Article:

Vieira, AR, Abar, L, Chan, DSM et al. (5 more authors) (2017) Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project. Annals of Oncology, 28 (8). pp. 1788-1802. ISSN 0923-7534

https://doi.org/10.1093/annonc/mdx171

Foods and beverages and colorectal cancer risk: a systematic review and meta-analysis of cohort studies, an update of the evidence of the WCRF-AICR Continuous Update Project

A R Vieira[1], L Abar[1], DSM Chan[1], S Vingeliene[1], E Polemiti[1], C Stevens[1], D Greenwood[2], T Norat[1]

Affiliations:
[1]Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom [2]Department of Public Health and General Practice, Faculty of Medicine, [2]Division of Biostatistics, University of Leeds, Leeds, United Kingdom

Correspondence to:
Ms Rita Vieira | Imperial College London| Department of Epidemiology and Biostatistics | School of Public Health Faculty of Medicine, room 501, 5th floor - Norfolk Place - St Mary's Campus London W2 1PG UK Tel: +44 207 5948589 |
Email: a.vieira@imperial.ac.uk

Word count abstract: 270
Word count text: 4397

Abstract

Objective: As part of the World Cancer Research Fund International Continuous Update Project, we updated the systematic review and meta-analysis of prospective studies to quantify the dose-response between foods and beverages intake and colorectal cancer risk.

Data Sources: PubMed and several databases up to May 31st 2015.

Study selection: Prospective studies reporting adjusted relative risk estimates for the association of specific food groups and beverages and risk of colorectal, colon and rectal cancer.

Data synthesis: Dose-response meta-analyses using random effect models to estimate summary relative risks (RRs).

Results: Results: 400 individual study estimates from 111 unique cohort studies were included. Overall, the risk increase of colorectal cancer is 12% for each 100g/day increase of red and processed meat intake (95%CI=4-21%, I^2=70%, pheterogeneity (ph)<0.01) and 7% for 10 g/day increase of ethanol intake in alcoholic drinks (95%CI=5-9%, I^2=25%, *ph*=0.21). Colorectal cancer risk decrease in 17% for each 90g/day increase of whole grains (95%CI=11-21%, I^2=0%, *ph*=0.30, 6 studies). For each 400 g/day increase of dairy products intake (95%CI=10-17%, I^2=18%, *ph*=0.27, 10 studies). Inverse associations were also observed for vegetables intake (RR per 100 g/day =0.98 (95%CI=0.96-0.99, I^2=0%, *ph*=0.48, 11 studies) and for fish intake (RR for 100g/day=0.89(95%CI=0.80-0.99, I^2=0%, *ph*=0.52, 11 studies), that were weak for vegetables and driven by one study for fish. Intakes of fruits, coffee, tea, cheese, poultry and legumes were not associated with colorectal cancer risk.

Conclusions: Our results reinforce the evidence that high intake of red and processed meat and alcohol increase the risk of colorectal cancer. Milk and whole grains may have a protective role against colorectal cancer. The evidence for vegetables and fish was less convincing.

Key words • Colorectal Cancer • Summary of the evidence • Meat • Wholegrains • Dairy • Alcohol • Review • Meta-analysis

Key message: Colorectal cancer is the third most common cancer in men and the second in women. The WCRF Panel judged in 2011 that there was strong evidence that red and processed meats and alcohol increase the risk of colorectal cancer and that foods containing dietary fibre and dairy products decrease the risk. The evidence for other foods and beverages was limited.

The evidence from prospective studies accumulated up to 2015 confirms the judgements of the WCRF Panel.

Introduction

Colorectal cancer is the third most common cancer in men (746,000 cases, 10.0% of total cancer) and the second in women (614,000 cases, 9.2% of total cancer) worldwide. Almost 55% of the cases occur in more developed regions. There is wide geographical variation in incidence across the world and the geographical patterns are very similar in men and women[1].

There is strong evidence that colorectal cancer aetiology is related to lifestyle, including diet. The World Cancer Research Fund International (WCRF) Continuous Update Project (CUP) reviewed the evidence from cohort studies and randomized controlled trials on diet, nutrition, adiposity, and physical activity and the risk of colorectal cancer accumulated up to 2010, and published a report in 2011 (available at http://www.wcrf.org/sites/default/files/Colorectal-Cancer-2011-Report.pdf and http://www.wcrf.org/). The Panel concluded there was strong evidence (convincing) that red and processed meat, alcoholic drinks in men, body fatness, abdominal fatness and adult attained height increase the risk of colorectal cancer and that physical activity and foods containing fibre decrease the risk of colorectal cancer. The evidence suggesting a protective effect of garlic, milk, calcium and alcoholic drinks (in women) was judged as probable.

As part of the WCRF-CUP, we updated the 2011 CUP systematic review and meta-analysis including articles published up to May 2015.

In this review we summarize the evidence on food groups and beverages for which more evidence was accumulated after the 2010 CUP SLR: whole grains foods, fruits and vegetables, legumes, red and processed meats, fish, poultry, dairy foods, milk, alcohol, coffee and tea). We specifically aimed to summarise the study results by conducting linear dose-response meta-analyses and to examine whether the associations were similar for colon and rectum and by sex and by geographic location.

Methods

Search strategy

Articles published before December 2005 were searched in different electronic databases including Pubmed, Embase, CAB Abstracts, ISI Web of Science, BIOSIS, LILACS, Cochrane library, CINAHL, AMED, National Research Register, and In Process Medline by reviewers at the Wageningen University. The protocol followed for the review can be found at: http://www.wcrf.org/int/research-we-fund/continuous-update-project-findings-reports/colorectal-bowel-cancer and includes the specific search criteria used.

Because all the relevant studies were identified by the PubMed search, the PubMed database was searched by the CUP team at Imperial College from January 2006 up to May 2015 using the same search strategy. Furthermore, the reference list of the included articles and published meta-analyses and reviews identified was screened for relevant studies. We followed standard criteria for reporting meta-analysis (PRISMA criteria)[2].

Study selection

The study inclusion criteria were 1) being a randomized controlled trial or prospective study with cohort, case-cohort or nested case-control design; 2) report adjusted estimates of the relative risk (RR) (e.g. hazard ratio, risk ratio or odds ratio) and 95% confidence intervals (CIs) for the association of foods and colorectal cancer incidence; 3) for dose-response meta-analysis, studies should provide a quantitative measure of the intake. When the same study published more than one article, we selected the newest publication with the largest number of cases. We included results of other pooled analysis in our analysis (Flowchart of study selection – Figure 1 and supplementary material).

Data extraction

The data of relevant articles was extracted to the WCRF-CUP database. The database contains the data of all relevant articles identified in the searches for the 2005 WCRF SLR and 2010 WCRF SLR. The data extracted for each article were: first author's last name, publication year, country where the study was conducted, the study name, follow-up period, sample size, sex, age, number of cases, dietary assessment method (type, number of food items and whether it had been validated), type of food, amount of intake, RRs and 95% CIs and adjustment variables. The search and extraction was conducted by the CUP team at Imperial College London.

Statistical methods

We updated the meta-analyses of the 2010 SLR when there were two new studies published from January 1st 2010 and sufficient data to estimate a dose-response association for at least five studies in total in the WCRF database. The primary analysis focused on associations between continuous intake levels of different foods and beverages (whole grains, fruit and vegetable, legumes, red and processed meat, red meat, processed meat, fish, poultry, dairy foods, milk, cheese, alcoholic drinks, coffee and tea) and risks of colorectal, colon or rectal cancers.

The statistical methods used are included under supplementary material.

Results

A total of 45 dose-response meta-analyses on 15 different foods or food groups using 400 individual study estimates from 111 unique cohort studies were included [6-99]. Meta-analyses included a median of 9 studies (ranging from 4 to 23 studies), with a median number of cases of 6662 (ranging from 729 to 31 551 cases).

This work is an update of the 2010 CUP SLR. The results from the 2005 SLR [100], the 2010 CUP SLR and the results of this analysis (2015CUP SLR) are in Table 1. Figure 2a, 2b and 2c represent the summary plots of all the main estimates for colorectal, colon and rectal cancer, respectively.

1- Foods associated with increased colorectal cancer risk

Red and processed meats

The consumption of red and processed meats was associated with an increase of risk of colorectal cancer (RR for 100 g/day increment=1.12; 95%CI=1.04-1.21, I^2=70%, pheterogeneity (*ph*)<0.01) (figure 2a) and colon cancer (RR per 100g/day=1.19 (95%CI=1.10-1.30, I^2=63%, 0.004) (figure 2b). A positive but not statistically significant association was observed with rectal cancer (RR per 100g/day=1.17 95%CI=0.99-1.39, I^2=48%, *ph*=0.08, 6 studies) (figure 2c)(table 1D).

For colorectal cancer, the associations were similar in men and women(supplementary table 1). For colon cancer the association was significant in men, but not in women (supplementary table 1).

Five studies investigated the association of red and processed meats with distal and proximal colon cancer [37,44,47,54,93], but there was not enough data for dose-response meta-analyses. A daily increment of 100g of red meat consumption corresponded to a 70% increase in distal colon cancer risk (multivariate RR =1.70(95%CI=1.31-2.21) [54]. For proximal cancer, no study reported significant associations.

Processed meats

Processed meat intake was associated with an increased risk of colorectal cancer (RR for 50 g/day increment=1.18(95%CI=1.10-1.28, I^2=11%, *p*=0.34) (figure 2a), and colon cancer (RR=1.23(95%CI=1.11-1.35, I^2=26%, *ph*=0.18) (figure 2b). For rectal cancer the positive association was marginally significant (RR=1.08, 95%CI=1.00-1.18, I^2=0%, *ph*=0.77, 10 studies) (figure 2c) (table 1D).

The summary relative risk of two studies in men was 1.11(95%CI=0.86-1.43, I^2=34%, *ph*=0.22) and for five studies in women the RR was 1.18 (95%CI=0.99-1.41, I^2=19%, *ph*=0.29) (supplementary table 1).

Six studies investigated the association of processed meats with risk of distal and proximal colon cancer, one study (NOWAC) [44] observed a significant association for distal colon cancer (*p*=0.02) and five studies observed a non-significant association [37,44,47,54,93,101].

Red meats

The association of red meat with colorectal cancer was marginally significant (RR for 100g/day increment=1.12, 95%CI=1.00-1.25.I^2=24%, *ph*=0.24, 8 studies) (figure 2a). Red meat was significantly associated with risk of colon cancer (RR for 100 g/day increment=1.22 (95%CI=1.06-1.39, I^2=12%, *ph*=0.33, 11 studies) (figure 2b) but not with rectal cancer (RR=1.13, 95%CI=0.96-1.34, I^2=0%, *ph*=0.52, 8 studies) (figure 2c) (table 1D).

For colorectal cancer a smaller number of studies could be included in the analysis stratified by sex. (supplementary table 1).

From the four studies with data on distal and proximal colon cancer none observed an association with red meat [38,44,47,101]. A Japanese study [47] observed a significant association between beef consumption and proximal cancer in women RR=2.52(95%CI=1.53-4.14, 28 vs 0.1 g/day) and distal colon cancer in men (1.58 (1.07, 2.34, 19 vs 0.2 g/day).

Alcohol

Each increase of 10g/day of alcohol intake (as ethanol in alcoholic beverages) (10g/day of ethanol is equivalent to a standard drink – 100ml of wine, 275ml of beer or 30ml of spirits) was associated with an increased risk of colorectal (RR=1.07(95%CI=1.05-1.09, I^2=25%, *ph*=0.21, 16 studies) (figure 2a), colon (RR=1.07(95%CI=1.05-1.09, I^2=34%, *ph*=0.13, 14 studies) (figure 2b) and rectal cancer (RR=1.08(95%CI=1.07-1.10, I^2=0%, *ph*=0.54, 11 studies) (figure 2c) (table

For colorectal cancer, the stratified analysis by sex showed an increased risk in men and a borderline significant increased risk in women. The evidence of association in women was stronger than in the previous 2011 SLR CUP review (table 1). For colon and rectal cancer alcohol intake was associated with a significant increase in women and men (supplementary table 2).

For five studies [48,51,59,62,64] with data on distal and proximal colon cancer, two observed a significant association with distal colon cancer, the Melbourne Cohort Study (RR=4.17(95%CI=1.63-10.66, ≥45 vs <50g/day) and the European Prospective Investigation into Cancer and Nutrition (EPIC) study RR=1.68 (95%=1.08-2.62, ≥60 vs 0.1-4.9g/day) [62,64] and two studies on women observed a significant association with proximal cancer, the Iowa Women's Health Study (IWHS) RR=1.12(0.71-1.77, ≥31 vs 0 g/day) and the Netherlands Cohort Study (NLCS) RR=2.28(95%CI=1.12-4.62, ≥30 vs 0 g/day) [48,59].

We identified eight studies on total alcoholic drinks and colorectal cancer. For each increase of alcoholic drink per day there was a 6% increased risk, with high heterogeneity, RR=1.06(95%CI=1.01-1.11, I^2=60%, *ph*=0.01).

2- Foods associated with a decreased colorectal cancer risk

Whole grains

Whole grains was associated with a decrease risk of colorectal cancer (RR for 90 g/day=0.83 (95%CI=0.79-0.89, I^2=18%, *ph*=0.30, 6 studies) (figure 2a) and a decrease risk of colon cancer (RR=0.82 (95%CI=0.73-0.92, I^2=0%, *ph*=0.49, 4 studies) (figure 2b). Whole grains intake was not associated with rectal cancer (RR=0.81 (95%CI=0.54-1.20, 91%, ph<0.0001, 3 studies) (figure 2c) (table 1A). No stratified analysis by sex could be conducted, only by geographic location (supplementary table 3).

One study observed a significant decrease risk between wholegrain foods and proximal colon cancer in men RR=0.55(95%CI=0.30-0.99) [67]. No significant association was observed for women or distal colon cancer.

Total dairy products and milk

Higher intake of dairy products was associated with a decreased risk of colorectal cancer (RR for 400 g/day =0.87 (95%CI=0.83-0.90, I^2=18%, *ph*=0.27, 10 studies) (figure 2a) and colon cancer RR= 0.87 (95%CI=0.81-0.94, I^2=24%, *ph*=0.25, 6 studies) (figure 2b). Dairy products were not associated with rectal cancer (table 1B).

For colorectal cancer similar associations were observed in men and women (supplementary table 4).

An increase of 200g/day of milk intake was associated with a decreased risk of colorectal (RR=0.94 (95%CI=0.92-0.96, I^2=0%, 0.97, 9 studies), colon cancer (RR=0.93 (95%CI=0.90-0.96, I^2=30%, *ph*=0.18, 9 studies) and rectal cancer (RR=0.94 (95%CI=0.91-0.97, I^2=0%, *ph*=0.93, 7 studies).

The association of milk intake with colorectal and colon cancer was significant in men, but not in women. For rectal cancer the association was significant in women, but not in men (supplementary table 4).

The consumption of dairy products was associated with a significant decrease risk of distal cancer in three European studies [8,96,102] and to proximal cancer in two European studies [8,96]. The EPIC study reported a RR=0.74 (95%CI=0.61-0.90) for distal cancer and a RR=0.75(95%CI=0.62-0.91, 490 vs 0-133.9 g/day) for proximal cancer [96]. The Cohort Study of Swedish Men reported a RR=0.43(95%CI=0.20-0.93) for distal cancer and a RR=0.37(95%CI=0.16-0.88, 7 vs 1.9 servings/day) for proximal cancer [8]. The Swedish Mammography Cohort observed a RR=0.28(95%CI=0.14-0.56) for distal cancer and a RR=0.84(95%CI=0.50-1.42, 4 vs 0.9 servings/day) for proximal colon cancer [102].

Vegetables

The consumption of 100g/day of vegetables was associated with a decreased risk in colorectal cancer, RR=0.98 (95%CI=0.96-0.99, I^2=0%, *ph*=0.48, 11 studies) (figure 2a) and colon cancer risk RR=0.97 (95%CI=0.95-0.99, I^2=0%, *ph*=0.77, 12 studies) (figure 2b). Most studies included in analysis observed a null association between vegetable consumption and colorectal cancer. The overall result was driven by one study with 40% of weight in the analysis [103]. When this study was excluded the overall result was no longer significant RR= 0.98 (95% CI=0.97-1.00). No association was identified with rectal cancer RR=0.99(95%CI=0.96-1.02), I^2=0%, *ph*=0.72, 8 studies) (table 1A).

For both colorectal and colon cancer the association remained significant in men but not in women. (supplementary table 5). Six studies provided data on proximal and distal cancer. No association was observed between vegetable intake and proximal or distal cancer [31,70,83,87-89]

Fish

An increase of 100g/day of fish was associated with an 11% decreased risk of colorectal RR=0.89(95%CI=0.80-0.99, I^2=0%, *ph*=0.52, 11 studies) (figure 2a). The overall result was driven by one study with 40% weight in the analysis [35]. When this study was excluded the overall result was no longer significant RR=0.94(95%CI=0.82-1.07). The analyses of fish and colon (RR=0.91(0.80-1.03, I^2=0%, *ph*=0.76, 11 studies)) (figure 2b) and rectal cancer 0.84(0.69-1.02, I^2=15%, *ph*=0.31, 10 studies)) (figure 2c) were not significant and the study results were inconsistent (table 1D).

For colorectal cancer the association remained significant in men, but not in women (supplementary table 6).

The results for colorectal cancer were non-significant for both subgroup of studies adjusting and not adjusting for meat intake, RR=0.98(0.84-1.14, I^2=0%, *ph*=0.76, 6 studies) and RR=0.76 (0.61-0.95, I^2=0%, *ph*=0.79, 5 studies) respectively.

Four studies from three publications provided data on proximal and distal cancer. No association was observed between fish intake and proximal or distal cancer [54,86,104].

3- Foods not associated with colorectal cancer

Analysis with 10 or more studies

The analysis on coffee and fruits included at least ten studies. Coffee was not significantly associated with colorectal cancer, colon or rectal cancer. The result per 1 cup/day was null for all the studies included in the analysis. In the dose-response analysis for colorectal cancer, per 1cup/day we observed a RR=1.00(95%CI=0.99-1.02, I^2=44%, *ph*=0.05, 14 studies) (figure 2a). For colon cancer the RR was 0.99(95%CI=0.97-1.01, I^2=49%, *ph*=0.03, 11 studies) (figure 2b). In this analysis we included a pooled analysis of 13 studies and 4439 colon cases from North America and Europe which also showed a null association per 250g/day of coffee (1.00(95% CI = 0.97-1.05)[99]. This pooled analysis also modelled coffee consumption as a continuous variable and no association was observed (for an increment of 250 g/d the pooled multivariable RR = 0.99, 95% CI = 0.97 to 1.02, *p*=0.45) [99]. For proximal cancer the RR was 0.99(95%CI=0.96-1.02, 64%, *ph*=0.25, 5 studies) and for distal cancer the RR was 0.99 (95%CI=0.97-1.01, 0%, *ph*=0.63, 5 studies). For rectal cancer the RR was 1.01(95%CI=1.00-1.03, I^2 =2%, *ph*=0.43, 15 studies) (table 1C).

Fruit intake was not associated with colorectal, colon or rectal cancer risk. The 13 studies included in the analysis showed inconsistent results. The RR for colorectal cancer per 100g/day of fruits was 0.96(95% CI = 0.93-1.00, I^2=68%, ph<0.0001, 13 studies) (figure 2a). For colon the RR was 0.98(95% CI = 0.96-1.01, I^2=38%, *ph*=0.09, 12 studies) (figure 2b). For rectal cancer the RR was 0.98(95% CI = 0.93-1.03, I^2=55%, *ph*=0.02, 9 studies) (figure 2c).

Six studies provided data on proximal and distal cancer. No association was observed between fruit intake and proximal or distal cancer [31,70,83,87-89].

We observed a significant non-linear association for fruits and vegetables which was consistent for colorectal, colon and rectal cancer. We observed a higher risk of cancer for lower intakes (≤300g/day) of fruits and vegetables and no further reductions in risk with intakes above 700 grams per day. Similar trends were observed for fruits and vegetables analysed separately.

Analysis with five to ten studies

The analysis on poultry, cheese and tea included between five and ten studies. Poultry intake was not associated with colorectal, colon or rectal cancer. All the studies included in analysis showed non-significant associations. The overall RR for colorectal cancer per 100g/day of poultry was 0.81(95% CI = 0.53-1.25, I^2=48%, *ph*=0.05, 7 studies) (figure 2a). For colon the RR=0.83(0.63-1.11, I^2=35%, *ph*=0.08, 10 studies) and for rectal cancer the RR=0.86(0.72-1.01, I^2=0%, *ph*=0.96, 6 studies) (figure 2b) (table 1D). The four studies [44,47,101,105] with data on proximal and distal cancer observed no association with poultry intake.

The consumption of 50g/day of cheese was not associated with colorectal RR=0.94 (95% CI = 0.87-1.02, I^2=10%, *ph*=0.36, 7 studies) (figure 2a) or colon cancer (RR=0.91 (95% CI = 0.80-1.03, I^2=19%, *ph*=0.29, 6 studies) (figure 2b). For rectal cancer the association was marginally significant, RR=0.95 (95% CI = 0.90-1.00, I^2=0% *ph*=0.96, 4 studies) (figure 2c) (table 1B). The results were driven by one study [96] with higher weight in the analyses of colorectal (69%) colon (62%) and rectal cancer (96%). The results of each individual study were inconsistent (table 1B).

Tea intake was not associated with colorectal, colon or rectal cancer risk. All studies showed non-significant dose-response associations. The summary RR for colorectal cancer per 1cup/day was 0.99(95% CI = 0.97-1.01, I^2=26%, *ph*=0.23, 8 studies) (figure 2a). For colon cancer the RR was 0.99(0.94-1.03, I^2=75%, ph<0.001, 6 studies) (figure 2b). For rectal cancer the RR was 0.99(0.97-1.02, I^2=0%, *ph*=0.47, 9 studies) (figure 2c) (table 1C). For proximal cancer the RR was 1.02(0.99-1.05, I^2=0%, *ph*=0.74, 4 studies), only one study showed a significant inverse association [15] and for distal cancer the RR was 1.07 (95%CI=0.97-1.05, 25%, *ph*=0.26, 4 studies), all studies showed a non-significant association.

Analyses with less than five studies

The analysis on legumes included less than five studies for colorectal, colon and rectal cancer. Studies showed results in different directions. The overall RR for colorectal cancer per 50g/day was 1.00 (95% CI = 0.95-1.06, I^2=33%, *ph*=0.2, 4 studies) (figure 2a). For colon cancer the RR was 0.97(95% CI = 0.83-1.15, I^2=55%, *ph*=0.04, 6 studies) (figure 2b). For rectal cancer the RR was 0.99(95% CI = 0.78-1.25, I^2=45%, *ph*=0.14, 4 studies) (figure 2c). The only study with data on proximal and distal cancer did not observe an association [87] (table 1C).

Heterogeneity between studies

Out of the 45 meta-analyses, twenty-seven (60%) meta-analyses had low heterogeneity, I^2 < 30%, ten meta-analyses (22%) had moderate heterogeneity, I^2 =30-50%, and seven (15%) had high heterogeneity, I^2 ≥50%. Only one meta-analysis (with non-significant results) had very high heterogeneity, I^2 > 75%.

Among the analyses with significant increase risk results five had low heterogeneity (I^2<30%) (processed meat, alcohol and colorectal cancer and red meat, processed meat and colon cancer) one had moderate heterogeneity (I^2 =30-50%) (alcohol and colon cancer) and two had high heterogeneity (I^2>50%) (red and processed meat and colorectal cancer and colon cancer).

The heterogeneity observed for red and processed meat can be explained by differences in the strength of the association between studies and not by differences in the direction of the association. The differences in assessment of red and processed meats in the studies and the confounder adjustment, on top of sex and geographic location, may partly explain the high level of heterogeneity observed.

From the analysis with significant decrease risk results all the nine analyses had low heterogeneity, ranging from 0 to 30%.

Small study effects (such as publication bias) and influence analysis

Among the 18 meta-analyses with significant results, two showed a significant p-value for Egger's test. In the analysis of red and processed meat and colon cancer (Egger's *p* value=0.02, 10 studies) and in the analysis of processed meat and colon cancer (Egger's *p* value<0.01, 12 studies). The statistically significance of the Egger's test is possibly not related to small study bias, as the asymmetry observed in the funnel plot appeared to be driven by one big study that explained the high heterogeneity in the analyses [45].

Among the meta-analyses with non-significant results, two showed evidence of small study bias, the analysis of coffee and colorectal cancer (Egger's *p* value=0.002, 14 studies) and the analysis of tea and rectal cancer (Egger's *p* value=0.04, 9 studies)

In influence analysis in which we excluded one study at a time from each analysis the summary estimates were not substantially altered for most of the exposures. The exception was for vegetables and fish, where one study with higher weight in the analysis driven the result.

Discussion

Foods associated with an increased risk of colorectal cancer were red and processed meat and alcohol. Foods associated with a decreased risk of colorectal cancer were whole-grains, vegetables, dairy and fish. Foods not associated with colorectal cancer risk were fruits, coffee, tea, poultry, cheese and legumes. Our results update and confirm the evidence graded in WCRF 2011 report.

Limitations of the study

Our meta-analysis has some limitations. There was moderate to high heterogeneity in some of the analyses (e.g. red and processed meat). In part, this could be attributable to the use of different definitions of red and processed meats between studies. In general, the meat item was a combination of red meat, such as beef, pork and lamb, and processed meat, such as hotdogs, luncheon meat and bacon. Although we cannot rule out residual confounding, most studies included in the meta-analyses adjusted results by smoking, alcohol consumption, BMI and physical activity in addition to age and sex.

Less than 50% of studies included in our meta-analysis stated that they used validated food-frequency questionnaires, and only EPIC study corrected the results for measurement error [35,64,96].
Another limitation of our analysis is publication bias, some studies do not publish results on all food types or colorectal cancer subtypes. In this analysis, publication or small study bias appeared to be explained by one outlying study, and when this study was excluded, the test for publication bias was no longer significant.

In general the evidence for rectal cancer was weaker than for colon and colorectal cancer which might be explained by the lower number of cases on rectal cancer reported in the studies included. For the distal and proximal cancer the data is limited and more studies are needed. One limitation of the analysis of fish and vegetables was the highest weight of one study in the analysis which has driven the overall result. When this study was excluded the results were no longer significant which is consistent with the results of previous pooled analyses. For vegetables, a pooled analysis of 14 cohort studies and 5838 colorectal cancer cases showed a non-significant association when comparing 300 vs 100g/day of vegetables RR=0.96 (95%CI=0.84-1.09) [106]. For fish the UK Dietary Cohort Consortium reported a RR for ≥30 vs < 1 g/day of white fish of 0.86 (95%CI=0.64–1.16) and for fatty fish the RR was 0.73 (95%CI=0.54–0.98). Non-significant results were observed for colon and rectal cancer [107].

Whenever it was possible we included previous pooled analyses in our analyses. A small pooled analysis, the UK Dietary Cohort Consortium which included seven UK cohort studies (579 cases and 1996 controls), reported no evidence of an association between red and processed meat consumption and colorectal cancer risk (odd ratios for a 50g/day increase in red and processed meat = 0.97, 95% CI = 0.84-1.12). Similar relationships were observed for colon and rectal cancers [107]. This is not in concordance with the significant positive associations observed in the current meta-analyses, as the authors argued that the null results might be due to the relatively low meat intake of the cohorts included (cut points of the highest quantiles of intake were only 80g/day, 50 g/day and 30 g/day for red and processed meat, red meat and processed meat respectively). Two of the cohorts (EPIC-Norfolk and EPIC-Oxford) participating in this consortium were included in our meta-analyses [35]. The IARC Monographs Programme evaluated red meat as probably carcinogenic to humans and processed meat as carcinogenic to humans[108].
We identified two pooled analyses on alcohol and colorectal cancer with inconsistent results. A pooled analysis of five Japanese cohort studies showed a significant positive association per 15g/day of alcohol in men 1.11 (95% CI = 1.09-1.14) and women 1.13 (95% CI = 1.06-1.20) [71]. We included this in our analysis. A pooled analysis of seven cohorts from the UK was not included in our analysis because of the overlap with the EPIC study [35]. This analysis showed non-significant results when comparing ≥45 vs 0 g/day in men 1.24(95% CI = 0.69-2.22) and women 1.52(95% CI= 0.56-4.10) [109].

No pooled analysis was identified on dairy products. One meta-analysis of 12 cohort studies from North America and Europe showed a significant decrease risk for highest compared to lowest analysis 0.84 (95%CI = 0.75-0.95) [110]. Another meta-analysis observed a 17% decrease risk of colorectal cancer per 400g/day of dairy 0.83 (95%CI = 0.78-0.88), 10 studies[111].

The Pooling Project on wholegrains and colorectal cancer, not included in our analysis because it only performed highest compared to lowest analysis, showed a borderline significant 8% decreased risk of colorectal cancer including 13 studies and 8081 cases, 0.92 (95% CI = 0.84-1.00)[112]. One meta-analysis of 6 cohort studies and 7941 cases showed a 21% decrease in the highest compared to lowest analysis RR=0.79 (95% CI = 0.72-0.86,0%, *ph*=0.30) and a 17% decrease risk in the dose-response analysis per 90g/day of wholegrains 0.83 (0.78-0.89), 18%, *ph*=0.30[113].

Although the analysis on whole grains and colorectal cancer included a lower number of cases (8320 cases) than the analyses of meat, alcohol or dairy products. All the six studies showed a decreased risk in colorectal cancer risk. Four studies showed a significant decreased risk ranging from 13 to 27%.

The benefit of whole grains may mainly be related to the content of fibre of these foods [114,115]. As part of the analysis of the 2015 CUP SLR, after including the results of the Pooling Project [112], we observed a borderline significant 7% decrease risk of colorectal cancer RR per 10g/day dietary fibre=0.93 (95%CI=0.87-1.00, 72%, *ph*<0.001, 21 studies, 16 562 cases).

The non-significant associations observed for fruit and coffee should not be interpret as lack of power to detect an association because there were at least ten studies in each analysis and the number of cases ranged from16385 to 20667. For poultry, tea, cheese and legumes the number of studies included in the analysis might have been low to have the statistical power to detect an association. The opposite direction of results of individual studies might be explained by different units of measurement or range of intakes.

Mechanisms

Further discuss of the mechanisms is included as supplementary material.

Strengths of the study

Strengths of the current study include the update, systematic review and meta-analysis of prospective studies that quantify the dose-response between foods and beverages intake and colorectal cancer risk, the detailed subgroup and sensitivity analysis and the comparison between SLR 2005, CUP SLR 2010 and CUP SLR 2015 results. The studies included had high quality, most adjusted for the main confounders for colorectal cancer (age, sex, BMI, smoking, alcohol, physical activity, calcium, fruit and vegetable intake and fibre), included a large number of cases with a low loss to follow-up, used FFQs to assess food intake and cancer registries to confirm cancer outcome.

Conclusion

In conclusion, our results reinforce the evidence that red and processed meat and alcohol increase the risk of colorectal cancer. Dairy products and whole grains have a protective role against colorectal cancer. The analysis of fish and vegetables showed low credibility because the results were mainly driven by one study in the analysis. Fruits and coffee were not associated with colorectal cancer.

Acknowledgments . This study is part of the WCRF International Continuous Update Project (http://www.wcrf.org/cancer_research/cup/index.php). The views expressed in this review are the opinions of the authors. They may not represent the views of WCRF International/American Institute of Cancer Research and may differ from those in future updates of the evidence related to diet, nutrition, physical activity and cancer risk. All authors had full access to the data in the study. We thank Dagfinn Aune, Associate Professor Bjørknes University College, Oslo, Norway, and Research Associate in the Department of Epidemiology and Biostatistics, School of Public Health, Imperial College London, London, United Kingdom for his contribution.

Funding: This work was funded by the World Cancer Research Fund (grant number 2007/SP01) as part of the Continuous Update Project. The sponsor of this study had no role in the decisions about the design or conduct of the study; the collection, management, analysis, or interpretation of the data; or the preparation, review, or approval of the manuscript.

Conflict of interest: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisation that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Legends:

Table 1 (A –D**)** Summary of results of dose-response meta-analysis for foods and beverages investigated in the 2015 CUP update by year of update (2005, 2010, 2015)

1A Results of dose-response meta-analysis for wholegrain, fruits and vegetables
1B Results of dose-response meta-analysis for dairy products, milk and cheese
1C results of dose-response meta-analysis for alcohol, coffee, tea and legumes
1D results of dose-response meta-analysis for meat, poultry and fish

Figure 1 Flowchart of study selection. Search period January 1st 2010-May 31st 2015

Figure 2A Dose-response meta-analysis of foods and beverages and risk of colorectal cancer

Figure 2B Dose-response meta-analysis of foods and beverages and risk of colon cancer

Figure 2C Dose-response meta-analysis of foods and beverages and risk of rectal cancer

Supplementary material for online only:
Study selection
Statistical methods
Subgroup analysis
Mechanisms
Supplementary table 1 – Subgroup analysis on red and processed meat
Supplementary table 2 – Subgroup analysis on alcohol as ethanol
Supplementary table 3 – Subgroup analysis on wholegrains
Supplementary table 4 – Subgroup analysis on dairy products and milk
Supplementary table 5 – Subgroup analysis on vegetables
Supplementary table 6 – Subgroup analysis on fish

Reference List

1. American Cancer Society. Cancer facts and figures 2015. Atlanta:American Cancer Society, 2015.

2. Moher D, Liberati A, Tetzlaff J et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Int J Surg 2010; 8(5): 336-41.

3. DerSimonian R, Laird N. Meta-analysis in clinical trials. Control Clin Trials 1986; 7(3): 177-88.

4. Orsini N, Bellocco R, Greenland S. Generalized least squares for trend estimation of summarized dose-response data. Stata Journal 2006; 6(1): 40-57.

5. Hamling J, Lee P, Weitkunat R et al. Facilitating meta-analyses by deriving relative effect and precision estimates for alternative comparisons from a set of estimates presented by exposure level or disease category. Stat Med 2008; 27(7): 954-70.

6. Dominianni C, Huang WY, Berndt S et al. Prospective study of the relationship between coffee and tea with colorectal cancer risk: The PLCO Cancer Screening Trial. Br J Cancer 2013.

7. Jarvinen R, Knekt P, Hakulinen T et al. Prospective study on milk products, calcium and cancers of the colon and rectum. Eur J Clin Nutr 2001; 55(11): 1000-7.

8. Larsson SC, Bergkvist L, Rutegard J et al. Calcium and dairy food intakes are inversely associated with colorectal cancer risk in the Cohort of Swedish Men. Am J Clin Nutr 2006; 83(3): 667-73.

9. Lee KJ, Inoue M, Otani T et al. Coffee consumption and risk of colorectal cancer in a population-based prospective cohort of Japanese men and women. Int J Cancer 2007; 121(6): 1312-8.

10. Lee SA, Shu XO, Yang G et al. Animal origin foods and colorectal cancer risk: a report from the Shanghai Women's Health Study. Nutr Cancer 2009; 61(2): 194-205.

11. Naganuma T, Kuriyama S, Akhter M et al. Coffee consumption and the risk of colorectal cancer: a prospective cohort study in Japan. Int J Cancer 2007; 120(7): 1542-7.

12. Nilsson LM, Winkvist A, Johansson I et al. Low-carbohydrate, high-protein diet score and risk of incident cancer; a prospective cohort study. Nutr J 2013; 12(1): 58.

13. Park Y, Leitzmann MF, Subar AF et al. Dairy food, calcium, and risk of cancer in the NIH-AARP Diet and Health Study. Arch Intern Med 2009; 169(4): 391-401.

14. Simons CC, Leurs LJ, Weijenberg MP et al. Fluid intake and colorectal cancer risk in the Netherlands Cohort Study. Nutr Cancer 2010; 62(3): 307-21.

15. Sinha R, Cross AJ, Daniel CR et al. Caffeinated and decaffeinated coffee and tea intakes and risk of colorectal cancer in a large prospective study. Am J Clin Nutr 2012.

16. Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. Cancer Causes Control 1994; 5(5): 401-8.

17. Su LJ, Arab L. Tea consumption and the reduced risk of colon cancer -- results from a national prospective cohort study. Public Health Nutr 2002; 5(3): 419-25.

18. Terry P, Wolk A. Tea consumption and the risk of colorectal cancer in Sweden. Nutr Cancer 2001; 39(2): 176-9.

19. Wie GA, Cho YA, Kang HH et al. Red meat consumption is associated with an increased overall cancer risk: a prospective cohort study in Korea. Br J Nutr 2014; 112(2): 238-47.

20. Bidel S, Hu G, Jousilahti P et al. Coffee consumption and risk of colorectal cancer. Eur J Clin Nutr 2010; 64(9): 917-23.

21. Brink M, Weijenberg MP, de Goeij AF et al. Meat consumption and K-ras mutations in sporadic colon and rectal cancer in The Netherlands Cohort Study. Br J Cancer 2005; 92(7): 1310-20.

22. Gaard M, Tretli S, Loken EB. Dietary factors and risk of colon cancer: a prospective study of 50,535 young Norwegian men and women. European Journal of Cancer Prevention 1996; 5(6): 445-54.

23. Klatsky AL, Armstrong MA, Friedman GD et al. The relations of alcoholic beverage use to colon and rectal cancer. Am J Epidemiol 1988; 128(5): 1007-15.

24. Kobayashi M, Tsubono Y, Otani T et al. Fish, long-chain n-3 polyunsaturated fatty acids, and risk of colorectal cancer in middle-aged Japanese: the JPHC study. Nutr Cancer 2004; 49(1): 32-40.

25. Nomura AM, Wilkens LR, Murphy SP et al. Association of vegetable, fruit, and grain intakes with colorectal cancer: the Multiethnic Cohort Study. Am J Clin Nutr 2008; 88(3): 730-7.

26. Park SY, Murphy SP, Wilkens LR et al. Calcium and vitamin D intake and risk of colorectal cancer: the Multiethnic Cohort Study. Am J Epidemiol 2007; 165(7): 784-93.

27. Sanjoaquin MA, Appleby PN, Thorogood M et al. Nutrition, lifestyle and colorectal cancer incidence: a prospective investigation of 10998 vegetarians and non-vegetarians in the United Kingdom. Br J Cancer 2004; 90(1): 118-21.

28. Schatzkin A, Mouw T, Park Y et al. Dietary fiber and whole-grain consumption in relation to colorectal cancer in the NIH-AARP Diet and Health Study. Am J Clin Nutr 2007; 85(5): 1353-60.

29. Sellers TA, Bazyk AE, Bostick RM et al. Diet and risk of colon cancer in a large prospective study of older women: an analysis stratified on family history (Iowa, United States). Cancer Causes Control 1998; 9(4): 357-67.

30. Sugawara Y, Kuriyama S, Kakizaki M et al. Fish consumption and the risk of colorectal cancer: the Ohsaki Cohort Study. Br J Cancer 2009; 101(5): 849-54.

31. Terry P, Giovannucci E, Michels KB et al. Fruit, vegetables, dietary fiber and risk of colorectal cancer. J Natl Cancer Inst 2001; 93(7): 525-33.

32. Tiemersma EW, Kampman E, Bueno de Mesquita HB et al. Meat consumption, cigarette smoking, and genetic susceptibility in the etiology of colorectal cancer: results from a Dutch prospective study. Cancer Causes Control 2002; 13(4): 383-93.

33. Yamada H, Kawado M, Aoyama N et al. Coffee Consumption and Risk of Colorectal Cancer: The Japan Collaborative Cohort Study. J Epidemiol 2014.

34. Allen NE, Beral V, Casabonne D et al. Moderate alcohol intake and cancer incidence in women. J Natl Cancer Inst 2009; 101(5): 296-305.

35. Bamia C, Lagiou P, Buckland G et al. Mediterranean diet and colorectal cancer risk: results from a European cohort. Eur J Epidemiol 2013.

36. Berndt SI, Platz EA, Fallin MD et al. Genetic variation in the nucleotide excision repair pathway and colorectal cancer risk. Cancer Epidemiol Biomarkers Prev 2006; 15(11): 2263-9.

37. Chao A, Thun MJ, Connell CJ et al. Meat consumption and risk of colorectal cancer. JAMA 2005; 293(2): 172-82.

38. Cross AJ, Ferrucci LM, Risch A et al. A large prospective study of meat consumption and colorectal cancer risk: an investigation of potential mechanisms underlying this association. Cancer Res 2010; 70(6): 2406-14.

39. Fung TT, Hu FB, Schulze M et al. A dietary pattern that is associated with C-peptide and risk of colorectal cancer in women. Cancer Causes Control 2012.

40. Kabat GC, Miller AB, Jain M et al. A cohort study of dietary iron and heme iron intake and risk of colorectal cancer in women. Br J Cancer 2007; 97(1): 118-22.

41. Kim J, Park S, Nam BH. The Risk of Colorectal Cancer is Associated with the Frequency of Meat Consumption in a Population-based Cohort in Korea. Asian Pac J Cancer Prev 2011; 12(9): 2371-6.

42. Oba S, Shimizu N, Nagata C et al. The relationship between the consumption of meat, fat, and coffee and the risk of colon cancer: a prospective study in Japan. Cancer Lett 2006; 244(2): 260-7.

43. Ollberding NJ, Wilkens LR, Henderson BE et al. Meat consumption, heterocyclic amines and colorectal cancer risk: The Multiethnic Cohort Study. Int J Cancer 2012.

44. Parr CL, Hjartaker A, Lund E et al. Meat intake, cooking methods, and risk of proximal colon, distal colon, and rectal cancer: The Norwegian Women and Cancer (NOWAC) cohort study. Int J Cancer 2013.

45. Ruder EH, Thiebaut AC, Thompson FE et al. Adolescent and mid-life diet: risk of colorectal cancer in the NIH-AARP Diet and Health Study. Am J Clin Nutr 2011; 94(6): 1607-19.

46. Shin A, Joo J, Yang HR et al. Risk prediction model for colorectal cancer: national health insurance corporation study, Korea. PLoS One 2014; 9(2): e88079.

47. Takachi R, Tsubono Y, Baba K et al. Red meat intake may increase the risk of colon cancer in Japanese, a population with relatively low red meat consumption. Asia Pac J Clin Nutr 2011; 20(4): 603-12.

48. Bongaerts BW, van den Brandt PA, Goldbohm RA et al. Alcohol consumption, type of alcoholic beverage and risk of colorectal cancer at specific subsites. Int J Cancer 2008; 123(10): 2411-7.

49. Bostick RM, Potter JD, Kushi LH et al. Sugar, meat, and fat intake, and non-dietary risk factors for colon cancer incidence in Iowa women (United States). Cancer Causes Control 1994; 5(1): 38-52.

50. Chen J, Stampfer MJ, Hough HL et al. A prospective study of N-acetyltransferase genotype, red meat intake, and risk of colorectal cancer. Cancer Res 1998; 58(15): 3307-11.

51. Cho E, Lee JE, Rimm EB et al. Alcohol consumption and the risk of colon cancer by family history of colorectal cancer. Am J Clin Nutr 2012; 95(2): 413-9.

52. Everatt R, Tamosiunas A, Virviciute D et al. Consumption of alcohol and risk of cancer among men: a 30 year cohort study in Lithuania. Eur J Epidemiol 2013.

53. Flood A, Velie EM, Sinha R et al. Meat, fat, and their subtypes as risk factors for colorectal cancer in a prospective cohort of women. Am J Epidemiol 2003; 158(1): 59-68.

54. Larsson SC, Rafter J, Holmberg L et al. Red meat consumption and risk of cancers of the proximal colon, distal colon and rectum: the Swedish Mammography Cohort. Int J Cancer 2005; 113(5): 829-34.

55. Lin J, Zhang SM, Cook NR et al. Dietary fat and fatty acids and risk of colorectal cancer in women. Am J Epidemiol 2004; 160(10): 1011-22.

56. Nan H, Lee JE, Rimm EB et al. Prospective study of alcohol consumption and the risk of colorectal cancer before and after folic acid fortification in the United States. Ann Epidemiol 2013.

57. Norat T, Bingham S, Ferrari P et al. Meat, fish, and colorectal cancer risk: the European Prospective Investigation into cancer and nutrition. J Natl Cancer Inst 2005; 97(12): 906-16.

58. Pietinen P, Malila N, Virtanen M et al. Diet and risk of colorectal cancer in a cohort of Finnish men. Cancer Causes Control 1999; 10(5): 387-96.

59. Razzak A, Oxentenko A, Vierkant RA et al. Alcohol Intake and Colorectal Cancer Risk by Molecularly-Defined Subtypes in a Prospective Study of Older Women. Cancer Prev Res (Phila) 2011.

60. Razzak AA, Oxentenko AS, Vierkant RA et al. Associations Between Intake of Folate and Related Micronutrients with Molecularly Defined Colorectal Cancer Risks in the Iowa Women's Health Study. Nutr Cancer 2012; 64(7): 899-910.

61. Willett WC, Stampfer MJ, Colditz GA et al. Relation of meat, fat, and fiber intake to the risk of colon cancer in a prospective study among women. N Engl J Med 1990; 323(24): 1664-72.

62. Akhter M, Kuriyama S, Nakaya N et al. Alcohol consumption is associated with an increased risk of distal colon and rectal cancer in Japanese men: the Miyagi Cohort Study. Eur J Cancer 2007; 43(2): 383-90.

63. Chyou PH, Nomura AM, Stemmermann GN. A prospective study of colon and rectal cancer among Hawaii Japanese men. Ann Epidemiol 1996; 6(4): 276-82.

64. Ferrari P, Jenab M, Norat T et al. Lifetime and baseline alcohol intake and risk of colon and rectal cancers in the European prospective investigation into cancer and nutrition (EPIC). Int J Cancer 2007; 121(9): 2065-72.

65. George SM, Park Y, Leitzmann MF et al. Fruit and vegetable intake and risk of cancer: a prospective cohort study. Am J Clin Nutr 2009; 89(1): 347-53.

66. Glynn SA, Albanes D, Pietinen P et al. Colorectal cancer and folate status: a nested case-control study among male smokers. Cancer Epidemiol Biomarkers Prev 1996; 5(7): 487-94.

67. Kyro C, Skeie G, Loft S et al. Intake of whole grains from different cereal and food sources and incidence of colorectal cancer in the Scandinavian HELGA cohort. Cancer Causes Control 2013.

68. Larsson SC, Giovannucci E, Bergkvist L et al. Whole grain consumption and risk of colorectal cancer: a population-based cohort of 60,000 women. Br J Cancer 2005; 92(9): 1803-7.

69. McCarl M, Harnack L, Limburg PJ et al. Incidence of colorectal cancer in relation to glycemic index and load in a cohort of women. Cancer Epidemiol Biomarkers Prev 2006; 15(5): 892-6.

70. McCullough ML, Robertson AS, Chao A et al. A prospective study of whole grains, fruits, vegetables and colon cancer risk. Cancer Causes Control 2003; 14(10): 959-70.

71. Mizoue T, Inoue M, Wakai K et al. Alcohol drinking and colorectal cancer in Japanese: a pooled analysis of results from five cohort studies. Am J Epidemiol 2008; 167(12): 1397-406.

72. Murata M, Takayama K, Choi BC et al. A nested case-control study on alcohol drinking, tobacco smoking, and cancer. Cancer Detect Prev 1996; 20(6): 557-65.

73. Toriola AT, Kurl S, Laukanen JA et al. Alcohol consumption and risk of colorectal cancer: the Findrink study. Eur J Epidemiol 2008; 23(6): 395-401.

74. Vogtmann E, Xiang YB, Li HL et al. Fruit and vegetable intake and the risk of colorectal cancer: results from the Shanghai Men's Health Study. Cancer Causes Control 2013.

75. Wu AH, Paganini Hill A, Ross RK et al. Alcohol, physical activity and other risk factors for colorectal cancer: a prospective study. Br J Cancer 1987; 55(6): 687-94.

76. Daniel CR, Cross AJ, Graubard BI et al. Prospective investigation of poultry and fish intake in relation to cancer risk. Cancer Prev Res (Phila) 2011.

77. English DR, MacInnis RJ, Hodge AM et al. Red meat, chicken, and fish consumption and risk of colorectal cancer. Cancer Epidemiol Biomarkers Prev 2004; 13(9): 1509-14.

78. Flood A, Velie EM, Chaterjee N et al. Fruit and vegetable intakes and the risk of colorectal cancer in the Breast Cancer Detection Demonstration Project follow-up cohort. Am J Clin Nutr 2002; 75(5): 936-43.

79. Hall MN, Chavarro JE, Lee IM et al. A 22-year prospective study of fish, n-3 fatty acid intake, and colorectal cancer risk in men. Cancer Epidemiol Biomarkers Prev 2008; 17(5): 1136-43.

80. Lin J, Zhang SM, Cook NR et al. Dietary intakes of fruit, vegetables, and fiber, and risk of colorectal cancer in a prospective cohort of women (United States). Cancer Causes Control 2005; 16(3): 225-33.

81. Michels KB, Edward G, Joshipura KJ et al. Prospective study of fruit and vegetable consumption and incidence of colon and rectal cancers. J Natl Cancer Inst 2000; 92(21): 1740-52.

82. Murff HJ, Shu XO, Li H et al. A prospective study of dietary polyunsaturated fatty acids and colorectal cancer risk in Chinese women. Cancer Epidemiol Biomarkers Prev 2009; 18(8): 2283-91.

83. Park Y, Subar AF, Kipnis V et al. Fruit and vegetable intakes and risk of colorectal cancer in the NIH-AARP diet and health study. Am J Epidemiol 2007; 166(2): 170-80.

84. Sato Y, Tsubono Y, Nakaya N et al. Fruit and vegetable consumption and risk of colorectal cancer in Japan: The Miyagi Cohort Study. Public Health Nutr 2005; 8(3): 309-14.

85. Shibata A, Paganini-Hill A, Ross RK et al. Intake of vegetables, fruits, beta-carotene, vitamin C and vitamin supplements and cancer incidence among the elderly: a prospective study. Br J Cancer 1992; 66(4): 673-9.

86. Song M, Chan AT, Fuchs CS et al. Dietary intake of fish, omega-3 and omega-6 fatty acids and risk of colorectal cancer: A prospective study in U.S. men and women. Int J Cancer 2014.

87. Steinmetz KA, Kushi LH, Bostick RM et al. Vegetables, fruit, and colon cancer in the Iowa Women's Health Study. Am J Epidemiol 1994; 139(1): 1-15.

88. van Duijnhoven FJ, Bueno-De-Mesquita HB, Ferrari P et al. Fruit, vegetables, and colorectal cancer risk: the European Prospective Investigation into Cancer and Nutrition. Am J Clin Nutr 2009; 89(5): 1441-52.

89. Voorrips LE, Goldbohm RA, van PG et al. Vegetable and fruit consumption and risks of colon and rectal cancer in a prospective cohort study: The Netherlands Cohort Study on Diet and Cancer. Am J Epidemiol 2000; 152(11): 1081-92.

90. Butler LM, Wang R, Koh WP et al. Prospective study of dietary patterns and colorectal cancer among Singapore Chinese. Br J Cancer 2008; 99(9): 1511-6.

91. Dik VK, Bueno-De-Mesquita HB, van Oijen MG et al. Coffee and tea consumption, genotype-based CYP1A2 and NAT2 activity and colorectal cancer risk-Results from the EPIC cohort study. Int J Cancer 2013.

92. Fung TT, Hu FB, Wu K et al. The Mediterranean and Dietary Approaches to Stop Hypertension (DASH) diets and colorectal cancer. Am J Clin Nutr 2010; 92(6): 1429-35.

93. Giovannucci E, Rimm EB, Stampfer MJ et al. Intake of fat, meat, and fiber in relation to risk of colon cancer in men. Cancer Res 1994; 54(9): 2390-7.

94. Kearney J, Giovannucci E, Rimm EB et al. Calcium, vitamin D, and dairy foods and the occurrence of colon cancer in men. Am J Epidemiol 1996; 143(9): 907-17.

95. Michels KB, Fuchs CS, Giovannucci E et al. Fiber intake and incidence of colorectal cancer among 76,947 women and 47,279 men. Cancer Epidemiol Biomarkers Prev 2005; 14(842-9.

96. Murphy N, Norat T, Ferrari P et al. Consumption of Dairy Products and Colorectal Cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC). PLoS One 2013; 8(9): e72715.

97. Nechuta S, Shu XO, Li HL et al. Prospective cohort study of tea consumption and risk of digestive system cancers: results from the Shanghai Women's Health Study. Am J Clin Nutr 2012; 96(5): 1056-63.

98. Singh PN, Fraser GE. Dietary risk factors for colon cancer in a low-risk population. Am J Epidemiol 1998; 148(8): 761-74.

99. Zhang X, Albanes D, Beeson WL et al. Risk of colon cancer and coffee, tea, and sugar-sweetened soft drink intake: pooled analysis of prospective cohort studies. J Natl Cancer Inst 2010; 102(11): 771-83.

100. 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.

101. Sato Y, Nakaya N, Kuriyama S et al. Meat consumption and risk of colorectal cancer in Japan: the Miyagi Cohort Study. Eur J Cancer Prev 2006; 15(3): 211-8.

102. Larsson SC, Bergkvist L, Wolk A. High-fat dairy food and conjugated linoleic acid intakes in relation to colorectal cancer incidence in the Swedish Mammography Cohort. Am J Clin Nutr 2005; 82(4): 894-900.

103. George SM, Park Y, Leitzmann MF et al. Fruit and vegetable intake and risk of cancer: a prospective cohort study. Am J Clin Nutr 2009; 89(1): 347-53.

104. Hirayama T. Association between alcohol consumption and cancer of the sigmoid colon: observations from a Japanese cohort study. Lancet 1989; 2(8665): 725-7.

105. Larsson SC, Wolk A. Meat consumption and risk of colorectal cancer: a meta-analysis of prospective studies. Int J Cancer 2006; 119(11): 2657-64.

106. Koushik A, Hunter DJ, Spiegelman D et al. Fruits, vegetables, and colon cancer risk in a pooled analysis of 14 cohort studies. J Natl Cancer Inst 2007; 99(19): 1471-83.

107. Spencer EA, Key TJ, Appleby PN et al. Meat, poultry and fish and risk of colorectal cancer: pooled analysis of data from the UK dietary cohort consortium. Cancer Causes Control 2010.

108. Bouvard V, Loomis D, Guyton KZ et al. Carcinogenicity of consumption of red and processed meat. Lancet Oncol 2015; 16(16): 1599-600.

109. Park JY, Dahm CC, Keogh RH et al. Alcohol intake and risk of colorectal cancer: results from the UK Dietary Cohort Consortium. Br J Cancer 2010; 103(5): 747-56.

110. Huncharek M, Muscat J, Kupelnick B. Colorectal cancer risk and dietary intake of calcium, vitamin D, and dairy products: a meta-analysis of 26,335 cases from 60 observational studies. Nutr Cancer 2009; 61(1): 47-69.

111. Aune D, Lau R, Chan DS et al. Dairy products and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Ann Oncol 2011.

112. Park Y, Hunter DJ, Spiegelman D et al. Dietary fiber intake and risk of colorectal cancer: a pooled analysis of prospective cohort studies. JAMA 2005; 294(22): 2849-57.

113. Aune D, Chan DS, Lau R et al. Carbohydrates, glycemic index, glycemic load, and colorectal cancer risk: a systematic review and meta-analysis of cohort studies. Cancer Causes Control 2012; 23(4): 521-35.

114. Scharlau D, Borowicki A, Habermann N et al. Mechanisms of primary cancer prevention by butyrate and other products formed during gut flora-mediated fermentation of dietary fibre. Mutat Res 2009; 682(1): 39-53.

115. Bingham SA. Mechanisms and experimental and epidemiological evidence relating dietary fibre (non-starch polysaccharides) and starch to protection against large bowel cancer. Proc Nutr Soc 1990; 49(2): 153-71.

116. Kyro C, Olsen A, Landberg R et al. Plasma alkylresorcinols, biomarkers of whole-grain wheat and rye intake, and incidence of colorectal cancer. J Natl Cancer Inst 2014; 106(1): djt352.

117. Larsson SC. Plasma alkylresorcinols as a biomarker for whole-grain intake and association with colorectal cancer. J Natl Cancer Inst 2014; 106(1): djt362.

118. Zhou L, Zahid M, Anwar MM et al. Suggestive evidence for the induction of colonic aberrant crypts in mice fed sodium nitrite. Nutr Cancer 2016; 68(1): 105-12.

119. Boffetta P, Hashibe M. Alcohol and cancer. Lancet Oncol 2006; 7(2): 149-56.

120. Giovannucci E, Rimm EB, Ascherio A et al. Alcohol, low-methionine--low-folate diets, and risk of colon cancer in men. J Natl Cancer Inst 1995; 87(4): 265-73.

121. Liu RH. Potential synergy of phytochemicals in cancer prevention: mechanism of action. J Nutr 2004; 134(12 Suppl): 3479S-85S.

122. Larsson SC, Kumlin M, Ingelman-Sundberg M et al. Dietary long-chain n-3 fatty acids for the prevention of cancer: a review of potential mechanisms. Am J Clin Nutr 2004; 79(6): 935-45.