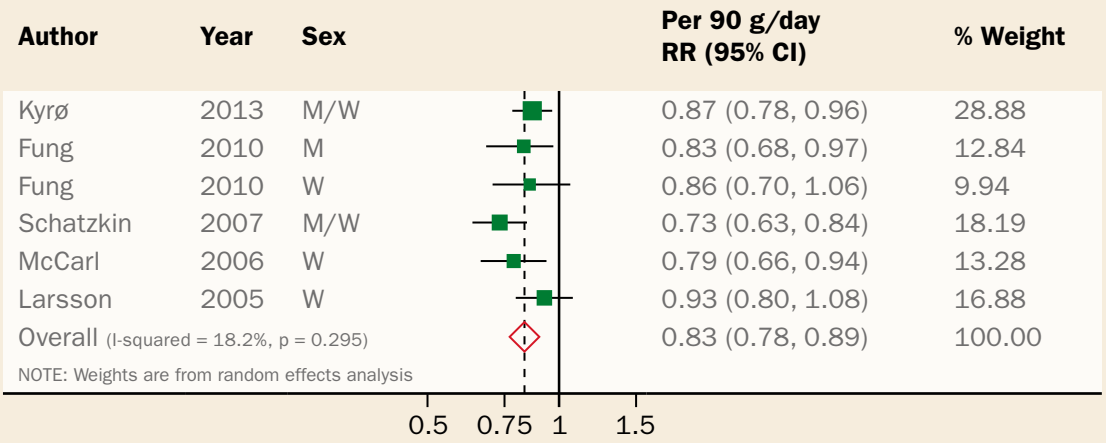
### 7.1 Wholegrains

*(Also see CUP Colorectal SLR 2016: Section 2.1.1.4)*

The CUP identified one new study, giving a total of six studies (five publications) [14-18] reviewing the evidence for wholegrains and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 10 and 11). Of the four studies included in an analysis comparing the highest and the lowest categories of intake, all reported inverse associations for colorectal cancer incidence, three of which were significant (see CUP Colorectal SLR 2016 Figure 2).

All six studies were included in the dose-response meta-analysis ($n$ = 8,320 cases), which showed a significant 17 per cent decreased risk per 90 grams of wholegrains per day (RR 0.83 (95% CI 0.78–0.89); see **Figure 1** (CUP Colorectal SLR 2016 Figure 3). Low heterogeneity ($I^2$ = 18%) was observed. The association remained significant across all sensitivity analyses.

**Figure 1: Dose-response meta-analysis of wholegrains intake and colorectal cancer per 90 grams per day**




When stratified by site, the inverse association was significant for colon cancer only (see **Table 1** and CUP Colorectal SLR 2016 Figures 8 and 12). Stratified analyses by region showed significant inverse associations in Europe and North America (see CUP Colorectal SLR Table 8).

**Table 1: Summary of CUP 2016 cancer site dose-response meta-analyses – wholegrains**

| Analysis | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|
| **Colon cancer** | Per 90 g/day | 0.82 (0.73–0.92) | 0% | 4 | 3,875 |
| **Rectal cancer** | Per 90 g/day | 0.82 (0.57–1.16) | 84% | 3 | 1,548 |

All studies adjusted for age, physical activity, BMI, alcohol consumption, smoking, red meat and hormone therapy in women (for more information, see CUP Colorectal SLR 2016 Tables 10 and 11).

All studies were included in the CUP analyses.

The CUP findings were consistent with the findings from the 2010 SLR, which also showed a significant inverse association (RR 0.83 (95% CI 0.79–0.89)). The CUP 2016 meta-analysis included more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

One published pooled analysis [19] and one published meta-analysis (reporting results from the 2010 CUP SLR) [20] of cohort studies on wholegrains and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. In the pooled analysis, no significant association was observed when comparing the highest consumers of wholegrains with the lowest consumers (see **Table 2**). The pooled analysis was not included in the CUP dose-response meta-analysis. Results from the CUP and the published pooled-analyses are presented in **Table 2**.

**Table 2: Summary of CUP 2016 meta-analysis and published pooled analysis wholegrains**

| Analysis | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|
| **CUP Colorectal SLR 2016** | Per 90 g/day | 0.83 (0.78–0.89) | 18% | 6 | 8,320 |
| **Pooling Project [19]** | Highest vs. lowest | 0.92 (0.84–1.00) | | 13 | 8,081 |

### Mechanisms

Wholegrains are a source of dietary fibre, which may reduce colorectal cancer risk through the intestinal microbiota's synthesis of short-chain fatty acids, reduced transit time or prevention of insulin resistance. Wholegrains are also a rich source of various bioactive compounds including vitamin E, selenium, copper, zinc, lignans, phytoestrogens and phenolic compounds [21]. Many of these compounds, which are largely found in the bran and germ of the grain, have plausible anti-carcinogenic properties. For instance, several phenolic acids have been shown in experimental studies to stimulate anti-oxidative activity [21,22]. Wholegrains may also protect against colorectal cancer by binding carcinogens and regulating glycaemic response.

### CUP Panel's conclusion:

The evidence for colorectal cancer was consistent, with a clear dose-response relationship showing a significant decreased risk with increased consumption of wholegrains, with low heterogeneity. One published pooled analysis reported no significant association. There is evidence of plausible mechanisms in humans. The CUP Panel concluded the following:

**Consumption of wholegrains probably protects against colorectal cancer.**

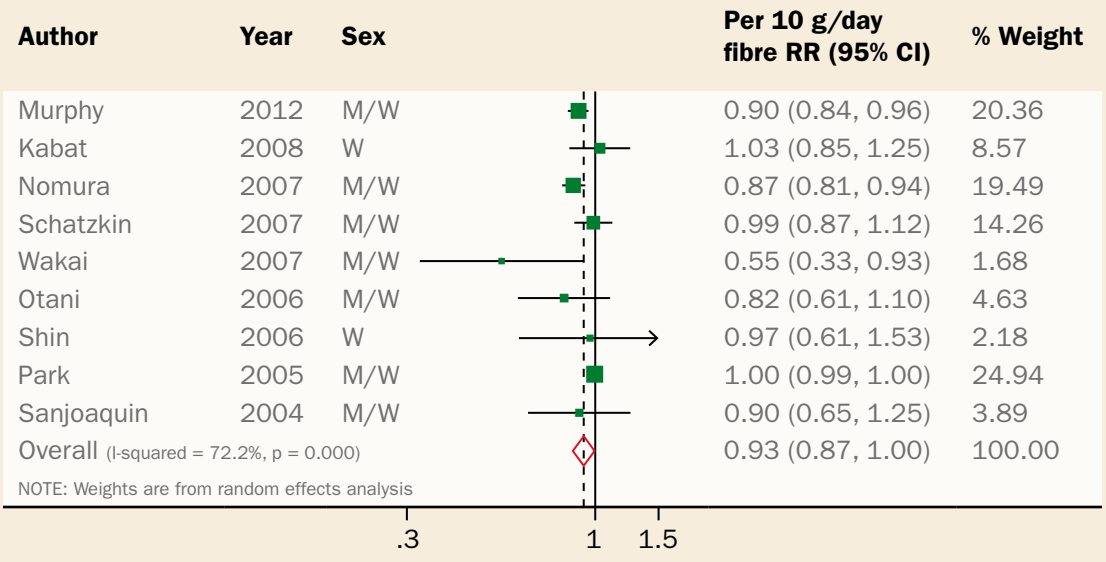
## 7.2 Foods containing dietary fibre

*(Also see CUP Colorectal SLR 2016: Section 5.1.2)*

The CUP identified one updated study (three new publications) [23-25], giving a total of 23 studies (27 publications) reviewing the evidence for foods containing dietary fibre and colorectal cancer (see CUP Colorectal SLR 2016 Tables 168 and 169, for a full list of references). Of 10 studies reporting on colorectal cancer incidence, six reported inverse associations, one of which was significant, and two reported non-significant positive associations when comparing the highest versus the lowest categories. Two studies reported inconsistent results for men and women. The Pooling Project [19], which contained 13 studies, reported a non-significant inverse association (see CUP Colorectal SLR 2016 Figure 294).

Twenty-one of the 23 studies (including the pooled analysis of 13 studies) were included in the dose-response meta-analysis (*n* = 16,562 cases), which showed no significant association per 10 grams of fibre per day (RR 0.93 (95% CI 0.87–1.00); see **Figure 2** (CUP Colorectal SLR 2016 Figure 295)). Overall, high heterogeneity was observed ($I^2$ = 72%); however, low heterogeneity was observed in analyses stratified by men, women, European and North American studies.

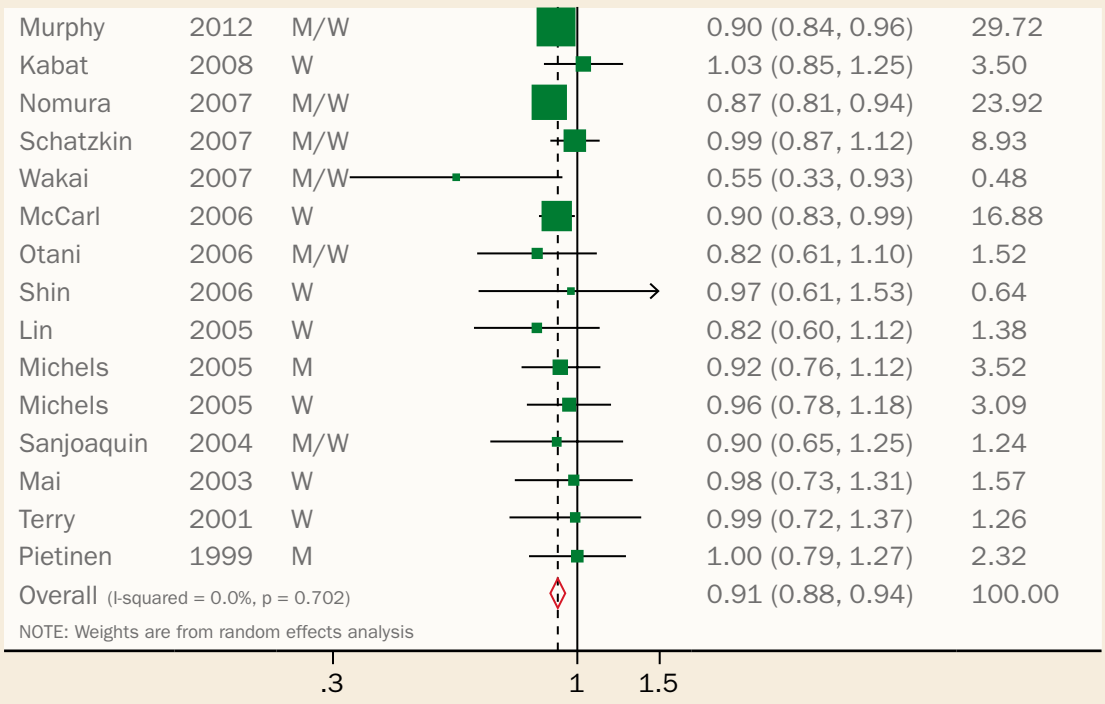
**Figure 2: Dose-response meta-analysis of foods containing dietary fibre intake and colorectal cancer per 10 grams per day**

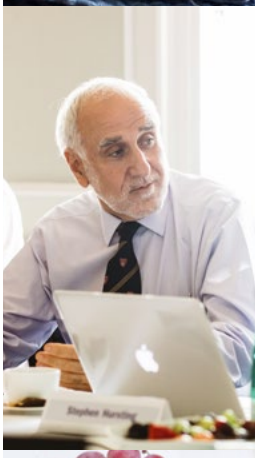



There was evidence of small study bias with Egger's test (p = 0.002; see CUP Colorectal SLR 2016 Figure 296). Visual inspection of the funnel plot showed asymmetry, with one study [25] reporting an association stronger than expected. The test for non-linearity was not significant, p = 0.06 (see CUP Colorectal SLR 2016 Figure 300 and Table 170).

In an analysis using the results of individual studies included in the Pooling Project, instead of using the overall Pooling Project result, fifteen studies (14,876 cases) were included and the overall result was similar to the result observed in the 2010 SLR (RR 0.91 (95% CI 0.88–0.94), $I^2$ = 0%, $p_{heterogeneity}$ = 0.70; see **Figure 3** and CUP Colorectal SLR 2016 Figure 301). This result was statistically significant with no heterogeneity.

**Figure 3: Dose-response meta-analysis of dietary fibre intake and colorectal cancer per 10 grams per day, including individual study results and not the overall Pooling Project result**



Significant inverse associations were observed for colorectal cancer risk in both men and women (see **Table 3** and CUP Colorectal SLR 2016 Figure 297). When stratified by geographical location, significant inverse associations were observed for colorectal cancer in North American and European populations (see CUP Colorectal SLR 2016 Figure 298). In studies that adjusted for folate intake, a result similar to the one reported for the overall CUP analysis for colorectal cancer incidence was observed (RR 0.92 (95% CI 0.85–1.00); see CUP Colorectal SLR 2016 Figure 299). When stratified by cancer site, no significant associations were observed for colon or rectal cancer risk (see **Table 3** and CUP Colorectal SLR 2016 Figures 304 and 313).

**Table 3: Summary of CUP 2016 cancer site dose-response meta-analyses – foods containing dietary fibre**

| Analysis | Sex | Increment/ Contrast | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 10 g/day | 0.89 (0.82–0.96) | 25% | 6 | - |
| | W | Per 10 g/day | 0.91 (0.87–0.96) | 0% | 11 | - |
| **Colon** | M/W | Per 10 g/day | 0.91 (0.84–1.00) | 69% | 21 | 12,601 |
| **Rectal** | M/W | Per 10 g/day | 0.93 (0.85–1.01) | 31% | 21 | 5,809 |

All studies adjusted for at least age, and most of the studies adjusted for most of the main colorectal cancer risk factors, including physical activity, BMI, alcohol consumption, smoking, red meat and hormone therapy in women (for more information, see CUP Colorectal SLR 2016 Tables 168 and 169).

One study [24] was not included in any of the CUP analyses because it reported interaction results only.

The results from the 2010 SLR also showed an inverse association for colorectal cancer, although statistical significance was reached (RR 0.90 (0.86–0.94), $I^2$ = 4%). The 2016 CUP meta-analysis included six more studies and over 3,000 more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

Two published pooled analyses [19, 25] and one meta-analysis [20] of cohort studies on fibre intake and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. One of the published pooled analyses [19] was included in the CUP dose-response meta-analysis. When the analyses were stratified by fibre type, no significant associations were observed. The other published pooled analysis reported significant associations for dietary fibre intake when comparing the highest- with the lowest-fibre consumers, assessed by food diaries [25]. The published meta-analysis [20] reported the results from the 2010 CUP SLR. Results from the 2016 CUP and the two published pooled-analyses are presented in **Table 4**.

**Table 4: Summary of CUP 2016 meta-analysis and published pooled analyses – dietary fibre**

| Analysis | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|
| **CUP Colorectal Cancer SLR 2016** | Per 10 g/day | 0.93 (0.87–1.00) | 72% | 21 | 16,562 |
| **Pooling Project [19]** | Cereal fibre, highest vs. lowest | 0.94 (0.86–1.03) | | 13 | |
| | Vegetable fibre, highest vs. lowest | 1.00 (0.93–1.08) | | | |
| | Fruit fibre, highest vs. lowest | 0.96 (0.89–1.04) | | | |
| **UK Dietary Cohort Consortium [25]** | Dietary fibre (intake density assessed by food diaries), highest vs. lowest | 0.66 (0.45–0.96) | | 7 | 579 |
| | Dietary fibre (intake density assessed by FFQ), highest vs. lowest | 0.88 (0.57–1.36) | | | |

## Mechanisms

Dietary fibre is fermented within the bowel, forming short-chain fatty acids, such as butyrate. Butyrate has been shown in experimental studies to have anti-proliferative effects [21, 27]. Other mechanisms by which greater dietary fibre intake may lower colorectal cancer risk include the reduction of intestinal transit time and increased faecal bulk, which would lessen the potential for faecal mutagens to interact with the colon mucosa, and a reduction of secondary bile acid production [21, 27]. High-fibre diets may also reduce insulin resistance, which is a risk factor for colorectal cancer [28]. Overall there is moderate mechanistic evidence linking dietary fibre intake with reduced risk of colorectal cancer.

### CUP Panel's conclusion:

The overall evidence was consistent showing a decreased risk of colorectal cancer with consumption of dietary fibre. The dose-response meta-analysis (including the summary estimate from the Pooling Project) showed no significant association with colorectal cancer risk; high heterogeneity was observed, which wasn't apparent in the stratified analyses, and there was evidence of small study bias. Analyses stratified by sex showed significant decreased risks. An analysis using the individual studies from the Pooling Project combined with the CUP showed a significant inverse association. There is evidence for plausible mechanisms operating in humans. The CUP Panel concluded the following:

**Consumption of foods containing dietary fibre probably protects against colorectal cancer.**

## 7.3 Fruits and non-starchy vegetables

*(Also see CUP Colorectal SLR 2016: Section 2.2)*

### 7.3.1 Fruits and non-starchy vegetables

The CUP identified three new studies (three publications) [29-31], giving a total of 13 studies (17 publications) reviewing the evidence for non-starchy vegetables and fruit and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 17 and 18).

Ten of the 17 studies were included in the dose-response meta-analysis (*n* = 10,999 cases), which showed a significant inverse association per 100 grams of non-starchy vegetables and fruit per day (RR 0.98 (95% CI 0.97–0.99); see CUP Colorectal SLR 2016 Figure 15). Low heterogeneity ($I^2$ = 14%) was observed. There was evidence of a non-linear relationship (p = 0.009) significant increased risks were observed for low intakes (below 300 grams per day) with significant decreased risk observed for intakes above 500 grams per day (see CUP Colorectal SLR 2016 Figure 19 and Table 19).

When stratified by sex, a significant inverse association was observed for men, no association was observed for women (see Table 5 and CUP Colorectal SLR 2016 Figure 16). No significant associations were observed in analyses stratified by geographical location (see CUP Colorectal SLR 2016 Figure 17). When stratified by cancer site, no associations were observed for colon or rectal cancer (see **Table 5** and CUP Colorectal SLR 2016 Figures 22 and 28).

**Table 5: Summary of CUP 2016 cancer site dose-response meta-analysis – fruit and non-starchy vegetables**

| Analysis | Sex | Increment/ Contrast | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 100 g/ day | 0.98 (0.96–0.99) | 0% | 4 | - |
| | W | Per 100 g/ day | 0.99 (0.97–1.01) | 42% | 7 | - |
| **Colon cancer** | M/W | Per 100 g/ day | 0.99 (0.97–1.00) | 0% | 12 | >6,045 |
| **Rectal cancer** | M/W | Per 100 g/ day | 0.99 (0.97–1.01) | 0% | 10 | >2,746 |

All studies adjusted for at least age, and most of the studies adjusted for most of the established colorectal cancer risk factors, including: age, physical activity, BMI, and alcohol consumption, smoking, red meat and hormone therapy in women (for more information, see CUP Colorectal SLR 2016 Tables 17 and 18).

All studies were included in the CUP analyses.

The CUP findings reached statistical significance, which was not seen in the 2010 SLR (RR 0.99 (95% CI 0.97–1.00)). The CUP meta-analysis includes three more studies and 1,000 more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

Results from one published pooled analysis [32] were identified reviewing the evidence for colorectal cancer. No significant association was observed when comparing the highest and lowest categories of intake. One published meta-analysis [33], results from the 2010 CUP SLR, was also identified.

## 7.3.2 Non-starchy vegetables

*(Also see CUP Colorectal SLR 2016: Sections 2.2.1)*

The CUP identified seven new or updated studies (six publications) [18, 29, 30, 34-36], giving a total of 23 studies (32 publications) reviewing the evidence for non-starchy vegetables and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 25 and 26). Of nine studies reporting on colorectal cancer incidence, eight reported inverse associations, one of which was significant, and one which was significant for men but not for women. One study reported a non-significant positive association when comparing the highest versus the lowest levels of intake (see CUP Colorectal SLR 2016 Figure 33).

Eleven of the 23 studies were included in the dose-response meta-analysis (*n* = 14,136 cases), which showed a statistically significant two per cent decreased risk per 100 grams of non-starchy vegetables per day (RR 0.98 (95% CI 0.96–0.99); see CUP Colorectal SLR 2016 Figure 34). No heterogeneity was observed ($I^2$ = 0%). When the reference category was 200 grams per day, there was evidence of a non-linear dose-response relationship ($p < 0.0001$) with significant increased risks observed for low intakes (below 100 grams per day) and significant decreased risks observed for intakes above 300 grams per day (see **Figure 4** and **Table 6**; CUP Colorectal SLR 2016 Figure 38 and Table 27).

**Figure 4: Non-linear dose-response association of non-starchy vegetable intake and colorectal cancer**

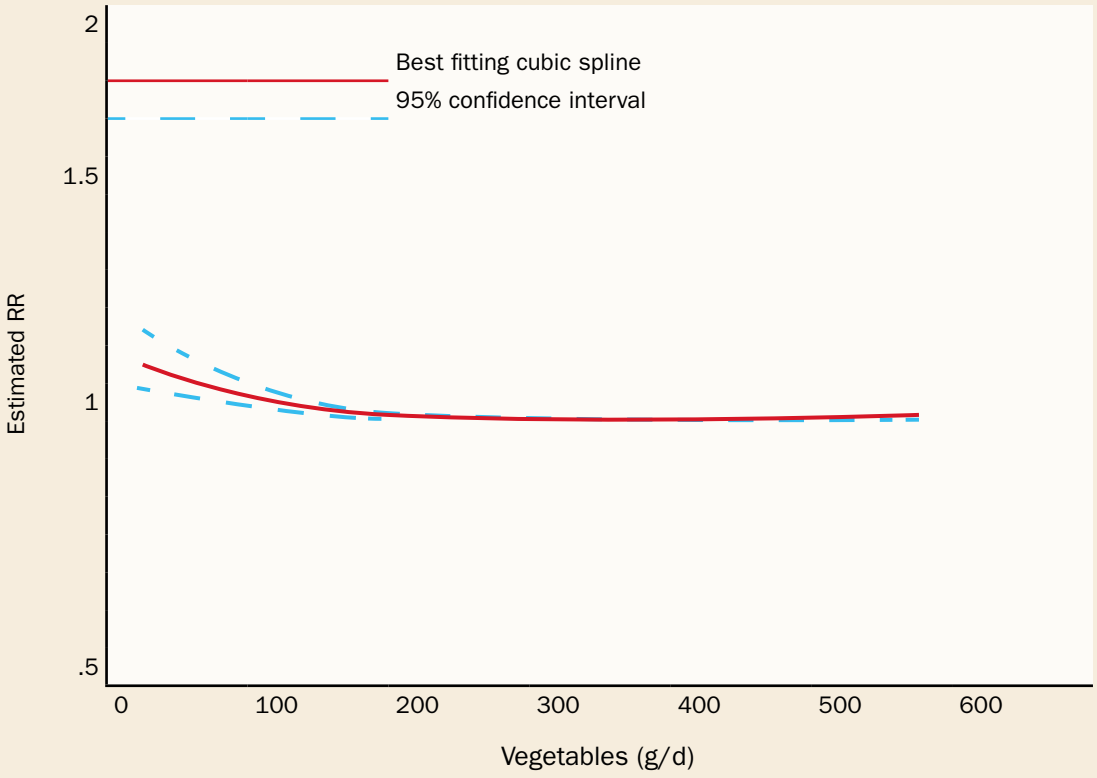


**Table 6: Non-linear dose-response estimates of non-starchy vegetable intake and colorectal cancer**

| g/day | RR (95% CI) |
|---|---|
| 22 | 1.16 (1.11–1.21) |
| 100 | 1.08 (1.06–1.10) |
| 200 | 1.00 |
| 300 | 0.96 (0.95–0.97) |
| 400 | 0.95 (0.95–0.96) |
| 500 | 0.96 (0.96–0.96) |

For colorectal cancer, analyses stratified by sex showed a significant inverse association for colorectal cancer in men but not women. Analyses stratified by geographical location showed significant inverse associations in North America (seven studies) and Asia (one study only). When stratified by cancer site, a significant inverse association was observed for colon cancer only (see **Table 7** and CUP Colorectal SLR 2016 Figures 35, 36, 41 and 47).

**Table 7: Summary of CUP 2016 cancer site dose-response meta-analyses – non-starchy vegetables**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 100 g/ day | 0.96 (0.93–0.99) | 33% | 5 | - |
| | W | Per 100 g/ day | 0.99 (0.96–1.01) | 0% | 7 | - |
| **Colon cancer** | M/W | Per 100 g/ day | 0.97 (0.95–0.99) | 0% | 12 | > 6,308 |
| **Rectal cancer** | M/W | Per 100 g/ day | 0.99 (0.96–1.02) | 0% | 8 | > 2,435 |

All studies adjusted for age, and most of the studies also adjusted for most of the established colorectal cancer risk factors, including: physical activity, BMI, alcohol consumption, smoking, red meat and hormone therapy in women (for full details, see CUP Colorectal SLR 2016 Tables 25 and 26).

Six studies were not included in any of the CUP analyses, four due to not reporting quantities [35, 37-39], one due to reporting less than three categories of intake [39] and one due to reporting insufficient data [29].

The CUP findings are consistent with those reported in the 2010 SLR, which reported the same significant inverse association (RR 0.98 (0.96–0.99), $I^2$ = 0%). The 2016 CUP meta-analysis included three more studies and nearly 2,000 more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

No pooled analyses on non-starchy vegetable consumption and colorectal cancer risk were identified. Two published meta-analyses of cohort studies on non-starchy vegetables and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. One [41] reported no significant association when comparing the highest and lowest categories of intake (RR 0.95 (95% CI 0.88–1.04), eight studies, $I^2$ = 19%, *n* = 7,916). The other published meta-analysis reported results from the 2010 CUP SLR [33].

### Mechanisms

Consumption of vegetables provides a large number of potential anti-tumorigenic agents such as dietary fibre, carotenoids, vitamins C and E, selenium, folic acid, dithiolthiones, glucosinolates and indoles, isothiocyanates, flavonoids, phenols, protease inhibitors, plant sterols, allium compounds, and limonene [42]. It is possible that a combination of these nutrients is responsible for the lower colorectal cancer risks associated with vegetable consumption. Mechanistic evidence supporting the inverse relationship between vegetables and colorectal cancer is moderate in strength.

### CUP Panel's conclusion:

Overall the evidence was limited but reasonably consistent. The dose-response meta-analysis showed a significant decreased risk of colorectal cancer. There was evidence of a non-linear dose-response relationship between colorectal cancer and non-starchy vegetable intake showing significant increased risks at low levels of intake (below 100 grams per day). There is evidence of plausible mechanisms in humans. The CUP Panel concluded the following:

**The evidence suggesting that low consumption of non-starchy vegetables increases the risk of colorectal cancer is limited.**

### 7.3.3 Fruits

*(Also see CUP Colorectal SLR 2016: Section 2.2.2)*

The CUP identified five new or updated studies (five publications) [18, 30, 34-36], giving a total of 21 studies (24 publications) reviewing the evidence for fruits and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 36 and 37). Of 11 studies reporting on colorectal cancer incidence, seven reported inverse associations, three of which were significant, three reported non-significant inverse associations and one reported a significant inverse association for men and a non-significant inverse association for women. Four studies reported non-significant positive associations when comparing the highest versus the lowest levels of intake (see CUP Colorectal SLR 2016 Figure 53).

Thirteen of the 21 studies were included in the dose-response meta-analysis (*n* = 16,355 cases), which showed no significant association per 100 grams of fruit per day (RR 0.96 (95% CI 0.93–1.00); see CUP Colorectal SLR 2016 Figure 54). High heterogeneity ($I^2$ = 68%) was observed that appeared to be explained by one study [38] reporting a much lower RR compared with the other studies. Although the test for small study bias was not significant (p = 0.07), visual inspection of the funnel plot suggested asymmetry, which appeared to be driven by the same study [38], and when excluded, the Egger's test was attenuated (p = 0.14) (see CUP Colorectal SLR 2016 Figure 57).

In the influence analysis, when the EPIC study [34] (with the largest weighting) was removed the summary RR reached significance (RR 0.95 (95% CI 0.92–0.99)). There was evidence of a non-linear relationship (p < 0.0001). When the reference category was 200 grams per day significant increased risks were observed for low intakes (below 100 grams per day) and significant decreased risks observed for intakes above 300 grams per day (see **Figure 5** and **Table 8**; CUP Colorectal SLR 2016 Figures 58 and 59).

**Figure 5: Non-linear dose-response association of fruit intake and colorectal cancer**

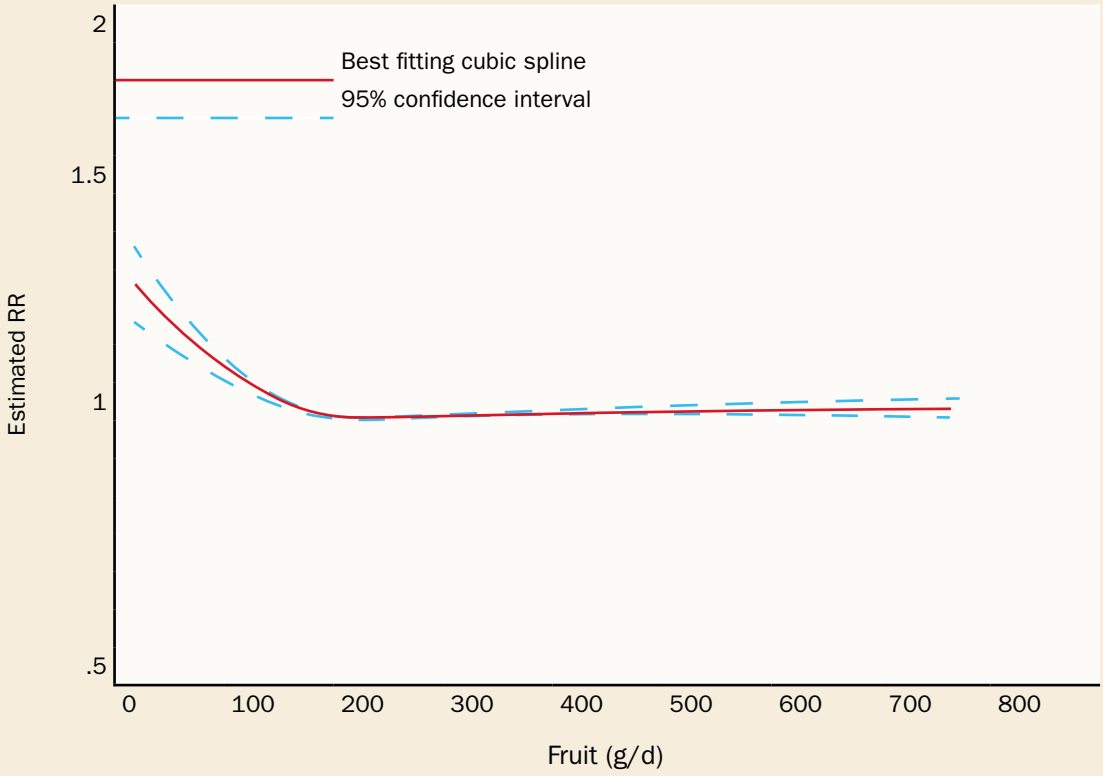



**Table 8: Non-linear dose-response estimates of fruit intake and colorectal cancer**

| g/day | RR (95% CI) |
|---|---|
| 2 | 1.21 (1.15–1.26) |
| 100 | 1.07 (1.05–1.09) |
| 200 | 1.00 |
| 300 | 0.99 (0.98–0.99) |
| 400 | 0.99 (0.98–0.99) |
| 500 | 0.99 (0.98–1.00) |

When stratified by sex, inverse associations were observed for colorectal cancer in both men and women and were significant for men only. Analyses stratified by geographical location showed inverse associations and were significant in Asia only (see CUP Colorectal SLR 2016 Figures 55 and 56). When stratified by cancer site, inverse associations were observed for colon and rectal cancer (see **Table 9** and CUP Colorectal SLR 2016 Figures 62 and 68).

**Table 9: Summary of CUP 2016 cancer site dose-response meta-analyses – fruit**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 100 g/ day | 0.96 (0.93–0.99) | 39% | 6 | - |
| | W | Per 100 g/ day | 0.96 (0.91–1.01) | 61% | 6 | - |
| **Colon cancer** | M/W | Per 100 g/ day | 0.98 (0.96–1.01) | 39% | 12 | >6,317 |
| **Rectal cancer** | M/W | Per 100 g/ day | 0.98 (0.93–1.03) | 55% | 9 | >2,444 |

Most of the studies adjusted for physical activity, BMI, alcohol consumption, smoking, red meat and hormone therapy in women (for more information, see CUP Colorectal SLR 2016 Tables 36 and 37).

Eight studies were not included in any of the CUP analyses. Four were excluded due to reporting outcome as mortality [43-46], three were excluded for not reporting quantities [35, 37, 39] and one was excluded for reporting fewer than three categories [40].

The CUP findings are similar to those from the 2010 SLR, which also showed an inverse association per 100 grams of fruit consumed per day (RR 0.97 (95% CI 0.94–0.99)) for eight studies, although the 2010 result reached statistical significance. The 2016 CUP update included five more studies and almost 4,000 more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

No pooled analyses were identified. Two published meta-analyses of cohort studies on fruits and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. One [41] reported a non-significant positive association when comparing the highest and lowest categories of intake (RR 1.01 (95% CI 0.86–1.18), eight studies, $I^2$ = n/a, *n* = 7,916). The other published meta-analysis reported results from the 2010 CUP SLR [33].

### Mechanisms

In addition to their fibre content, fruits are a rich source of vitamins C and E as well as numerous bioactive compounds which may have anti-tumorigenic potential. These include folic acid, flavonoids, polyphenols and limonene. Many of these compounds have potent anti-oxidative properties which could inhibit cellular damage and exposure to reactive oxygen species [47].

### Proposed CUP Panel's conclusion

The evidence for consumption of fruit was limited but generally consistent. The dose-response meta-analysis showed no significant association with colorectal cancer. There was evidence of a non-linear dose-response of colorectal cancer and fruit intake showing significant increased risks at low levels of intake (below 100 grams per day). There is evidence of plausible mechanisms in humans. The CUP Panel concluded the following:

**The evidence suggesting that low consumption of fruit increases the risk of colorectal cancer is limited.**

## 7.4 Foods containing vitamin C

*(Also see CUP Colorectal SLR 2016: Section 5.5.9)*

### Colon cancer

Evidence presented in this section is for colon cancer as no analyses for colorectal or rectal cancer were possible due to a lack of evidence.

The CUP identified three new or updated cohort studies (three publications) [47-49] and one pooled analysis of 13 studies [51] giving a total of 18 studies (13 publications) assessing foods containing vitamin C and colon cancer (see CUP Colorectal SLR 2016 Tables 278 and 279, for a full list of references). Of five studies reporting on incidence, three reported inverse associations, two of which were significant when comparing the highest versus the lowest categories. One study reported a non-significant positive association and one reported inconsistent results for men and women. A pooled analysis of 13 studies reported a non-significant positive association (see CUP Colorectal SLR Figure 487). There were enough studies to conduct analysis on colon cancer incidence but not colorectal or rectal cancer incidence.

Six studies were included in the dose-response meta-analysis ($n$ = 4,391 cases), which showed a six per cent decreased risk per 40 milligrams per day (RR 0.94 (95% CI 0.89–0.99); see CUP Colorectal SLR 2016 Figure 488). Moderate heterogeneity was observed ($I^2$ = 50%, $p_{heterogeneity}$ = 0.08) for all studies combined. Two studies [52, 53] were not included in any of the CUP analyses due to reporting insufficient data.

Most of the studies adjusted for physical activity, BMI, alcohol consumption, smoking, red meat and hormone therapy in women (for more information, see CUP Colorectal SLR 2016 Tables 278 and 279).

All studies were included in the CUP analyses.

No updated analysis was conducted in the 2010 SLR. The CUP findings are stronger than those observed in the 2005 SLR which showed no significant association (RR 0.99 (95% CI 0.97–1.02) per 10 mg/day, $I^2$ = 68%).

### Published pooled analyses and meta-analyses

One published pooled analysis [51] was identified in the CUP Colorectal SLR 2016 and included 13 studies not included in the CUP dose-response meta-analysis. No significant association was observed in the multivariate adjusted model comparing the highest with the lowest consumers of dietary vitamin C. In the same pooled analysis, the result for total vitamin C also showed no significant association (RR 0.86 (95% CI 0.74–1.00), > 600 vs. ≤ 100 mg/day). The pooled analysis was not included in the CUP dose-response meta-analysis. Results from the CUP Colorectal SLR 2016 and the published pooled analysis are presented in **Table 10**.

**Table 10: Summary of CUP 2016 highest vs. lowest meta-analysis and published pooled analysis – foods containing vitamin C**

| Study | Increment/ Contrast | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|
| **CUP colon cancer** | Per 40 mg/day | 0.94 (0.89–0.99) | 50% | 6 | 4,391 |
| **Pooling Project of Prospective Studies of Diet and Cancer [51] - colon cancer** | Highest vs. lowest | 1.06 (0.95–1.18) | - | 14 | 5,454 |

### Mechanisms

There is biological plausibility to support a protective effect of vitamin C on colorectal cancer development. Vitamin C is a potent antioxidant, reducing levels of reactive oxygen species, inhibiting lipid peroxidation and reducing nitrates [47]. Vitamin C has also been shown to inhibit formation of carcinogens in experimental models and to protect DNA from mutagenic insults [54].

### CUP Panel's conclusion

The evidence was limited but generally consistent and the dose response meta-analysis showed a significant decreased risk per 40 milligrams per day for colon cancer. There was evidence of moderate heterogeneity. One published pooled analysis reported no significant association. No analysis for colorectal or rectal cancer was possible. There is evidence of plausible mechanisms in humans. The CUP Panel concluded the following:

**The evidence suggesting that consumption of foods containing vitamin C decreases the risk of colon cancer is limited.**

## 7.5 Red and processed meat

This section includes evidence for red and processed combined, red meat and processed meat.

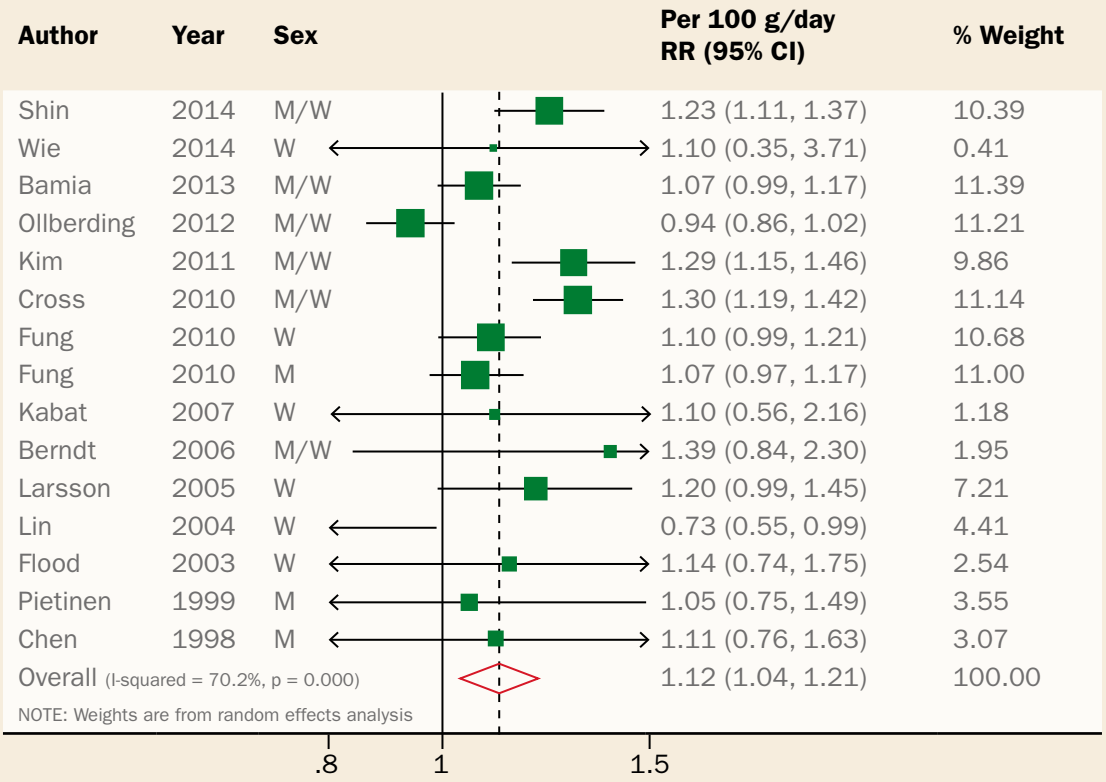
### 7.5.1 Red and processed meat

*(Also see CUP Colorectal SLR 2016: Section 2.5.1)*

The CUP identified nine new or updated studies (eight publications) [18, 31, 34, 55-59], giving a total of 19 studies (20 publications) assessing red and processed meat and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 55 and 56).

Fifteen studies were included in the dose-response meta-analysis (*n* = 31,551 cases which showed a 12 per cent increased risk per 100 grams per day (RR 1.12 (95% CI 1.04–1.21); see **Figure 6** and CUP Colorectal SLR 2016 Figure 83). High heterogeneity was observed ($I^2$ = 70%).

**Figure 6: Dose-response meta-analysis of red and processed meat and colorectal cancer per 100 grams per day**



When stratified by sex, positive associations were observed for men and women, significant for men only (see CUP Colorectal SLR 2016 Figure 85). Positive associations were observed in analyses stratified by geographical location, significant in Asia and Europe (see CUP Colorectal SLR 2016 Figure 86). When stratified by cancer site, positive associations were observed for colon and rectal cancer, significant for colon only (see **Table 11** and CUP Colorectal SLR 2016 Figures 90 and 97).

**Table 11: Summary of CUP 2016 cancer site dose-response meta-analysis – red and processed meat**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 100 g/ day | 1.10 (1.02–1.18) | 0% | 4 | - |
| | W | Per 100 g/ day | 1.13 (1.00–1.29) | 47% | 8 | - |
| **Colon cancer** | M/W | Per 100 g/ day | 1.19 (1.10–1.30) | 63% | 10 | 10,010 |
| **Rectal cancer** | M/W | Per 100 g/ day | 1.17 (0.99–1.39) | 48% | 6 | 3,455 |

Most studies included in the meta-analyses adjusted results by smoking, alcohol consumption, BMI and physical activity in addition to age and sex (for more information, see CUP Colorectal SLR 2016 Tables 55 and 56).

The CUP findings were similar to those reported in the 2010 SLR (RR 1.16 (95% CI 1.04–1.30)) – although the effect size was smaller in the updated analysis. The CUP meta-analysis includes six more studies and almost 20,000 more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

Results from one published pooled analysis [60] were identified reviewing the evidence for colorectal cancer. No significant association was observed in the dose-response analysis (RR 0.97 (95% CI 0.84–1.12). Two published meta-analyses were also identified. One [61] reported a significant positive association when comparing the highest with the lowest levels of intakes (RR 1.11 (95% CI 1.03–1.19)), and the other reported the results from the 2010 CUP SLR [62].

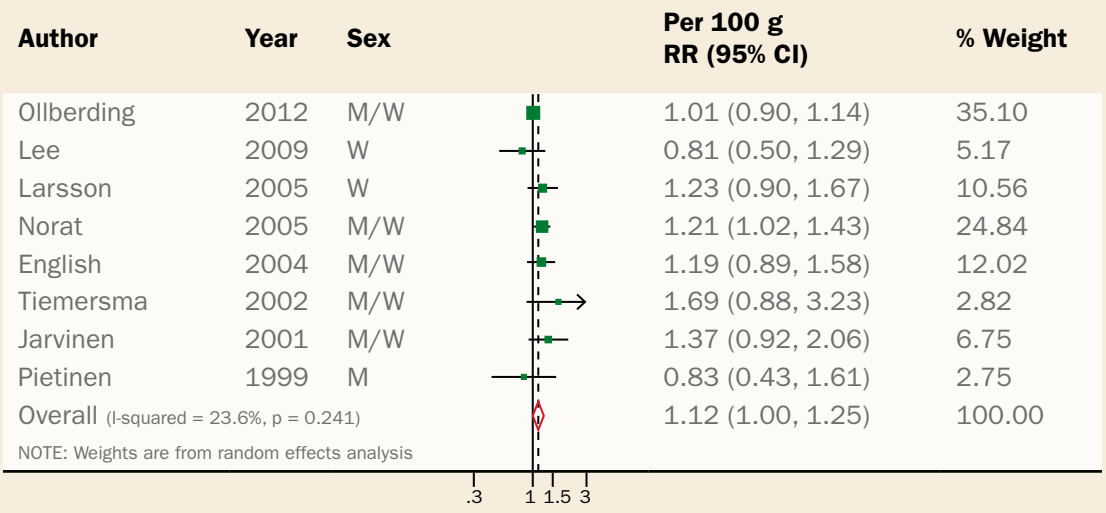
## 7.5.2 Red Meat

*(Also see CUP Colorectal SLR 2016: Section 2.5.1.3)*

The CUP identified four new studies (eight publications) [24, 36, 56, 57, 59, 63-65], giving a total of 14 studies (20 publications) assessing red meat and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016, Tables 79 and 80). Of 13 studies reporting on colorectal cancer incidence, 12 reported non-significant positive associations and one reported a non-significant inverse association when comparing the highest versus the lowest levels of intake (see CUP Colorectal SLR Figure 124).

Eight studies were included in the dose-response meta-analysis (*n* = 6,662 cases), which showed no significant association (RR 1.12 (95% CI 1.00–1.25)) per 100 grams per day; see **Figure 7** and CUP Colorectal SLR 2016 Figure 125). Low heterogeneity was observed ($I^2$ = 24%). In sensitivity analyses, summary RRs ranged from 1.09 (95% CI 0.96–1.25) when EPIC [66] (25 per cent of the weight) was omitted to 1.19 (95% CI 1.06–1.34) when MEC [57] (35 per cent of the weight) was omitted.

**Figure 7: Dose-response meta-analysis of red meat and colorectal cancer per 100 grams per day**




When stratified by sex, positive but not significant associations were also observed for colorectal cancer (see **Table 12** and CUP Colorectal SLR 2016 Figure 128). Analyses stratified by geographical location showed positive associations and were significant in Europe (see CUP Colorectal SLR 2016 Figure 128). When stratified by cancer site, a significant positive association was observed for colon only (see Table 12 and CUP Colorectal SLR 2016 Figures 133 and 140).

**Table 12: Summary of CUP 2016 cancer site dose-response meta-analyses – red meat**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 100 g/ day | 1.28 (0.49–3.34) | 64% | 2 | - |
| | W | Per 100 g/ day | 1.02 (0.78–1.33) | 11% | 4 | - |
| **Colon cancer** | M/W | Per 100 g/ day | 1.22 (1.06–1.39) | 12% | 11 | 4,081 |
| **Rectal cancer** | M/W | Per 100 g/ day | 1.13 (0.96–1.34) | 0% | 8 | 1,772 |

Three studies [43, 67, 68] were not included in any of the CUP analyses as all three reported mortality as the outcome.

All studies were adjusted for multiple different confounders (for more information, see CUP Colorectal SLR 2016 Tables 79 and 80).

The 2016 CUP findings are less strong than those from the 2010 SLR, which showed a 17 per cent increased risk per 100 grams of red meat per day (RR 1.17 (95% CI 1.05–1.31)). The CUP meta-analysis included the same number of studies as the 2010 SLR but over 2,000 more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

Results from three published pooled analyses [60, 69, 70] and two published meta-analyses [61, 62] reporting on red meat intake and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. All three published pooled analyses reported no significant associations and were not included in the CUP dose-response meta-analysis. The UK Dietary Cohort Consortium of cohort studies reported no significant associations although the average intake of red and processed meat was low, and there were a high number of vegetarians in the cases. Two meta-analyses were published after the 2010 SLR. One [61] combined nine studies with different outcomes (colorectal, colon and rectal cancer) and reported no significant association (RR 1.05 (95% CI 0.98–1.12)) when comparing the highest with the lowest categories of red meat consumption. The other meta-analysis reported the results of the 2010 CUP SLR [62]. Results from the CUP meta-analysis and published pooled analyses are presented in **Table 13**.

**Table 13: Summary of CUP 2016 meta-analysis and published pooled analyses – red meat**

| Analysis | Outcome | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **CUP Colorectal Cancer SLR 2016** | Colorectal cancer | Per 100 g/ day | 1.12 (1.00–1.25) | 24% | 8 | 6,662 |
| **Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and Colon Cancer Family Registry (CCFR) [69]** | Colorectal cancer | Per 1 serving/day | 1.05 (0.94–1.18) | - | 7 nested case-control studies | 3,488 |
| **GECCO and CCFR [70]** | Colorectal cancer | Highest vs. lowest | 1.06 (0.90–1.24)* | - | 5 nested case-control studies | 2,564 |
| **UK Dietary Cohort Consortium [60]**** | Colorectal cancer | Per 50 g/ day | 1.01 (0.84–1.22) | - | 7 | 579 |

* Relationship was not modified by NAT2 enzyme activity (based on polymorphism at rs1495741).

** The average intake of red meat was low, 38.2 g/day in men and 28.7 g/day in women controls and there were a high number of vegetarians in the cases.

## Mechanisms

Cooking meats at high temperatures results in the formation of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs), both of which have been linked to colorectal cancer development in experimental studies [71]. In addition, haem iron, which is present at high levels in red meat, has been shown to promote colorectal tumorigenesis by stimulating the endogenous formation of carcinogenic N-nitroso compounds [72]. There is moderate mechanistic evidence to support a relationship between high consumption of red meat and colorectal cancer.

## CUP Panel's conclusion

The evidence for red meat consistently showed a positive association in the dose-response meta-analyses in colorectal, colon and rectal cancer. The result was positive, but not significant, for colorectal and rectal cancers and significant for colon cancer, with low heterogeneity. Three published pooled analyses reported no significant associations but were consistent in the direction of effect. There is evidence of plausible mechanisms operating in humans. The CUP Panel concluded the following:

**Consumption of red meat is probably a cause of colorectal cancer.**

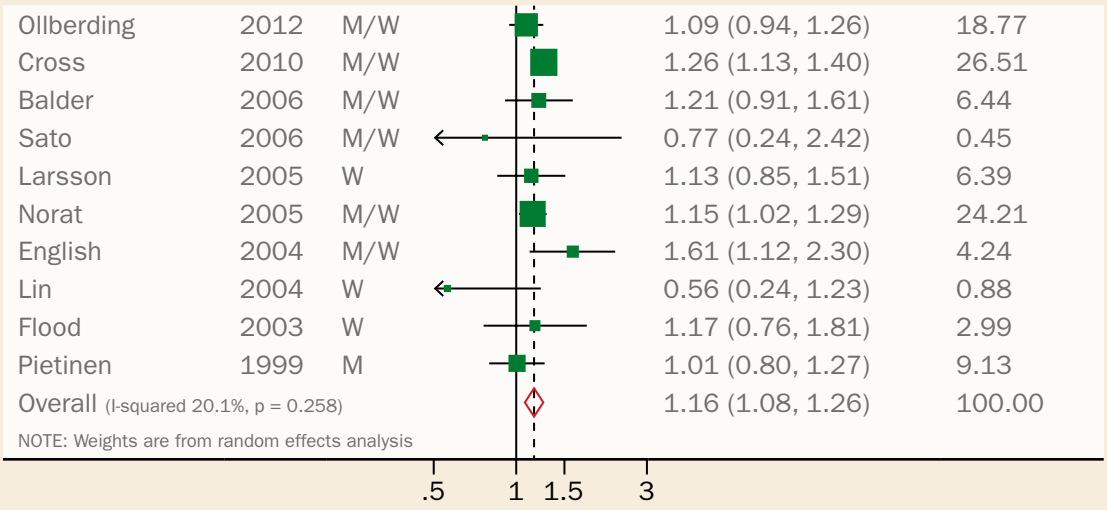
### 7.5.3 Processed meat

*(Also see CUP Colorectal SLR 2016: Section 2.5.1.2)*

The CUP identified four new or updated studies (four publications) [24, 56, 57, 59], giving a total of 13 studies (32 publications) reviewing the evidence for processed meat and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 67 and 68). Of the 12 studies reporting on colorectal cancer incidence, nine reported positive associations, three of which were significant, and three reported non-significant inverse associations when comparing the highest versus lowest levels of intake (see CUP Colorectal SLR 2016 Figure 103).

Ten of the 13 studies were included in the dose-response meta-analysis (*n* = 10,738 cases), which showed a 16 per cent increased risk per 50 grams of processed meat per day (RR 1.16 (95% CI 1.08–1.26); see **Figure 8** and CUP Colorectal SLR 2016 Figure 104). There was evidence of low heterogeneity ($I^2$ = 20%, $p_{heterogeneity}$ = 0.258).

**Figure 8: Dose-response meta-analysis of processed meat and colorectal cancer per 50 grams per day**




When stratified by sex, positive but not significant associations were also observed for colorectal cancer (see **Table 14** and CUP Colorectal SLR 2016 Figure 106). Analyses stratified by geographical location showed positive associations, which were significant in Europe only (see CUP Colorectal SLR 2016 Figure 107). When stratified by cancer site, positive associations were observed for colon and rectal cancer, significant for colon cancer risk only (see **Table 14** and CUP Colorectal SLR 2016 Figures 111 and 118).

**Table 14: Summary of CUP 2016 cancer site dose-response meta-analyses – processed meat**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 50 g/day | 1.11 (0.86–1.43) | 34% | 2 | - |
| | W | Per 50 g/day | 1.18 (0.99–1.41) | 19% | 5 | - |
| **Colon cancer** | M/W | Per 50 g/day | 1.23 (1.11–1.35) | 26% | 12 | 8,599 |
| **Rectal cancer** | M/W | Per 50 g/day | 1.08 (1.00–1.18) | 0% | 10 | 3,029 |

Processed meat was generally described as processed meat, preserved meat or cured meat, but individual items included in the meat group could vary between the studies. Most studies included in the meta-analyses adjusted results by smoking, alcohol consumption, BMI, physical activity, age and sex (for more information, see CUP Colorectal SLR 2016 Tables 67 and 68).

Two studies [43, 67] were not included in any of the CUP analyses as both studies reported mortality as the outcome.

The CUP findings are similar to the result from the 2010 SLR (RR 1.18 (95% CI 1.10–1.28)). The 2016 CUP meta-analysis included one more study than the 2010 SLR.

### Published pooled analyses and meta-analyses

Two published pooled analyses [60, 69] (not included in the CUP dose-response meta-analysis) and two published meta-analyses [62, 73] reported on processed meat intake and colorectal cancer risk. One of the pooled analyses reported a significant positive association and one reported no significant association. One meta-analysis [73] reported significant positive associations for colorectal cancer (RR 1.10 (95% CI 1.05–1.15)), and the other reported the result from the CUP 2010 SLR [62]. Results from the CUP and the published pooled analyses are presented in **Table 15**.

**Table 15: Summary of CUP 2016 and published pooled analyses – processed meat**

| Analysis | Comparison | RR (95% CI) | $I^2$/P-trend | No. Studies | No. Cases |
|---|---|---|---|---|---|
| **CUP Colorectal Cancer SLR 2016** | Per 50 g/day | 1.16 (1.08–1.26) | 20% | 10 | 10,738 |
| **Genetics and Epidemiology of Colorectal Cancer Consortium (GECCO) and Colon Cancer Family Registry (CCFR) [69]** | Per 1 serving/ day | 1.48 (1.30–1.70) | - | 7 | 3,488 |
| **UK Dietary Cohort Consortium [60]** | Per 50g/day | 0.88 (0.68–1.15) | 0.36 | 7 | 579 |

## Mechanisms

Overall it is likely that a combination of mechanisms contribute to higher risk of colorectal cancer among individuals consuming high quantities of processed meat. Similar to red meat, processed meat is rich in fat, protein and haem iron, which can promote tumorigenesis through the mechanisms described under red meat [71]. Processed meats, such as sausages, are often cooked at high temperatures, which can lead to increased exposure to HCAs and PAHs. Processed meat is invariably higher in fat content than red meat which may stimulate tumorigenesis through synthesis of secondary bile acids; however, human data supporting this hypothesis are weak. Processed meat is also a source of exogenously derived N-nitroso compounds which may have carcinogenic potential [74].

## CUP Panel's conclusion:

There is generally consistent evidence showing an increased risk of colorectal cancer with increased consumption of processed meat. The dose-response meta-analysis showed a significant increased risk of colorectal cancer per 50 grams per day. Two published pooled analyses reported positive associations, one of which was significant. There is robust evidence for mechanisms operating in humans. The CUP Panel concluded the following:

**Consumption of processed meat is a convincing cause of colorectal cancer**

## 7.6 Foods containing haem iron

*(Also see CUP Colorectal SLR 2016: Section 5.6.2)*

The CUP identified six new or updated studies (five publications) [24, 59, 75-77], giving a total of eight studies (seven publications) reviewing the evidence on haem iron and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 289 and 290). Of six studies reporting on colorectal cancer incidence, five reported non-significant positive associations (a combined estimate was reported for two studies) and one reported inconsistent results by sex when comparing the highest versus lowest levels (see CUP Colorectal SLR 2016 Figure 492).

Six of the eight studies were included in the dose-response meta-analysis (*n* = 6,070 cases), which showed no significant association (RR 1.04 (95% CI 0.98–1.10)), (see CUP Colorectal SLR 2016 Figure 493). No heterogeneity was observed ($I^2$ = 0%, $p_{heterogeneity}$ = 0.81). There was evidence of a non-linear association (p = 0.001) with a significant increase in risk for higher levels of haem iron (see **Figure 9** and **Table 16**; CUP Colorectal SLR Figure 497 and Table 291). Significant increased risks were observed beyond 0.6 milligrams of haem iron per day; 3 ounces of cooked sirloin steak contains 2.9 milligrams of haem iron.

**Figure 9: Non-linear dose-response association of foods containing haem iron and colorectal cancer**

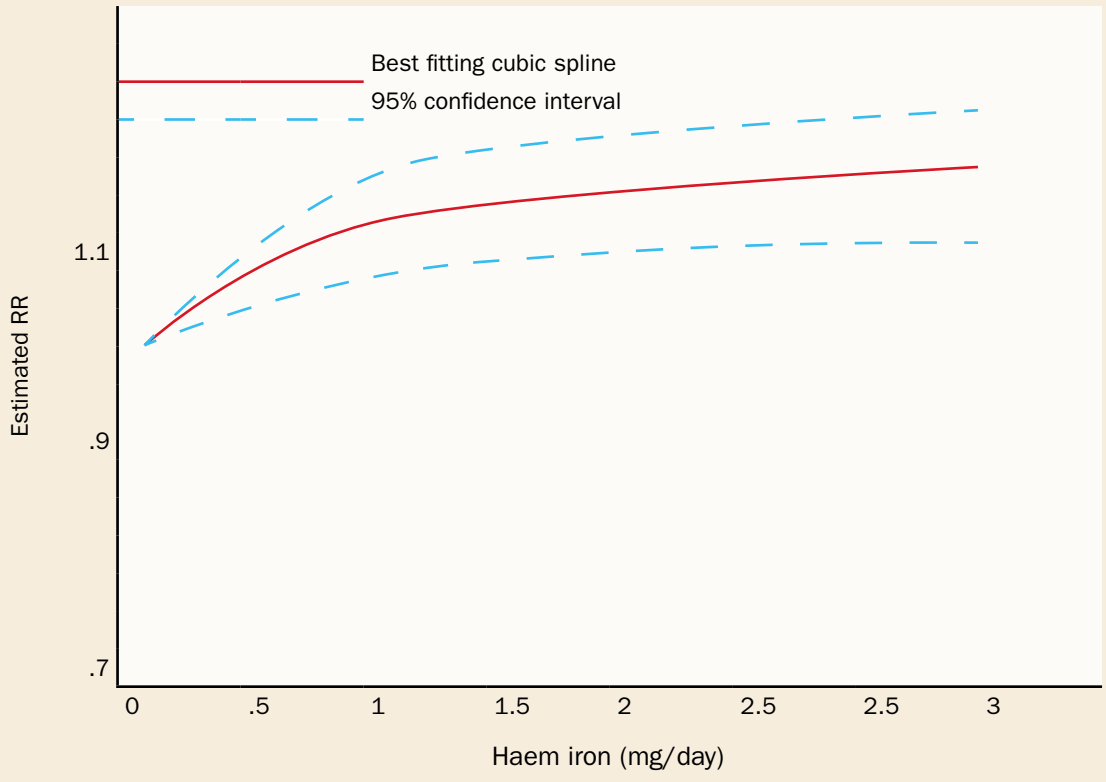
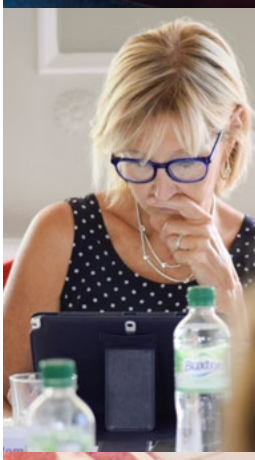


**Table 16: Non-linear dose-response estimates of foods containing haem iron and colorectal cancer**

| Haem iron (mg/day) | RR (95% CI) |
|---|---|
| 0 | 1.00 |
| 0.6 | 1.09 (1.05–1.13) |
| 1.01 | 1.15 (1.09–1.21) |
| 1.4 | 1.18 (1.11–1.25) |
| 2.19 | 1.21 (1.12–1.30) |



When stratified by sex, no significant associations for colorectal cancer risk were observed in either men or women. No significant associations were observed for colorectal cancer when stratified by geographical location. When stratified by cancer site, no significant associations were observed for colon or rectal cancer (see **Table 17** and CUP Colorectal SLR 2016 Figures 496, 497, 501 and 507).

**Table 17: Summary of CUP 2016 cancer site dose-response meta-analyses – haem iron**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 1 mg/day | 1.02 (0.92–1.13) | 0% | 3 | - |
| | W | Per 1 mg/day | 1.04 (0.96–1.12) | 0% | 4 | - |
| **Colon cancer** | M/W | Per 1 mg/day | 1.07 (0.99–1.17) | 37% | 8 | 6,780 |
| **Rectal cancer** | M/W | Per 1 mg/day | 1.09 (0.98–1.21) | 0% | 6 | 2,293 |

One study [24] was not included in any of the CUP analyses due to reporting insufficient data.

The studies adjusted for most known confounding factors (for more information, see CUP Colorectal SLR 2016 Tables 289 and 290).

The CUP findings are similar to those from the 2010 SLR, which also showed no significant association per 1 mg/day (RR 1.04 (95% CI 0.97–1.12)). The CUP meta-analysis included double the number of studies and over 1,000 more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

Results from one published meta-analysis [78] on haem iron and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. This meta-analysis of eight cohort studies (same cohort studies that were included in the CUP analyses) reported a significant positive association when comparing the highest with the lowest levels of intake (RR 1.14 (95% CI 1.04–1.24)).

### Mechanisms

Higher consumption of meat and meat products may increase exposure to greater quantities of bio-available haem iron to those not at risk of iron deficiency. Iron is involved in processes of oxygen transport, oxidative phosphorylation, DNA synthesis and cell growth. However, increased intake of iron is thought to augment reactive oxygen species synthesis by acting as a catalyst in free radical generating pathways in the colon. In turn, reactive oxygen species can induce lipid peroxidation and cellular and DNA damage [79].

### CUP Panel's conclusion:

The evidence for consumption of foods containing haem was limited, and no significant associations were observed between haem iron and colorectal, colon or rectal cancer. For colorectal cancer, there was evidence of a non-linear association with a significant increase in risk for higher levels of haem iron. One published meta-analysis reported a significant positive association when comparing the highest with the lowest levels of intake. There is evidence of plausible mechanisms in humans. The CUP Panel concluded the following:

**The evidence suggesting that consumption of foods containing haem iron increases the risk of colorectal cancer is limited.**

## 7.7 Fish

*(Also see CUP Colorectal SLR 2016: Section 2.5.2)*

The CUP identified four new or updated studies (six publications) [34, 36, 59, 65, 80, 81], giving a total of 18 studies (41 publications) reviewing the evidence on fish and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 100 and 101). Of 15 studies reporting on colorectal cancer incidence, seven reported inverse associations, three of which were significant, when comparing the highest versus the lowest levels of intake. Seven studies reported non-significant positive associations and one reported inconsistent results by sex (see CUP Colorectal SLR 2016 Figure 161).

Eleven of the 18 studies were included in the dose-response meta-analysis ($n$ = 10,356 cases), which showed an 11 per cent decreased risk per 100 grams per day (RR 0.89 (95% CI 0.80–0.99); see CUP Colorectal SLR 2016 Figure 162). No heterogeneity was observed ($I^2$ = 0%, $p_{heterogeneity}$ = 0.521). Sensitivity analysis was conducted and summary RRs ranged from 0.86 (95% CI = 0.76–0.97) when the Ohsaki Cohort Study [82] was omitted to 0.94 (95% CI = 0.82–1.07) when EPIC [34], which holds 40 per cent of the weight in the analysis, was omitted.

Inverse associations were also observed for colorectal cancer stratified by sex and were significant in men. No significant associations were observed in analyses stratified by geographical location. No significant association was observed when analyses were adjusted for meat intake. When stratified by cancer site, inverse but not significant associations were observed for colon and rectal cancer (see **Table 18** and CUP Colorectal SLR 2016 Figures 165, 166, 167 170 and 177).

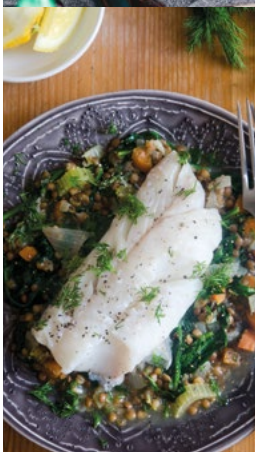


**Table 18: Summary of CUP 2016 cancer site dose-response meta-analyses – fish**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 100 g/ day | 0.83 (0.71–0.98) | 11% | 6 | - |
| | W | Per 100 g/ day | 0.96 (0.82–1.12) | 0% | 7 | - |
| **Colon cancer** | M/W | Per 100 g/ day | 0.91 (0.80–1.03) | 0% | 11 | 10,512 |
| **Rectal cancer** | M/W | Per 100 g/ day | 0.84 (0.69–1.02) | 15% | 10 | 3,944 |

Exposure definition varied from general fish intake, fish meals intake, and fish and shellfish intake to seafood consumption. Most studies did not differentiate the amount of fish intake by n-3 fatty acids content. Most studies adjusted the results for multiple confounders (for more information, see CUP Colorectal SLR 2016 Tables 100 and 101).

Three studies adjusted for fruit intake [34, 82, 83] and three studies for vegetable intake [34, 83, 84].

Two studies [43, 45] were not included in any of the CUP analyses due to reporting mortality as the outcome.

The 2010 SLR did not find a significant association (RR 0.88 (95% CI 0.74–1.06)). The CUP update included two more studies and more than double the number of cases.

### Published pooled analyses and meta-analyses

Results from one published pooled analysis [60] and one published meta-analysis [85] on fish and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. The pooled analysis reported inverse but not significant associations in continuous analyses for both white and oily fish. This pooled analysis was not included in the CUP dose-response meta-analysis. The meta-analysis reported a non-significant inverse association in dose-response analysis (RR 0.99 (95% CI 0.97–1.01)). Results from the CUP Colorectal SLR 2016 and the published pooled analysis are presented in **Table 19**.

**Table 19: Summary of CUP 2016 meta-analysis and published pooled analysis – fish**

| Analysis | Increment/ Contrast | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|
| **CUP Colorectal Cancer SLR 2016** | Per 100 g/day | 0.89 (0.80–0.99) | 0% | 11 | 10,356 |
| **UK Dietary Cohort Consortium [60]** | White fish per 50 g/day | 0.92 (0.70–1.21) | - | 7 | 579 |
| | Oily fish per 50 g/day | 0.89 (0.70–1.13) | - | | |

### Mechanisms

Experimental studies suggest that long-chain n-3 polyunsaturated fatty acids (PUFAs) found in fish, such as eicosapentaenoic acid and docosahexaenoic acid, suppress the development of colorectal cancer [86, 87]. Long-chain n-3 PUFAs have been shown to influence inflammatory pathways by the suppression of n-6 PUFA derived eicosanoid synthesis. There are limited mechanistic data for a link between fish consumption and colorectal cancer risk in humans.

### CUP Panel's conclusion:

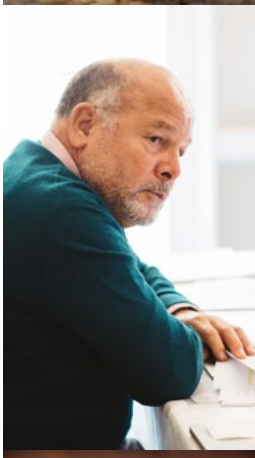
The evidence for consumption of fish was limited but generally consistent. The dose-response meta-analysis showed a significant decreased risk of colorectal cancer risk. However, when the EPIC study which contributed 40 per cent of the weight was removed in a sensitivity analysis, the result was no longer significant. One published pooled analysis reported no significant association for white or oily fish consumption and colorectal cancer risk. There is evidence of plausible mechanisms in humans.

The CUP Panel concluded the following:

**The evidence suggesting that consumption of fish decreases the risk of colorectal cancer is limited.**

## 7.8 Dairy products

This category includes evidence on the following exposures: dairy products, milk, cheese and dietary calcium.



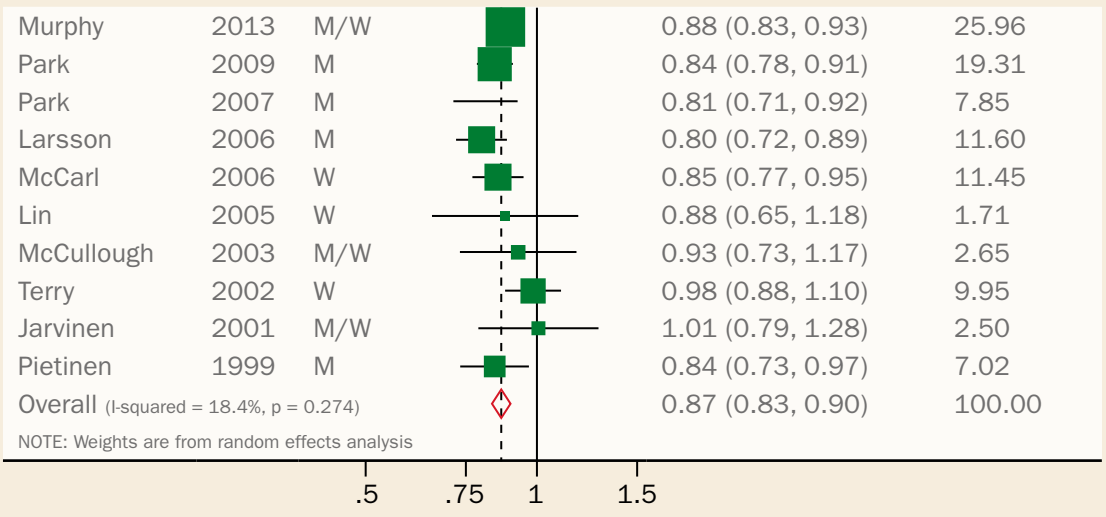
### 7.8.1 Dairy products

*(Also see CUP Colorectal SLR 2016: Section 2.7)*

The CUP identified one new study (two publications) [34, 88], giving a total of 14 studies (16 publications) reviewing the evidence for dairy products and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 106 and 107). Of 12 studies reporting on colorectal cancer incidence, ten reported inverse associations, five of which were significant when comparing the highest versus the lowest levels of intake. One study reported a non-significant positive association and one reported no effect (RR 1.00), (see CUP Colorectal SLR 2016 Figure 184).

Ten of the 14 studies were included in the dose-response meta-analysis ($n$ = 14,859 cases), which showed a 13 per cent decreased risk per 400 grams per day (RR 0.87 (95% CI 0.83–0.90); see **Figure 10** and CUP Colorectal SLR 2016 Figure 185). Low heterogeneity was observed ($I^2$ = 18%, $p_{heterogeneity}$ = 0.274).

**Figure 10: Dose-response meta-analysis of dairy products and colorectal cancer per 400 grams per day**



Non-linear dose-response meta-analysis revealed a significant non-linear association (p = 0.003), with the association slightly stronger at lower levels of intake (see **Figure 11** and **Table 20**; CUP Colorectal SLR 2016 Figure 189 and Table 108).

**Figure 11: Non-linear dose-response association of dairy products and colorectal cancer**

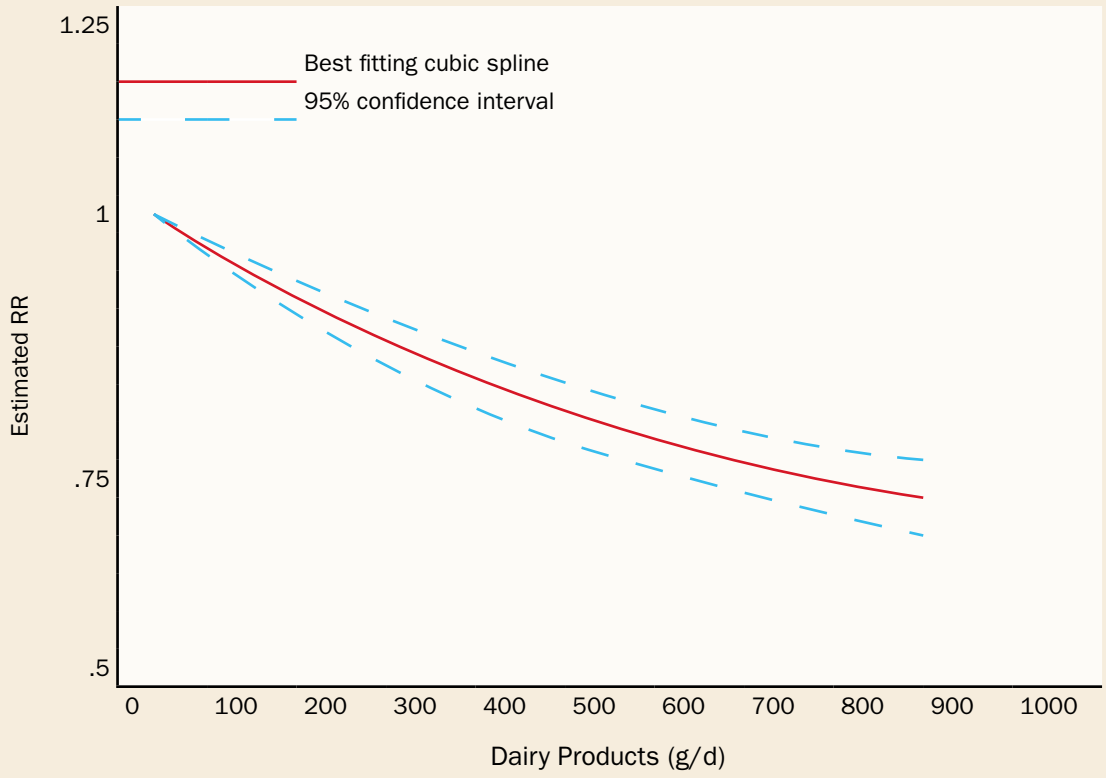



**Table 20: Non-linear dose-response estimates of dairy products and colorectal cancer**

| Dairy products (g/day) | RR (95% CI) |
|---|---|
| 23.3 | 1.00 |
| 100 | 0.95 (0.94–0.96) |
| 200 | 0.90 (0.88–0.92) |
| 300 | 0.86 (0.84–0.88) |
| 400 | 0.82 (0.80–0.85) |
| 500 | 0.79 (0.77–0.82) |

Significant inverse associations were observed for colorectal cancer stratified by sex. Significant inverse associations were observed in North American and European populations. When stratified by cancer site, inverse associations were observed for colon and rectal cancer, significant for colon only (see **Table 21** and CUP Colorectal SLR 2016 Figures 187, 188, 193 and 198).

**Table 21: Summary of CUP 2016 cancer site dose-response meta-analyses – dairy products**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 400 g/ day | 0.84 (0.80–0.89) | 0% | 5 | - |
| | W | Per 400 g/ day | 0.86 (0.78–0.96) | 56% | 6 | - |
| **Colon cancer** | M/W | Per 400 g/ day | 0.87 (0.81–0.94) | 24% | 6 | 3,991 |
| **Rectal cancer** | M/W | Per 400 g/ day | 0.93 (0.82–1.06) | 49% | 5 | 2,152 |

All studies adjusted for age, and most of the studies also adjusted for most of the established colorectal cancer risk factors, including physical activity, BMI, alcohol consumption, smoking, red meat and hormone therapy in women (for more information, see CUP Colorectal SLR 2016 Tables 106 and 107).

Four studies were not included in any of the analyses; two [39, 40] did not report sufficient data, one [45] reported mortality as an outcome and one [89] reported household intake only.

The CUP findings are similar to those from the 2010 SLR, which showed a 15 per cent decreased risk per 400 grams per day (RR 0.85 (95% CI 0.81–0.90)). The CUP meta-analysis included one more study and 5,000 more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

Results from two published meta-analyses [90, 91] on dairy product consumption and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. One analysis [90] reported a significant inverse association when comparing the highest and lowest categories of intake (RR 0.84 (95% CI 0.75–0.95)). The other meta-analysis was the results from the CUP 2010 SLR [91].

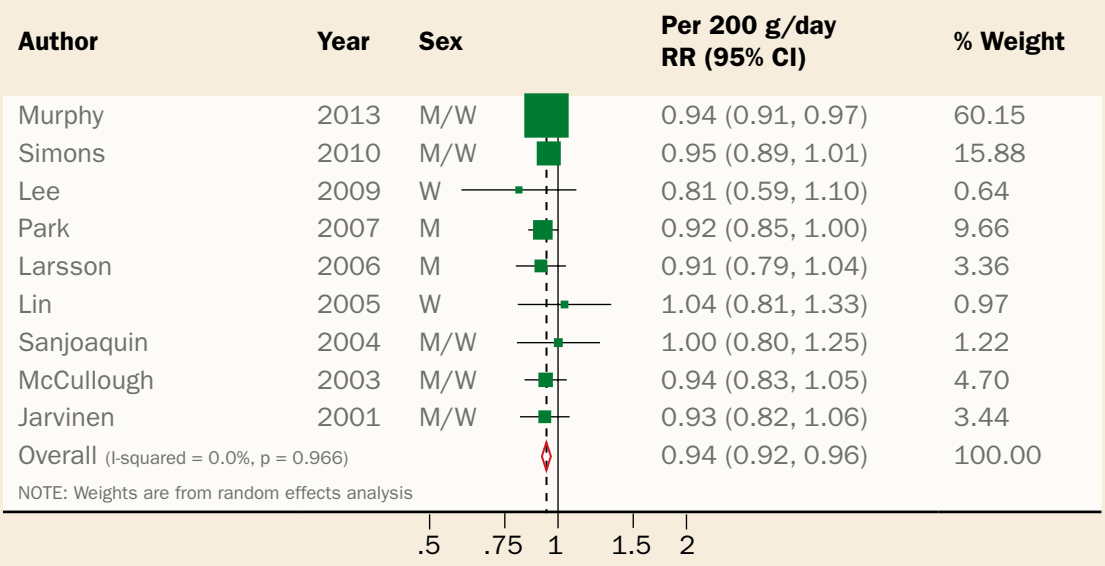
## 7.8.2 Milk

*(Also see CUP Colorectal SLR 2016: Section 2.7.1)*

The CUP identified two new studies (three publications) [49, 88, 92], giving a total of 13 studies (15 publications) reviewing the evidence for milk and colorectal cancer (for a full list of references see CUP Colorectal SLR 2016 Tables 114 and 115). Of 11 studies reporting on colorectal cancer incidence, seven reported inverse associations, two of which were significant, and two of which reported inverse associations significant only in men. Two reported a non-significant positive association (see CUP Colorectal SLR 2016 Figure 200).

Nine of the 13 studies were included in the dose-response meta-analysis (*n* = 10,738 cases), which showed a six per cent decreased risk per 200 grams per day (RR 0.94 (95% CI 0.92–0.96); see **Figure 12** and CUP Colorectal SLR 2016 Figure 201). No heterogeneity was observed ($I^2$ = 0%, $p_{heterogeneity}$ = 0.966).

**Figure 12: Dose-response meta-analysis of milk and colorectal cancer per 200 grams per day**




When stratified by sex, inverse associations for colorectal cancer were observed for men and women, significant in men. Analyses by geographical location showed inverse associations, significant in Europe and North America. When stratified by cancer site, significant inverse associations were observed for colon and rectal cancer (see **Table 22** and CUP Colorectal SLR 2016 Figures 202, 203, 208 and 213 respectively).

**Table 22: Summary of CUP 2016 cancer site dose-response meta-analysis – milk**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 200 g/ day | 0.92 (0.87–0.98) | 0% | 3 | - |
| | W | Per 200 g/ day | 0.96 (0.89–1.03) | 0% | 4 | - |
| **Colon cancer** | M/W | Per 200 g/ day | 0.93 (0.91–0.96) | 30% | 9 | 8,149 |
| **Rectal cancer** | M/W | Per 200 g/ day | 0.94 (0.91–0.97) | 0% | 7 | 3,599 |

All studies adjusted for age, and most of the studies adjusted for most of the established colorectal cancer risk factors, including physical activity, BMI, alcohol consumption, smoking, red meat and hormone therapy in women (for more information, see CUP Colorectal SLR 2016 Tables 114 and 115).

Three studies [43, 89, 93] were not included in any of the CUP analyses. Two reported mortality as the outcome and one reported total household dietary intake only.

The CUP findings are similar to those from the 2010 SLR, which also showed a significant inverse association although the risk estimate was smaller (RR 0.90 (95% CI 0.85–0.94)). The CUP meta-analysis included over double the number of cases of colorectal cancer.

### Published pooled analyses and meta-analyses

Results from one published pooled analysis [94] and three meta-analyses [90, 91, 95] on milk consumption and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. Two meta-analyses [90, 95] reported significant inverse associations when comparing the highest with the lowest consumers of milk (RR 0.90 (95% CI 0.83–0.97) and RR 0.85 (95% CI 0.77–0.93) respectively). The other meta-analysis reported the results from the CUP 2010 SLR [91]. The pooled analysis also reported a significant inverse association when comparing the highest with the lowest consumers of milk. Results from the CUP Colorectal SLR 2016 and the published pooled analysis are presented in **Table 23**.

**Table 23: Summary of CUP 2016 meta-analysis and published pooled analysis – milk**

| Study | Increment/ Contrast | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|
| **CUP Colorectal Cancer SLR 2016** | Per 200 g/day | 0.94 (0.92–0.96) | 0% | 9 | 10,738 |
| **The Pooling Project [94]** | Per 200 g/day | 0.95 (0.92–0.97) | | 10 | 4,992 |
| **CUP additional analysis: meta-analysis of The Pooling Project studies [94] combined with non-overlapping studies from the CUP** | Per 200 g/day | 0.94 (0.93–96) | 0% | 18 | 13,373 |

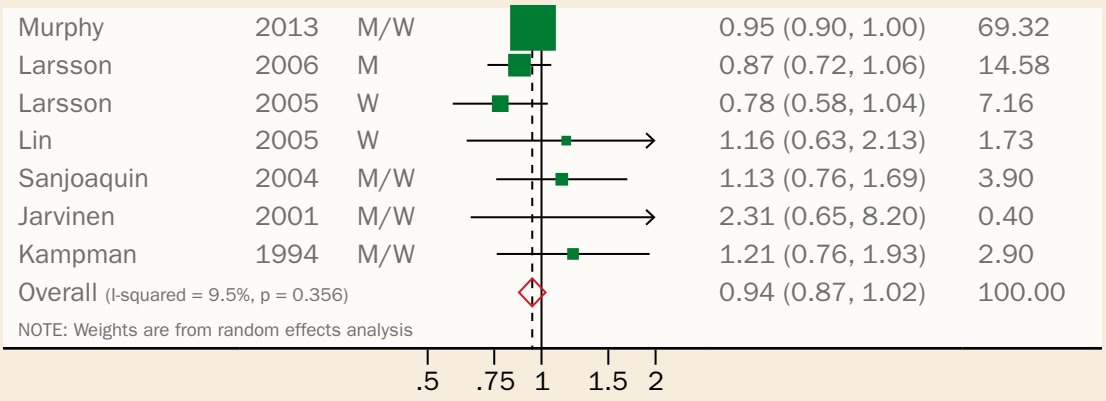
### 7.8.3 Cheese

*(Also see CUP Colorectal SLR 2016: Section 2.7.2)*

The CUP identified one updated study (one publication) [88], giving a total of nine studies (10 publications) reviewing the evidence for cheese and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 tables 121 and 122). Of seven studies reporting on colorectal cancer incidence, five reported inverse associations, two of which were significant and two of which reported non-significant positive associations when comparing the highest versus the lowest levels of intake (see CUP Colorectal SLR 2016 Figure 218).

Seven of the nine studies were included in the dose-response meta-analysis ($n$ = 6,462 cases), which showed no association (RR 0.94 (95% CI 0.87–1.02); see **Figure 13** and CUP Colorectal SLR 2016 Figure 219). Low heterogeneity was observed ($I^2$ = 10%, $p_{heterogeneity}$ = 0.356).

**Figure 13: Dose-response meta-analysis of cheese and colorectal cancer per 50 grams per day**




The test for non-linearity was significant (p = 0.047), showing a trend towards increased risk at low levels and a decreased risk of colorectal cancer at higher levels, although the risk estimates never reached statistical significance (see **Figure 14** and **Table 24**; CUP Colorectal SLR Figures 221 and 222).

**Figure 14: Non-linear dose-response association of cheese and colorectal cancer**

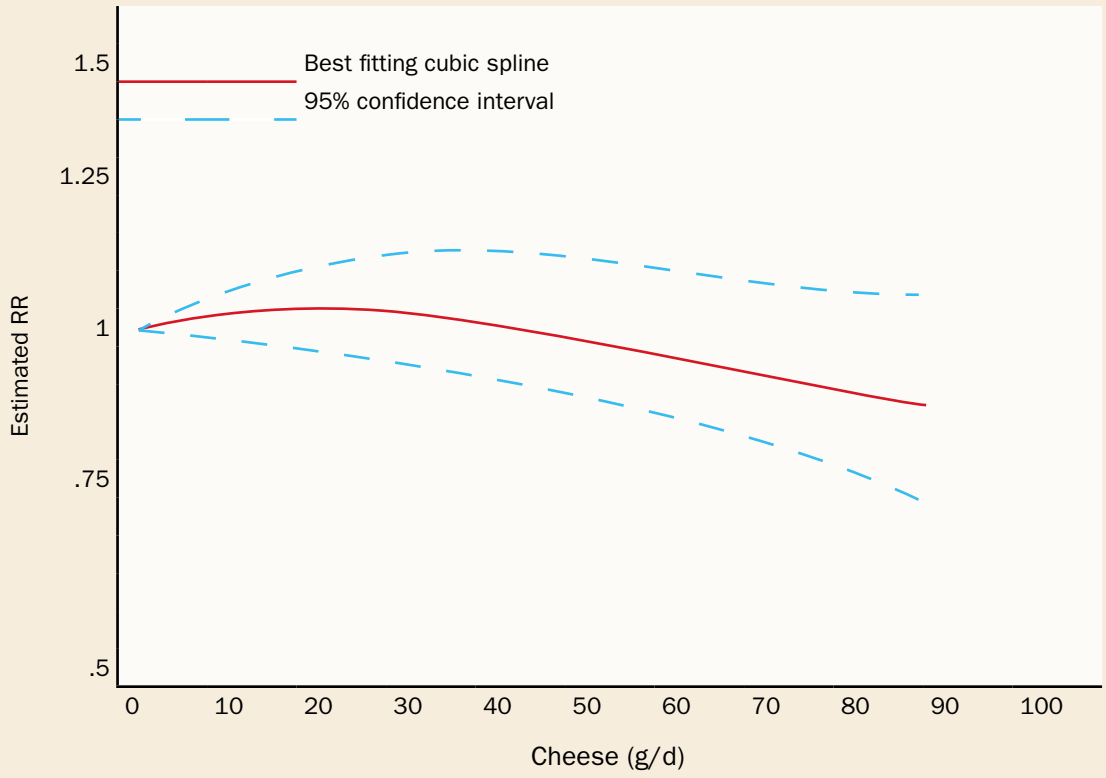



**Table 24: Non-linear dose-response estimates of cheese and colorectal cancer**

| Cheese (g/day) | RR (95% CI) |
|---|---|
| 0 | 1.00 |
| 10 | 1.02 (0.98–1.07) |
| 20 | 1.04 (0.96–1.12) |
| 30 | 1.04 (0.94–1.14) |
| 40 | 1.02 (0.91–1.14) |
| 50 | 0.99 (0.88–1.11) |
| 60 | 0.96 (0.84–1.09) |
| 70 | 0.92 (0.80–1.06) |
| 80 | 0.89 (0.75–1.04) |
| 90 | 0.86 (0.71–1.03) |

When stratified by sex, inverse but not significant associations for colorectal cancer were observed for men and women. Analyses by geographical location showed no significant associations in Europe or Asia (see CUP Colorectal SLR Table 119) When stratified by cancer site, inverse associations were observed for colon and rectal cancer (see **Table 25** and CUP Colorectal SLR 2016 Figures 220, 225 and 231 respectively and Table 119).

**Table 25: Summary of CUP 2016 cancer site dose-response meta-analysis – cheese**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 50 g/day | 0.87 (0.72–1.06) | n/a | 1 | - |
| | W | Per 50 g/day | 0.87 (0.61–1.23) | 27% | 2 | - |
| **Colon cancer** | M/W | Per 50 g/day | 0.91 (0.80–1.03) | 19% | 6 | 3,958 |
| **Rectal cancer** | M/W | Per 50 g/day | 0.95 (0.90–1.00) | 0% | 4 | 2,101 |

All studies adjusted for age, and most of the studies adjusted for most of the established colorectal cancer risk factors, including physical activity, BMI, alcohol consumption, smoking, red meat and hormone therapy in women (for more information, see CUP Colorectal SLR 2016 Tables 121 and 122).

Two [43, 93] studies were not included in any of the CUP analyses. Both reported mortality as the outcome.

The CUP findings are different to those from the 2005 SLR (no analysis was conducted for the 2010 SLR), which showed no significant association (RR 1.11 (95% CI 0.88–1.39)). The CUP meta-analysis included five more studies and almost 6,000 more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

Results from one published pooled analysis [94] and two meta-analyses [91, 95] on cheese consumption and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. One meta-analysis [95] reported non-significant results when comparing the highest with the lowest consumers of cheese (RR 1.11 (95% CI 0.90–1.36). The other meta-analysis reported the results from the CUP 2010 SLR [91]. The pooled analysis (not included in the CUP dose-response meta-analysis) reported no significant association in highest versus lowest analysis. Results from the CUP Colorectal SLR 2016 and the published pooled analysis are presented in **Table 26**.

**Table 26: Summary of CUP 2016 meta-analysis and published pooled analysis – cheese**

| Study | Increment/ Contrast | RR (95% CI) | $I^2$ | No. Studies | No. cases |
|---|---|---|---|---|---|
| **CUP Colorectal SLR 2016** | Per 50 g/day | 0.94 (0.87–1.02) | 10% | 7 | 6,462 |
| **The Pooling Project [94]** | ≥ 25 vs. < 5 g/ day | 1.10 (0.98–1.24) | n/a, p = 0.37 | 10 | 7,157 |

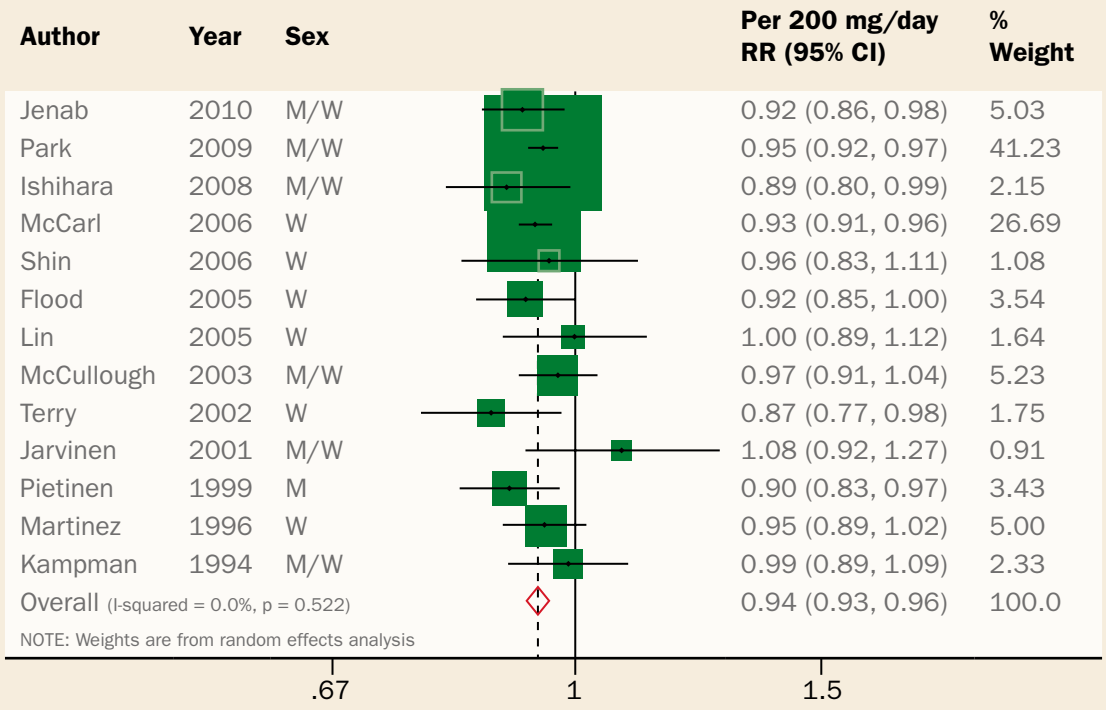
## 7.8.4 Dietary calcium

*(Also see CUP Colorectal SLR 2016: Section 5.6.3 and appendix 4)*

The CUP identified one new study (two publications) [88, 96], giving a total of 20 studies (26 publications) reviewing the evidence for dietary calcium and colorectal cancer (for details, see CUP Colorectal SLR 2016 appendix 4). Of 11 studies comparing the highest and lowest levels of intake, ten reported inverse associations, three of which were significant, and two reported results stratified by sex, which were significant only in men. One study reported a non-significant positive association. A pooled analysis [94] of ten studies reported a significant inverse association (see CUP Colorectal SLR 2016 Figure 490).

No new dose-response meta-analysis was conducted. In the 2010 SLR, 13 studies were included in a dose-response meta-analysis (*n* = 11,519 cases), which showed a six per cent decreased risk per 200 milligrams per day (RR 0.94 (95% CI 0.93–0.96); see **Figure 15** and CUP Colorectal SLR appendix 4). No heterogeneity was observed ($I^2$ = 0%, $p_{heterogeneity}$ = 0.522).

**Figure 15: Dose-response, meta-analysis of dietary calcium and colorectal cancer per 200 milligrams per day**




In the 2010 SLR, when stratified by cancer site, inverse associations were observed for colon and rectal cancer, significant for colon only. Significant inverse associations were also observed for colorectal cancer stratified by sex (see **Table 27** and CUP Colorectal SLR 2016 appendix 4).

**Table 27: Summary of CUP 2010 cancer site dose-response meta-analyses – dietary calcium**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 200 mg/day | 0.93 (0.88–0.99) | 52% | 3 | - |
| | W | Per 200 mg/day | 0.93 (0.91–0.95) | 0% | 9 | - |
| **Colon cancer** | M/W | Per 200 mg/day | 0.93 (0.89–0.97) | 10% | 10 | 2,738 |
| **Rectal cancer** | M/W | Per 200 mg/day | 0.94 (0.86–1.02) | 35% | 8 | 1,173 |

Three studies were not included in any of the analyses [97-99] due to not reporting sufficient data.

### Published pooled analyses and meta-analyses

Results from one published pooled analysis [94] on dietary calcium and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. The pooled analysis (not included in the 2010 CUP dose-response meta-analysis) reported a significant inverse association when comparing the highest and lowest levels of intake. Results from the CUP Colorectal SLR 2016 and the published pooled analysis are presented in **Table 28**.

**Table 28: Summary of CUP 2016 meta-analysis and published pooled analysis – dietary calcium**

| Study | Increment/ Contrast | RR (95% CI) | $I^2$ | No. Studies | No. cases |
|---|---|---|---|---|---|
| **CUP Colorectal SLR 2010** | Per 200 mg/day | 0.94 (0.93–0.96) | 0% | 10 | 11,519 |
| **The Pooling Project [94]** | Highest vs. Lowest | 0.86 (0.78–0.95) | n/a, p = 0.02 | 10 | 4,992 |

### Mechanisms

Observed inverse associations between intake of dairy products and colorectal cancer development have been largely attributed to their content of calcium (see mechanisms in section 7.9). In addition to calcium, lactic acid–producing bacteria may also protect against colorectal cancer [100], while the casein and lactose in milk may increase calcium bioavailability [101]. Other constituents or bio-active compounds in dairy products, such as lactoferrin, vitamin D (from fortified dairy products) or the short-chain fatty acid butyrate may also impart some colorectal cancer protective functions [100], but these require much better elucidation.

### CUP Panel's conclusion:

The evidence was consistent for dairy products, milk, cheese and dietary calcium in showing a decreased risk of colorectal cancer with higher consumption. The dose-response meta-analyses for dairy products, milk and dietary calcium were statistically significant with no or little heterogeneity. Evidence for cheese was less strong than for the other exposures. One published pooled analysis reported significant inverse associations when comparing the highest with the lowest levels of intake of milk and dietary calcium. There is evidence of plausible mechanisms in humans. The CUP Panel concluded the following:

**Consumption of dairy products probably protects against colorectal cancer.**

## 7.9 Calcium supplements

*(Also see CUP Colorectal SLR 2016: Section 5.5.10 and appendix 5)*

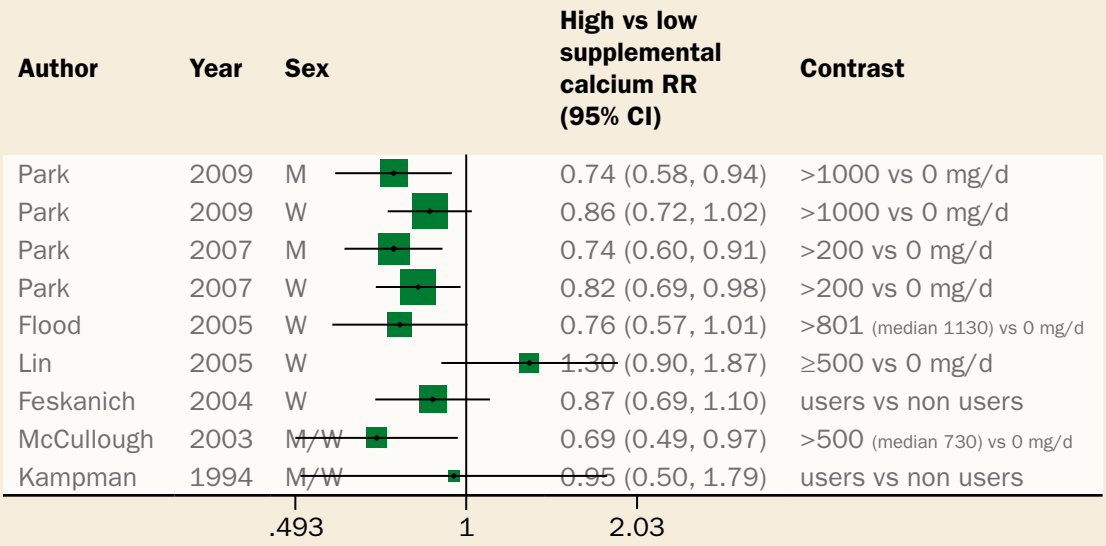
### Randomised controlled trial

The Women's Health Initiative [102] was a double-blind, placebo-controlled clinical trial of 1,000 mg elemental calcium carbonate plus 400 IU of vitamin D3 daily, with an average intervention period of seven years, in 36,282 postmenopausal women in the United States. The main outcome was hip fracture, and secondarily, total fracture and colorectal cancer. No significant associations with colorectal cancer risk were observed for calcium and vitamin D supplementation compared with placebo use in all trial participants (RR 1.06 (95% CI 0.85–1.32)) and after excluding women using personal calcium or vitamin D supplements at baseline (RR 0.81 (95% CI 0.58–1.13)).

### Prospective cohort studies

Only one update study [102] was identified after the 2010 SLR. This study in postmenopausal women reported the age-adjusted incidence as 0.11 per cent in non-users of supplements (174 incident cases) and 0.08 per cent (88 incident cases) in vitamin D and calcium supplement users after 7.2 years of follow-up, on average. No significant association was reported for colorectal cancer for calcium and vitamin D supplementation compared with no supplement use (RR 0.83 (95% CI 0.61–1.12)).
No dose-response meta-analysis was conducted for the 2016 SLR. In the 2010 SLR, seven studies (seven publications) were identified that reviewed the evidence on calcium supplements and colorectal cancer. Five studies reported inverse associations, two of which were significant when comparing the highest and lowest levels of intake. One reported a non-significant positive association and one reported inconsistent results by sex (see **Figure 16**; CUP Colorectal Cancer SLR 2016 appendix 5).

**Figure 16: Highest versus lowest analysis of calcium supplement intake and colorectal cancer**




### Published pooled and meta-analyses

One published meta-analysis of cohort studies [90] was identified in the 2010 SLR. It reported a significant inverse association for colon and colorectal cancer when comparing the highest with the lowest levels of intake (RR 0.76 (95% CI 0.65–0.89)).

### Mechanisms

A long-standing mechanism proposed for calcium action against colorectal cancer is its ability to bind unconjugated bile acids and free fatty acids, diminishing their toxic effects on the colorectum [103]. More recent cell culture studies suggest that it may also reduce cell proliferation and promote cell differentiation, likely by influencing different cell-signalling pathways [104]. Calcium may also prevent colonic K-ras mutations and inhibit haem-induced promotion of colon carcinogenesis [105, 106].

### CUP Panel's conclusion:

The evidence was generally consistent and showed inverse associations across a range of intakes (200–1000mg). The RCT reported a non-significant inverse association for calcium and vitamin D supplementation compared to placebo use after excluding women using personal calcium or vitamin D supplements at baseline. Although no dose-response meta-analysis could be conducted, six of the eight cohort studies reported inverse associations. There is evidence of plausible mechanisms in humans. The CUP Panel concluded the following:

**Taking calcium supplements probably protects against colorectal cancer.**

## 7.10 Vitamin D

This section includes the evidence for foods containing vitamin D, supplemental vitamin D and plasma/serum vitamin D.

### 7.10.1 Foods containing vitamin D

*(Also see CUP Colorectal SLR 2016: Section 5.5.10 and appendix 6)*

The CUP identified one new study (one publication) [107], giving a total of 15 studies reviewing the evidence on foods containing vitamin D and colorectal cancer.

No new dose-response meta-analysis was conducted. The 2010 SLR reported a significant five per cent decreased risk per 100 IU per day (RR 0.95 (95% CI 0.93–0.98), $I^2$ = 11%, *n* = 5,171, 10 studies; see CUP Colorectal SLR 2016 appendix 6).

### 7.10.2 Vitamin D supplements

*(Also see CUP Colorectal SLR 2016: Section 5.5.10 and appendix 6)*

#### Colon cancer

The CUP identified one new study (one publication) [102], giving a total of three prospective cohort studies reviewing the evidence on supplemental vitamin D and colon cancer (see information above). No new dose-response meta-analysis was conducted. The 2010 SLR reported a significant seven per cent decreased risk per 100 IU/day (RR 0.93 (95% CI 0.88–0.98), *n* = 415, two studies; see CUP Colorectal Cancer SLR 2016 appendix 6). No dose-response analysis was possible for colorectal or rectal cancer.

### 7.10.3 Plasma or serum vitamin D

*(Also see CUP Colorectal SLR 2016: Section 5.5.10)*

The CUP identified seven new studies (11 new publications) [108-118], giving a total of 12 studies (15 publications) reviewing the evidence for plasma or serum vitamin D and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 227 and 228). Of 11 studies reporting on colorectal cancer incidence, eight reported inverse associations, four of which were significant, two reported positive associations, one of which was significant and one study reported inconsistent results for men and women when comparing the highest versus the lowest levels of serum plasma vitamin D (see CUP Colorectal SLR 2016 Figure 412).

Eleven of the 12 studies were included in the dose-response meta-analysis (*n* = 4,801 cases), which showed no significant association per 30 nanomoles per litre (RR 0.92 (95% CI 0.85–1.00); see CUP Colorectal SLR 2016 Figure 414). Moderate heterogeneity ($I^2$ = 54%, $p_{heterogeneity}$ = 0.021) was observed, explained by the direction of effect.

Although there was no evidence of small study bias with Egger's test (p = 0.90; see CUP Colorectal SLR 2016 Figure 415), visual inspection of the funnel plot shows that two studies were outliers [109, 118], with one reporting a much larger significant inverse association that the other studies and one reporting a significant positive association.

When stratified by sex, no significant associations were observed for men and women and the direction of effect varied (see **Table 29** and CUP Colorectal SLR 2016 Figure 416). Analysis by geographical location for colorectal cancer showed inverse, but not significant, associations in Europe, North America and Asia (see CUP Colorectal SLR Figure 417). When stratified by cancer site, inverse associations were observed for colon and rectal cancer (see **Table 29** and CUP Colorectal SLR 2016 Figures 422 and 427).

**Table 29: Summary of CUP 2016 cancer site dose-response meta-analyses – plasma or serum vitamin D**

| Analysis | Sex | Increment/ Contrast | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 30 nmol/l | 1.05 (0.88–1.26) | 60% | 3 | - |
| | W | Per 30 nmol/l | 0.83 (0.53–1.30) | 84% | 2 | - |
| **Colon cancer** | M/W | Per 30 nmol/l | 0.90 (0.81–1.01) | 63% | 9 | 2,037 |
| **Rectal cancer** | M/W | Per 30 nmol/l | 0.83 (0.69–1.00) | 43% | 7 | 1,579 |

All studies were multiple adjusted for different confounders (for more information, see CUP Colorectal SLR 2016 Tables 227 and 228).

One study [117] was not included in any analyses as it reported mortality as the outcome.

The CUP findings showed an inverse association, which was also observed in the 2010 CUP SLR, but the results from the previous SLR were significant (RR 0.96 (95% CI 0.94–0.97)). The CUP meta-analysis included five more studies and over 2,000 more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

Two published meta-analyses on plasma or serum vitamin D levels and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. One [119] reporting on case-control and cohort studies showed a significant inverse association per 10 nanograms per millilitre (RR 0.85 (95% CI 0.79–0.91)) and one [113], when comparing the highest with the lowest levels of serum 25-hydroxyvitamin D, also reported a significant inverse association (RR 0.66 (95% CI 0.54–0.81)).

### Mechanisms

Underlying mechanisms for an effect of vitamin D on colorectal cancer have been studied mostly in in vitro and experimental models, and there are limited data in humans. These studies suggest a role for circulating vitamin D, through its active form, 1α,25-dihydroxyvitamin D3[1,25(OH)2D3], in control of cell growth, by reducing proliferation and by inducing differentiation and apoptosis [120]. Other purported mechanisms of vitamin D action pertain to improved innate and adaptive immune function, inhibition of angiogenesis, reduced inflammation and regulation of microRNA expression with higher vitamin D status [120-122].

### CUP Panel's conclusion:

The evidence for vitamin D was limited but generally consistent. For foods containing vitamin D, the 2010 dose-response meta-analysis showed a significant decreased risk of colorectal cancer risk. For supplemental vitamin D, the dose-response meta-analysis showed a significant decreased risk of colon cancer. For plasma/serum vitamin D, the dose-response meta-analysis showed no significant association with colorectal cancer. Two published meta-analyses reported significant inverse associations. The Panel noted plasma/serum vitamin D status can be influenced by sun exposure, obesity, seasonality, smoking and measurement error. There is evidence of plausible mechanisms in humans. The CUP Panel concluded the following:

**The evidence suggesting that vitamin D that decreases the risk of colorectal cancer is limited.**

## 7.11 Multivitamin supplements

*(Also see CUP Colorectal SLR 2016: Section 5.5.13)*

### Randomised Controlled Trials

The CUP identified one RCT, the Physicians' Health Study II [123], a randomised, double-blind, placebo-controlled, 2 x 2 x 2 x 2 factorial trial of daily multivitamin supplementation, vitamin E (400-IU synthetic tocopherol), vitamin C (500 mg synthetic ascorbic acid) and beta-carotene (50 mg Lurotin) that included 14,641 male physicians in the United States of 50 years of age or older. The trial investigated benefits and risks of supplementation for total cancer (excluding non-melanoma skin cancer), with prostate, colorectal, and other site-specific cancers among secondary endpoints, cardiovascular disease, eye disease, and cognitive function, colorectal cancer was a secondary outcome. Treatment started in 2001, and the multivitamin component continued until 2011. The trial reported no significant associations for colorectal cancer incidence; see **Table 30**.

**Table 30: Summary of RCT – multivitamin supplement**

| Study Name & Intervention | Supplementation | Outcome | RR (95% CI) | P-Value | No. Cases | |
|---|---|---|---|---|---|---|
| | | | | | Inter-vention | Control |
| **Physicians Health Study [123]** | Vitamin E (400 IU synthetic tocopherol), vitamin C (500 mg synthetic ascorbic acid) and beta-carotene (50 mg Lurotin) | Incidence | 0.89 (0.68-1.17) | 0.39 | 99 | 111 |

The CUP identified five new or updated cohort studies (four publications) [124–127] giving a total of 11 studies (12 publications) assessing multivitamin supplements and colorectal cancer (for a full list of references, see Tables 241 and 242). Of 11 studies reporting on colorectal cancer incidence, six reported inverse associations, three of which were significant (one paper reported combined results for two studies). Three studies reported non-significant positive associations and one reported no effect (RR 1.00) when comparing users of multivitamin supplements with non-users (see CUP Colorectal SLR 2016 Figure 432).

No dose-response meta-analysis could be conducted. All 11 studies were included in an analysis comparing users of multivitamin supplements with non-users (*n* = 8,072 cases), which showed a significant decreased risk (RR 0.88 (95% CI 0.79–0.98)) (CUP Colorectal SLR 2016 Figure 432). There was evidence of moderate heterogeneity ($I^2$ = 47%).

All studies adjusted for age (for more information, see CUP Colorectal SLR 2016 Tables 241 and 242).

One study [67] was not included in any of the CUP analyses due to reporting insufficient data.

No previous analyses were conducted on multivitamin supplements and colorectal cancer risk.

### Published pooled analyses and meta-analyses

Results from one published meta-analysis [128] reporting on multivitamin supplement use and colorectal and colon cancer risk were identified in the CUP Colorectal SLR 2016. The meta-analysis reported a significant inverse association with colorectal cancer incidence when comparing multivitamin supplement users with non-users (RR 0.92 (95% CI 0.87–0.97)).

### Mechanisms

Multivitamin supplements consist of a combination of several or in some instances many vitamins, making it challenging to determine what specifically is the active ingredient. Numerous vitamins contained in multivitamin supplements have been shown to capture free radicals and reactive oxygen species and to prevent lipid peroxidation [128].

### CUP Panel's conclusion:

The evidence for use of multivitamin supplements was limited but generally consistent. One RCT in men reported a non-significant inverse association for multivitamin supplementation compared with placebo. The analysis of highest versus lowest users of supplements showed a significant decreased risk of colorectal cancer. One published meta-analysis on colorectal and colon cancer reported significant inverse associations. There is evidence of plausible mechanisms in humans. The CUP Panel concluded the following:

**The evidence suggesting that taking multivitamin supplements decreases the risk of colorectal cancer is limited.**

## 7.12 Alcoholic drinks

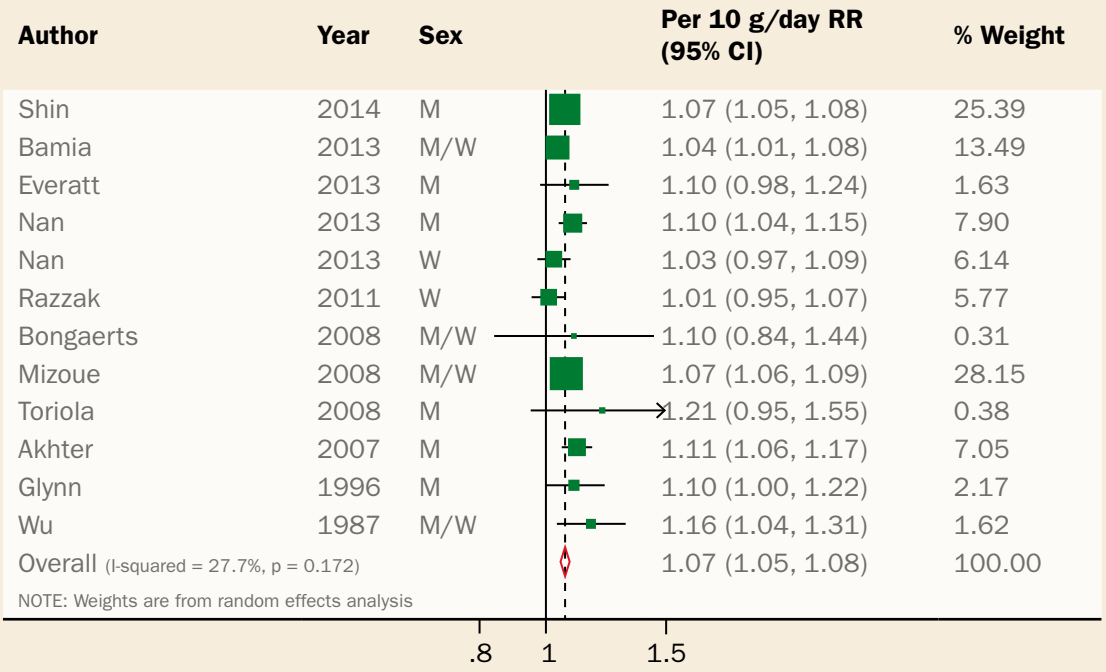
*(Also see CUP Colorectal SLR 2016: Sections 5.4 and 3.7.1)*

### Alcohol as ethanol

The CUP identified 11 new or updated studies (21 publications) [24, 29, 34, 36, 55, 92, 129-142], giving a total of 19 studies (26 publications) reviewing the evidence for alcohol (as ethanol) and colorectal cancer risk (for a full list of references, see CUP Colorectal SLR 2016 Tables 218 and 219). Of 12 studies reporting on colorectal cancer incidence, ten reported positive associations, six of which were significant, and two reported inconsistent results for men and women when comparing the highest versus the lowest levels of intake. A pooled analysis [143] of five Japanese studies reported a significant positive association (see CUP Colorectal SLR 2016 Figure 387).

Sixteen of the 19 studies were included in the dose-response meta-analysis ($n$ = 15,896 cases), which showed a seven per cent increased risk per 10 grams of ethanol per day (RR 1.07 (95% CI 1.05–1.08); see **Figure 17** and CUP Colorectal SLR 2016 Figure 388). Low heterogeneity was observed, $I^2$ = 28% ($p_{heterogeneity}$ = 0.172).

**Figure 17: Dose-response meta-analysis of alcohol (as ethanol) and colorectal cancer per 10 grams per day**




There was evidence of a non-linear dose-response relationship (p = 0.01). No significant risk increase was observed at low intake levels (up to 20 grams per day). Significant increased risks were observed for 30 grams per day and above, where the relationship was positive and appeared linear (see **Figure 18** and **Table 31** and CUP Colorectal SLR 2016 Figure 392 and Table 220).

**Figure 18: Non-linear dose-response associations of alcohol (as ethanol) intake and colorectal cancer**

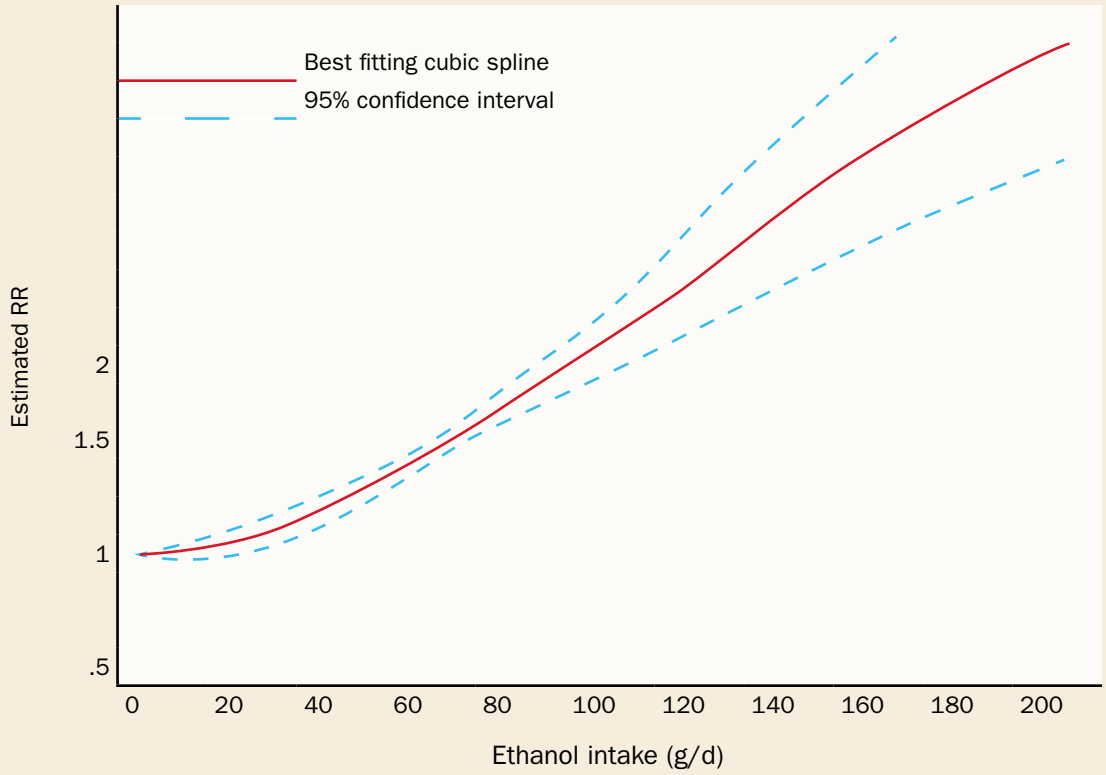



**Table 31: Non-linear dose-response estimates of alcohol (as ethanol) intake and colorectal cancer**

| Alcohol (g/day) | RR (95% CI) |
|---|---|
| 0 | 1.00 |
| 10 | 1.02 (0.98–1.07) |
| 20 | 1.07 (1.00–1.16) |
| 30 | 1.15 (1.06–1.26) |
| 40 | 1.25 (1.14–1.36) |
| 50 | 1.41 (1.31–1.52) |
| 60 | 1.60 (1.51–1.69) |

When stratified by sex, positive associations for colorectal cancer were observed in both men and women, significant for men (see **Table 32** and CUP SLR Figure 390). In analyses stratified by geographical location, significant positive associations were observed for Europe, North America and Asia (see CUP SLR Figure 391). When stratified by cancer site, significant positive associations were observed for colon and rectal cancer. Significant positive associations were also observed in the analyses stratified by sex in both colon and rectal cancer (see **Table 32** and CUP Colorectal SLR 2016 Figures 396, 398, 402 and 404).

**Table 32: Summary of CUP 2016 cancer site dose-response meta-analysis – alcohol as ethanol**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 10 g/day | 1.08 (1.06–1.09) | 0% | 14 | - |
| | W | Per 10 g/day | 1.04 (1.00–1.07) | 44% | 10 | - |
| **Colon cancer** | M/W | Per 10 g/day | 1.07 (1.05–1.09) | 34% | 14 | 12,051 |
| | M | Per 10 g/day | 1.08 (1.06–1.10) | 37% | 12 | - |
| | W | Per 10 g/day | 1.05 (1.02–1.09) | 0% | 10 | - |
| **Rectal cancer** | M/W | Per 10 g/day | 1.08 (1.07–1.10) | 0% | 11 | 7,763 |
| | M | Per 10 g/day | 1.09 (1.06–1.12) | 25% | 10 | - |
| | W | Per 10 g/day | 1.09 (1.04–1.15) | 0% | 8 | - |

When stratified by type of drink significant positive associations were observed for wine, beer and spirits (see **Table 33** and CUP Colorectal SLR 2016 Figures 407, 409 and 411 respectively).

**Table 33: Summary of CUP 2016 type of drink dose-response meta-analyses – alcohol as ethanol**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Wine (colorectal or colon cancer)** | M/W | Per 10 g/day | 1.04 (1.01–1.08) | 0% | 6 | - |
| **Beer (colorectal cancer)** | M/W | Per 10 g/day | 1.08 (1.05–1.11) | 0% | 5 | - |
| **Spirits (colorectal cancer)** | M/W | Per 10 g/day | 1.08 (1.02–1.14) | 0% | 4 | - |

All studies were adjusted for multiple different confounders (for more information, see CUP Colorectal SLR 2016 Tables 218 and 219).

Four studies were excluded from the analysis; three [99, 144, 145] reported mean exposures only and one [29] reported insufficient data.

The CUP findings are similar to those from the 2010 SLR, which also showed a significant increased risk although the risk estimate was larger in the 2010 analysis (RR 1.10 (95% CI 1.06–1.13)). The 2016 CUP meta-analysis included double the number of studies and over 10,000 more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

Results from two published pooled analyses [139, 143] on alcohol as ethanol and colorectal cancer risk were identified in the CUP Colorectal SLR 2016. Both analyses reported positive associations. These were not included in the CUP dose-response meta-analysis. Results from the CUP and the published pooled-analyses are presented in **Table 34.**

**Table 34: Summary of CUP 2016 meta-analysis and published pooled analyses – alcohol as ethanol**

| Study | Increment/ Contrast | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|
| **CUP Colorectal Cancer SLR 2016** | Per 10 g/day | 1.07 (1.05–1.08) | 28% | 16 | 15,896 |
| **UK Dietary Cohort Consortium [139]** | ≥ 45 vs. 0 g/ day, men | 1.24 (0.69–2.22) | | 7 | 579 |
| | ≥45 vs. 0 g/ day, women | 1.52 (0.56–4.10) | | | |
| **Japanese Pooling Project 2008 [143]** | Per 15 g/day, men | 1.11 (1.09–1.14) | | 5 | 1,724 |
| | Per 15 g/day, women | 1.13 (1.06–1.20) | | | 1,078 |

### Alcohol as drinks

Analysis conducted per one drink per day increase showed positive associations for colorectal, colon and rectal cancer. Results from the CUP meta-analyses are presented in **Table 35.**

**Table 35: Summary of CUP 2016 meta-analyses – alcoholic drinks**

| Analysis | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|
| **Colorectal cancer** | Per 1 drink/day | 1.06 (1.00–1.11) | 60% | 8 | 36,942 |
| **Colon cancer** | Per 1 drink/day | 1.11 (0.90–1.36) | 98% | 8 | 5,207 |
| **Rectal cancer** | Per 1 drink/day | 1.08 (1.00–1.17) | 62% | 5 | 963 |

## Mechanisms

The mechanisms of action for an effect of chronic alcohol consumption on colorectal cancer development appear to be diverse and are not well elucidated. Acetaldehyde, a toxic metabolite of ethanol oxidation, can be carcinogenic to colonocytes [146]. Higher ethanol consumption can also induce oxidative stress through increased production of reactive oxygen species which are genotoxic and carcinogenic [147]. Alcohol may also act as a solvent for cellular penetration of dietary or environmental (e.g., tobacco) carcinogens, affect hormone metabolism or interfere with retinoid metabolism and with DNA repair mechanisms [148].

## CUP Panel's conclusion:

There was consistent epidemiological evidence, with low heterogeneity, for a positive association between alcohol consumption and colorectal cancer. The association for alcohol as ethanol was still apparent when stratified by specific cancer site as significant increased risk was observed for colorectal, colon and rectal cancer. There was evidence of a non-linear association for colorectal cancer, with significant positive associations for intakes of 30 grams per day and above. The CUP findings were supported by one published pooled analysis, which reported significant positive associations for both men and women across all cancer sites. Another published pooled analysis reported no significant association. There is robust evidence for mechanisms operating in humans. The CUP Panel concluded the following:

**Consumption of alcoholic drinks is a convincing cause of colorectal cancer. This is based on evidence for intakes above 30 grams per day (about two drinks a day).**

## 7.13 Physical activity

This section includes the evidence for total physical activity and recreational physical activity.

*Note: A variety of measures were used to collect the data on physical activity, so it was not possible to conduct dose-response meta-analyses. Study results were therefore summarised for the highest compared with the lowest physical activity category.*

### 7.13.1 Total physical activity

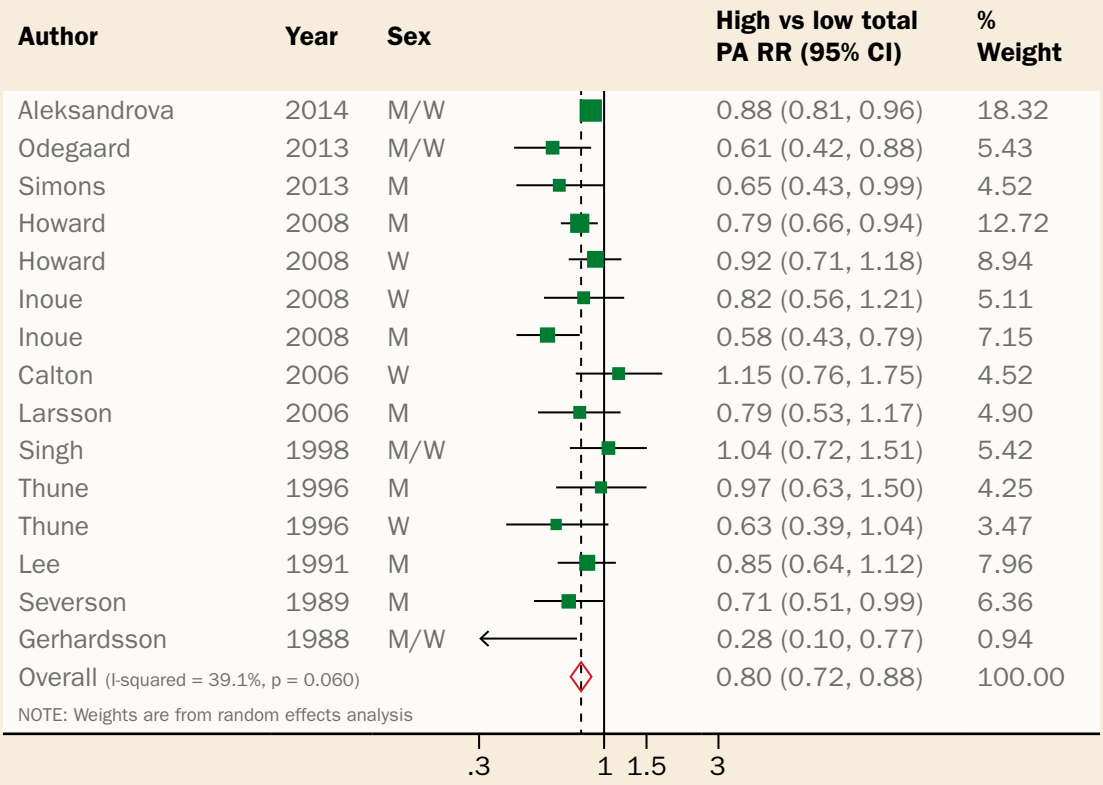
*(Also see CUP Colorectal SLR 2016: Sections 6.1)*

#### Colon cancer

The CUP identified three new or updated studies (three publications) [134, 149, 150], giving a total of 13 studies (15 publications) reviewing the evidence for total physical activity and colon cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 299 and 300).

The new studies presented the results in different units; therefore a dose-response meta-analysis was not conducted. Twelve of the 13 studies were included in an analysis comparing the highest and lowest total physical activity levels ($n$ = 8,396 cases), which showed a 20 per cent significant decreased risk (RR 0.80 (95% CI 0.72–0.88); see **Figure 19** and CUP Colorectal SLR 2016 Figure 512). There was evidence of moderate, but not significant heterogeneity ($I^2$ = 39%, $p_{heterogeneity}$ = 0.06).

**Figure 19: Highest versus lowest analysis of total physical activity and colon cancer**




Analyses for other cancer sites showed a significant inverse association for colorectal cancer when comparing the highest and lowest level of physical activity. No significant association was observed for rectal cancer (see **Table 36** and CUP SLR Figures 511 and 513).

**Table 36: Summary of CUP 2016 cancer site highest versus lowest meta-analysis – physical activity**

| Analysis | Sex | Comparison | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M/W | Highest vs. lowest | 0.81 (0.69–0.95) | 48% | 6 | 5,607 |
| **Rectal cancer** | M/W | Highest vs. lowest | 1.04 (0.92–1.18) | 9% | 9 | 2,326 |

Most studies adjusted for multiple confounders, three studies adjusted for age only [151-153], one study adjusted for age and BMI [154], and one study for age and sex [155], (for more information, see CUP Colorectal SLR 2016 Tables 299 and 300).

Two studies were not included in any of the CUP analyses – one [156] did not measure levels of physical activity and one [29] reported only continuous estimates.

The 2010 SLR also reported a significant inverse association for colon cancer (RR 0.92 (95% CI 0.86–0.99)). The 2016 CUP analysis effect size is bigger and included more than double the number of studies and cases of colon cancer.

### Published pooled and meta-analyses

No published pooled or meta-analyses were identified.

## 7.13.2 Recreational physical activity

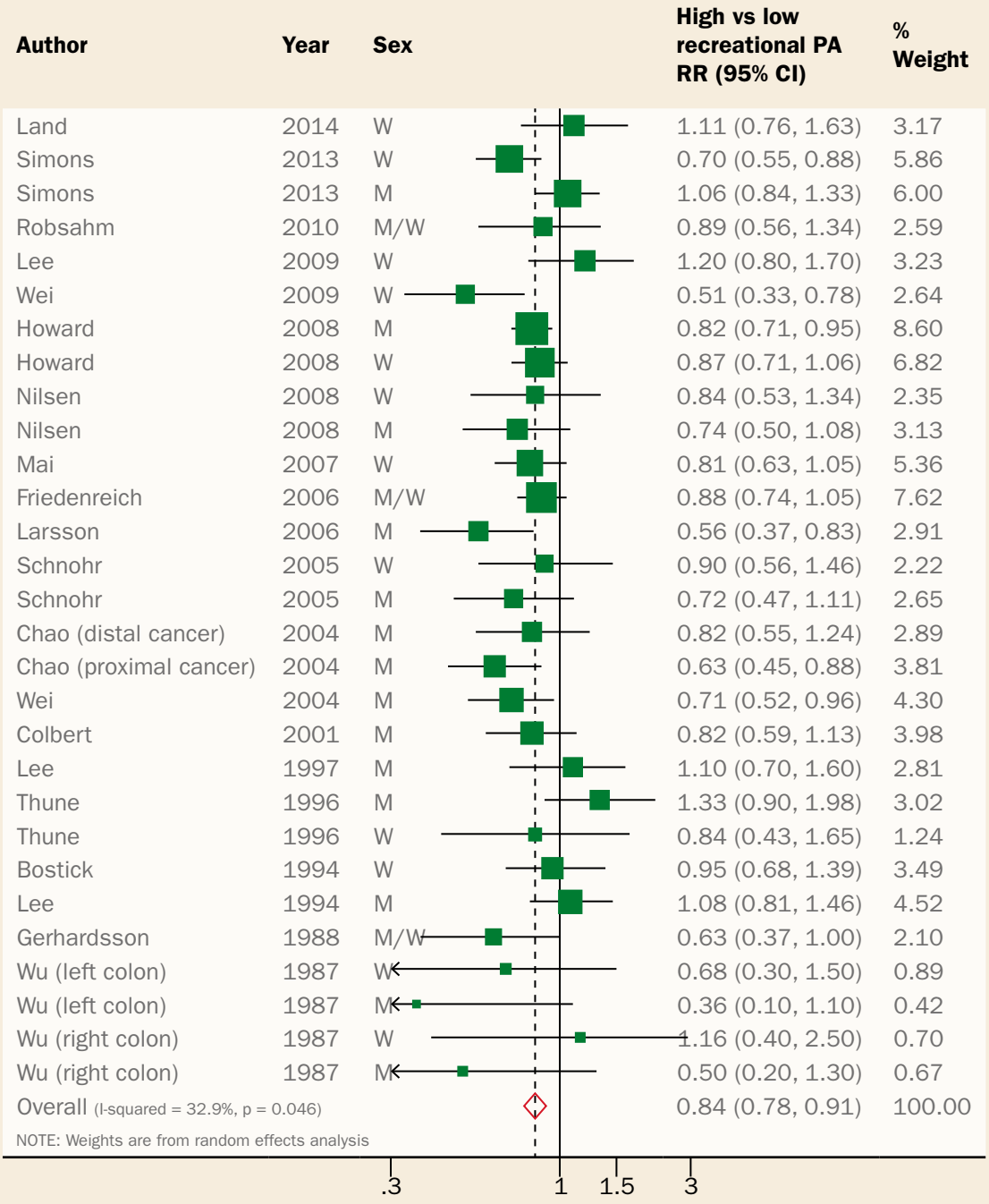
*(Also see CUP Colorectal SLR 2016: Sections 6.1.1.2)*

### Colon cancer

The CUP identified four new or updated studies (four publications) [150, 157-159], giving a total of 21 studies (26 publications) reviewing the evidence for recreational physical activity and colon cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 307 and 308).

The new studies presented the results in different units; therefore a dose-response meta-analysis was not conducted. Twenty of the 25 studies were included in an analysis comparing the highest and lowest recreational physical activity levels (*n* = 10,258 cases), which showed a 16 per cent significant decreased risk (RR 0.84 (95% CI 0.78–0.91); see **Figure 20** and CUP Colorectal SLR 2016 Figure 514). There was evidence of moderate heterogeneity ($I^2$ = 33%, $p_{heterogeneity}$ = 0.046).

**Figure 20: Highest versus lowest analysis of recreational physical activity and colon cancer**




Due to lack of data, no updated analysis was performed for colorectal cancer. Analyses for rectal cancer showed no significant association when comparing the highest and lowest level of recreational physical activity (RR 0.95 (95% CI 0.85–1.07), $I^2$ = 26%, *n* = 4,560 (see CUP Colorectal SLR 2016 Figure 515)).

Five studies were not included in any of the CUP analyses, three due to the outcome being mortality [159-161] and two [162, 163] because they did not report sufficient data.

Most studies adjusted for multiple confounders; three studies adjusted for age only [151-153], one study adjusted for age and BMI [154], and one study for age and sex [155], (for more information, see CUP Colorectal SLR 2016 Tables 307 and 308).

The 2010 SLR reported no significant association for colon cancer (RR 0.98 (95% CI 0.96–1.00)). The CUP analysis included four times as many studies and almost five times as many cases of colon cancer and reached statistical significance.

### Published pooled and meta-analyses

Results from three published meta-analyses [164-166] reporting on recreational physical activity and colon cancer were identified. All analyses reported inverse associations. Results from the CUP and the published meta-analyses are presented in **Table 37**.

**Table 37: Summary of CUP 2016 meta-analysis and published meta-analyses – recreational physical activity**

| Study | Cancer Site | Sex | Highest vs Lowest RR (95% CI) | $I^2$/ P-Value | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **CUP Colorectal Cancer SLR 2016** | Colon cancer | M/W | 0.84 (0.78–0.91) | 33% | 20 | 10,258 |
| **Boyle, 2012 [166]** | Proximal colon cancer | M/W | 0.73 (0.66–0.81) | 31%, 0.06 | 12 cohort and 9 case-control studies | |
| | Distal colon cancer | | 0.74 (0.68–0.80) | 0%, 0.47 | | |
| **Yang, 2010 [165]** | Colon cancer | M | 0.74 (0.61–0.90) | 0.14 | 28 | |
| | | W | 0.99 (0.95–1.02) | 0.41 | | |
| **Harris, 2009 [164]** | Colon cancer | M | 0.80 (0.67–0.96) | 54.1%, 0.01 | 15 | 7,873 |
| | | W | 0.86 (0.76–0.98) | 0%, 0.88 | | |

### Mechanisms

Physical activity reduces body fatness and therefore has a beneficial effect on colorectal cancer risk, possibly through a reduction in insulin resistance and inflammation – both of which have been linked to colorectal cancer development [167-173]. However, it is unclear whether physical activity that is not accompanied by weight loss has a significant impact on these pathways. Other mechanisms by which physical activity may lower

colorectal cancer risk include stimulating digestion and reducing transit time through the intestine [174], though robust data to support this mechanism in humans is limited. Overall, mechanistic data to support a link between physical activity and colorectal cancer are moderate in strength.

### CUP Panel's conclusion:

The evidence is strong and consistently shows significant inverse associations when comparing the highest and lowest levels of total and recreational physical activity and colon cancer incidence. A significant inverse association was observed for total physical activity and colorectal cancer; no significant associations were observed for rectal cancer and either total or recreational physical activity when comparing the highest and the lowest levels of activity. For recreational physical activity and colon cancer risk, three published meta-analyses reported inverse associations. There is robust evidence for mechanisms operating in humans. However, dose-response relationships could not be determined. The CUP Panel concluded the following:

**Physical activity convincingly protects against colon cancer.**

## 7.14 Body fatness

*(Also see CUP Colorectal SLR 2016: Sections 8.1.1, 8.2.1, 8.2.3)*

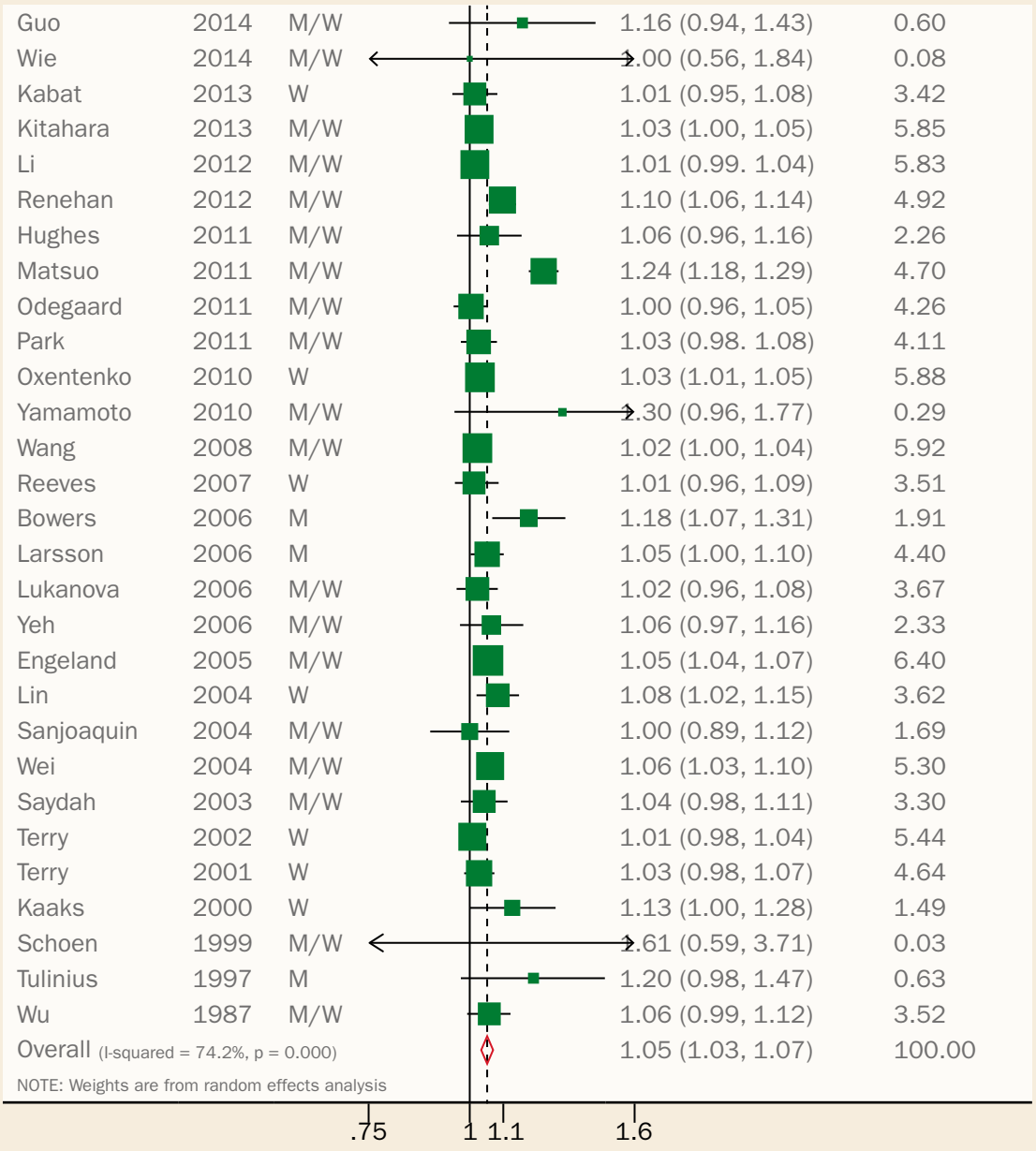
The CUP Panel interpreted body mass index (BMI), waist circumference and waist-to-hip ratio as measures of body fatness. The Panel is aware that these anthropometric measures are imperfect and do not distinguish between lean and fat mass.

### Body mass index

The CUP identified 24 new studies (28 publications) [55, 64, 175-200], giving a total of 57 studies (75 publications) reviewing the evidence for BMI and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 322 and 323). Of 36 studies reporting on colorectal cancer incidence, 23 reported positive associations, ten of which were significant when comparing the highest and the lowest BMI categories. Six reported non-significant inverse associations and five reported inconsistent results by sex. One pooled analysis [201] of eight cohort studies reported a significant positive association for men and a non-significant positive association for women (see CUP Colorectal SLR 2016 Figure 519).

Thirty-eight of the 57 studies were included in the dose-response meta-analysis ($n$ = 71,089 cases), which showed significant five per cent increased risk per 5 kg/m$^2$ (RR 1.05 (95% CI 1.03–1.07); see **Figure 21** (CUP Colorectal SLR 2016 Figure 520)). High heterogeneity ($I^2$ = 74%, $p < 0.001$) was observed. There was no indication of small study bias with Egger's test ($p = 0.16$) (see Figure 521); however, the funnel plot was asymmetric. Visual inspection of the funnel and forest plot shows that the asymmetry is driven by the smaller studies [195, 202, 203] – a study in northern China [176] and the Japanese pooled analysis of eight cohorts [201] that reported stronger associations than the average.

**Figure 21: Dose-response meta-analysis of BMI and colorectal cancer per 5 kg/m²**




The test for non-linearity was significant, $p \leq 0.01$. Colorectal cancer risk increased with greater BMI throughout the range observed; however, the association appears to be stronger above 27 kg/m² (see **Figure 22** and **Table 38** and CUP Colorectal SLR 2016 Figure 525 and Table 324).

**Figure 22: Non-linear analysis of BMI and colorectal cancer per 5 kg/m²**

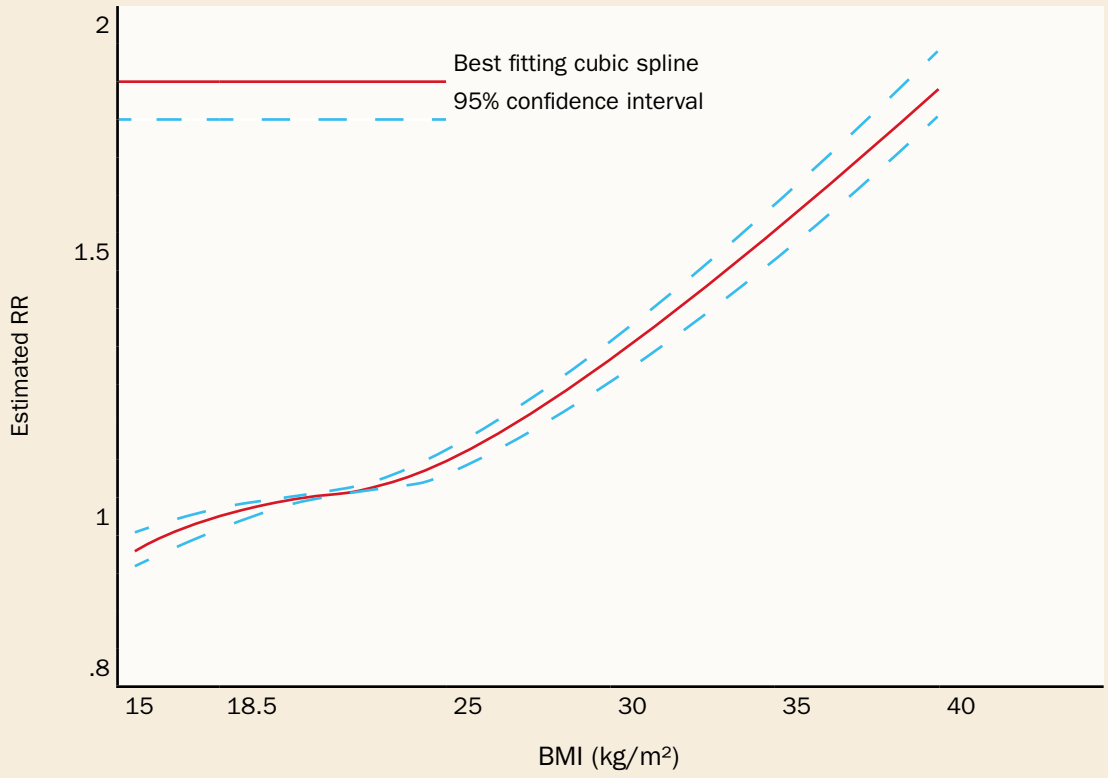



**Table 38: Non-linear estimates of BMI and colorectal cancer**

| BMI (kg/m²) | RR (95% CI) |
|---|---|
| 18.75 | 0.98 (0.98–0.99) |
| 20.29 | 1.00 |
| 23.75 | 1.05 (1.03–1.06) |
| 25.25 | 1.08 (1.06–1.10) |
| 27.50 | 1.15 (1.13–1.18) |
| 31.20 | 1.34 (1.29–1.38) |

Significant positive associations were observed for colorectal cancer in both men and women. Analyses by geographical location showed significant positive associations in North American and European populations and no significant association for Asian populations. When stratified by cancer site, significant positive associations were observed for colon, proximal colon, distal colon and rectal cancer (see **Table 39** and CUP Colorectal SLR 2016 Figures 522, 523, 528, 533, 536 and 541).

**Table 39: Summary of CUP 2016 cancer site dose-response meta-analyses – BMI**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 5 kg/m$^2$ | 1.08 (1.04–1.11) | 83% | 20 | |
| | W | Per 5 kg/m$^2$ | 1.05 (1.02–1.08) | 83% | 24 | |
| **Colon cancer** | M/W | Per 5 kg/m$^2$ | 1.07 (1.05–1.09) | 72% | 41 | 72,605 |
| **Proximal colon cancer** | M/W | Per 5 kg/m$^2$ | 1.05 (1.03–1.08) | 44% | 20 | 8,437 |
| **Distal colon cancer** | M/W | Per 5 kg/m$^2$ | 1.08 (1.04–1.11) | 52% | 20 | 14,985 |
| **Rectal cancer** | M/W | Per 5 kg/m$^2$ | 1.02 (1.01–1.04) | 59% | 35 | 67,732 |

All studies were adjusted for multiple confounders. About half of the studies (31) used measured height and weight to calculate BMI, 27 studies used self-reported height and weight, and six studies used BMI from medical records (for more information, see CUP Colorectal SLR 2016 Tables 322 and 323).

Fourteen studies were not included in any of the CUP analyses. Four [99, 204–206] reported mean exposure only, three [207-209] did not report RRs, two [185, 188] reported gene interactions only, one [210] only reported two categories of results, one [199] did not report the number of cases by category, one [191] reported an outcome of mucinous cancer, one [186] had a study population with type II diabetes and another [197] had a study population with cardiovascular disease.

The 2010 SLR reported results per 1 kg/m$^2$ and showed a larger effect size – two per cent increased risk per 1 kg/m$^2$ (RR 1.02 (95% CI 1.02–1.03)). The CUP meta-analysis included 15 more studies and over 8,000 more cases of colorectal cancer.

### Published pooled analyses and meta-analyses

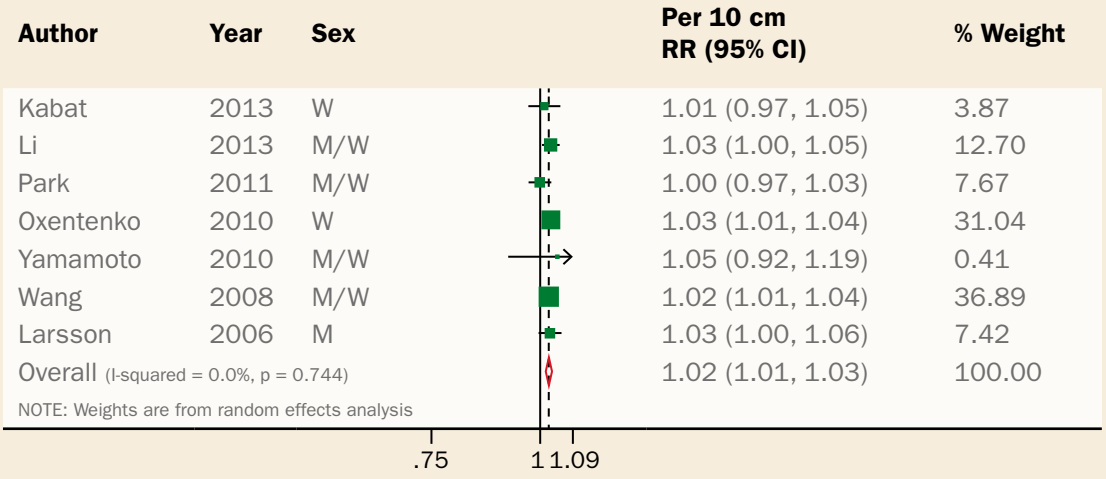
One published pooled analysis of eight Japanese studies [201] on BMI and colorectal cancer risk was identified, showing significant increased risk per 1 kg/m$^2$ in both men and women (RR 1.03 (95% CI 1.02–1.04) and RR 1.07 (95% CI 1.05–1.08) respectively) and was included in the CUP dose-response meta-analysis. One published meta-analysis [211] was identified in the CUP Colorectal SLR 2016 which reported a significant positive association comparing obese with normal BMIs (RR 1.33 (95% CI 1.25–1.42), $I^2$ = 69%, *n* = 41 studies).

### Waist circumference

The CUP identified nine new or updated studies (13 publications) [177, 184, 185, 187, 188, 190, 194-196, 200, 212-214], giving a total of 13 studies (18 publications) reviewing the evidence for waist circumference and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 332 and 333). Of 10 studies reporting on colorectal cancer incidence, nine reported positive associations, three of which were significant when comparing the highest and the lowest categories. One study reported inconsistent results by sex (see CUP Colorectal SLR 2016 Figure 547).

Eight of the 13 studies were included in the dose-response meta-analysis (*n* = 4,301 cases), which showed a significant two per cent increased risk per 10 centimetres of waist circumference with no heterogeneity ($I^2$ = 0%, p < 0.001) (RR 1.02 (95% CI 1.01–1.03); see **Figure 23** (CUP Colorectal SLR 2016 Figure 548)).

**Figure 23: Dose-response meta-analysis of waist circumference and colorectal cancer per 10 centimetres**




Positive associations were observed for colorectal cancer in both men and women, and were significant in women only (see **Table 40** and CUP Colorectal SLR 2016 Figure 550). Analyses by geographical location showed significant positive associations in North American and Asian populations (see CUP Colorectal SLR 2016 Figure 551). When stratified by cancer site, positive associations were observed for colon and rectal cancer, and were significant for colon cancer (see **Table 40** and CUP Colorectal SLR 2016 Figures 554 and 561).

**Table 40: Summary of CUP 2016 cancer site dose-response meta-analysis – waist circumference**

| Analysis | Sex | Increment | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 10 cm | 1.02 (1.00–1.04) | 47% | 4 | |
| | W | Per 10 cm | 1.03 (1.02–1.04) | 0% | 5 | |
| **Colon cancer** | M/W | Per 10 cm | 1.04 (1.02–1.06) | 63% | 10 | 3,613 |
| **Rectal cancer** | M/W | Per 10 cm | 1.02 (1.00–1.03) | 0% | 6 | 1,579 |

In all studies the RR estimates were adjusted for main potential confounders (for more information, see CUP Colorectal SLR 2016 Tables 332 and 333).

One study [188] was not included in any of the CUP analyses due to reporting gene-interaction information only.

The CUP findings showed a smaller summary risk estimate than those from the 2010 SLR (RR 1.03 (95% CI 1.02–1.04), $I^2$ = 0%, three studies, *n* = 1,798). The CUP meta-analysis included five more studies and more than double the number of cases of colorectal cancer.

### Published pooled analyses and meta-analyses

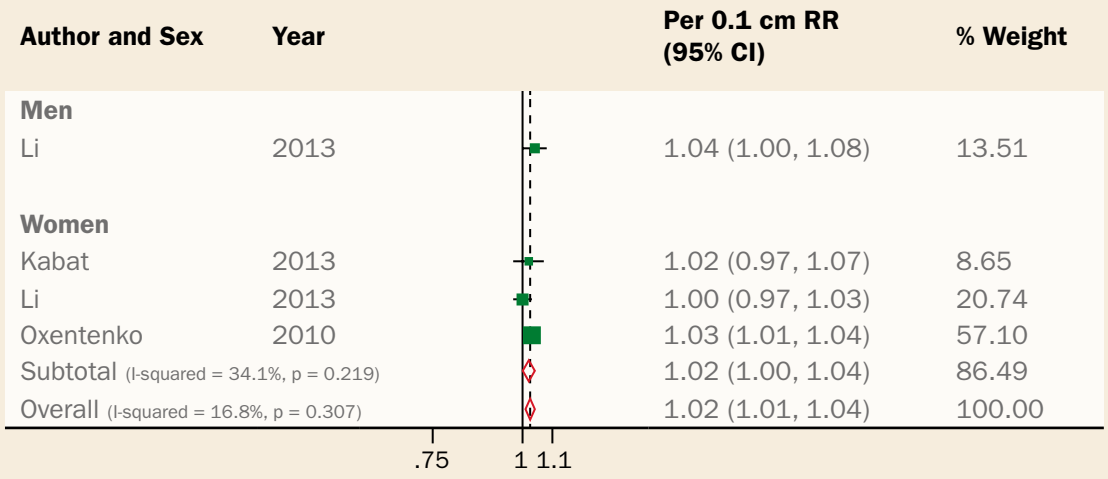
One published meta-analysis [211] was identified in the CUP Colorectal SLR 2016 which reported a significant positive association comparing highest versus lowest waist circumference (RR 1.45 (95% CI 1.33–1.60), $I^2$ = 11%, 54 studies).

### Waist-hip ratio

The CUP identified five new studies or updated (six publications) [177, 184, 185, 194, 196, 213], giving a total of six studies (10 publications) reviewing the evidence for waist-hip ratio and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 336 and 337). Of five studies reporting on colorectal cancer incidence, four reported positive associations, two of which were significant when comparing the highest and the lowest categories. One study reported inconsistent results by sex (see CUP Colorectal SLR 2016 Figure 565).

Four of the six studies were included in the dose-response meta-analysis (*n* = 2,564 cases), which showed significant two per cent increased risk per 0.1 unit of waist-hip ratio (RR 1.02 (95% CI 1.01–1.04); see **Figure 24** (CUP Colorectal SLR 2016 Figure 566)). Low heterogeneity was observed ($I^2$ = 17%, p = 0.307).

**Figure 24: Dose-response meta-analysis of waist-hip ratio and colorectal cancer per 0.1 unit**




When stratified by cancer site, a significant positive association was observed for colon cancer (RR 1.20 (95% CI 1.09–1.32), $I^2$ = 87%, six studies, *n* = 2,481; CUP Colorectal SLR 2016 Figure 570). For rectal cancer, four studies were identified. No new dose-response meta-analysis was conducted; the 2010 SLR reported a non-significant increase risk (RR 1.20 (95% CI 1.07–1.34), $I^2$ = 0%, three studies, *n* = 970).

The relative risks estimates in all studies were adjusted for potential confounders (for more information, see CUP Colorectal SLR 2016 Tables 336 and 337).

One study [185] was not included in any of the CUP analyses due to reporting only gene interaction data.

The summary risk estimate from the CUP was much smaller than the 2010 SLR (RR 1.17 (95% CI 1.09–1.25), $I^2$ = 0%, three studies, *n* = 1,785). The CUP included one more study, but the other three had been superseded by more recent publications that reported much lower risk estimates than included in the 2010 SLR.

### Published pooled analyses and meta-analyses

No published pooled or meta-analyses were identified.

### Mechanisms

Higher body fatness is associated with increased levels of insulin, which can promote cell growth and inhibit apoptosis and has been linked to greater risk of colorectal cancer in human [167-169] and experimental studies [170, 171]. Body fatness also stimulates the body's inflammatory response, which can also promote colorectal cancer development [172, 173]. Overall, there are convincing mechanistic data supporting a link between body fatness and colorectal cancer.

### CUP Panel's conclusion:

The evidence for colorectal cancer was consistent in the direction of effect, with a clear dose-response relationship showing a significant increased risk with increased BMI; high heterogeneity was observed. There was evidence of a non-linear dose-response, where the risk increase is higher above 27 kg/m$^2$ for colorectal cancer. The CUP findings were supported by one published meta-analysis. Significant positive associations were observed for colorectal in the dose-response analysis for waist circumference, supported by one published meta-analysis, and for waist-hip ratio. There is robust evidence for mechanisms in humans. The CUP Panel concluded the following:

**Greater body fatness is a convincing cause of colorectal cancer.**

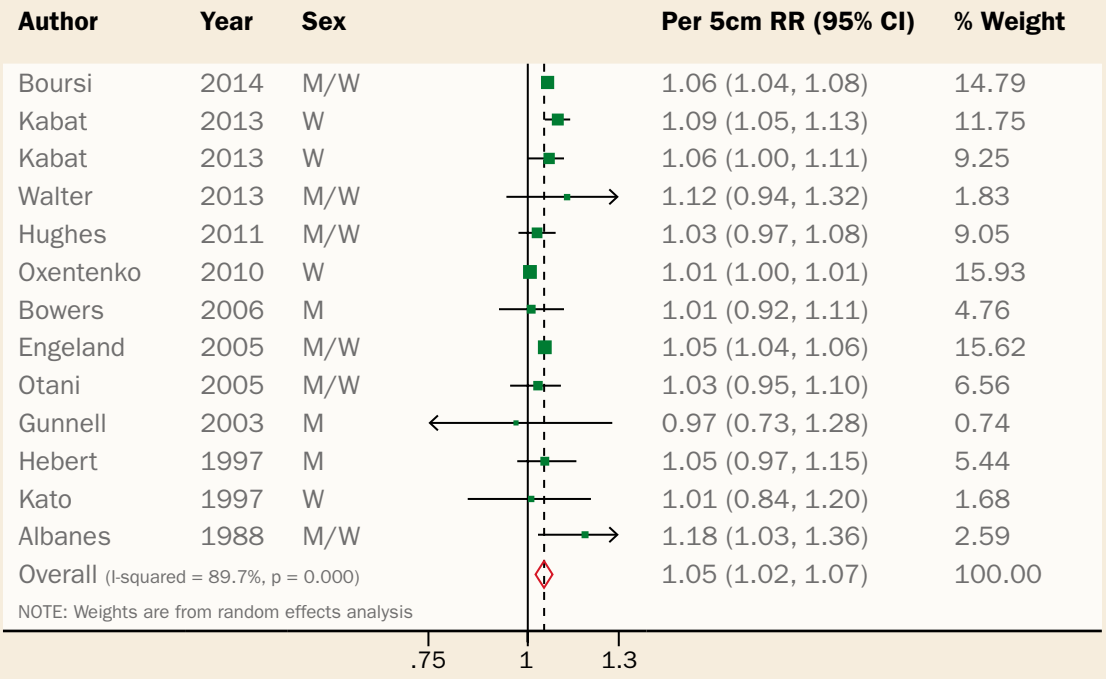
## 7.15 Adult attained height

*(Also see CUP Colorectal SLR 2016: Sections 8.3.1)*

The CUP identified nine new or updated studies (10 publications) [55, 181, 185, 187, 188, 194, 215-218], giving a total of 20 studies (26 publications) reviewing the evidence for height and colorectal cancer (for a full list of references, see CUP Colorectal SLR 2016 Tables 344 and 345). Of 11 studies reporting on colorectal cancer incidence, eight reported positive associations, five of which were significant. One reported a non-significant inverse association, one reported no effect (RR 1.00) and one reported inconsistent results by sex (see CUP Colorectal SLR 2016 Figure 574).

Thirteen of the 20 studies were included in the dose-response meta-analysis (*n* = 65,880 cases), which showed a significant five per cent increased risk per five centimetre increase in height (RR 1.05 (95% CI 1.02–1.07); see **Figure 25** (CUP Colorectal SLR 2016 Figure 575). High heterogeneity ($I^2$ = 90%, p < 0.001) was observed, partly explained by the stronger association in women compared with men and the slightly stronger association observed in studies in North America compared with studies in Europe. There was evidence of publication or small study bias (p = < 0.001; see CUP Colorectal SLR Figure 576) with one small study [219] reporting an inverse, but not significant association.

**Figure 25: Dose-response meta-analysis of height and colorectal cancer per 5 centimetres**




For colorectal cancer, analyses stratified by sex showed significant positive associations for both men and women (see **Table 41** and CUP Colorectal SLR 2016 Figure 577). For colorectal cancer, analyses stratified by geographical location showed significant positive associations in European and North American populations (see CUP SLR Figure 578). When stratified by cancer site, significant positive associations were observed for colon and rectal cancer (see **Table 41** and CUP Colorectal SLR 2016 Figures 582 and 589).

**Table 41: Summary of CUP 2016 cancer site dose-response meta-analysis – adult attained height**

| Analysis | Sex | | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|---|
| **Colorectal cancer** | M | Per 5 cm | 1.04 (1.03–1.05) | 0% | 8 | |
| | W | Per 5 cm | 1.06 (1.02–1.09) | 92% | 9 | |
| **Colon cancer** | M/W | Per 5 cm | 1.05 (1.04–1.07) | 90% | 14 | 85,589 |
| **Rectal cancer** | M/W | Per 5 cm | 1.03 (1.01–1.06) | 60% | 13 | 25,005 |

All studies were adjusted for multiple different confounders (for more information, see CUP Colorectal SLR 2016 Tables 344 and 345).

One study [185] was not included in any of the CUP analyses as it reported gene interaction data only.

The CUP findings are similar to those from the 2010 SLR (which also showed a five per cent increased risk per five centimetres). The CUP meta-analysis included five more studies.

### Published pooled analyses and meta-analyses

One published pooled analysis [220] on height and colorectal cancer risk was identified in the CUP Colorectal SLR 2016 which reported a significant positive association per 6.5 centimetres. This was not included in the CUP dose-response meta-analysis. Results from the CUP and the published pooled analysis are presented in **Table 42**.

**Table 42: Summary of CUP 2016 meta-analysis and published pooled analysis – adult attained height**

| Analysis | Increment/ Contrast | RR (95% CI) | $I^2$ | No. Studies | No. Cases |
|---|---|---|---|---|---|
| **CUP Colorectal Cancer SLR 2016** | Per 5 cm | 1.05 (1.02–1.07) | 90% | 13 | 65,880 |
| **Emerging risk factors collaboration [220]** | Per 6.5 cm | 1.07 (1.03–1.11) | 12% | 121 | 4,855 deaths |

## Mechanisms

The proposed mechanisms by which higher adult attained height is linked to higher risk of colorectal cancer include greater exposure to growth factors such as growth hormone and insulin-like growth factors in childhood and early adulthood [221, 222], and excess calorie consumption in early life. Taller people have more cells and thus there is greater opportunity for mutations leading to cancer development [223]. In addition, taller adults also have longer intestines; therefore, there may be greater potential for exposure to mutagenic or cancer-promoting agents. Overall there are moderate mechanistic data supporting greater adult height as a risk factor for colorectal cancer.

### CUP Panel's conclusion:

The evidence for colorectal cancer was consistent in the direction of effect, with a clear dose-response relationship showing a significant increased risk with increased height. There was evidence of high heterogeneity, in stratified analyses the high heterogeneity was observed in the analysis on women and was due to the size of the effect. One published pooled analysis also reported a significant positive association. There is robust evidence for mechanisms operating in humans. The CUP Panel concluded the following:

**Developmental factors leading to greater linear growth (marked by adult attained height) are a convincing cause of colorectal cancer.**

## 7.16 Other

Other exposures were evaluated. However, data were either of too low quality or too inconsistent, or the number of studies too few to allow conclusions to be reached. This list of exposures judged as 'limited – no conclusion' is summarised in the matrix on **page 8**.

The evidence for garlic, previously judged as 'probable decreases risk', and the evidence for foods containing animal fats and foods containing sugars, previously judged as 'limited-suggestive increases risk' in the 2011 Colorectal Cancer Report [3], were less consistent, and the Panel could not draw any conclusions on the updated evidence.

Evidence for the following exposures previously judged as 'limited – no conclusion' in the 2011 Colorectal Cancer Report remained unchanged after updating the analyses with new data identified in the CUP Colorectal SLR 2016: glycaemic index, folate, vitamin E, selenium, dietary pattern.

The following exposure, which was also previously too limited to draw conclusions in the 2011 CUP Colorectal Report and not updated as part of the CUP Colorectal SLR 2016 due to a lack of new evidence, remained 'limited – no conclusion': low fat.

In addition, evidence for the following exposures, which were not reviewed in the 2011 CUP Colorectal Report, have been judged as 'limited - no conclusion': cereals (grains) and their products, potatoes, poultry, shellfish and other seafood, fatty acid composition, cholesterol, dietary n-3 fatty acid from fish, legumes, non-dairy sources of calcium, sugar (sucrose), coffee, tea, caffeine, carbohydrate, total fat, starch, glycaemic load, vitamin A, vitamin B6, methionine, beta-carotene, alpha-carotene, lycopene, retinol, energy intake, meal frequency.

# 8. Comparison with the 2011 CUP Colorectal Cancer Report

Much of the new evidence in this report was on wholegrains, vitamin D, foods containing vitamin C, fish, multivitamin supplements, and low intakes of fruit and non-starchy vegetables. Overall the Panel noted the consistency in the findings of strong evidence (convincing or probable) from the 2011 CUP Report and this CUP update.

# 9. Conclusions

The Continuous Update Project (CUP) Panel judges as follows:

## Convincing evidence

**Physical activity: Physical activity convincingly protects against colon cancer.**

**Processed meat: Consumption of processed meat is a convincing cause of colorectal cancer.**

**Alcoholic drinks: Consumption of alcoholic drinks is a convincing cause of colorectal cancer. This is based on evidence for intakes above 30 grams per day (about two drinks a day).**

**Body fatness: Greater body fatness is a convincing cause of colorectal cancer.**

**Adult attained height: Developmental factors leading to greater linear growth (marked by adult attained height) are a convincing cause of colorectal cancer.**

## Probable evidence

**Wholegrains: Consumption of wholegrains probably protects against colorectal cancer.**

**Dietary fibre: Consumption of foods containing dietary fibre probably protects against colorectal cancer.**

**Dairy products: Consumption of dairy products probably protects against colorectal cancer.**

**Calcium supplements: Taking calcium supplements probably protects against colorectal cancer.**

**Red meat: Consumption of red meat is probably a cause of colorectal cancer.**

### Limited – suggestive evidence

**Foods containing vitamin C: The evidence suggesting that foods containing vitamin C decreases the risk of colon cancer is limited.**

**Fish: The evidence suggesting that consumption of fish decreases the risk of colorectal cancer is limited.**

**Vitamin D: The evidence suggesting that vitamin D decreases the risk of colorectal cancer is limited.**

**Multivitamin supplements: The evidence suggesting that taking multivitamin supplements decreases the risk of colorectal cancer is limited.**

**Non-starchy vegetables: The evidence suggesting that low consumption of non-starchy vegetables increases the risk of colorectal cancer is limited.**

**Fruits: The evidence suggesting that low consumption of fruit increases the risk of colorectal cancer is limited.**

**Foods containing haem iron: The evidence suggesting that consumption of foods containing haem iron increases the risk of colorectal cancer is limited.**

For a full description of the definitions of, and criteria for, the terminology of 'convincing', 'probable', 'limited – suggestive', 'limited – no conclusion' and 'substantial effect on risk unlikely', see the **Appendix** on page 106.

The Cancer Prevention Recommendations were reviewed by the CUP Panel and published in 2018. Please see Recommendations and public health and policy implications for further details.

Each conclusion on the likely causal relationship between an exposure and the risk of cancer forms a part of the overall body of evidence that is considered during the process of making Cancer Prevention Recommendations. Any single conclusion does not represent a recommendation in its own right. The 2018 Cancer Prevention Recommendations are based on a synthesis of all these separate conclusions, as well as other relevant evidence.

# Abbreviations

| | |
|---|---|
| **AICR** | American Institute for Cancer Research |
| **BMI** | Body mass index |
| **CI** | Confidence interval |
| **CUP** | Continuous Update Project |
| **DNA** | Deoxyribonucleic acid |
| **EPIC** | European Prospective Investigation into Cancer and Nutrition |
| **FAP** | Familial adenomatous polyposis |
| **HNPCC** | Hereditary non-polyposis colorectal cancer |
| **IARC** | International Agency for Research on Cancer |
| **MEC** | Multiethnic Cohort |
| ***n*** | Number of cases |
| **PUFA** | Poly-unsaturated fatty acids |
| **RR** | Relative risk |
| **SLR** | Systematic literature review |
| **WCRF** | World Cancer Research Fund |

# Acknowledgements

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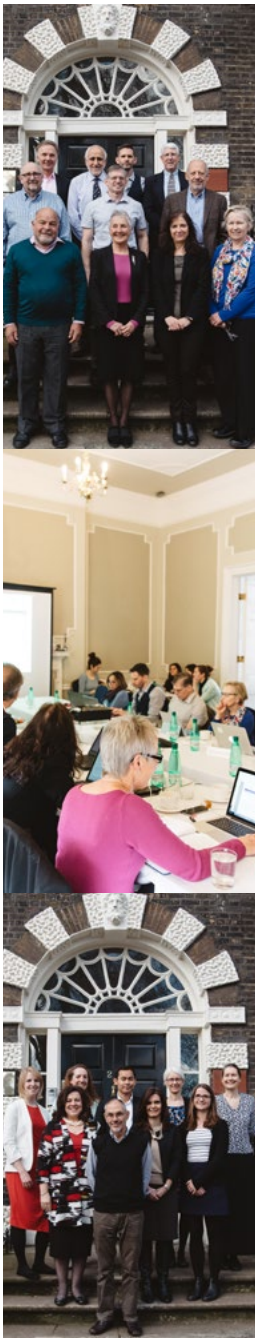

# Glossary

### Adenocarcinoma

Cancer of glandular epithelial cells.

### Adenosquamous carcinoma

A type of cancer that contains two types of cells: squamous cells (thin, flat cells that line certain organs) and gland-like cells.

### Adjustment

A statistical tool for taking into account the effect of known confounders (see confounder).

### Antioxidant

A molecule that inhibits the oxidation of other molecules. Oxidation is a chemical reaction involving the loss of electrons, which can produce free radicals. In turn, these radicals can start chain reactions, which can cause damage or death to cells (see free radicals).

### Apoptosis

A process occurring during the normal life cycle of a cell that leads to programmed cell death when the cell reaches senescence, or when errors in DNA replication occur. Failure of apoptosis can lead to populations of cells with damaged DNA that can increase the risk of cancer.

### Bias

In epidemiology, consistent deviation of an observed result from the true value in a particular direction (systematic error) due to factors pertaining to the observer or to study design or analysis (see selection bias).

### Bioactive compounds

Compounds that have an effect on a living organism, tissue or cell. In nutrition, bioactive compounds are distinguished from essential nutrients.

### Body mass index (BMI)

Body weight expressed in kilograms divided by the square of height expressed in metres (BMI = kg/m2). Provides an indirect measure of body fatness. Also known as Quetelet's Index.

### Caecum

A pouch connected to the junction of the small and large intestines.

### Carcinogen

Any substance or agent capable of causing cancer.

### Case-control study

An epidemiological study in which the participants are chosen based on their disease or condition (cases) or lack of it (controls), to test whether distant or recent history of an exposure such as smoking, genetic profile, alcohol consumption or dietary intake is associated with the risk of disease.

### Cell differentiation

The process by which a less specialised cell becomes a more specialised cell type.

### Cell proliferation

The process that results in an increase of the number of cells and is defined by the balance between cell divisions and cell loss through cell death or differentiation.

### Chronic

A health condition or disease that is persistent or long lasting.

### Cohort study

A study of a (usually large) group of people whose characteristics are recorded at recruitment (and sometimes also later), followed up for a period of time during which outcomes of interest are noted. Differences in the frequency of outcomes (such as disease) within the cohort are calculated in relation to different levels of exposure to factors of interest – for example, smoking, alcohol consumption, diet and exercise. Differences in the likelihood of a particular outcome are presented as the relative risk, comparing one level of exposure with another.

### Colon

Part of the large intestine extending from the cecum to the rectum.

### Colonocyte

An epithelial cell of the colon.

### Confidence interval (CI)

A measure of the uncertainty in an estimate, usually reported as 95 per cent confidence interval (CI), which is the range of values within which there is a 95 per cent chance that the true value lies. For example, the effect of smoking on the relative risk of lung cancer may be expressed as 10 (95% CI 5–15). This means that the estimate of the relative risk was calculated as 10 and that there is a 95 per cent chance that the true value lies between 5 and 15.

### Confounder

A variable that is associated with both an exposure and a disease but is not in the causal pathway from the exposure to the disease. If not adjusted for within a specific epidemiological study, this factor may distort the apparent exposure–disease relationship. An example is that smoking is related both to coffee drinking and to risk of lung cancer, and thus unless accounted for (adjusted) in studies, might make coffee drinking appear falsely as a cause of lung cancer.

### Countries characterised by higher indices of development and/or income

As defined by the World Bank, countries with a gross average annual national product of more than an agreed figure per head (in 2017, this was US$12,476). This term is more precise than, and used in preference to, 'economically developed countries'.

### Countries characterised by lower indices of development and/or income

As defined by the World Bank, countries with a gross average annual national product of less than an agreed figure per head (in 2017, this was US$1,025). This term is more precise than, and used in preference to, 'economically developing countries'.

### Deoxyribonucleic acid (DNA)

The double-stranded, helical molecular chain found within the nucleus of each cell, which carries the genetic information.

### Dietary fibre

Constituents of plant cell walls that are not digested in the small intestine. Several methods of analysis are used, which identify different components. The many constituents that are variously included in the definitions have different chemical and physiological features that are not easily defined under a single term. The different analytical methods do not generally characterise the physiological impact of foods or diets. Non-starch polysaccharides are a consistent feature and are fermented by colonic bacteria to produce energy and short chain fatty acids including butyrate. The term 'dietary fibre' is increasingly seen as a concept describing a particular aspect of some dietary patterns.

### Dose-response

A term derived from pharmacology that describes the degree to which an effect changes as the level of an exposure changes, for instance, intake of a drug or food (see Second Expert Report Box 3.2).

### Exposure

A factor to which an individual may be exposed to varying degrees, such as intake of a food, level or type of physical activity, or aspect of body composition.

### Free radicals

An atom or group of atoms that have one or more unpaired electrons. A prominent feature of radicals is that they have high chemical reactivity, which explains their normal biological activities and how they inflict damage on cells. There are many types of radicals, but those of most importance in biological systems are derived from oxygen and known collectively as reactive oxygen species.

### Genotoxic

Chemical agents that damage the genetic information within a cell, causing mutations, which may lead to cancer.

### Heterocyclic amines and polycyclic aromatic hydrocarbons

Potentially carcinogenic chemicals formed when muscle meat, including beef, pork, fish or poultry, is cooked using high-temperature methods.

### Heterogeneity

A measure of difference between the results of different studies addressing a similar question. In meta-analysis, the degree of heterogeneity may be calculated statistically using the $I^2$ test.

### Immune response

The production of antibodies or specialised cells in response to foreign proteins or other substances.

### Incidence rates

The number of new cases of a condition appearing during a specified period of time expressed relative to the size of the population; for example, 60 new cases of breast cancer per 100,000 women per year.

### Inflammation

The immunologic response of tissues to injury or infection. Inflammation is characterized by accumulation of white blood cells that produce several bioactive chemicals (cytokines), causing redness, pain, heat and swelling.

### Lipid peroxidation

The oxidative degradation of lipids, when free radicals 'steal' electrons from the lipids in cell membranes, resulting in cell damage.

### Localised cancer

A malignancy limited to the organ of origin.

### Meta-analysis

The process of using statistical methods to combine the results of different studies.

### Metastasis or metastatic disease

The spread of a cancer from its site of origin to other tissues not directly neighbouring it.

### More developed regions

As defined by IARC, all regions of Europe plus Northern America, Australia, New Zealand and Japan.

### Mutation

A permanent change of the nucleotide sequence of the genome (an organism's complete set of DNA).

### Nested case-control study

A case-control study in which cases and controls are drawn from the population of a cohort study; often used for studies of prospectively collected information or biological samples.

### Odds ratio

A measure of the risk of an outcome such as cancer, associated with an exposure of interest, used in case-control studies; approximately equivalent to relative risk.

### Pathogenesis

The origin and development of disease; the mechanisms by which causal factors increase the risk of disease.

### Polymorphisms

Common variations (in more than one per cent of the population) in the DNA sequence of a gene.

### Pooled analysis

In epidemiology, a type of study in which original individual-level data from two or more original studies are obtained, combined and re-analysed.

### Processed meat

Meat (usually red meat) that is preserved by smoking, curing or salting, or by the addition of preservatives. Definitions vary between countries and studies as to what precisely is included.

### Randomised controlled trial (RCT)

A study in which a comparison is made between one intervention (often a treatment or prevention strategy) and another (control). Sometimes the control group receives an inactive agent (a placebo). Groups are randomised to one intervention or the other, so that any difference in outcome between the two groups can be ascribed with confidence to the intervention. Sometimes, neither investigators nor subjects know to which intervention they have been randomised; this is called ‘double-blinding’.

### Rectum

The final section of the large intestine, terminating at the anus.

### Regionalised cancer

Tumor extension beyond the limits of the organ of origin without being distant.

### Relative risk (RR)

The ratio of the rate of an outcome (e.g., disease (incidence) or death (mortality)) among people exposed to a factor, compared with the rate among the unexposed; usually used in cohort studies.

### Selection bias

Bias arising from the procedures used to select study participants and from factors influencing participation.

### Short chain fatty acids

Fatty acids with fewer than six carbon atoms, which are produced when bacteria ferment fibre in the colon.

### Statistical significance

The probability that any observed result has or has not occurred by chance.

Conventionally, a probability of less than five per cent ($p < 0.05$) that a study result has occurred by chance is considered 'statistically significant' (see confidence interval).

### Systematic literature review (SLR)

A means of compiling and assessing published evidence that addresses a scientific question with a predefined protocol and transparent methods. May or may not include meta-analysis.

### Tumour-suppressor genes

Normal genes that slow down cell division, repair DNA mistakes, or promote apoptosis or programmed cell death. When tumour suppressor gene function is impaired, cells can accumulate errors in DNA that can lead to cancer.

### Waist-hip ratio (WHR)

A measure of body shape indicating central (abdominal) fat distribution.

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# Appendix: Criteria for grading evidence for cancer prevention

See also Judging the evidence, section 8.

Adapted from Chapter 3 of the 2007 Second Expert Report. Listed here are the criteria agreed by the Panel that were necessary to support the judgements shown in the matrices. The grades shown here are 'convincing', 'probable', 'limited – suggestive', 'limited – no conclusion', and 'substantial effect on risk unlikely'. In effect, the criteria define these terms.

These criteria were used in a modified form for breast cancer survivors (see CUP Breast cancer survivors report 2014).

## CONVINCING (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a convincing causal (or protective) relationship, which justifies making recommendations designed to reduce the risk of cancer. The evidence is robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- No substantial unexplained heterogeneity within or between study types or in different populations relating to the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.
- Presence of a plausible biological gradient ('dose-response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- Strong and plausible experimental evidence, either from human studies or relevant animal models, that typical human exposures can lead to relevant cancer outcomes.

## PROBABLE (STRONG EVIDENCE)

Evidence strong enough to support a judgement of a probable causal (or protective) relationship, which generally justifies recommendations designed to reduce the risk of cancer.

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- No substantial unexplained heterogeneity between or within study types in the presence or absence of an association, or direction of effect.
- Good-quality studies to exclude with confidence the possibility that the observed association results from random or systematic error, including confounding, measurement error and selection bias.
- Evidence for biological plausibility.

## LIMITED – SUGGESTIVE

Evidence that is too limited to permit a probable or convincing causal judgement but is suggestive of a direction of effect. The evidence may be limited in amount or by methodological flaws but shows a generally consistent direction of effect. This judgement is broad and includes associations where the evidence falls only slightly below that required to infer a probably causal association through to those where the evidence is only marginally strong enough to identify a direction of effect. This judgement is very rarely sufficient to justify recommendations designed to reduce the risk of cancer; any exceptions to this require special, explicit justification.

All of the following are generally required:

- Evidence from at least two independent cohort studies or at least five case-control studies.
- The direction of effect is generally consistent though some unexplained heterogeneity may be present.
- Evidence for biological plausibility.

## LIMITED – NO CONCLUSION

Evidence is so limited that no firm conclusion can be made. This judgement represents an entry level and is intended to allow any exposure for which there are sufficient data to warrant Panel consideration, but where insufficient evidence exists to permit a more definitive grading. This does not necessarily mean a limited quantity of evidence. A body of evidence for a particular exposure might be graded ‘limited – no conclusion’ for a number of reasons. The evidence may be limited by the amount of evidence in terms of the number of studies available, by inconsistency of direction of effect, by methodological flaws (for example, lack of adjustment for known confounders) or by any combination

of these factors. When an exposure is graded 'limited – no conclusion', this does not necessarily indicate that the Panel has judged that there is evidence of no relationship. With further good-quality research, any exposure graded in this way might in the future be shown to increase or decrease the risk of cancer. Where there is sufficient evidence to give confidence that an exposure is unlikely to have an effect on cancer risk, this exposure will be judged 'substantial effect on risk unlikely'.

There are also many exposures for which there is such limited evidence that no judgement is possible. In these cases, evidence is recorded in the full CUP SLRs on the World Cancer Research Fund International website (**dietandcancerreport.org**). However, such evidence is usually not included in the summaries.

## SUBSTANTIAL EFFECT ON RISK UNLIKELY (STRONG EVIDENCE)

Evidence is strong enough to support a judgement that a particular food, nutrition or physical activity exposure is unlikely to have a substantial causal relation to a cancer outcome. The evidence should be robust enough to be unlikely to be modified in the foreseeable future as new evidence accumulates.

All of the following are generally required:

- Evidence from more than one study type.
- Evidence from at least two independent cohort studies.
- Summary estimate of effect close to 1.0 for comparison of high- versus low-exposure categories.
- No substantial unexplained heterogeneity within or between study types or in different populations.
- Good-quality studies to exclude, with confidence, the possibility that the absence of an observed association results from random or systematic error, including inadequate power, imprecision or error in exposure measurement, inadequate range of exposure, confounding and selection bias.
- Absence of a demonstrable biological gradient ('dose-response').
- Absence of strong and plausible experimental evidence, from either human studies or relevant animal models, that typical human exposure levels lead to relevant cancer outcomes.

Factors that might misleadingly imply an absence of effect include imprecision of the exposure assessment, insufficient range of exposure in the study population and inadequate statistical power. Defects such as these and in other study design attributes might lead to a false conclusion of no effect.

The presence of a plausible, relevant biological mechanism does not necessarily rule out a judgement of 'substantial effect on risk unlikely'. But the presence of robust evidence from appropriate animal models or humans that a specific mechanism exists or that typical exposures can lead to cancer outcomes argues against such a judgement.

Because of the uncertainty inherent in concluding that an exposure has no effect on risk, the criteria used to judge an exposure 'substantial effect on risk unlikely' are roughly equivalent to the criteria used with at least a 'probable' level of confidence. Conclusions of 'substantial effect on risk unlikely' with a lower confidence than this would not be helpful and could overlap with judgements of 'limited – suggestive' or 'limited – no conclusion'.

## SPECIAL UPGRADING FACTORS

These are factors that form part of the assessment of the evidence that, when present, can upgrade the judgement reached. An exposure that might be deemed a 'limited – suggestive' causal factor in the absence, for example, of a biological gradient, might be upgraded to 'probable' if one were present. The application of these factors (listed below) requires judgement, and the way in which these judgements affect the final conclusion in the matrix are stated.

Factors may include the following:

- Presence of a plausible biological gradient ('dose-response') in the association. Such a gradient need not be linear or even in the same direction across the different levels of exposure, so long as this can be explained plausibly.
- A particularly large summary effect size (an odds ratio or relative risk of 2.0 or more, depending on the unit of exposure) after appropriate control for confounders.
- Evidence from randomised trials in humans.
- Evidence from appropriately controlled experiments demonstrating one or more plausible and specific mechanisms actually operating in humans.
- Robust and reproducible evidence from experimental studies in appropriate animal models showing that typical human exposures can lead to relevant cancer outcomes.

# Our Cancer Prevention Recommendations

**Be a healthy weight**
Keep your weight within the healthy range and avoid weight gain in adult life

**Be physically active**
Be physically active as part of everyday life – walk more and sit less

**Eat a diet rich in wholegrains, vegetables, fruit and beans**
Make wholegrains, vegetables, fruit, and pulses (legumes) such as beans and lentils a major part of your usual daily diet

**Limit consumption of 'fast foods' and other processed foods high in fat, starches or sugars**
Limiting these foods helps control calorie intake and maintain a healthy weight

**Limit consumption of red and processed meat**
Eat no more than moderate amounts of red meat, such as beef, pork and lamb. Eat little, if any, processed meat

**Limit consumption of sugar sweetened drinks**
Drink mostly water and unsweetened drinks

**Limit alcohol consumption**
For cancer prevention, it's best not to drink alcohol

**Do not use supplements for cancer prevention**
Aim to meet nutritional needs through diet alone

**For mothers: breastfeed your baby, if you can**
Breastfeeding is good for both mother and baby

**After a cancer diagnosis: follow our Recommendations, if you can**
Check with your health professional what is right for you

**Not smoking and avoiding other exposure to tobacco and excess sun are also important in reducing cancer risk.**

**Following these Recommendations is likely to reduce intakes of salt, saturated and trans fats, which together will help prevent other non-communicable diseases.**

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