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Meat consumption and risk of colorectal cancer: A meta-analysis of prospective studies

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Accumulating epidemiologic evidence indicates that high consumption of red meat and of processed meat may increase the risk of colorectal cancer. We quantitatively assessed the association between red meat and processed meat consumption and the risk of colorectal cancer in a meta-analysis of prospective studies published through March 2006. Random-effects models were used to pool study results and to assess dose-response relationships. We identified 15 prospective studies on red meat (involving 7,367 cases) and 14 prospective studies on processed meat consumption (7,903 cases). The summary relative risks (RRs) of colorectal cancer for the highest *vs.* the lowest intake categories were 1.28 (95% confidence interval (CI) = 1.15–1.42) for red meat and 1.20 (95% CI = 1.11–1.31) for processed meat. The estimated summary RRs were 1.28 (95% CI = 1.18–1.39) for an increase of 120 g/day of red meat and 1.09 (95% CI = 1.05–1.13) for an increase of 30 g/day of processed meat. Consumption of red meat and processed meat was positively associated with risk of both colon and rectal cancer, although the association with red meat appeared to be stronger for rectal cancer. In 3 studies that reported results for subsites in the colon, high consumption of processed meat was associated with an increased risk of distal colon cancer but not of proximal colon cancer. The results of this meta-analysis of prospective studies support the hypothesis that high consumption of red meat and of processed meat is associated with an increased risk of colorectal cancer.

Key words: cohort studies; meat; meta-analysis; prospective studies; systematic review

High consumption of red meat and processed meat has been associated with increased risk of colorectal cancer in many epidemiologic studies, although the associations were usually not statistically significant. A meta-analysis of prospective studies published through June 1999 reported that a daily increase of 100 g of red meat or 25 g of processed meat was associated with a 17% and 49%, respectively, increased risk of colorectal cancer.[1] Similar associations between red meat and processed meat consumption with colorectal cancer risk were found in another meta-analysis,[2] which included both case–control and prospective studies published through 1999. These 2 meta-analyses did not report prospective results for colon and rectal cancer separately, and there is evidence that colon and rectal cancers as well as those in the proximal and distal colon may have distinct etiologies.[3–5]

Ten prospective studies[4–13] have since 1999 been published on red meat and/or processed meat consumption in relation to risk of colorectal cancer. The current meta-analysis updates and expands the previous meta-analyses[1,2] to include all prospective studies on this issue published through March 2006. This meta-analysis includes up to 6 times as many cases of colorectal cancer as the 2 earlier meta-analyses, thus providing more precise risk estimates. Herein, we also report summary results for colon and rectal cancer separately as well as for subsites in the colon (i.e., proximal and distal colon).

Material and methods

Assembly of literature

To be included in this meta-analysis, studies had to (*i*) use a prospective study design and (*ii*) provide relative risks with corresponding confidence intervals (or data to calculate them) of the association of red meat or processed meat consumption with incidence of or mortality from colon, rectal or colorectal cancer. We omitted studies that reported results only for total meat (including chicken or fish). Studies were identified by searching MEDLINE for literature published in any language from 1966 through March 2006, using the search terms meat, foods, diet, colorectal, colon, rectal, cancer, neoplasm, prospective, cohort and exploded variants. References in the retrieved publications as well as those in previous meta-analyses,[1,2] were checked for any other pertinent studies.

We identified 23 publications that reported results from prospective studies on red meat and/or processed meat consumption in relation to risk of colon or colorectal cancer.[4–26] Four publications[14–17] were excluded because they were superseded by later publication.[4,6,9] There were 2 publications based on the Iowa Women's Health.[18,25] The earlier publication by Bostick *et al.*[18] was included in the meta-analysis because this study focused on meat consumption and adjusted for more covariates than the latter publication by Sellers *et al.*[25] (the latter publication presented results stratified by family history of colon cancer[25]). The remaining 18 publications[4–13,18–24,26] were included in the meta-analysis.

Data extraction

We extracted the following data from each publication: the first author's last name, the year of publication, the country in which the study was performed, the sample size, the age of the participants at cohort entry, the method of assessment of diet, the years of follow-up, the categories of meat consumption, the variables controlled for in the multivariate models, and the relative risks and 95% CI for colorectal cancer associated with red meat and processed meat consumption. From each study, we extracted the relative risks that reflected the greatest degree of control for potential confounders.

Statistical analysis

We used the reported relative risk (RR) as the measure of association of red meat or processed meat consumption with colorectal cancer risk. Reported RRs and corresponding standard errors (SEs) were transformed to their natural logarithms to stabilize the variances and to normalize the distributions. The SEs were derived from the confidence intervals (CIs) provided in each study. We quantified the relations between red meat and processed meat consumption with colorectal cancer risk with the method of DerSimonian and Laird[27] by use of the assumptions of a random-effects model, which considers both within-study and between-study variation. For studies that provided separate RRs for colon and rectal cancer[4,6,7,9] and/or for women and men,[7,26] we pooled the RRs, weighted by the inverse of the variance, within each study.

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TABLE I – CHARACTERISTICS OF PROSPECTIVE STUDIES OF RED MEAT AND PROCESSED MEAT CONSUMPTION AND COLORECTAL CANCER RISK[1]

Study and country	Study participants; age at cohort entry	Exposure assessment	Follow-up years (mean)[2]	No. of cases by cancer site	Adjusted RR (95% CI)[3]		Adjustments
					Red meat[4]	Processed meat	
Bostick *et al*., 1994[18]; Iowa Women's Health Study, USA	35,215 women; 55–69 years	127-item FFQ[5]	1986–1990 (4 years)	212 CC	1.04 (0.62–1.76) CC	1.51 (0.72–3.17) CC	Age, height, parity, vitamin A supplement use, intakes of energy and total vitamin E
Gaard *et al*., 1996[26]; Norwegian National Health Screening Service, Norway	50,535 women and men; 20–53 years	80-item FFQ[5]	1977–1991 (11.4 years)	143 CC	NA	2.51 (1.14–5.55) CC[6]	Age
Kato *et al*., 1997[21]; New York University Women's Health Study, USA	14,727 women; 34–65 years	70-item FFQ	1985–1994 (7.1 years)	100 CRC	1.23 (0.68–2.22) CRC	1.09 (0.59–2.02) CRC	Age, place of enrollment, education, energy intake
Chen *et al*., 1998[19]; Physicians' Health Study, USA	Nested case–control study of 212 male cases and 221 male controls; 40–84 years	20-item FFQ[5]	1982–1994	212 CRC	1.17 (0.68–2.02) CRC	NA	Age, smoking
Hsing *et al*., 1998[20]; Lutheran Brotherhood Study, USA	17,633 men; ≥35 years	35-item FFQ	1966–1986	145 CRC[7] 120 CC[7]	1.9 (0.9–4.3) CRC 1.8 (0.8–4.4) CC	NA	Age, smoking, alcohol, energy intake
Singh and Fraser, 1998[24]; Adventist Health Study, USA	32,051 women and men; ≥25 years	55-item FFQ[5]	1976–1982	157 CC[8]	1.41 (0.90–2.21) CC	NA	Age, sex, family history, smoking, BMI, physical activity, aspirin use, alcohol
Pietinen *et al*., 1999[23]; ATBC Cancer Prevention Study, Finland	27,111 male smokers; 50–69 years	276-item FFQ[5]	1988–1995 (8 years)	185 CRC	1.1 (0.7–1.7)	1.2 (0.7–1.8) CRC	Age, supplement group, education, smoking years, BMI, physical activity, alcohol, calcium intake
Knekt *et al*., 1999[22]; Finnish Mobile Clinic Health Examination Survey, Finland	9,985 women and men; 15–99 years	1 year dietary history interview	1966–1990	73 CRC	NA	1.84 (0.98–3.47) CRC	Age, sex, geographic area, smoking, energy intake
Järvinen *et al*., 2001[12]; Finnish Mobile Clinic Health Examination Survey, Finland	9,959 women and men; 15–99 years	1 year dietary history interview	1966–1999	109 CRC 63 CC 46 RC	1.50 (0.77–2.94) CRC 1.34 (0.57–3.15) CC 1.82 (0.60–5.52) RC	NA	Age, sex, occupation, geographic area, smoking, BMI, intakes of energy, vegetables, fruits and cereals
Tiemersma *et al*., 2002[13]; Monitoring Project on Cardiovascular Disease Risk Factors, The Netherlands	Nested case–control study of 102 cases and 537 controls; 20–59 years	Short FFQ[5]	1987–1998 (8.5 years)	102 CRC	1.6 (0.9–2.9) CRC	NA	Age, sex, height, alcohol, energy intake
Flood *et al*., 2003[11]; Breast Cancer Detection Demonstration Project, USA	45,496 women; 40–93 years	62-item FFQ[5]	1987–1998 (8.5 years)	487 CRC	1.10 (0.83–1.45) CRC	1.00 (0.76–1.31) CRC	Age, energy intake
Wei *et al*., 2004[4]; Nurses' Health Study, USA	87,733 women; 30–55 years	61-item FFQ[5]	1980–2000	876 CRC 672 CC 204 RC	1.21 (0.72–2.03) CRC[6] 1.31 (0.73–2.36) CC 0.92 (0.31–2.71) RC	1.10 (0.64–1.88) CRC[6] 1.32 (0.95–1.83) CC 0.72 (0.33–1.59) RC	Age, history of endoscopy, family history, smoking, height, BMI, physical activity, intakes of alcohol, calcium and folate

(*Continued*)

TABLE I – CHARACTERISTICS OF PROSPECTIVE STUDIES OF RED MEAT AND PROCESSED MEAT CONSUMPTION AND COLORECTAL CANCER RISK[1] (CONTINUED)

Study and country	Study participants; age at cohort entry	Exposure assessment	Follow-up years (mean)[2]	No. of cases by cancer site	Adjusted RR (95% CI)[3]		Adjustments
					Red meat[4]	Processed meat	
Wei *et al.*, 2004[4]; Health Professionals Follow-Up Study, USA	46,632 men; 40–75 years	131-item FFQ[5]	1986–1999	602 CRC 467 CC 135 RC	1.24 (0.78–1.96) CRC[6] 1.35 (0.80–2.27) CC 0.90 (0.34–2.45) RC	1.23 (0.87–1.73) CRC[6] 1.27 (0.87–1.85) CC 1.06 (0.48–2.33) RC	Age, history of endoscopy, family history, smoking, height, BMI, physical activity, intakes of alcohol, calcium and folate
Kojima *et al.*, 2004[7]; Japan Collaborative Cohort Study, Japan	107,824 women and men; 40–79 years	33-item FFQ[5]	1988–1999 (9.9 years)	457 CRC[7] 284 CC[7] 173 RC[7]	NA	1.18 (0.87–1.62) CRC[6] 1.20 (0.79–1.82) CC[6] 1.16 (0.72–1.86) RC[6]	Age, sex, education, family history, smoking, BMI, walking, alcohol
English *et al.*, 2004[10]; Melbourne Collaborative Cohort Study, Australia	37,112 women and men; 40–69 years	121-item FFQ	1990–2002 (9 years)	451 CRC 283 CC 169 RC	1.4 (1.0–1.9) CRC 1.1 (0.7–1.6) CC 2.3 (1.2–4.2) RC	1.5 (1.1–2.0) CRC 1.3 (0.9–1.9) CC 2.0 (1.1–3.4) RC	Age, sex, country of birth, intakes of energy, fat and cereals
Larsson *et al.*, 2005[5]; Swedish Mammography Cohort, Sweden	61,433 women; 40–75 years	67-item FFQ[5]	1987–2003 (13.9 years)	733 CRC 389 CC 234 PCC 155 DCC 230 RC	1.32 (1.03–1.68) CRC 1.41 (0.92–2.16) CC[6] 1.03 (0.67–1.60) PCC 2.22 (1.34–3.68) DCC 1.28 (0.83–1.98) RC	1.07 (0.85–1.33) CRC 1.06 (0.83–1.35) CC[6] 1.02 (0.69–1.52) PCC 1.39 (0.86–2.24) DCC 0.90 (0.60–1.34) RC	Age, education, BMI, intakes of energy, alcohol, saturated fat, calcium, folate, fruits, vegetables and whole grain foods
Chao *et al.*, 2005[9]; Cancer Prevention Study II Nutrition Cohort, USA	148,610 women and men; 50–74 years	68-item FFQ[5]	1992–2001	1667 CRC 1197 CC 667 PCC 408 DCC 470 RC	1.36 (0.93–2.00) CRC[6] 1.15 (0.90–1.46) CC 1.27 (0.91–1.76) PCC 0.71 (0.47–1.07) DCC 1.71 (1.15–2.52) RC	1.16 (0.96–1.40) CRC[6] 1.13 (0.91–1.41) CC 0.97 (0.72–1.29) PCC 1.39 (0.94–2.05) DCC 1.26 (0.86–1.83) RC	Age, sex, smoking, education, hormone therapy use (women), BMI, physical activity, multivitamin use, aspirin use, intakes of energy, alcoholic beverages, fruits, vegetables and high-fiber grain foods
Norat *et al.*, 2005[8]; EPIC, Europe[9]	478,040 women and men; 35–70 years	88- to 266-item FFQ[5]	1992–1998 (4.8 years)	1329 CRC 855 CC 351 PCC 391 DCC 474 RC	1.35 (0.96–1.88) CRC 1.17 (0.78–1.77) CC 1.03 (0.56–1.91) PCC 1.51 (0.76–3.02) DCC 1.75 (0.98–3.10) RC	1.42 (1.09–1.86) CRC 1.30 (0.92–1.84) CC 1.19 (0.70–2.01) PCC 1.48 (0.87–2.53) DCC 1.62 (1.04–2.50) RC	Age, sex, center, smoking, height, weight, physical activity, alcohol, energy intake
Lüchtenborg *et al.*, 2005[6]; Netherlands Cohort study, The Netherlands	Case-cohort 2,948 women and men; 55–69 years	150-item FFQ[5]	1989–1994	588 CRC 434 CC 154 RC	NA	1.13 (0.87–1.47) CRC[6] 1.17 (0.86–1.59) CC 1.04 (0.64–1.68) RC	Age, sex, family history, smoking, BMI, energy intake

[1]BMI, body mass index; CI, confidence interval; CRC, colorectal cancer; CC, colon cancer; DCC, distal colon cancer; FFQ, food-frequency questionnaire; NA, not available; PCC, proximal colon cancer; RC, rectal cancer; RR, relative risk.–[2]Means are shown when reported in the article.–[3]Highest *vs.* lowest consumption category.–[4]Relative risks for total red meat (fresh red meat plus processed meat) were chosen when provided; otherwise, relative risks for fresh red meat were included.–[5]Undertook validation of dietary assessment.–[6]The relative risk (and its 95% CI) was derived by pooling the sex- and/or subsite-specific relative risks (weighted by the inverse of the variance).–[7]Fatal cancer cases.–[8]Including 22 cancers in the rectosigmoid junction.–[9]European Prospective Investigation into Cancer and Nutrition (EPIC) includes subjects from 10 European countries: Denmark, France, Germany, Greece, Italy, Netherlands, Norway, Spain, Sweden and United Kingdom.

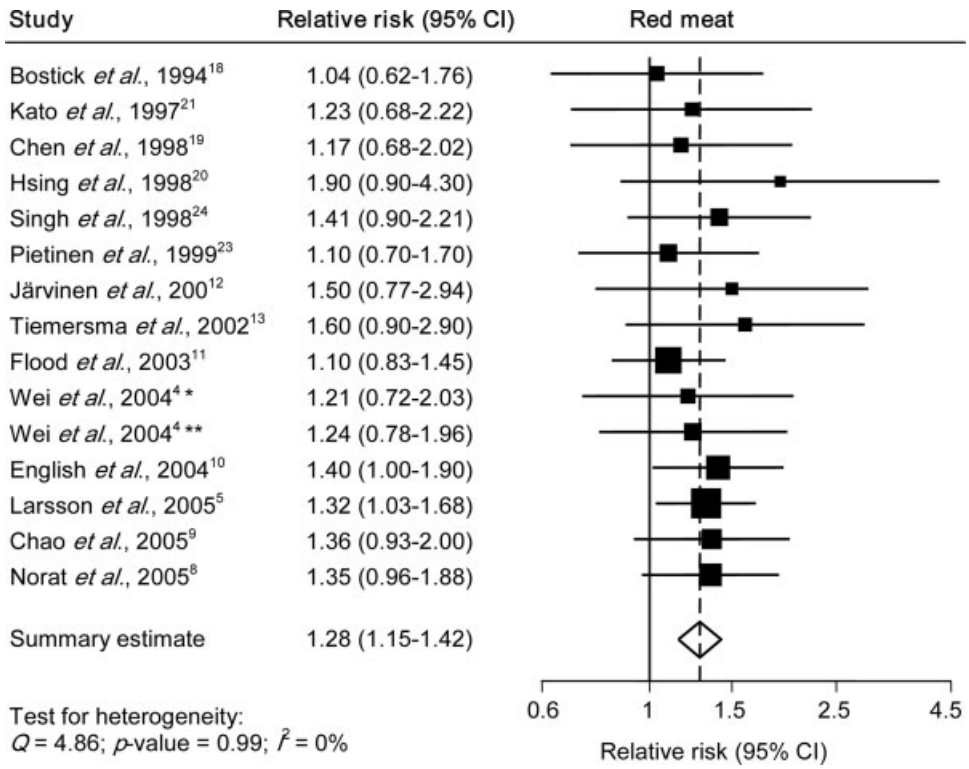

Figure 1 – Relative risks of colorectal cancer comparing the highest with the lowest category of red meat consumption. Studies are ordered by year of publication. Squares represent study-specific relative risks (RRs) and the sizes of the squares reflect the statistical weight that each study contributed to the summary estimate; horizontal lines represent 95% confidence intervals (CIs); diamond represents the summary estimate and its 95% CI. *Nurses' Health Study; **Health Professionals Follow-Up Study.

For the dose-response meta-analysis, we used the method proposed by Greenland and coworkers[28,29] to compute study-specific slopes (linear trends) from the correlated natural log of the RRs across categories of meat intake. This method requires that the distribution of cases and noncases (or person-time) and the RR with its variance estimate for at least 3 quantitative exposure categories are known. For studies that did not provide the number of cases and noncases in each consumption category, we estimated the slopes using variance-weighted least squares regression. Because the studies included in our meta-analysis used different units to report meat consumption (i.e., grams, servings or frequencies), we rescaled meat consumption into grams per day. We used 120 g as the approximate average portion size for red meat and 50 g as the average portion size for processed meat.[2] For the study by Gaard *et al.*,[26] 120 g was used as the average portion size for sausage. For each study, the median or mean level of consumption for each category was assigned to each corresponding RR. When the median or mean consumption was not reported, we assigned the midpoint of the upper and lower bound in each category as the average intake. If the upper bound was not provided, we assumed that it had the same amplitude as the preceding category.

We used the Q and I^2 statistics[30] to examine statistical heterogeneity among the studies included in the meta-analysis. For the Q statistic, heterogeneity was considered present for $p \leq 0.1$. I^2 is the proportion of total variation contributed by between-study variation.[30] We conducted subgroup analyses to examine potential sources of heterogeneity by cancer site, sex, study location, start of follow-up, length of follow-up, the year of publication and control for potential confounders. Publication bias was assessed with the use of funnel plots and with the Egger's regression asymmetry test[31] ($p \leq 0.1$ was considered representative of statistically significant publication bias). The potential influence that unpublished studies could have on the summary results was examined using a trim and fill analysis.[32] Statistical analyses were performed using Stata (release 9.0; StataCorp, College Station, TX).

Results

Characteristics of studies

Characteristics of the 19 prospective studies (1 publication[4] had 2 independent cohorts, which were included as 2 separate studies) included in the meta-analysis are shown in Table I. Two studies[13,19] were case–control studies nested within prospective cohorts. Nine studies were conducted in the United States, 8 in Europe and 1 each in Australia and Japan. The study population in 10 studies included men and women, 4 consisted entirely of men, and 5 consisted of only women. The cohort sizes ranged from 9,959 to 478,040, and the number of cases ranged from 73 to 1,667.

Red meat (highest vs. lowest category)

All 15 studies that examined the association between red meat consumption and risk of colorectal cancer found a positive relationship (Fig. 1). Combined, the 15 studies included 1,042,824 participants and 7,367 cases. There was no heterogeneity among studies ($Q = 4.86$; $p = 0.99$; $I^2 = 0\%$). The summary RR of colorectal cancer was 1.28 (95% CI = 1.15–1.42) for subjects in the highest category of red meat consumption compared with those in the lowest category. Summary results did not change materially when we excluded the 2 nested case–control studies[13,19] (RR = 1.28; 95% CI = 1.15–1.42) or the 2 studies based on colorectal cancer mortality[7,20] (RR = 1.27; 95% CI = 1.14–1.42). The association

TABLE II – SUMMARY RELATIVE RISKS OF COLORECTAL CANCER BY RED MEAT AND PROCESSED MEAT CONSUMPTION (HIGHEST *VS.* LOWEST CATEGORY)

	Red meat					Processed meat				
	n^1	RR (95% CI)	Q^2	p-value^2	I^2 (%)^2	n^1	RR (95% CI)	Q^2	p-value^2	I^2 (%)^2
Cancer subsite										
Colon	9	1.21 (1.05–1.40)	2.35	0.97	0	10	1.21 (1.09–1.34)	5.81	0.76	0
Proximal colon	3	1.15 (0.91–1.47)	0.72	0.70	0	3	1.02 (0.82–1.26)	0.44	0.80	0
Distal colon	3	1.31 (0.62–2.79)	12.36	0.002	83.8	3	1.41 (1.09–1.84)	0.04	0.98	0
Rectum	7	1.56 (1.25–1.95)	4.82	0.57	0	8	1.20 (0.98–1.46)	9.06	0.25	22.7
Sex										
Men	5	1.26 (1.02–1.54)	1.53	0.82	0	5	1.27 (1.06–1.52)	0.82	0.94	0
Colon	3	1.36 (1.04–1.77)	0.49	0.78	0	4	1.34 (1.08–1.67)	0.74	0.86	0
Rectum	1	–	–	–	–	2	1.02 (0.64–1.63)	0.01	0.91	0
Women	6	1.16 (1.01–1.34)	2.28	0.81	0	8	1.07 (0.94–1.23)	4.91	0.67	0
Colon	4	1.14 (0.91–1.43)	1.96	0.58	0	6	1.14 (0.95–1.37)	5.97	0.31	16.2
Rectum	2	1.22 (0.82–1.83)	0.31	0.58	0	2	1.06 (0.50–2.23)	1.72	0.19	42.0
Study location										
Europe	5	1.32 (1.12–1.57)	1.22	0.88	0	6	1.27 (1.06–1.52)	7.69	0.17	35.0
United States	9	1.23 (1.06–1.42)	2.86	0.94	0	6	1.13 (0.99–1.29)	1.69	0.63	0
Other[3]	1	–	–	–	–	2	1.34 (1.06–1.69)	1.19	0.28	0
Start of follow-up										
Before 1985	5	1.36 (1.06–1.75)	1.30	0.86	0	2	1.38 (0.84–2.28)	1.47	0.23	32.1
After 1985	10	1.27 (1.13–1.42)	3.30	0.95	0	12	1.20 (1.10–1.31)	10.55	0.48	0
Length of follow-up										
<10 years	9	1.26 (1.11–1.42)	3.40	0.91	0	9	1.21 (1.09–1.33)	6.18	0.63	0
≥10 years	6	1.31 (1.10–1.57)	1.34	0.93	0	5	1.27 (1.00–1.62)	6.22	0.18	35.7
Publication year										
1994–2000	6	1.23 (0.99–1.53)	2.22	0.82	0	5	1.44 (1.10–1.90)	3.85	0.43	0
2001–2006	9	1.30 (1.15–1.47)	2.47	0.96	0	9	1.18 (1.08–1.29)	6.73	0.57	0
Type of meat[4]										
Total red meat	8	1.24 (1.09–1.42)	3.33	0.85	0	–	–	–	–	–
Fresh red meat only	9	1.22 (1.08–1.37)	5.62	0.69	0	–	–	–	–	–
Adjustment for potential confounders										
Physical activity and BMI										
Yes	6	1.29 (1.09–1.53)	0.88	0.97	0	6	1.22 (1.08–1.38)	1.71	0.89	0
BMI only	2	1.34 (1.07–1.69)	0.12	0.73	0	2	1.10 (0.92–1.30)	0.10	0.76	0
No	7	1.25 (1.06–1.47)	3.61	0.73	0	6	1.37 (1.06–1.78)	8.73	0.12	42.7
Smoking										
Yes	9	1.31 (1.12–1.53)	2.10	0.98	0	8	1.22 (1.09–1.36)	3.66	0.82	0
No	6	1.26 (1.09–1.45)	2.63	0.76	0	6	1.23 (1.00–1.51)	8.61	0.13	41.9
Alcohol intake										
Yes	9	1.33 (1.16–1.52)	2.19	0.98	0	7	1.19 (1.07–1.32)	2.73	0.84	0
No	6	1.21 (1.02–1.44)	1.98	0.85	0	7	1.29 (1.06–1.58)	9.43	0.15	36.3
Total energy intake										
Yes	10	1.30 (1.15–1.47)	4.00	0.91	0	9	1.20 (1.08–1.33)	8.93	0.35	10.4
No	5	1.23 (0.99–1.52)	0.63	0.96	0	5	1.24 (1.03–1.50)	3.36	0.50	0
Calcium intake										
Yes	4	1.25 (1.05–1.50)	0.52	0.91	0	4	1.12 (0.95–1.33)	0.53	0.91	0
No	11	1.30 (1.14–1.48)	4.25	0.94	0	10	1.25 (1.11–1.40)	10.98	0.28	18.1

[1]n, number of prospective studies.–[2]Heterogeneity test.–[3]One study each in Australia[10] and Japan[7].–[4]Four studies[5,8,18,23] reported results for both total red meat (fresh red meat plus processed meat) and fresh red meat, 4 studies[9,11,19,20] reported results only for total red meat and 5 studies[4,10,13,24] reported results only for fresh red meat; 2 studies[12,21] were excluded because the meat items included in red meat were not specified.

with red meat consumption was stronger for rectal cancer than for colon cancer (p-heterogeneity between cancer sites = 0.06), but did not differ significantly by subsite in the colon (p-heterogeneity between subsites = 0.75) (Table II). Positive relationships of comparable strengths were present in all subgroups according to sex, study location, start of follow-up, length of follow-up, publication year and definition of red meat (Table II). Stratification by adjustment for potential confounders, including physical activity and body mass index, smoking and intakes of alcohol, total energy and calcium showed no significant differences in the summary RRs between studies that did control for these variables and those that did not (Table II). When we restricted the analysis to studies that adjusted for physical activity, body mass index, smoking and any of the considered dietary variables (alcohol, energy or calcium intake)[4,8,9,23,24] the summary RR of colorectal cancer comparing the highest with the lowest intake categories of red meat was 1.29 (95% CI = 1.09–1.53). The funnel plot did not provide strong evidence for publication bias (p = 0.42 by Egger's test).

Processed meat (highest vs. lowest category)

The 14 studies that investigated the association between processed meat consumption and colorectal cancer risk (involving 1,153,401 participants and 7,903 cases) did not show substantial heterogeneity (Q = 12.41; p = 0.50; I^2 = 0%). The summary RR of colorectal cancer was 1.20 (95% CI = 1.11–1.31) for individuals in the highest relative to the lowest category of processed meat consumption (Fig. 2). High *vs.* low consumption of processed meat was associated with an increased risk of both colon and rectal cancer (Table II). Only 3 studies[5,8,9] reported results for subsites in the colon. In these studies, high consumption of processed meat was associated with an increased risk of distal colon cancer but not of proximal colon cancer (p-heterogeneity between

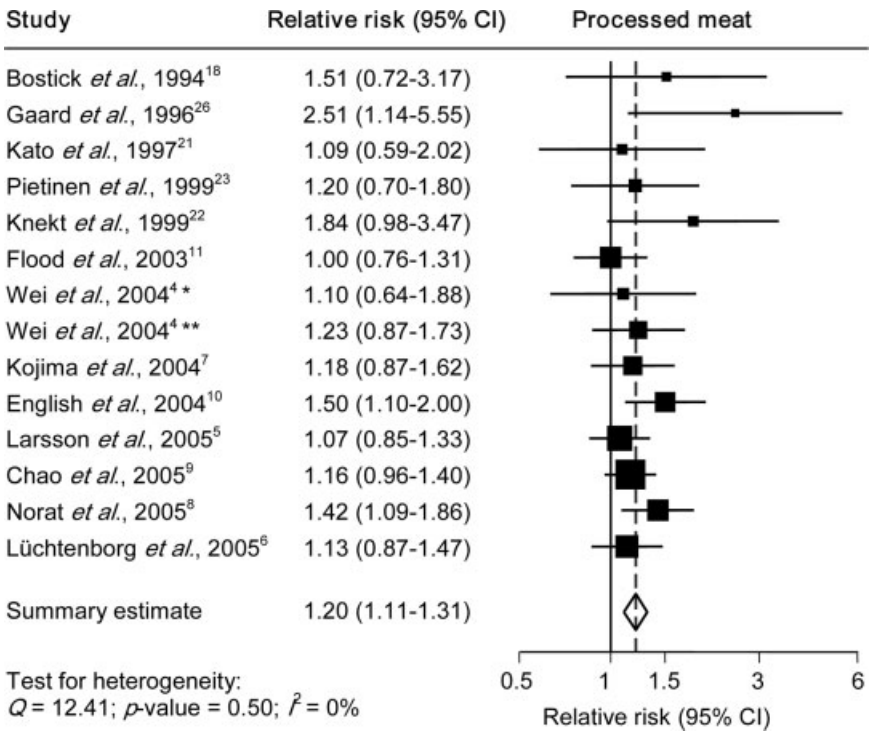

FIGURE 2 – Relative risks of colorectal cancer comparing the highest with the lowest category of processed meat consumption. Studies are ordered by year of publication. Squares represent study-specific relative risks (RRs) and the sizes of the squares reflect the statistical weight that each study contributed to the summary estimate; horizontal lines represent 95% confidence intervals (CIs); diamond represents the summary estimate and its 95% CI. *Nurses' Health Study; **Health Professionals Follow-Up Study.

TABLE III – DOSE-RESPONSE RELATIONSHIPS BETWEEN RED MEAT OR PROCESSED MEAT CONSUMPTION AND COLORECTAL CANCER RISK

	Red meat, 120 g/day					Processed meat, 30 g/day				
	n^1	RR (95% CI)	Q^2	p-value^2	I^2 (%)^2	n^1	RR (95% CI)	Q^2	p-value^2	I^2 (%)^2
All studies	14	1.28 (1.18–1.39)	8.82	0.79	0	11	1.09 (1.05–1.13)	6.42	0.78	0
Colon cancer	10	1.24 (1.12–1.38)	8.39	0.50	0	9	1.10 (1.05–1.16)	4.14	0.85	0
Rectal cancer	7	1.63 (1.24–2.14)	12.08	0.06	50.3	7	1.07 (0.98–1.18)	8.05	0.23	25.5
Europe	5	1.33 (1.17–1.50)	3.06	0.55	0	5	1.08 (1.03–1.14)	3.12	0.54	0
United States	8	1.24 (1.10–1.39)	4.91	0.67	0	4	1.08 (1.02–1.14)	0.86	0.84	0

[1]n, number of prospective studies.–[2]Heterogeneity test.

subsites = 0.06). There were no significant differences (p-heterogeneity > 0.10) in the summary RRs between subgroups defined by sex, study location, start of follow-up, length of follow-up or year of publication (Table II). In addition, stratifying the studies by adjustment for potential confounders, there were no significant differences between subgroups. Restricting the analysis to studies that adjusted for physical activity, body mass index, smoking and any of the considered dietary variables (alcohol, energy or calcium intake)[4,7–9,23] yielded a summary RR of 1.22 (95% CI = 1.08–1.38). The funnel plot suggested a possible absence of negative studies involving small sample sizes (p = 0.08 by Egger's test). According to the trim and fill analysis, 2 such studies may be missing. Adding those missing studies to the meta-analysis gave a summary RR of 1.19 (95% CI = 1.08–1.31).

Dose-response meta-analysis

For the dose-response meta-analysis of red meat consumption, 14 studies[4,5,8–13,18–20,23,24] were included, whereas 1 study[21] was excluded because red meat consumption could not be quantified. The estimated summary RR of colorectal cancer for an increase in red meat consumption of 120 g/day was 1.28 (95% CI = 1.18–1.39), without heterogeneity among studies (Table III). The summary RR was greater for rectal cancer than for colon cancer (p-heterogeneity between cancer sites = 0.07); there was heterogeneity among study results for rectal cancer (Table III).

Eleven studies[4–8,10,11,18,23,26] were included in the dose-response meta-analysis of processed meat consumption. Three studies[9,21,22] were excluded because processed meat consumption could not be quantified. The estimated summary RR of colorectal cancer for an increase in processed meat consumption of 30 g/day was 1.09 (95% CI = 1.05–1.13), without heterogeneity among studies (Table III). The summary RRs were similar for colon and rectal cancer, and for studies conducted in Europe and in the United States (Table III).

Discussion

Findings of this meta-analysis involving almost 8,000 cases from 19 prospective studies show consistent associations between high consumption of red meat and of processed meat and an increased risk of colorectal cancer. Individuals in the highest category of red meat or processed meat consumption had a 28% and 20%, respectively, higher risk of colorectal cancer compared with those in the lowest intake categories. High consumption of red meat and processed meat was associated with an increased risk of both colon and rectal cancer, although the association with red meat was more pronounced for rectal cancer. The positive associa-

tion with processed meat consumption was stronger for distal colon cancer than for proximal colon cancer. Results were consistent for women and men, and for studies carried out in Europe and in the United States.

Our meta-analysis has several strengths. First, our quantitative assessment was based on prospective studies, which tend to be less susceptible to bias (e.g., recall and selection bias) than retrospective case–control studies. Moreover, most of the included studies, particularly those published since 2004, had a large sample size. Hence, meta-analysis of these studies provides high statistical power for estimating the relationship between meat consumption and colorectal cancer risk. The relatively large number of included studies also allowed us to perform subgroup analyses according to study characteristics.

As a meta-analysis of observational studies, our findings have several limitations. First, this type of meta-analysis leaves the possibility of confounding as a potential explanation for the observed associations. Nevertheless, the associations between meat consumption and colorectal cancer risk persisted when we restricted the analysis to studies that adjusted for major potential confounders. A second limitation is that our findings were likely to be influenced by imprecise measurement of meat consumption. Categorization of exposures that are measured with nondifferential error may produce differential misclassification and may bias the relative risk toward or away from the null value.[33,34] Hence, misclassification of meat consumption in the original studies might have lead to an underestimate or an overestimate of the summary relative risks estimates. Finally, because our meta-analysis was based on published studies, the possibility of publication bias could be of concern. Studies with null results or small sample sizes are less likely to be published.[35] There was suggestion of publication bias in the literature for processed meat consumption. However, adjusting for unpublished studies had negligible effect on the summary results.

In general, our findings for red meat consumption and risk of colorectal cancer are in accord with those of 2 previous meta-analyses,[1,2] but are more precise because of a larger number of cases. In the 2 earlier meta-analyses, for prospective studies (including 2,100–2,500 cases), an increase in red meat consumption of 100–120 g/day was associated with a 17–22% increased risk of colorectal cancer.[1,2] In the present meta-analysis, the magnitude of the relationship of processed meat consumption with colorectal cancer risk was weaker than in the earlier meta-analyses,[1,2] which estimated a 49–54% increase in risk of colorectal cancer (including about 1,200 cases) for an increment in processed meat consumption of 25–30 g/day.

Several hypotheses have been proposed to explain the relationship between red meat or processed meat consumption and colorectal cancer risk. Red meat contains higher amounts of heme iron than white meat. Heme damages the colonic mucosa and stimulates epithelial proliferation in animal studies.[36] Heme iron intake has been positively associated with the risk of colon cancer in prospective cohort studies.[37,38] Ingestion of red meat and heme iron supplementation has been shown to increase fecal concentrations of *N*-nitroso compounds (NOCs),[39–41] many of which are potent animal carcinogens.[42] The positive association with processed meat consumption may be partly due to NOCs already present in the meat. Meat cooked at high temperatures also contains other potential mutagens and carcinogens in the form of heterocyclic amines (HCAs) and polycyclic aromatic hydrocarbons (PAHs). The cancer risk posed to humans by HCAs and PAHs may depend on the extent to which these compounds are activated by metabolic enzymes.[43] The fat content of meat may influence the risk of colorectal cancer by increasing the production of secondary bile acids,[44] which may promote colon carcinogenesis.[45] However, epidemiologic studies have generally not shown an association between fat intake and colon cancer risk.[46]

Several lines of evidence indicate that cancers occurring in the proximal and distal colon may have distinct etiologies.[3,47–49] Proximal and distal colon cancers display differences in incidence by geographic region, age and sex.[3] There are also differences between subsites with regard to pH,[50] apoptotic index,[3] metabolism of bile acids,[3] bacterial composition and bacterial metabolic capacity[51,52] and expression of carcinogen metabolizing enzymes.[3] All 3 studies that reported results for subsites in the colon showed that the positive relationship between processed meat consumption and cancer risk was stronger for distal colon than for proximal colon.[5,8,9] In this regard, it is noteworthy that levels of the promutagenic lesion O^6-methyldeoxyguanosine, a marker of exposure to NOCs, have been found to be higher in tissues from the distal colon than from the proximal colon.[53]

In summary, results of this meta-analysis support the hypothesis that high consumption of red meat and processed meat may increase the risk of colon and rectal cancer. Whether the association with red meat or processed meat consumption varies according to subsites in the colorectum warrants further investigation.

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