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Meat subtypes and their association with colorectal cancer: Systematic review and meta-analysis

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Associations between specific red meat subtypes and risk of colorectal cancer (CRC) have been investigated in a number of epidemiological studies. However, no publication to date has summarised the overall epidemiological evidence. We conducted a systematic review and meta-analysis of prospective studies (cohort, nested case-control or case-cohort studies), which reported relative risk (RR) estimates and 95% confidence intervals (CI) for the association between intake of meat subtypes with colorectal, colon or rectal cancer or colorectal adenoma risk. PubMed and ISI Web of Science were searched up until August 1, 2014. Nineteen studies examined meat subtypes (5 beef, 5 pork, 2 lamb, 1 veal and 19 poultry) and associations with colorectal, colon or rectal cancer risk and 4 studies examined associations with adenoma risk (1 beef and 4 poultry). Comparing highest versus lowest intake, beef consumption was associated with an increased risk of CRC (RR = 1.11, 95% CI = 1.01 to 1.22) and colon cancer (RR = 1.24, 95% CI = 1.07 to 1.44), but no association was found with rectal cancer (RR = 0.95, 95% CI = 0.78 to 1.16). Higher consumption of lamb was also associated with increased risk of CRC (RR = 1.24, 95% CI = 1.08 to 1.44). No association was observed for pork (RR = 1.07, 95% CI = 0.90 to 1.27), but some between study heterogeneity was observed. No association was observed for poultry consumption and risk of colorectal adenomas or cancer. This meta-analysis suggests that red meat subtypes differ in their association with CRC and its sub sites. Further analysis of data from prospective cohort studies is warranted, especially regarding the role of pork.

Mini Review

Many epidemiological studies have evaluated the association between red and processed meat and colorectal cancer (CRC) risk.[1–4] In 2007, the World Cancer Research Fund/American Institute for Cancer Research (WCRF/AICR) in the report, "Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective" judged red and processed meat to be a convincing risk factor for CRC, recommending to limit the intake of red meat and to avoid processed meat.[5] The most recent systematic review and meta-analysis from 2011 supports this conclusion that a high intake of red and processed meat significantly increases the risk of CRC.[1]

A number of mechanisms have been proposed to explain the association between red and processed meat with CRC. Potential factors such as heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH) arising in meat cooked at high temperatures,[6,7] heme iron[8] or nitrates and nitrites used in meat processing[9] have all been hypothesised to play a role. Although the exact mechanism is still unknown, the role of HCA and PAH has been questioned since these chemical components are also contained in poultry and fish cooked at high temperatures.[10,11] Poultry and fish, however, were not associated with increased CRC risk in previous epidemiological studies, so the association of HCA and PAH with CRC remains unclear.[5] Red meat is abundant in heme iron which has been suggested to mediate the formation of intestinal carcinogenic compounds.[12] It has been hypothesised that since different red meats contain differing amounts of heme iron, the risk for CRC may therefore vary according to the red meat subtype.[13] A more recent hypothesis proposed to explain the relation of red meat consumption and CRC suggests that a specific bovine infectious factor may be involved in CRC development.[14] Based on the fact that chemical carcinogens (HCA and PAH) as the sole player in

Key words: colorectal cancer, meat subtypes, red meat, poultry, meta-analysis

Abbreviations: CHD: coronary heart disease; CI: confidence intervals; CRC: colorectal cancer; DM: diabetes mellitus; HCA: heterocyclic amines; PAH: polycyclic aromatic hydrocarbons; RR: relative risk; WCRF/AICR: World Cancer Research Fund/American Institute for Cancer Research

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CRC risk have been questioned and the fact that the increased risk for CRC is restricted to populations with high beef consumption the author concludes that a specific beef factor may contaminate the meat which could then be potentially carcinogenic upon transmission to humans.[14]

Associations between specific red meat subtypes (*i.e.,* beef, lamb, pork or veal) and risk of CRC have been investigated in a number of epidemiological studies.[13,15–18] No publication to date has summarised the overall epidemiological evidence according to meat subtypes. Thus, we conducted a comprehensive systematic review and meta-analysis to summarize and quantify the associations between meat subtypes and CRC, based on prospective cohort studies.

Material and Methods

Data sources and search strategy

A systematic literature search was conducted in PubMed and ISI Web of Science without language restrictions until 1 August 2014 to identify eligible studies. The search terms used were (colorectal OR colon OR rectum OR rectal) and (cancer OR neoplasm OR carcinoma OR adenoma) and (meat OR "red meat" OR beef OR pork OR lamb OR veal OR poultry OR chicken OR turkey OR "processed meat") and (cohort OR "case control" OR "follow up" OR prospective OR "cross sectional" OR randomized) and ["relative risk" OR risk OR rate OR ratio OR incidence]. The reference lists of identified studies were also searched for additional relevant studies. The systematic literature review was conducted according to the criteria set out by the PRISMA and MOOSE guidelines.[19,20]

Study selection

Studies were eligible for inclusion in the systematic review if they were prospective (cohort, nested case-control or case-cohort) studies in humans and reported relative risk (RR) estimates (hazard ratios, risk ratios or odds ratios) with corresponding 95% confidence intervals (CI) for the association of meat subtypes with colorectal, colon or rectal cancer risk and/or colorectal adenoma risk. We have focused the main analysis of this review on the prospective cohort studies because they provide the most reliable level of available evidence and are less prone to recall and selection bias. Also, assessment of diet at baseline in a cohort study was considered more reliable and relevant than assessment of past or current dietary habits in case-control studies.

Meat subtypes included beef, veal, lamb, pork and poultry (chicken/turkey). Studies, which reported on "white meat," were included if the white meat category only included poultry and not fish. The author of one study was contacted to clarify the definition of white meat.[21]

Two reviewers (PC, MH) independently performed the study selection based on the selection criteria. Disagreements were resolved by discussing and reviewing the issue. The review was restricted to original articles published in English. Studies were excluded if they had no data on specific meat subtypes, if the study focussed on adenoma recurrence or serrated polyps only or if the study was conducted in special risk groups (*e.g.,* familial cases and young onset CRC cases). We excluded studies published as abstracts or commentaries as the information contained was insufficient for our assessment.

Data extraction

Two reviewers (PC, VW) carried out the extraction of data from eligible studies. Data were independently extracted onto a data extraction form which included the following information: first author's last name, year of publication, country, study name, study size, number of cases, sex, age, follow up time, dietary assessment and comparison groups, adjustment for confounders and the RR estimates with the corresponding 95% CI for the highest *versus* lowest level of intake for each reported meat subtype. We extracted the RRs from the most adjusted multivariate model. Disagreements in data extraction were solved through further discussion and review.

Quality assessment

A quality assessment of included studies was carried out by two reviewers (PC, VW). A maximum of 4 points was assigned to each CRC risk study (clear description of study population, recruitment and follow up; consideration of age, sex and other lifestyle factors in a multivariate analysis; extensive dietary assessment including amount of intake; clear definition of meat subtypes) and a maximum of 5 points for studies assessing risk of adenomas (additionally: assessment of adenoma presence based on medical records).

Statistical analysis

After assessment of the quality criteria, those studies which met the first two criteria (clear description of study participants and consideration of age, sex and other lifestyle factors in a multivariate analysis) were included in the meta-analysis.

In this meta-analysis, we compared the highest *versus* lowest category of meat subtype consumption as different studies reported different exposure categories for meat consumption (*e.g.,* quartiles, tertiles, yes or no etc.). RR estimates were pooled using the random effects models according to methods described by DerSimonian and Laird, which take into account both within and between study heterogeneity.[22] When a study provided risk estimates for CRC stratified by sex or cancer sub site only (colon or rectal; proximal colon or distal colon), we first pooled the estimates using a fixed effect model to get an overall summary RR for the meat subtype and included the pooled result in the random effects meta-analysis.[23] One study[24] reported RRs for poultry with skin and poultry without skin so we pooled the two RR estimates together using a fixed effect model to get a summary RR for overall poultry intake, which was then included in the meta-analysis. Further meta-analyses were conducted stratified by cancer sub site, sex and geographic location.

To evaluate heterogeneity of included studies, we calculated Cochran's Q test, I^2 statistic and tau squared.[25]

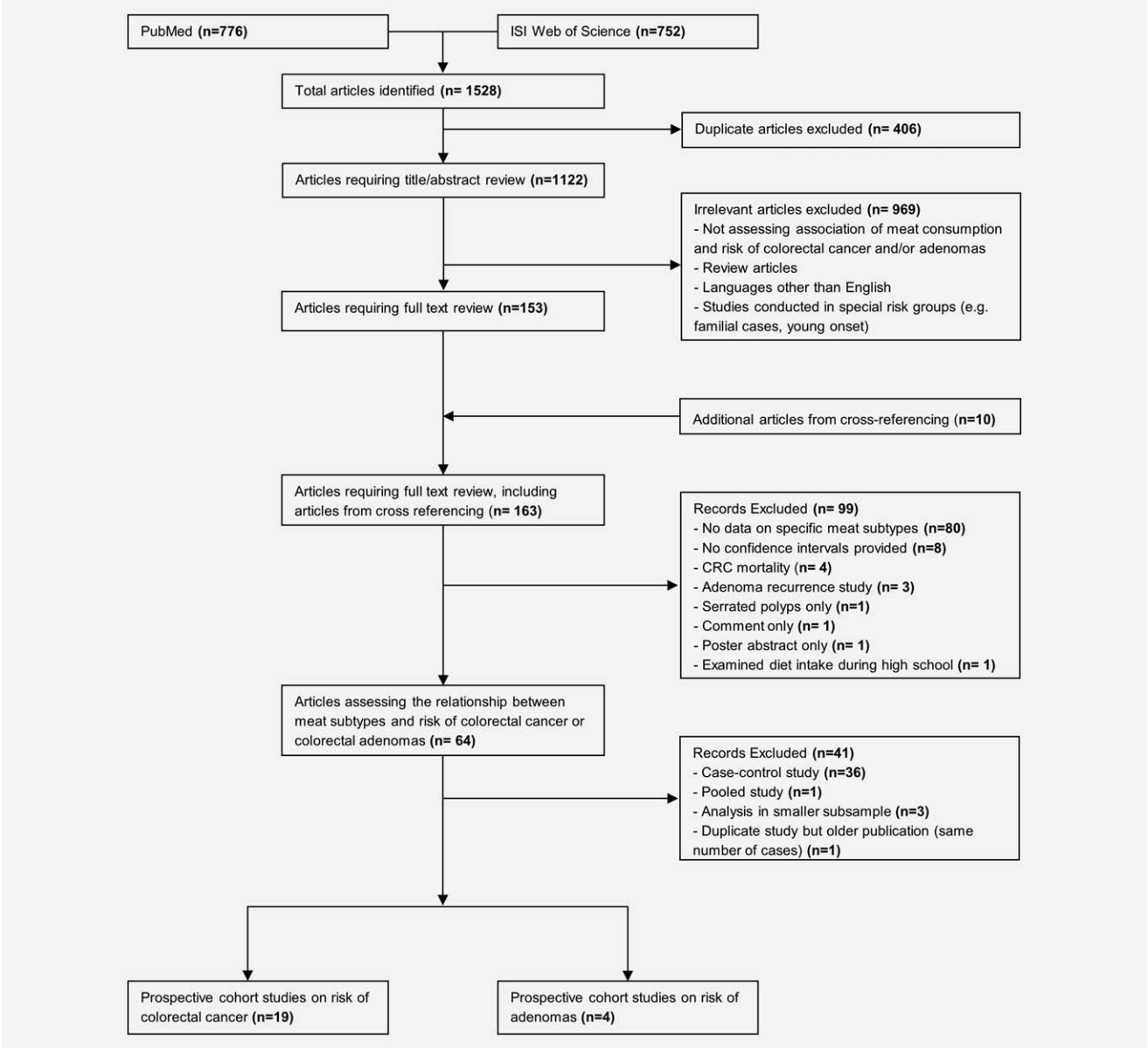

Figure 1. Flow diagram of systematic literature search.

Indication for publication bias was assessed with funnel plots.[26] Sensitivity analyses were conducted by omitting one study at a time and examining the influence of each individual study on the overall RR.

Although we excluded the case-control studies from our systematic review, we conducted quality assessment and meta-analyses for meat subtypes analyzed in case-control studies to check the consistency of the results across the study types. All analyses were conducted using R version 3.1.0,[27] and the R package "meta" version 3.5-1.[28]

Results

Search results

We identified 23 publications that examined the relationship between meat subtypes (beef, veal, pork, lamb or poultry) and colorectal, colon or rectal cancer or adenoma risk in the systematic literature search (Fig. 1). Among these publications, 19 prospective cohort studies assessed meat subtypes and CRC risk (1 case-cohort study, 2 nested case-control and 16 cohort studies; Supporting Information Table S1) and 4 prospective cohort studies assessed meat subtypes and adenoma risk (Supporting Information Table S2).

Five articles each assessed the association between beef and pork intake and risk of CRC,[13,15–18] two articles assessed the association between lamb and CRC risk[13,15] and one article assessed the association between veal consumption and CRC risk.[13] Nineteen articles described the association between poultry intake and risk of CRC.[13,15–18,24,29–41] Four articles described the association between poultry intake[21,42–44] and risk of colorectal adenomas, whilst only

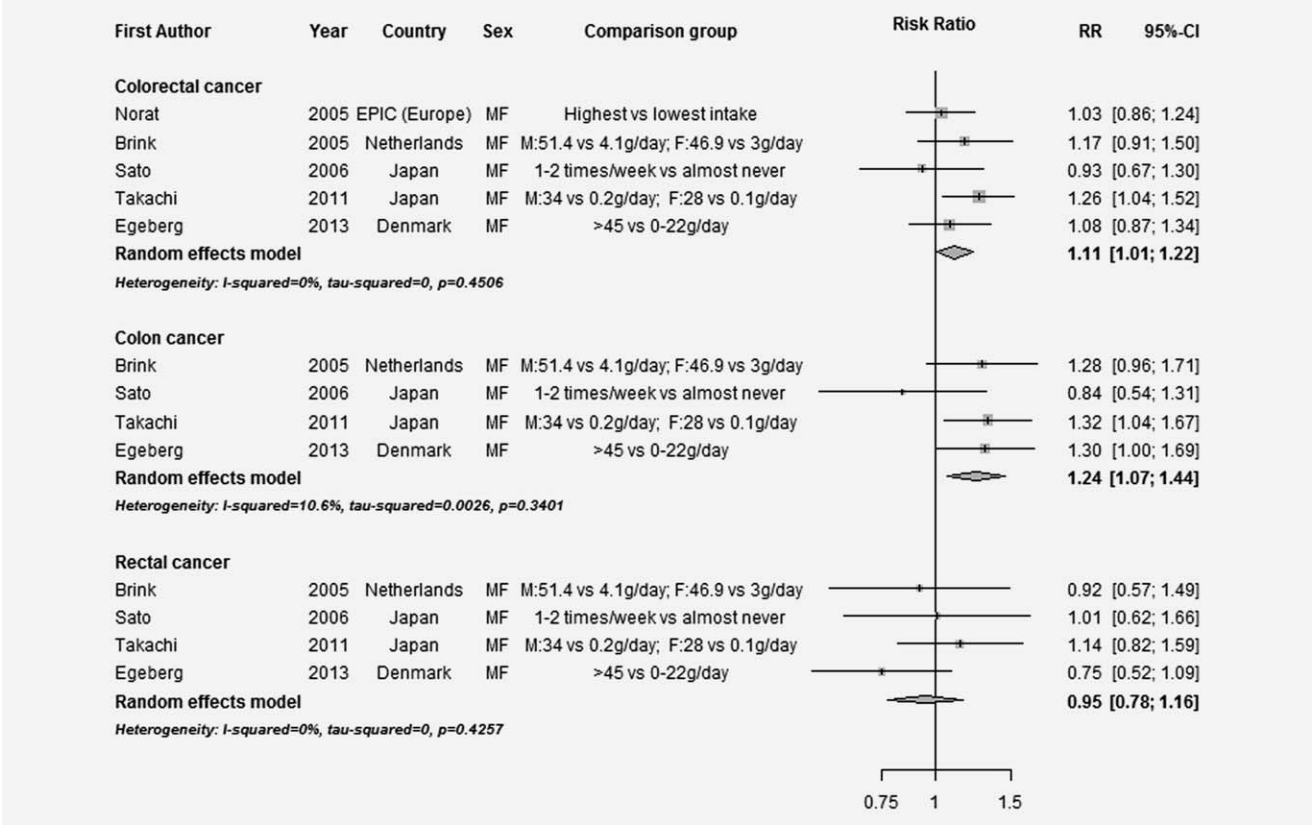

Figure 2. Meta-analysis of colorectal, colon and rectal cancer for highest *vs*. lowest category of beef intake (From Refs. 13, 15–18).

one article assessed beef consumption and colorectal adenoma risk.[42]

Study characteristics

Among the 19 eligible articles assessing meat subtypes and CRC risk there were 9 cohorts of men and women, 3 male cohorts and 7 female cohorts. The 19 studies comprised data from 15,183 CRC patients and had study sizes ranging from 639 to 492,186 participants. Seven of the studies assessing meat subtypes and CRC risk were from the USA, eight were from Europe (including a multinational cohort – EPIC), three were from Asia and one study was from Australia. Two of the included European studies[13,29] were also in parts sub cohorts of the multinational EPIC study.[15] However, our overall results were unchanged for all meat subtypes when the results of the EPIC study were omitted.

A total of 38,137 subjects including 2,546 colorectal adenoma cases were involved in the meta-analysis assessing meat subtypes and colorectal adenoma risk. Three of the studies were conducted in male and female cohorts, whilst one study was conducted in a male cohort. Three of the adenoma cohorts were carried out in the USA and the other one in Europe.

The mean score for the quality assessment of the included studies assessing meat consumption and CRC risk was 3.42 out of 4 (Supporting Information Table S3). Every study provided a clear description of study participants, recruitment and follow up. Only one study[41] did not consider or adjust its effect measures for at least age, sex and other lifestyle factors and was therefore excluded from the meta-analysis.

The mean score for the quality assessment of the included studies assessing meat subtypes and adenoma risk was 3.75 out of 5 (Supporting Information Table S3). All studies considered or adjusted the effect measures for at least age, sex and other lifestyle factors and provided a clear description of the study population, recruitment and follow up. None of the four studies provided clear descriptions of the amounts in each meat category.

Beef consumption and risk of CRC

Two of the five prospective cohort studies reporting on beef intake provided an overall result for CRC risk[15,16] and the remaining three studies provided results stratified by cancer sub site, *i.e.,* colon and rectal cancer.[13,17,18] Overall, beef consumption was related to increased risk of CRC (RR = 1.11, 95% CI = 1.01 to 1.22) and colon cancer (RR = 1.24, 95% CI = 1.07 to 1.44) but not rectal cancer (RR = 0.95, 95% CI = 0.78 to 1.16; Fig. 2). No significant heterogeneity was observed for the colorectal, colon or rectal cancer risk studies and no indication of publication bias was observed from the

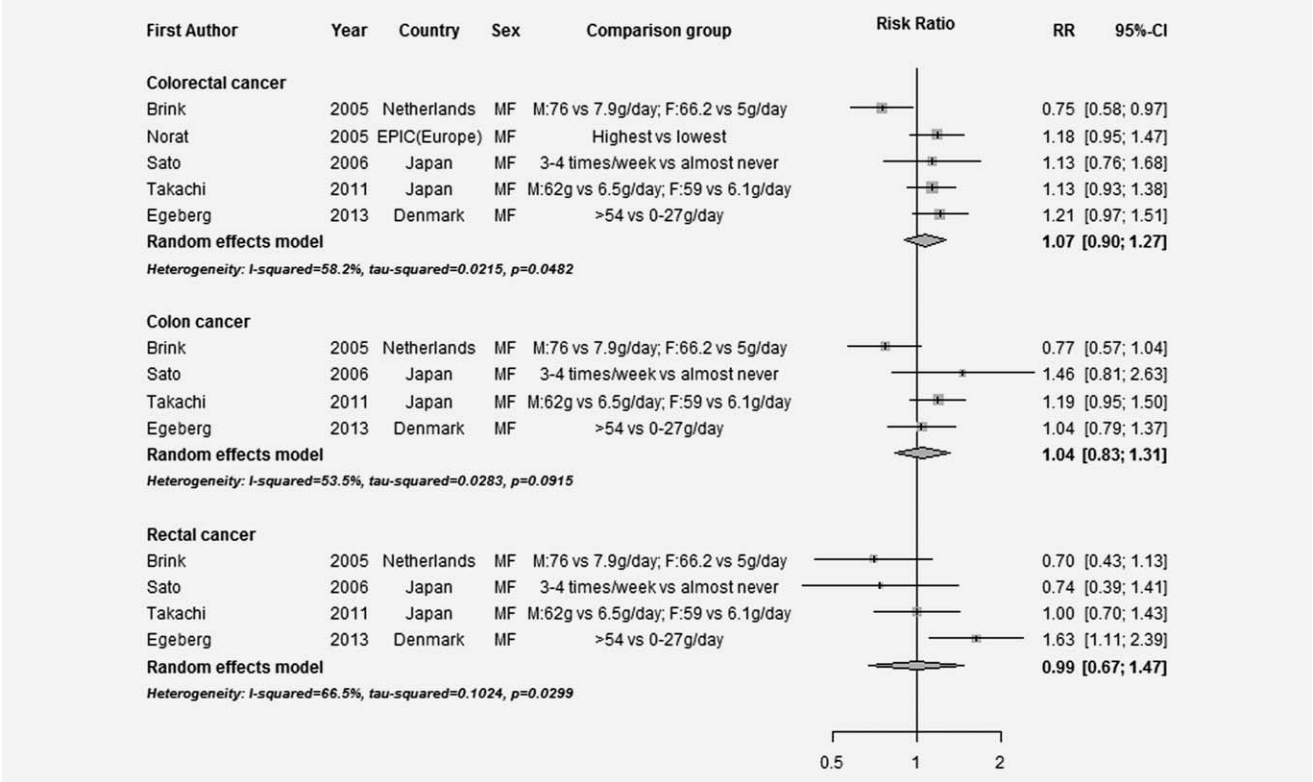

Figure 3. Meta-analysis of colorectal, colon and rectal cancer for highest *vs*. lowest category of pork intake (From Refs. 13, 15–18).

funnel plots (Supporting Information Fig. S1). In meta-analyses of case-control studies, beef consumption tended to be associated with an increased risk of CRC although the result was not statistically significant (RR = 1.84, 95% CI = 0.93 to 3.63; Supporting Information Fig. S5).

Pork consumption and risk of CRC

Two prospective cohort studies provided overall results for CRC risk[15,16] whilst the remaining 3 studies provided results stratified by colon and rectal cancer.[13,17,18] The summary RRs for the highest *versus* lowest pork intake were 1.07 (95% CI = 0.90 to 1.27), 1.04 (95% CI = 0.83 to 1.31) and 0.99 (95% CI = 0.67 to 1.47) for colorectal, colon and rectal cancer, respectively (Fig. 3). There was moderate to high heterogeneity between the studies. In sensitivity analyses, only removal of the case cohort study[18] considerably reduced the observed heterogeneity ($I^2 = 0\%$, $p_{\text{heterogeneity}} = 0.971$) and an increased risk of CRC was observed across the four remaining studies (RR = 1.17, 95% CI = 1.04 to 1.31). The funnel plots indicated potential publication bias for studies assessing rectal cancer risk. There was suggestion of small studies with a positive association missing, however the number of studies was small so this must be interpreted with caution (Supporting Information Fig. S2). The meta-analysis of case-control studies showed no association of pork consumption with CRC risk similar to the overall result for the cohort studies (RR = 1.03, 95% CI = 0.83 to 1.27; Supporting Information Fig. S5).

Lamb and veal consumption and risk of CRC

Only two prospective cohort studies[13,15] described the association between lamb consumption and CRC risk which were both included in the highest *versus* lowest intake meta-analysis. One article[15] presented an overall result for CRC risk whilst the other[13] provided results stratified by cancer sub site. We found a significant association between lamb intake and risk of CRC (RR = 1.24, 95% CI = 1.08 to 1.44). There was no study heterogeneity ($I^2 = 0\%$, $p_{\text{heterogeneity}} = 0.834$). In meta-analyses of case-control studies, the pooled RR for lamb consumption and CRC risk was similar (RR = 1.32, 95% CI = 1.03 to 1.69; Supporting Information Fig. S5). We could not perform meta-analysis on veal consumption as only one study[13] reported an association with colon and rectal cancer risk (RR = 1.01, 95% CI = 0.79 to 1.28, RR = 1.18, 95% CI = 0.85 to 1.64, respectively; Table 1). Also, no case-control study was available on the association of veal intake and CRC risk.

Poultry consumption and risk of CRC

All 19 articles provided results for associations of poultry intake and either colorectal,[15,16,29,31–39] colon[13,15–18,24,29–33,36,40,41] and/or rectal cancer risk[13,15–18,24,29–33,36,41] and were included in the

Table 1. Summary RRs of prospective cohort studies comparing highest *versus* lowest intakes of meat subtypes with respect to CRC risk, stratified by geographic location

Stratification variable	*n*	RR (95% CI)	I^2	*p* values I^2
Beef				
Europe				
CRC	3	1.08 (0.95–1.22)	0%	0.722
Colon cancer	2	1.29 (1.06–1.57)	0%	0.079
Rectal cancer	2	0.81 (0.60–1.08)	0%	0.509
Asia				
CRC	2	1.12 (0.84–1.49)	58.8%	0.119
Colon cancer	2	1.10 (0.71–1.70)	67.6%	0.079
Rectal cancer	2	1.10 (0.83–1.45)	0%	0.691
Pork				
Europe				
CRC	3	1.03 (0.77–1.38)	78.2%	0.010
Colon cancer	2	0.90 (0.67–1.21)	52.1%	0.148
Rectal cancer	2	1.08 (0.47–2.48)	86.1%	0.007
Asia				
CRC	2	1.13 (0.95–1.35)	0%	1
Colon cancer	2	1.22 (0.99–1.51)	0%	0.525
Rectal cancer	2	0.93 (0.68–1.27)	0%	0.424
Poultry				
Europe				
CRC	8	0.94 (0.85–1.05)	32.5%	0.168
Colon cancer	6	0.98 (0.82–1.17)	45.7%	0.101
Rectal cancer	6	0.96 (0.80–1.14)	0%	0.713
Asia				
CRC	3	1.08 (0.92–1.25)	0%	0.416
Colon cancer	3	1.14 (0.94–1.38)	0%	0.499
Rectal cancer	3	0.97 (0.75–1.27)	0%	0.479
North America				
CRC	4	0.93 (0.86–1.01)	0%	0.713
Colon cancer	3	0.97 (0.89–1.06)	0%	0.485
Rectal cancer	1	0.84 (0.72–0.98)	–	–
Australia				
CRC	1	0.70 (0.60–1.00)	–	–
Colon cancer	1	0.70 (0.50–1.10)	–	–
Rectal cancer	1	0.70 (0.50–1.20)	–	–
Lamb				
Europe				
CRC	2	1.24 (1.08–1.44)	0%	0.834
Veal				
Europe				
Colon cancer	1	1.01 (0.79–1.28)	–	–
Rectal cancer	1	1.18 (0.85–1.64)	–	–

Abbreviations: CI: confidence interval; CRC: colorectal cancer; *n*: number of studies; RR: relative risk

meta-analysis. We found no association between poultry intake and risk of CRC (RR = 0.96, 95% CI = 0.88 to 1.04) and study heterogeneity was low (Fig. 4). Results stratified by CRC sub site suggested an inverse association with rectal cancer (RR = 0.89, 95% CI = 0.80 to 0.98) but no association with colon cancer risk (RR = 1.00, 95% CI = 0.90 to 1.11). Funnel plots did not indicate publication bias for studies on colorectal, colon and rectal cancer risk, respectively (Supporting Information Fig. S3). The meta-analysis of case-control studies also indicated no association of poultry consumption with CRC risk (RR = 0.93, 95% CI = 0.74 to 1.17; Supporting Information Fig. S5).

Subgroup analysis by geographic location

The association between beef consumption and colon cancer risk was statistically significant in European studies (RR = 1.29, 95% CI = 1.06 to 1.57), but not in studies from Asia (RR = 1.10, 95% CI = 0.71 to 1.70; Table 1). Conversely, the association of pork and colon cancer risk observed in studies from Asia (RR = 1.22, 95% CI = 0.99 to 1.51) was different to the studies from Europe (RR = 0.90, 95% CI = 0.67 to 1.21). However, in most stratified analyses the number of studies was low and in some there was moderate to high heterogeneity. No difference was seen for associations with poultry intake when stratified by the geographical regions. With respect to sex, it was only possible to perform stratified meta-analyses for poultry intake, but results likewise did not suggest an association with CRC risk (results not shown).

Meat subtypes and risk of colorectal adenomas

A meta-analysis could only be performed for the four cohort studies,[21,42–44] which assessed the association of poultry intake and colorectal adenoma risk. The summary RR for highest *versus* lowest intake was 0.97 (95% CI = 0.86 to 1.10; Supporting Information Fig. S6). No study heterogeneity or publication bias was observed (Supporting Information Fig. S4). Beef intake and association with colorectal adenomas was reported in only one cohort study (RR = 1.09, 95% CI = 0.84 to 1.41).[42] Results from case-control studies, which assessed poultry intake and risk of adenomas were consistent with the cohort studies (RR = 0.90, 95% CI = 0.69 to 1.18; Supporting Information Fig. S7). We were also able to conduct meta-analyses of case-control studies, which assessed beef intake (RR = 1.56, 95% CI = 1.15 to 2.10; Supporting Information Fig. S7). Pork intake and association with colorectal adenomas was only reported in one eligible study (RR = 2.30, 95% CI = 1.08 to 4.90).[45]

Discussion

In this meta-analysis, red meat subtypes differed in their association with risk of CRC and its sub sites. When comparing the highest *versus* the lowest intake, beef was associated with an 11% increased risk of CRC and a 24% increased risk of colon cancer but no association with rectal cancer was observed. Also, lamb consumption was associated with increased CRC risk, although this finding was based on only

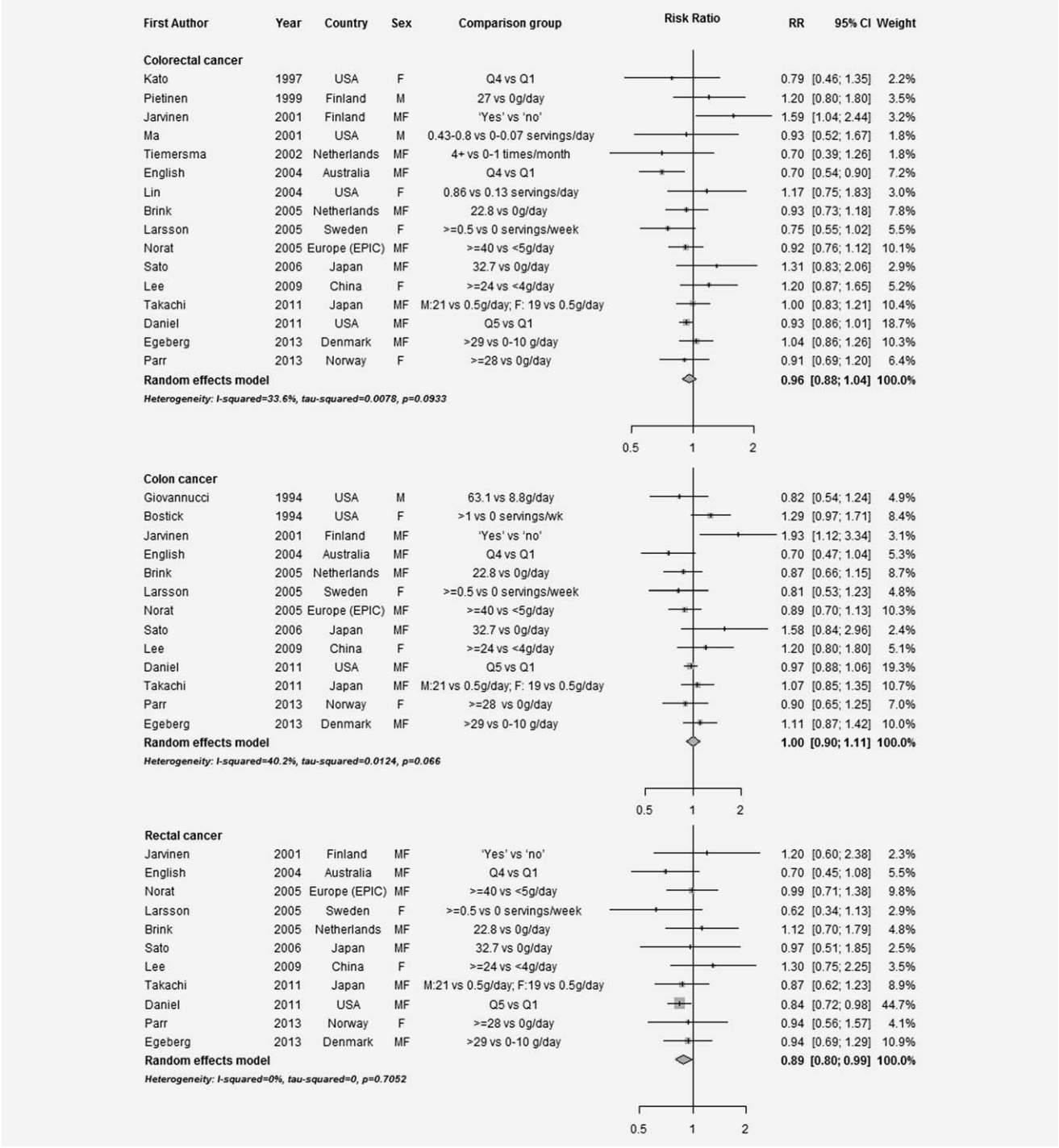

Figure 4. Meta-analysis of colorectal, colon and rectal cancer for highest *vs*. lowest category of poultry intake (From Refs. 13, 15–18, 24, 29–40).

two studies. Pork consumption showed no overall association with CRC risk, neither in meta-analysis of cohort nor of case-control studies. Poultry intake was consistently not associated with increased risk of CRC, its sub sites or its precursors. Only one study investigated associations with veal consumption but no statistically significant effect was observed.

Although no review to date has focussed specifically on meat subtypes and CRC risk, an increased risk has been observed between red and processed meat and CRC in several systematic reviews and meta-analyses.[1–4,46,47] In the most recent systematic review and meta-analysis, high red meat intake was associated with a 10% increased risk of CRC and an 18% increased risk of colon cancer, but no significant

association was found for rectal cancer.[1] The results from our meta-analysis particularly for beef consumption are of similar magnitude in terms of increased risk compared with these previous results and we also found no association with rectal cancer. Further evidence that red and processed meat is associated with colorectal carcinogenesis was presented in two previous systematic reviews and meta-analyses, which evaluated colorectal adenoma risk.[48,49] Both reviews concluded that increased intake of red and processed meat was associated with increased risk of colorectal adenomas.[48,49] Additionally, one of the reviews presented some results from subgroup analyses of eight case-control studies which supported a positive association of adenomas with beef and pork intake.[48] Of these studies, one study was excluded from our meta-analysis because hyperplastic polyps were considered along with adenomas,[50] and one study was excluded as it did not fulfil the quality criteria of adjusting for age, sex and other lifestyle factors.[51] The remaining six studies which provided results for pork intake[45] and/or beef intake[45,52–56] were included in our meta-analysis of case-control studies and showed an association with increased risk of adenomas.

Although a large number of studies have assessed poultry intake and CRC risk, the WCRF/AICR report from 2007 concluded that the evidence was "too limited in amount, consistency or quality to draw any conclusions."[5] The results from a review, which was published whilst we were conducting our systematic review and meta-analysis, assessing the relationship between poultry intake and CRC reported a summary RR, comparing the highest with the lowest level of poultry intake of 0.90 (95% CI = 0.82 to 1.00).[57]In addition, an earlier meta-analysis suggested that there was no association between risk of CRC and poultry intake.[2] After assessment of studies for relevant quality criteria, our results comparing the highest *versus* lowest intakes of poultry are clearly in line with both meta-analyses. Likewise, our result comparing highest *versus* lowest intakes of poultry and colorectal adenoma risk are in line with the results from a recent meta-analysis,[58] which concluded that poultry intake is not associated with the risk of colorectal adenomas. Although we did not find an overall association with poultry intake and risk of CRC, poultry intake was inversely associated with risk of rectal cancer, with low between study heterogeneity. Residual confounding has been suggested to explain this association since poultry consumption has been associated with an overall healthier diet and lifestyle.[57,59]

Epidemiological and experimental evidence supports the hypothesis that heme iron in red meat plays a role in CRC carcinogenesis.[8,60] A meta-analysis which compared the highest *versus* lowest category of heme iron consumption found an 18% increased risk of colon cancer with higher intake of heme iron.[8] Our meta-analysis supports these results since we found a 24% increased risk of colon cancer with beef consumption, which has a higher heme iron content (mean heme iron in cooked beef 2.63 ± 0.5 mg/100 g) compared with veal (mean heme iron in cooked veal 1.33 ± 0.6 mg/100 g) or pork (mean heme iron in cooked pork 0.39 ± 0.2 mg/100 g).[61] Since pork has a much lower heme iron content compared with beef or lamb (mean heme iron in cooked lamb 1.68 ± 0.4 mg/100 g) this could perhaps explain why we did not observe an association with pork consumption in our meta-analysis. Although the results from the meta-analysis of case-control studies supported this finding, our meta-analysis of prospective studies on pork consumption indicated moderate to high heterogeneity. In sensitivity analyses, we observed a positive association between pork and risk of CRC when one study was excluded[18] and it is unclear whether this study is a true outlier. Therefore, more prospective studies are needed to corroborate the potential lack of association with pork consumption.

Bovine infectious factors have been hypothesised to be involved in colorectal carcinogenesis since CRC seems to be restricted to populations with high beef consumption and different cultures use different meat preparation and cooking methods, which could also play a role.[14] We were only able to compare beef and pork consumption in Europe and Asia but the number of studies was limited. However, the amounts of meat intake compared in the different regions varied; the highest categories of beef intake in the Asian studies (median intake 7.4 g and 34 g/day)[16,17] was much lower than those in the European studies (median intake 51.4 and >45 g/day)[13,18] and therefore it is possible that the comparatively lower meat consumption among the Asian studies was insufficient to see an association. Overall, given the modest effects observed for highest *versus* lowest intakes, beef consumption alone seems unlikely to explain the large international variation of CRC incidence.

Besides the evidence linking red meat with CRC, there is limited evidence that red meat is associated with cancers of the oesophagus, lung, pancreas or endometrium[5] and a recent meta-analysis found that the risks of coronary heart disease (CHD) and diabetes mellitus (DM) were increased with high consumption of processed meat (RR of CHD per 50 g/day- = 1.42, 95% CI = 1.07 to 1.89; RR of DM per 50 g/day- = 1.19, 95% CI = 1.11 to 1.27) but not of unprocessed red meat (RR of CHD per 100 g/day = 1.00, 95% CI = 0.81 to 1.23; RR of DM per 100 g/day = 1.16, 95% CI = 0.92 to 1.46).[62] Current dietary recommendations from the WCRF/AICR suggest limiting intake of red meat and avoiding processed meat.[5] However, since red meat is an important source of dietary protein and essential nutrients such as iron and zinc, knowledge of the types of red meat which are associated with CRC are important to further clarify dietary recommendations.

Strengths and limitations

The major strengths of our systematic review and meta-analysis include the comprehensive search strategy, adherence to criteria for conducting and reporting meta-analysis of observational studies,[19,20] and the qualitative assessment of the studies. In addition, we have provided a comprehensive

overview of CRC risk by including both studies assessing adenomas as well as CRC risk. A further strength of our meta-analysis is that it is the first to summarise and evaluate the association of meat subtypes and CRC risk. Finally, since we restricted the systematic review and meta-analysis to the use of cohort studies, we have minimized recall and selection bias which case-control studies are liable to.

This meta-analysis also has limitations. Although we were able to conduct meta-analyses for meat subtypes, it would have been desirable to have a larger number of studies particularly for beef and pork intake. At least 30 prospective studies have investigated the association of red and processed meat and CRC yet only 5 studies reported results for red meat subtypes (beef and pork). Although we did not detect publication bias in the funnel plots, publication bias and selective reporting would still be possible in this meta-analysis, if studies with available information on meat subtypes did not publish results because no significant differences between meat subtypes emerged or because no or no statistically significant associations were observed. Also, only few studies reported on meat subtypes other than beef, pork and poultry and few eligible studies were available addressing adenoma risk.

Secondly, despite conducting a comprehensive qualitative assessment of the studies which included assessment of the covariates (age, sex and other lifestyle factors), covariates still varied across the studies and thus we cannot exclude the effect of residual confounding. A further limitation of our study is the lack of consistency in the definitions of the reference and comparison groups of meat subtypes in the studies. The definitions of the reference groups in the studies ranged from "lowest intake" to "almost never" to "<27 g/day" and the exposed group ranged from 'highest intake" to "3–4 times per week" to ">54 g/day," which made it difficult to compare the overall results and to conduct a dose response analysis. Nevertheless, we used the RRs for the highest *versus* the lowest intake in each category to potentially reduce some bias. Finally, despite our comprehensive search strategy, we cannot rule out the possibility of having missed a relevant study particularly as we excluded those reported in languages other than English.

Conclusion

In conclusion, this meta-analysis suggests that red meat subtypes differ in their association with risk of CRC and its sub sites and that poultry intake is not associated with risk of CRC or its precursors. Beef and lamb consumption were associated with a moderately increased risk of CRC but no association was observed with pork consumption. Due to the limited number of studies and the heterogeneity of results regarding the association with pork consumption from the existing cohort studies, these findings need to be confirmed in future studies and meta-analyses. Generally, to further assess the association of red meat intake with risk of CRC and other related outcomes, additional large scale cohort studies investigating specific meat subtypes are warranted especially regarding the role of pork.

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