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

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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%, $I^2=70\%$, heterogeneity ($ph)<0.01$) 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](http://www.wcrf.org/sites/default/files/Colorectal-Cancer-2011-Report.pdf) and [http://www.wcrf.org/](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, \( I^2 = 70\% \), heterogeneity \((p_h)<0.01\) (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, \( I^2 = 48\% \), \( p_h=0.08 \), 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, \( I^2 = 26\% \), \( p_h=0.18 \)) (figure 2b). For rectal cancer the positive association was marginally significant (RR=1.08, 95%CI=1.00-1.18, \( I^2 = 0\% \), \( p_h=0.77 \), 10 studies) (figure 2c) (table 1D).

The summary relative risk of two studies in men was 1.11(95%CI=0.86-1.43, \( I^2 = 34\% \), \( p_h=0.22 \)) and for five studies in women the RR was 1.18 (95%CI=0.99-1.41, \( I^2 = 19\% \), \( p_h=0.29 \)) (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, $I^2=24\%$, $p_h=0.24$, 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, $I^2=12\%$, $p_h=0.33$, 11 studies) (figure 2b) but not with rectal cancer (RR=1.13, 95%CI=0.96-1.34, $I^2=0\%$, $p_h=0.52$, 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, $I^2=25\%$, $p_h=0.21$, 16 studies) (figure 2a), colon (RR=1.07 (95%CI=1.05-1.09, $I^2=34\%$, $p_h=0.13$, 14 studies) (figure 2b) and rectal cancer (RR=1.08 (95%CI=1.07-1.10, $I^2=0\%$, $p_h=0.54$, 11 studies) (figure 2c) (table 2).

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% CI=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, $I^2=60\%$, $p_{h}=0.01$).

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, $I^2=18\%$, $p_{h}=0.30$, 6 studies) (figure 2a) and a decrease risk of colon cancer (RR=0.82 (95%CI=0.73-0.92, $I^2=0\%$, $p_{h}=0.49$, 4 studies) (figure 2b). Whole grains intake was not associated with rectal cancer (RR=0.81 (95%CI=0.54-1.20, 91%, $p_{h}<0.0001$, 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, $I^2=18\%$, $p_{h}=0.27$, 10 studies) (figure 2a) and colon cancer RR= 0.87 (95%CI=0.81-0.94, $I^2=24\%$, $p_{h}=0.25$, 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, $I^2=30\%$, $p_{h}=0.18$, 9 studies) and rectal cancer (RR=0.94 (95%CI=0.91-0.97, $I^2=0\%$, $p_{h}=0.93$, 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, I²=0%, p<0.48, 11 studies) (figure
2a) and colon cancer risk RR=0.97 (95% CI=0.95-0.99, I²=0%, p<0.77, 12 studies)
(figures 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), I²=0%, p<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, I²=0%, p<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,
I²=0%, p<0.76, 11 studies)) (figure 2b) and rectal cancer 0.84 (0.69-1.02, I²=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, I²=0%, ph=0.76, 6
studies) and RR=0.76 (0.61-0.95, I²=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 1 cup/day we observed a RR=1.00 (95% CI=0.99-1.02, $I^2=44\%$, $p_{H}=0.05$, 14 studies) (figure 2a). For colon cancer the RR was 0.99 (95% CI=0.97-1.01, $I^2=49\%$, $p_{H}=0.03$, 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%, $p_{H}=0.25$, 5 studies) and for distal cancer the RR was 0.99 (95% CI=0.97-1.01, 0%, $p_{H}=0.63$, 5 studies). For rectal cancer the RR was 1.01 (95% CI=1.00-1.03, $I^2=2\%$, $p_{H}=0.43$, 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, $I^2=68\%$, $p<0.0001$, 13 studies) (figure 2a). For colon the RR was 0.98 (95% CI = 0.96-1.01, $I^2=38\%$, $p_{H}=0.09$, 12 studies) (figure 2b). For rectal cancer the RR was 0.98 (95% CI = 0.93-1.03, $I^2=55\%$, $p_{H}=0.02$, 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 ($\leq$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, $I^2=48\%$, $p_{H}=0.05$, 7 studies) (figure 2a). For colon the RR=0.83 (0.63-1.11, $I^2=35\%$, $p_{H}=0.08$, 10 studies) and for rectal cancer the RR=0.86 (0.72-1.01, $I^2=0\%$, $p_{H}=0.96$, 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%C.I=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, \( I^2 \geq 50\% \). 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,%, 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.

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Conflict of interest: All authors have completed the ICMJE uniform disclosure form at http://www.icmje.org/doi_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:


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 1\textsuperscript{st} 2010-May 31\textsuperscript{st} 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
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