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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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23 **Abstract**

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

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

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

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

34 **Results:** Results: 400 individual study estimates from 111 unique cohort studies
35 were included. Overall, the risk increase of colorectal cancer is 12% for each
36 100g/day increase of red and processed meat intake (95%CI=4-21%, $I^2=70\%$,
37 pheterogeneity (ph)<0.01) and 7% for 10 g/day increase of ethanol intake in
38 alcoholic drinks (95%CI=5-9%, $I^2=25\%$, $ph=0.21$). Colorectal cancer risk decrease in
39 17% for each 90g/day increase of whole grains (95%CI=11-21%, $I^2=0\%$, $ph=0.30$, 6
40 studies). For each 400 g/day increase of dairy products intake (95%CI=10-17%,
41 $I^2=18\%$, $ph=0.27$, 10 studies). Inverse associations were also observed for
42 vegetables intake (RR per 100 g/day =0.98 (95%CI=0.96-0.99, $I^2=0\%$, $ph=0.48$, 11
43 studies) and for fish intake (RR for 100g/day=0.89(95%CI=0.80-0.99, $I^2=0\%$,
44 $ph=0.52$, 11 studies), that were weak for vegetables and driven by one study for fish.
45 Intakes of fruits, coffee, tea, cheese, poultry and legumes were not associated with
46 colorectal cancer risk.

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

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

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

59
60 The evidence from prospective studies accumulated up to 2015 confirms the
61 judgements of the WCRF Panel.

62 **Introduction**

63
64 Colorectal cancer is the third most common cancer in men (746,000 cases, 10.0% of
65 total cancer) and the second in women (614,000 cases, 9.2% of total cancer)
66 worldwide. Almost 55% of the cases occur in more developed regions. There is wide
67 geographical variation in incidence across the world and the geographical patterns
68 are very similar in men and women[1].

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

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

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

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94 **Methods**

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96 Search strategy

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

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

110

111 Study selection

112 The study inclusion criteria were 1) being a randomized controlled trial or prospective
113 study with cohort, case-cohort or nested case-control design; 2) report adjusted
114 estimates of the relative risk (RR) (e.g. hazard ratio, risk ratio or odds ratio) and 95%
115 confidence intervals (CIs) for the association of foods and colorectal cancer
116 incidence; 3) for dose-response meta-analysis, studies should provide a quantitative
117 measure of the intake. When the same study published more than one article, we
118 selected the newest publication with the largest number of cases. We included
119 results of other pooled analysis in our analysis (Flowchart of study selection – Figure
120 1 and supplementary material).

121 Data extraction

122 The data of relevant articles was extracted to the WCRF-CUP database. The
123 database contains the data of all relevant articles identified in the searches for the
124 2005 WCRF SLR and 2010 WCRF SLR. The data extracted for each article were:
125 first author's last name, publication year, country where the study was conducted,
126 the study name, follow-up period, sample size, sex, age, number of cases, dietary
127 assessment method (type, number of food items and whether it had been validated),
128 type of food, amount of intake, RRs and 95% CIs and adjustment variables. The
129 search and extraction was conducted by the CUP team at Imperial College London.

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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)<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 =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 =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 =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 =0.22) and for five studies in women the RR was 1.18 (95%CI=0.99-1.41, $I^2=19\%$, p =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].

1

2 **Red meats**

3 The association of red meat with colorectal cancer was marginally significant (RR for
4 100g/day increment=1.12, 95%CI=1.00-1.25, $I^2=24\%$, $ph=0.24$, 8 studies) (figure 2a).
5 Red meat was significantly associated with risk of colon cancer (RR for 100 g/day
6 increment=1.22 (95%CI=1.06-1.39, $I^2=12\%$, $ph=0.33$, 11 studies) (figure 2b) but not
7 with rectal cancer (RR=1.13, 95%CI=0.96-1.34, $I^2=0\%$, $ph=0.52$, 8 studies) (figure
8 2c) (table 1D).

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

11 From the four studies with data on distal and proximal colon cancer none observed
12 an association with red meat [38,44,47,101]. A Japanese study [47] observed a
13 significant association between beef consumption and proximal cancer in women
14 RR=2.52(95%CI=1.53-4.14, 28 vs 0.1 g/day) and distal colon cancer in men (1.58
15 (1.07, 2.34, 19 vs 0.2 g/day).

17 **Alcohol**

18 Each increase of 10g/day of alcohol intake (as ethanol in alcoholic beverages)
19 (10g/day of ethanol is equivalent to a standard drink – 100ml of wine, 275ml of beer
20 or 30ml of spirits) was associated with an increased risk of colorectal
21 (RR=1.07(95%CI=1.05-1.09, $I^2=25\%$, $ph=0.21$, 16 studies) (figure 2a), colon
22 (RR=1.07(95%CI=1.05-1.09, $I^2=34\%$, $ph=0.13$, 14 studies) (figure 2b) and rectal
23 cancer (RR=1.08(95%CI=1.07-1.10, $I^2=0\%$, $ph=0.54$, 11 studies) (figure 2c) (table

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

29 For five studies [48,51,59,62,64] with data on distal and proximal colon cancer, two
30 observed a significant association with distal colon cancer, the Melbourne Cohort
31 Study (RR=4.17(95%CI=1.63-10.66, ≥ 45 vs < 50 g/day) and the European
32 Prospective Investigation into Cancer and Nutrition (EPIC) study RR=1.68
33 (95%CI=1.08-2.62, ≥ 60 vs 0.1-4.9g/day) [62,64] and two studies on women observed a
34 significant association with proximal cancer, the Iowa Women's Health Study (IWHS)
35 RR=1.12(0.71-1.77, ≥ 31 vs 0 g/day) and the Netherlands Cohort Study (NLCS)
36 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 $RR=1.00(95\%CI=0.99-1.02, I^2=44\%, ph=0.05, 14 \text{ studies})$ (figure 2a). For colon cancer the RR was $0.99(95\%CI=0.97-1.01, I^2=49\%, ph=0.03, 11 \text{ studies})$ (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 $RR = 0.99, 95\% CI = 0.97 \text{ to } 1.02, p=0.45$) [99]. For proximal cancer the RR was $0.99(95\%CI=0.96-1.02, 64\%, ph=0.25, 5 \text{ studies})$ and for distal cancer the RR was $0.99 (95\%CI=0.97-1.01, 0\%, ph=0.63, 5 \text{ studies})$. For rectal cancer the RR was $1.01(95\%CI=1.00-1.03, I^2=2\%, ph=0.43, 15 \text{ studies})$ (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 $0.96(95\% CI = 0.93-1.00, I^2=68\%, ph<0.0001, 13 \text{ studies})$ (figure 2a). For colon the RR was $0.98(95\% CI = 0.96-1.01, I^2=38\%, ph=0.09, 12 \text{ studies})$ (figure 2b). For rectal cancer the RR was $0.98(95\% CI = 0.93-1.03, I^2=55\%, ph=0.02, 9 \text{ studies})$ (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 ($\leq 300\text{g/day}$) 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 $0.81(95\% CI = 0.53-1.25, I^2=48\%, ph=0.05, 7 \text{ studies})$ (figure 2a). For colon the $RR=0.83(0.63-1.11, I^2=35\%, ph=0.08, 10 \text{ studies})$ and for rectal cancer the $RR=0.86(0.72-1.01, I^2=0\%, ph=0.96, 6 \text{ studies})$

(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).

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

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

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

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

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

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

23 **Discussion**

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

30 **Limitations of the study**

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

1 Less than 50% of studies included in our meta-analysis stated that they used
 2 validated food-frequency questionnaires, and only EPIC study corrected the results
 3 for measurement error [35,64,96].
 4 Another limitation of our analysis is publication bias, some studies do not publish
 5 results on all food types or colorectal cancer subtypes. In this analysis, publication
 6 or small study bias appeared to be explained by one outlying study, and when this
 7 study was excluded, the test for publication bias was no longer significant.
 8
 9 In general the evidence for rectal cancer was weaker than for colon and colorectal
 10 cancer which might be explained by the lower number of cases on rectal cancer
 11 reported in the studies included. For the distal and proximal cancer the data is limited
 12 and more studies are needed. One limitation of the analysis of fish and vegetables
 13 was the highest weight of one study in the analysis which has driven the overall
 14 result. When this study was excluded the results were no longer significant which is
 15 consistent with the results of previous pooled analyses. For vegetables, a pooled
 16 analysis of 14 cohort studies and 5838 colorectal cancer cases showed a non-
 17 significant association when comparing 300 vs 100g/day of vegetables RR=0.96
 18 (95%CI=0.84-1.09) [106]. For fish the UK Dietary Cohort Consortium reported a RR
 19 for ≥ 30 vs < 1 g/day of white fish of 0.86 (95%CI=0.64–1.16) and for fatty fish the RR
 20 was 0.73 (95%CI=0.54–0.98). Non-significant results were observed for colon and
 21 rectal cancer [107].
 22
 23 Whenever it was possible we included previous pooled analyses in our analyses. A
 24 small pooled analysis, the UK Dietary Cohort Consortium which included seven UK
 25 cohort studies (579 cases and 1996 controls), reported no evidence of an
 26 association between red and processed meat consumption and colorectal cancer
 27 risk (odd ratios for a 50g/day increase in red and processed meat = 0.97, 95% CI =
 28 0.84-1.12). Similar relationships were observed for colon and rectal cancers [107].
 29 This is not in concordance with the significant positive associations observed in the
 30 current meta-analyses, as the authors argued that the null results might be due to
 31 the relatively low meat intake of the cohorts included (cut points of the highest
 32 quantiles of intake were only 80g/day, 50 g/day and 30 g/day for red and processed
 33 meat, red meat and processed meat respectively). Two of the cohorts (EPIC-Norfolk
 34 and EPIC-Oxford) participating in this consortium were included in our meta-
 35 analyses [35]. The IARC Monographs Programme evaluated red meat as probably
 36 carcinogenic to humans and processed meat as carcinogenic to humans[108].
 37 We identified two pooled analyses on alcohol and colorectal cancer with inconsistent
 38 results. A pooled analysis of five Japanese cohort studies showed a significant
 39 positive association per 15g/day of alcohol in men 1.11 (95% CI = 1.09-1.14) and
 40 women 1.13 (95% CI = 1.06-1.20) [71]. We included this in our analysis. A pooled
 41 analysis of seven cohorts from the UK was not included in our analysis because of
 42 the overlap with the EPIC study [35]. This analysis showed non-significant results
 43 when comparing ≥ 45 vs 0 g/day in men 1.24(95% CI = 0.69-2.22) and women
 44 1.52(95% CI= 0.56-4.10) [109].

1 No pooled analysis was identified on dairy products. One meta-analysis of 12 cohort
2 studies from North America and Europe showed a significant decrease risk for
3 highest compared to lowest analysis 0.84 (95%CI = 0.75-0.95) [110]. Another meta-
4 analysis observed a 17% decrease risk of colorectal cancer per 400g/day of dairy
5 0.83 (95%CI = 0.78-0.88), 10 studies[111].

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

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

18
19 The benefit of whole grains may mainly be related to the content of fibre of these
20 foods [114,115]. As part of the analysis of the 2015 CUP SLR, after including the
21 results of the Pooling Project [112], we observed a borderline significant 7%
22 decrease risk of colorectal cancer RR per 10g/day dietary fibre=0.93 (95%CI=0.87-
23 1.00, 72%, *ph*<0.001, 21 studies, 16 562 cases).

24 The non-significant associations observed for fruit and coffee should not be interpret
25 as lack of power to detect an association because there were at least ten studies in
26 each analysis and the number of cases ranged from 16385 to 20667. For poultry, tea,
27 cheese and legumes the number of studies included in the analysis might have been
28 low to have the statistical power to detect an association. The opposite direction of
29 results of individual studies might be explained by different units of measurement or
30 range of intakes.

31 **Mechanisms**

32 Further discuss of the mechanisms is included as supplementary material.

34 **Strengths of the study**

35 Strengths of the current study include the update, systematic review and meta-
36 analysis of prospective studies that quantify the dose-response between foods and
37 beverages intake and colorectal cancer risk, the detailed subgroup and sensitivity
38 analysis and the comparison between SLR 2005, CUP SLR 2010 and CUP SLR
39 2015 results. The studies included had high quality, most adjusted for the main
40 confounders for colorectal cancer (age, sex, BMI, smoking, alcohol, physical activity,
41 calcium, fruit and vegetable intake and fibre), included a large number of cases with

1 a low loss to follow-up, used FFQs to assess food intake and cancer registries to
2 confirm cancer outcome.

3 4 **Conclusion**

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

10
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15 from those in future updates of the evidence related to diet, nutrition, physical activity
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27
28
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34 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

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