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MEAT CONSUMPTION AND COLORECTAL CANCER RISK: DOSE-RESPONSE META-ANALYSIS OF EPIDEMIOLOGICAL STUDIES

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The hypothesis that consumption of red and processed meat increases colorectal cancer risk is reassessed in a meta-analysis of articles published during 1973–99. The mean relative risk (RR) for the highest quantile of intake *vs.* the lowest was calculated and the RR per gram of intake was computed through log-linear models. Attributable fractions and preventable fractions for hypothetical reductions in red meat consumption in different geographical areas were derived using the RR log-linear estimates and prevalence of red meat consumption from FAO data and national dietary surveys. High intake of red meat, and particularly of processed meat, was associated with a moderate but significant increase in colorectal cancer risk. Average RRs and 95% confidence intervals (CI) for the highest quantile of consumption of red meat were 1.35 (CI: 1.21–1.51) and of processed meat, 1.31 (CI: 1.13–1.51). The RRs estimated by log-linear dose-response analysis were 1.24 (CI: 1.08–1.41) for an increase of 120 g/day of red meat and 1.36 (CI: 1.15–1.61) for 30 g/day of processed meat. Total meat consumption was not significantly associated with colorectal cancer risk. The risk fraction attributable to current levels of red meat intake was in the range of 10–25% in regions where red meat intake is high. If average red meat intake is reduced to 70 g/week in these regions, colorectal cancer risk would hypothetically decrease by 7–24%.

Key words: *meat; colorectal cancer; attributable risk; preventable fraction*

Experimental and epidemiological studies have shown that food and nutrition modify colorectal cancer risk. The scientific evidence has been evaluated and summarised in recommendations by different expert groups that conclude that red meat consumption is likely to be related to increased risk of colorectal cancer. In 1996, the Colon Cancer Panel of the World Health Organisation-consensus conference on Nutrition in Prevention and Therapy on Cancer[1] concluded that consumption of red meat and processed meat was probably associated with increased risk for colorectal cancer and recommended that consumption of fish and poultry should be preferred to red meat. In the same year, the Centre national d'Ètudes et de Recommandations sur la Nutrition et l'Alimentation (CNERNA) in France published an evaluation of the scientific data on nutrition and cancer, in which the experts concluded that a diet poor in vegetables and rich in meat or fat of animal origin (excepting fish) is usually associated with an increased risk of colon cancer.[2] More recently, 2 major reports by the World Cancer Research Fund (WCRF)/American Institute for Cancer Research Report (AICR)[3] and the Working Group on Diet and Cancer of the Committee on Medical Aspects of Food and Nutrition Policy (COMA)[4] of the United Kingdom, recommended that western populations should decrease their consumption of red meat and increase consumption of vegetables in order to reduce colorectal cancer risk. Both panels agreed that the epidemiological results on meat were not consistent, but recognised that the studies conducted so far found either increased colorectal cancer risk or no association with risk, while no study has found a reduction in risk associated with high meat consumption.

Several hypotheses have been developed to explain the association between colorectal cancer risk and red meat.[5] The fat content of red meat could influence colon cancer risk by increasing the excretion of bile acids, whose products may act as tumour promoters by a non-specific irritant effect that increases cell proliferation in the colonic mucosa.[6,7] Other products of fat digestion, such as diacylglycerides, could selectively induce mitogenesis of adenomas and some carcinoma cells.[8] Fat could act by increasing saturated fatty acid content, or decreasing polyunsaturated fatty acid content in cell membranes leading to a reduction of the number and activity of insulin receptors.[9,10] Hyperinsulinemia could act as a growth factor and tumor promoter[11,12] and recent epidemiological evidence supports the association of insulin resistance with colon cancer risk.[13] The meat fat-hypothesis is consistent with the finding that lean beef did not promote colon carcinogenesis in rats[14] and that high consumption of beef could increase the concentration of secondary faecal bile acids.[15,16] Nevertheless, epidemiological studies have failed to show a consistent relationship between fat intake and colorectal cancer.[5,17]

During digestion, dietary protein is broken down into amino acids that are further degraded to ammonia, which may be carcinogenic to the colon.[18] There is, however, very limited evidence that protein per se increases colorectal cancer risk and some epidemiological studies have even reported a protective association between dietary protein and colon cancer. A possible explanation for this unexpected finding is that low intake of methionine may contribute to DNA methylation abnormalities, which might appear to be important in the initiation and progression of colon cancer.[19] Meat can be a major source of protein, but there is no evidence of an effect of meat protein on colorectal cancer risk.

Red meat has a higher iron content than white meat. Dietary iron enhances lipid peroxidation in the mouse colon and augments dimethylhydrazine-induced colorectal tumours in mice and rats[20] but the results of epidemiological studies are still insufficient.[21,22]

Red meat intake[23] enhances the production of endogenous promoters and possible carcinogens[24,25] such as *N*-nitroso compounds (NOC), which have been shown to induce the formation of DNA adducts in human colonocytes.[26] The same effect has not been observed with white meat.[23,27] NOC are also formed endogenously because the amines and amides produced primarily by bacterial decarboxylation of amino acids can be *N*-nitrosated in the presence of a nitrosating agent.[28–30] Nitrosamines have been detected in foods with added nitrates or nitrites, including salt-preserved fish and meat and in food processed by smoking or direct-fire dry-

Abbreviations: 95% CI, 95% confidence intervals; AP, attributable proportion; EPIC, European Prospective Investigation into Cancer and Nutrition; FAO, Food and Agricultural Organisation; FFQ, food frequency questionnaire; HCA, heterocyclic amines; NOC, *N*-nitroso compounds; PAH, polycyclic aromatic hydrocarbons; PP, preventable proportion; RR, relative risk.

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ing.[31,32] Supplements of nitrate have been shown to elevate faecal NOC levels.[27]

A mechanism that has attracted particular attention is the formation of heterocyclic amines (HCA) and polycyclic aromatic hydrocarbons (PAH) in meat when it is cooked at high temperature for a long time or over an open flame. HCA and particularly the 2-amino-1-methyl-6-phenylimidazo (4,5-b) pyridine (PhIP) and the 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) are powerful mutagens and carcinogenic in mice, rats and non-human primates in a wide variety of organs, mainly the liver, but also skin, lung, colon and mammary gland.[23,33] The carcinogenic potential of heterocyclic amines in humans has not been established. PAHs are widely believed to make a substantial contribution to the overall burden of cancer in humans via tobacco smoking, occupational and environmental exposures. The major dietary sources of PAHs are cereals and vegetables rather than meat due to environmental contamination, except where there is high consumption of meat cooked over an open flame, as when barbecuing.[34,35] Information on dietary practices, such as cooking methods (frying, broiling, smoking and barbecuing), meat doneness and surface browning has been used to evaluate the potential relationship of dietary exposure to HCAs and PAHs with colorectal cancer or colorectal adenoma risk,[36–50] but the epidemiological evidence is still limited and many methodological issues need to be solved. The fact that the metabolism of heterocyclic amines can be more or less efficient depending on the genetic variability of at least three enzymes involved in *N*-acetylation (NAT1, NAT2 and CYP1a2) makes the problem more complex and data from epidemiological studies[45,51–57] on acetylation status and colorectal cancer risk are sparse and somewhat conflicting.

In this article, the epidemiological literature on meat and colorectal cancer is reviewed and the results quantitatively summarized with two purposes. The first is to reassess the status of the meat/colorectal cancer hypothesis based on the global epidemiological evidence. The second aim is to provide estimates of the proportion of colorectal cancer attributable to current red meat consumption, as well as estimates of the effect that hypothetical changes in red meat consumption could have on colorectal cancer incidence in different geographical areas of the world, assuming that the association is causal and that the simulated change in meat consumption levels could be achieved.

MATERIAL AND METHODS

Search methods

The criteria for inclusion of epidemiological studies were: case-control or cohort studies evaluating the relationship between total meat, red meat or processed meat and colon, rectal or colorectal cancer risk; in males, females or in both sexes combined; with incidence or mortality as the endpoint; providing the information required for the statistical analysis; published in English between 1973 and 1999 and referenced in the Medline database (National Library of Medicine, Washington, DC). Besides the MEDLINE search, we systematically examined the list of references in the identified articles.

The definition of exposure varied between studies. In most of the articles, total meat (sometimes simply called meat) included white and red meat from all sources while in others, fresh meat only was considered. Red meat was sometimes defined as the intake of beef, veal, pork, mutton and lamb consumed fresh, whereas in others, processed red meat was also included as part of the red meat group. Processed meat was defined in our article as the group including any of the following foods: ham, raw ham, cured or smoked bacon, sausage, cured or smoked lunch meat, salami, nitrite-treated meats and meat-products. "Charcuterie" and "delicatessen" were also considered equivalent to "processed meat."

Statistical methods

The overall effect-size statistics estimated were the average of the logarithm of the observed relative risks (estimated as the odds ratio in most of the studies) associated to the highest versus the lowest level of consumption, as reported in the papers. The RR was weighted by the inverse of its variance. A random effect meta-analysis was performed in situations where heterogeneity was present[58] to incorporate the between-study component of variance in the weight.[59] Only studies reporting RR estimates with confidence intervals or quantitative information allowing their computation were included in the meta-analysis.

For the dose-response analysis, the method proposed by Greenland and Longnecker[60] was used, that accounts for the correlation between risk estimates for separate exposure levels depending on the same reference group. The summary estimate was the pooled coefficient b in the linear-logistic regression model $\ln RR = bX$, where X is the difference of meat intake between each category and the reference category. The individual slopes of each study were combined by weighted average, using the inverse of their variances as weights. Random effect models were assumed when there was evidence of heterogeneity. 95% confidence intervals (CI) were calculated for the common regression slopes. An SAS macro was written for this purpose.

We extracted from the studies the risk estimates that reflected the greatest degree of controlling for confounders (*i.e.*, risk factors or energy). The method required that the number of case subjects, the number of control subjects, the adjusted logarithm of the RR and its variance estimates for three or more exposure levels were known. Some extra-computation was performed to complete the required data, provided that the paper gave the information to do so. If this was not possible, the paper was not included in the dose-response analysis. The log-rank test of Begg and Mazumdar[61] were used to explore publication bias.

Interstudy variation was analyzed by performing subgroup identification[62] and meta-regression analysis[60] using the Genmod procedure in SAS. The main sources of heterogeneity examined were design (case-control or cohort), site (colon, rectum or colorectal), geographical area (USA, Europe or other), gender (males, females or both genders combined) and meat definition (fresh meat and fresh plus processed meat together).

Rescaling of exposure

For the dose-response analysis the intake was rescaled to grams per day. If the highest category was open-ended, the open-ended boundary was calculated using as interval length the width of the closest interval. When the lowest category was open-ended, the lowest boundary was considered as zero. The value of X of each category was then calculated as the mid-point of the logarithm of the boundaries, retransformed to grams per day.

When the exposures were expressed on a qualitative scale (*e.g.*, high, medium, low), we used the mean consumption and the variance given in the article to estimate midpercentiles of each category assuming lognormal distribution. When exposure was expressed as the frequency of consumption, we used 120 g as the approximate average "portion size" of meat and of red meat and 50 g as "serving size." The portion size of processed meat was 50 g as well. We based our decision on the results of the Continuing Survey of Food Intakes by Individuals 1989–91 of the United States[63] and preliminary results of the Dietary Survey of the European Prospective Investigation into Cancer and Nutrition (EPIC) (Riboli, unpublished data).[64]

Fraction of colorectal cancer risk attributable to red meat consumption

We obtained estimates of the proportion of risk attributable to red meat consumption (AP) using the relative risks estimated with the dose-response curve associated to quartiles of consumption of red meat using non-consumption as reference category. The formula provided by Miettinen was applied.[65]

As estimates of the prevalence of red meat consumption by geographical area, we used per caput intakes provided in Food Balance Sheets by the Food and Agricultural Organisation (FAO, http://apps.fao.org), corrected for overestimation with data published from 18 national dietary surveys.[66,67] The correction factor was computed as the ratio between the per caput calorie intake estimated in a dietary survey in a given country and the per caput calorie intake published by the FAO for that country in the same year as the survey. Caloric intake was chosen to deduce an overall "correction factor," even if its overestimation is not exactly the same as for red meat, because energy values were available in all the surveys. For geographical areas for which we were not able to find dietary surveys, the correction factor of the closest region was applied (Appendix 1). A ratio of male/female consumption was computed in the surveys providing the information and its average applied for those regions for which this information was not available.

Quartiles of consumption were calculated assuming a lognormal distribution. To do that, we applied the total coefficient of variation of red meat consumption by gender estimated in the EPIC cohort study, that is, 83% for women and 85% for men.

Finally, the exercise included an estimation of the proportion of cancer cases that could potentially be prevented assuming a hypothetical reduction in red meat consumption in each population to an average of 70 g/week, *i.e.*, a small portion of red meat once a week. The preventable proportion (PP) was estimated as proposed by Miettinen.[65]

Attributable risk could not be estimated for processed meat consumption because we could not find estimates of processed meat consumption worldwide.

RESULTS

Characteristics of studies

Thirty-four case-control studies[37,39,41,43,47,54,68–95] and 14 cohort studies[19,40,42,44,48,50,57,96–102] were identified in our search. The main characteristics of the studies are presented in Appendix 2. Fourteen case-control studies were carried out in Europe, 11 in the USA (including 2 in Hawaii), 3 in Japan, 2 in Australia and 1 each in Canada, China, Singapore and Argentina. Nine out of the 14 cohort studies were conducted in USA, 2 of which were based on Adventist Populations. Four cohorts were European and 1 was Japanese. Twenty-two of the case-control studies reported results on colon cancer risk, but only 16 provided also results on rectal cancer risk. Twelve studies reported the results for the 2 sites combined and not separately for colon and rectum. Ten case-control studies gave the results separately for men and women and 2 case-control studies were carried out only in men. The remaining reported odds ratios for both sexes combined. Seven of the cohorts reported results for colorectal cancer, only 1 analysed colon and rectal cancer separately and 6 focused only on colon cancer. Four cohort studies were carried out in men; 3 in women and 3 cohort studies reported the results separately for both men and women.

Total meat was defined as fresh plus processed meat in 19 studies, whereas only fresh meat was evaluated in 8 studies. Fish was reported together with meat in 4 case-control studies and eggs in 2. Red meat was defined as fresh beef, pork and lamb consumption in 13 studies whereas processed red meat was also included in this category in 11 studies.

Total meat

Twenty-one case-control and 6 cohort studies investigated total meat consumption and colorectal cancer risk, of which 3 case-control and one cohort study found a significant positive association. Only 1 study found a significantly reduced colorectal cancer risk for meat consumption.

Average relative risk

All cohort studies were included in the estimation of the average RR. Three case-control studies were excluded for the following reasons: odds ratios reported only when they were significant,[84] no confidence intervals,[80] or no odds ratios provided.[37] The excluded RR were not significant with the exception of a study reporting a significant risk decrease for cancer of the rectum, but not of the colon[80] and the significant values found in another study for 2 of the 8 odds ratios reported.[84]

The pooled estimate of the average RR was 1.14 (95% CI 0.99–1.31) (Fig. 1). There was evidence of lack of homogeneity when all studies were considered together. The estimates by subgroups together with the results of the heterogeneity tests are given in Table I. Only one cohort study on an Adventist population[42] found a significant association. In this study, both red meat and white meat contributed independently to a risk increase of 85% in subjects consuming meat once a week or more often, compared with non-consumers. Studies in which meat was defined as fresh meat have a lower average relative risk (RR: 1.01; 95% CI: 0.64–1.60) than studies defining meat as fresh plus processed meat (1.16; 95% CI: 1.01–1.34). The subgroups of cohort studies, the subgroups of males, females and of cancer of the rectum were the only subgroups not heterogeneous.

Dose-response meta-analysis

Eighteen studies (5 cohort and 13 case-control) were included in the dose-response meta-analysis and 9 were excluded, of which 2[84,93] found a significant risk increase associated with high consumption. In addition to 3 case-control studies that were excluded from the previous analysis,[37,80,84] 7 more studies were excluded because the exposure was classified in 2 categories[69,71,74] or because the distribution of cases and control subjects by exposure level[78,87,93,97] was not provided.

Among the 18 studies included in the meta-analysis, only 4 case-control and 1 cohort study reported exposure in grams per day. For case-control studies the inter-quantile mean range of intake was 126 g/day for studies reporting consumption in g/day

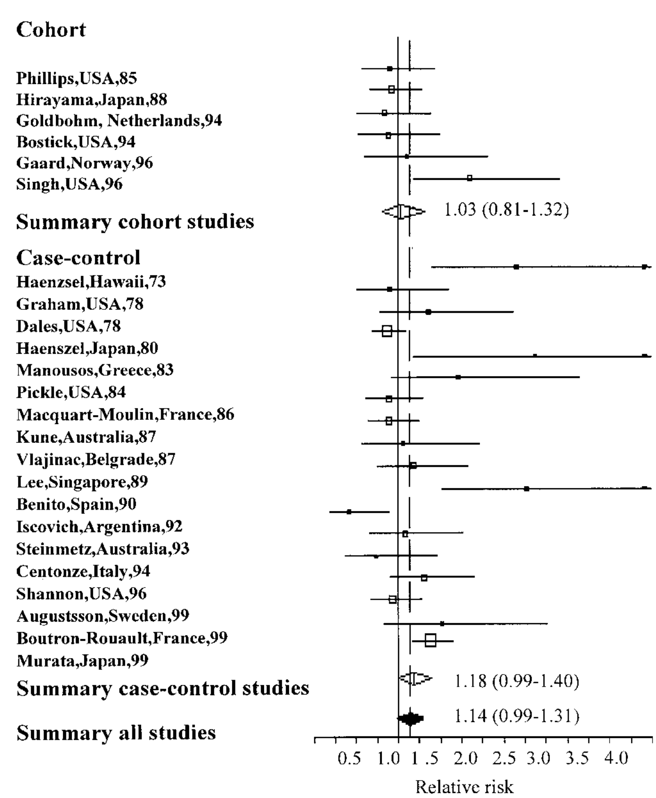

FIGURE 1 – Relative risks (highest vs. lowest category) for case-control and cohort studies (meat).

TABLE I – AVERAGE RELATIVE RISK FOR HIGHEST *VERSUS* LOWEST LEVEL OF INTAKE OF TOTAL MEAT, RED MEAT AND PROCESSED MEAT[1]

Sub-groups	Total meat			Red meat			Processed meat		
	RR (95% CI)	*n*	*p* Het.	RR (95% CI)	*n*	*p* Het.	RR (95% CI)	*n*	*p* Het.
All studies	1.14 (0.99–1.31)	24	<0.001	1.35 (1.21–1.51)	23	<0.001	1.31 (1.13–1.51)	23	<0.001
Case-control	1.18 (0.99–1.40)	18	<0.001	1.36 (1.17–1.59)	14	<0.001	1.29 (1.09–1.52)	16	<0.001
Cohort	1.03 (0.81–1.32)	6	0.14	1.27 (1.11–1.45)	9	0.45	1.39 (1.09–1.76)	7	0.85
Colon	1.09 (0.90–1.33)	15	0.01	1.32 (1.18–1.48)	19	<0.001	1.22 (1.06–1.39)	15	<0.001
Rectum	1.31 (1.00–1.73)	5	0.24	1.36 (1.17–1.57)	7	0.23	1.21 (0.98–1.50)	5	0.14
Males	1.05 (0.85–1.30)	7	0.64	1.40 (1.20–1.64)	9	0.64	1.57 (1.27–1.93)	7	0.22
Females	1.01 (0.81–1.25)	7	0.32	1.13 (0.85–1.50)	8	0.03	1.17 (0.95–1.44)	7	0.85
Europe	1.20 (0.88–1.63)	8	<0.001	1.46 (1.22–1.75)	7	0.03	1.39 (1.12–1.74)	10	0.001
USA	1.32 (1.03–1.70)	8	0.05	1.30 (1.12–1.52)	13	0.002	1.38 (1.10–1.73)	10	<0.001
Fresh meat only	1.01 (0.64–1.60)	6	0.001	1.28 (1.11–1.47)	13	0.003			
Fresh and processed meat	1.16 (1.08–1.34)	18	0.004	1.49 (1.26–1.77)	11	0.02			

[1]*n*, number of studies. *p* Het., *p* heterogeneity test.

TABLE II – DOSE-RESPONSE ANALYSIS[1]

	Total meat			Red meat			Processed meat		
	RR (95% CI)	*n*	*p* Het.	RR (95% CI)	*n*	*p* Het.	RR (95% CI)	*n*	*p* Het.
All studies	1.12 (0.98–1.30)	18	<0.001	1.24 (1.08–1.41)	17	<0.001	1.36 (1.15–1.61)	16	<0.001
Case-control	1.10 (0.94–1.29)	13	<0.001	1.26 (1.02–1.55)	8	<0.001	1.37 (1.13–1.66)	9	0.002
Cohort	0.99 (0.71–1.39)	5	0.18	1.22 (1.05–1.41)	9	0.17	1.54 (1.10–2.17)	7	0.001
Colon	1.10 (0.83–1.45)	14	0.02	1.23 (1.04–1.46)	14	0.01	1.32 (1.02–1.70)	8	0.10
Rectum	1.89 (1.02–3.51)	5	0.01	1.64 (0.64–4.21)	2	0.11		—	
Males	1.07 (0.85–1.34)	6	0.25	1.36 (1.18–1.55)	9	0.12	1.48 (1.08–2.04)	6	<0.001
Females	0.87 (0.72–1.09)	6	0.47	1.11 (0.78–1.56)	8	0.03	1.44 (1.10–1.89)	4	0.69
Europe	1.26 (1.05–1.51)	9	0.14	1.56 (1.07–2.26)	5	0.01	1.39 (1.09–1.77)	8	<0.001
USA	1.04 (0.75–1.45)	5	0.01	1.22 (1.05–1.41)	10	<0.001	1.54 (1.32–1.78)	6	0.63
Fresh meat only	1.01 (0.71–2.19)	6	0.03	1.19 (0.91–1.55)	8	<0.001			
Fresh and processed meat	1.15 (0.99–1.35)	12	0.001	1.28 (1.11–1.48)	9	0.01			

Relative risks for a consumption of 120 g/day (meat and red meat) or 30 g/day (processed meat) *vs.* no consumption.–[1]*n*, number of studies. *p* Het.: *p* heterogeneity test.

and slightly lower, 114 g/day for studies where the rescaling was applied. In cohort studies the mean ranges were 100 g/day and 94 g/day respectively.

The results for all studies combined and for subgroups are given in Table II. The RR estimated from the beta pooling that is associated with a consumption of 120 g/day of meat compared to no consumption is RR: 1.12 (95% CI: 0.98–1.30). On average, the epidemiological studies included in the analysis found no increase in colorectal cancer risk associated with this level of meat intake. The publication bias test was not statistically significant ($p = 0.58$).

There is heterogeneity between all studies, but homogeneity is not rejected for cohort studies. Meta-regressions using the beta estimates for each study as the dependent variable, and the design, geographical area, cancer site, sex and meat definition as explanatory variables were tested in different models using as weight the inverse of the variance of the beta estimate. The only significant predictor of beta was geographical area, with North American studies finding lower slopes than studies from other geographical areas. When the two variables, geographical area and meat definition were included together in the model, the difference between American studies and the other geographical areas disappeared. The slope for studies on fresh meat was lower than for fresh plus processed meat, but they were not significantly different.

Red meat

Fifteen case-control and 9 cohort studies investigated red meat. Six case-control studies reported a significant risk increase or significant trend associated with higher levels of red meat intake. In 2 of them the association was significant for cancer of the rectum but not for the colon. In 1 study there was a significant trend in females but not in males or in both sexes combined. Two out of 9 cohort studies reported relative risks significantly higher than 1.

Average relative risk

Only 1 case-control study,[80] which did not provide confidence intervals, was excluded from the analysis (Fig. 2). In contrast with the results for total meat, the estimated averaged RR for red meat was significantly higher than one (RR: 1.35; 95% CI: 1.21–1.51). As for total meat, homogeneity was not rejected for cohort studies, while case-control studies were heterogeneous and, on average, provided higher RR estimates than cohort studies (Table I). The subgroups of European and North American studies are internally heterogeneous, with Europeans having a larger average relative risk. Within North American studies, cohort studies have a larger average relative risk (RR: 1.45; 95% CI: 1.20–1.76) than case-control studies (RR: 1.28; 95% CI: 0.87–1.89). Studies on males and on cancer of the rectum were homogeneous. For the remaining subgroups homogeneity was rejected. When considering the definition of exposure, a higher average RR was obtained from studies that included processed meat in the red meat group (RR: 1.49; 95%CI: 1.26–1.77), compared to studies that did not (RR: 1.28; 95% CI: 1.11–1.47).

Dose-response meta-analysis

Eighteen studies (9 case-control and 9 cohort) were included in the dose-response meta-analysis whereas 5 studies had to be excluded. The reasons for exclusion are: no confidence interval,[80] only 2 levels of exposure,[74,90] no distribution of cases and control subjects by exposure level[87] and RR not reported.[39] One of the excluded studies found a significant risk increase associated with high consumption[90] and the others found no significant risk increase. The inter-quantile mean ranges of intake were 116 g/day for 3 cohort studies that reported intake in g/day and 101 g/day for the remaining cohort studies for which we estimated intake by

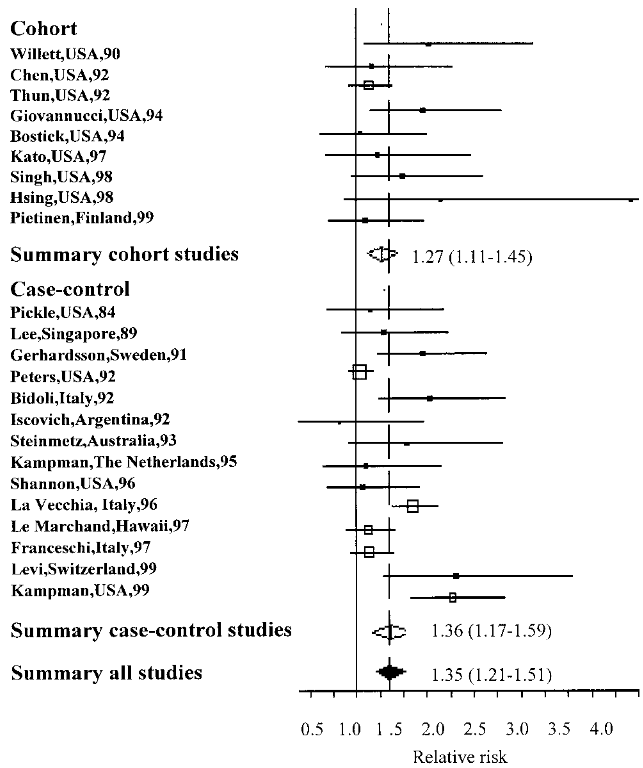

FIGURE 2 – Relative risks (highest *vs.* lowest category) for case-control and cohort studies (red meat).

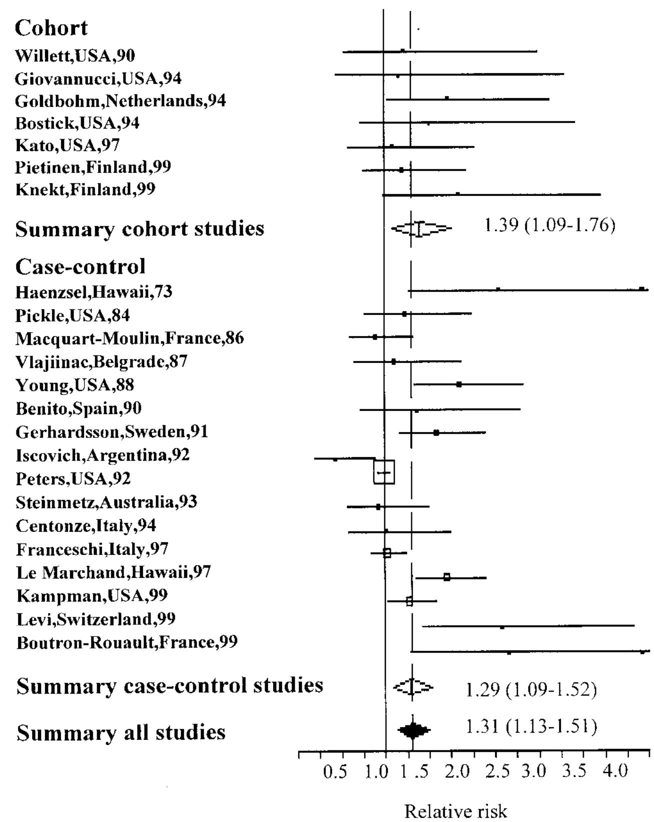

FIGURE 3 – Relative risks (highest *vs.* lowest category) for case-control and cohort studies (processed meat).

rescaling. The three case-control studies that reported intake in g/day had the same inter-quantile mean range as the remaining case-control studies after rescaling (93 g/day).

The results are presented in Table II. The estimated risk associated with consumption of 120 g/day of red meat compared to no consumption was 1.24 (95% CI: 1.08–1.41). Based on the studies included in the meta-analysis, there was no evidence of publication bias ($p = 0.52$). There was heterogeneity between all studies together but homogeneity was not rejected for cohort studies (p-heterogeneity $= 0.17$). In the meta-regression analysis, only the model with geographical area as predictor produced statistically significant estimates: the estimate of relative risk was higher for European than for North American studies. The significance of geographical area disappeared when meat definition was included in the model.

The dose-response was stronger and statistically significant for studies that included processed meat in the red meat group (RR: 1.28; 95%CI: 1.11–1.48) compared to studies that investigated only fresh red meat, for which the estimated risk was not significant (RR: 1.19 95% CI: 0.91–1.55). If the American studies are considered separately, studies evaluating only fresh meat reported lower risks on average (RR: 1.05; 95%CI: 0.55–2.00) than studies where the red meat category included processed meats (RR: 1.24; 95%CI: 1.07–1.43) but the homogeneity was rejected for both groups. The results are similar for European studies, where the RR estimated for studies on fresh red meat is lower (RR: 1.41; 95%CI: 0.91–2.20) than for studies on fresh red meat plus processed meat (RR: 2.07; 95% CI: 1.25–3.42).

Processed meat

Processed meat was evaluated in 29 studies, 22 case-controls and 7 cohorts. Two cohort studies found a significant trend, one cohort found a significantly increased risk for consumption between 2 and 4 times/week compared to no consumption and 12 case-control studies reported odds ratios significantly higher than 1.

Average relative risks

Six studies were not included in the estimation of the average relative risks because either they did not provide confidence intervals,[69,75,80] each type of processed meat was evaluated separately[79,85] or the number of subjects was very small.[82] The average RR for the 23 studies included in the analysis was 1.31 (95% CI: 1.13–1.51) (Fig. 3). The results were heterogeneous and, similarly to what was found for total meat and red meat, homogeneity was not rejected within cohort studies. Subgroup analysis within case-control studies showed that homogeneity was not rejected for the subgroups of males, females and for rectal cancer (Table I).

Dose-response meta-analysis

Sixteen studies (9 case-control and 7 cohort) were included in the dose-response meta-analysis and 13 case-control studies were excluded, of which 6 studies had also been excluded from the previous average RR estimation. The reasons for exclusion were: only 2 categories of exposure,[74,78,88] RR estimated only for the highest level of consumption[37,41] and distribution of case and control subjects not provided.[39,87] Five of the excluded studies reported a significant risk increase associated with increased consumption, 1 a non-significant decrease and the remainder found non-significant risk increases. There is no evidence of publication bias ($p = 0.75$). The mean range of intake for case-control studies was 39 g/day for the 3 studies that reported intake quantitatively and 34 g/day when rescaled; for cohort studies the mean range was 60 g/day (2 cohorts) and 30 g/day respectively.

The association estimated with the pooled dose-response meta-analysis was stronger for processed meat than for any other meat type considered in this study (Fig. 4). The relative risk estimated for a consumption of 30 g/day compared with no consumption was 1.36 (95% CI: 1.15–1.61) (Table II). The same relative risk would be associated with a consumption of 170 g/day of red meat, according to the results of the dose-response meta-analysis on red meat. Overall, the studies are not homogenous (p-heterogeneity < 0.001), but heterogeneity was not rejected for cohort studies. None of the variables evaluated in the meta-regression analysis explained the heterogeneity.

Estimation of the fraction prevented by current consumption of red meat worldwide

The per caput intake of red meat by geographical area estimated for 1995 is presented in Table III. The regions with the lowest correction factor, *i.e.*, with the highest discrepancy between FAO data and current consumption, are Europe, United States and High Income Asia (correction factors of 0.69, 0.60 and 0.70 respectively). These discrepancies can be explained in part because food waste in these countries is high and possibly because the surveys from which the correction factors were deduced are of better quality. The correction factor for Middle East Asia was similar to the value for Europe and America, but was based only on a survey in Turkey. FAO per caput intakes were lower than the mean consumption reported in dietary surveys for India and for males in Low Income Asia, China, India, South America, Caribbean, North Africa and Sub-Saharan Africa.

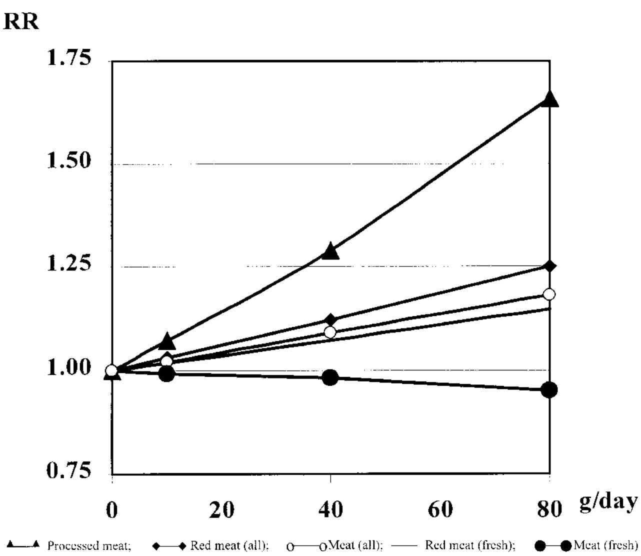

FIGURE 4 – Dose-response analysis of relative risk of colorectal cancer for meat consumption.

The proportion of colorectal cancer incidence attributable to current levels of red meat intake was computed using the beta-pooled estimates in the dose-response analysis. The same slope was used for all geographical areas and for both sexes for two main reasons: first the overall estimate had the advantage of being based on a larger number of studies and second, the subgroups defined by geographical area and by sex were not homogeneous.

The proportion of cancer risk attributable to current red meat consumption compared to non-consumption, as well as the preventable proportion simulating a shift of average consumption to 70 g/week are presented in Table III. The attributable proportion ranges from almost 25% for men in some countries of South America, followed by Australia and New Zealand (19.6%) and North America (13.9%) where consumption of red meat is high, to 2–3% in Chinese and Indian women, who eat very little red meat. When a hypothetical reduction to an average consumption of 70 g/week is simulated, the proportion of preventable risk ranges from 25–11.9% in men and from 17.2–7.5% in women in countries where the consumption is very high. In countries where the contribution of red meat to the diet is very low, as in India, Africa and some regions of Asia, less than 5% of the incidence could be potentially prevented.

DISCUSSION

The quantitative summary of the published literature on the risk of colorectal cancer and meat consumption suggests that high intakes of red meat and of processed meat are associated with increased risk of colorectal cancer. No significant association was found for total meat consumption and colorectal cancer risk. These results are consistent for case-control and cohort studies, for American, European and Asian studies (with the exception of one Argentinean study), for studies on males, females and both genders combined, and for studies on colon, rectal and colorectal cancer.

The use and interpretation of meta-analysis in epidemiology has raised methodological debates and controversial opinions. The most obvious limitation is that results are combined from studies conducted with different methods in different populations, resulting in heterogeneity. In our meat-analyses, heterogeneity was more often present within case-control than within cohort studies, which

TABLE III – PROPORTION OF COLORECTAL CANCER RISK ATTRIBUTABLE TO CURRENT RED MEAT CONSUMPTION AND PROPORTION PREVENTABLE BY REDUCING PER CAPUT RED MEAT CONSUMPTION TO 10 GRAMS PER DAY[1]

World regions	Males			Females		
	Red meat per caput g/day	AP %	PP %	Red meat per caput g/day	AP %	PP %
North America	85.9	13.9	11.9	57.7	9.5	7.5
Central America	41.5	11.1	9.1	30.2	5.1	3.1
Caribbean	26.0	4.2	2.4	18.9	3.2	1.2
Argentina, Uruguay, Paraguay	168.1	25.6	23.7	122	19.2	17.2
Rest of South America	70.3	11.5	9.5	51	8.4	6.5
North and Central Europe	47.3	7.8	5.9	35.0	5.8	3.9
Southern Europe	59.0	9.7	7.7	43.7	7.3	5.3
Eastern Europe	45.3	7.5	5.6	34.8	5.8	3.9
ex-URSS Asia	33.8	5.6	3.7	26.0	4.4	2.4
Middle east Asia	21.6	3.6	1.7	15.7	2.7	0.7
High income Asia	26.6	0.4	2.5	19.3	3.2	1.3
Middle income Asia	14.3	2.4	0.5	10.4	1.7	NC
Low income Asia	26.9	4.5	2.6	19.5	3.5	1.3
China	12.8	2.2	0.2	9.3	1.6	NC
India	15.1	2.6	0.6	11.0	1.9	0.0
North Africa	30.0	5.0	3.1	21.7	3.7	1.7
Subsaharan Africa	20.7	3.5	1.5	15.0	2.5	0.6
Australia, New Zealand	125.7	19.6	17.7	84.1	13.6	11.6
Oceania	41.0	6.8	4.9	29.7	5.0	3.0

[1]NC, not computed because per caput consumption is 10 g/day or less; AP, proportion attributable; PP, proportion preventable.

could be explained to some extent by the fact that most of the cohorts are North-American and used similar methodologies for dietary assessment. Case-control studies from North America and also from Europe remained heterogeneous, however, when studies in the two geographical areas were analyzed separately. Homogeneity was not always rejected when composing subgroups by sex and by cancer site. It is not clear how much of it could be explained by publication bias, because it may be that results are reported separately by sex or cancer site only when they correspond to a certain expectation.

Even though the effect-size estimates differed slightly between case-control and cohort studies, recall bias is very unlikely to account for the positive association we found between red and processed meat and colorectal cancer risk because the directionality of the summary measure of association was the same for both types of studies. Differences between the 2 study designs can partially explain the differences. The time interval between the period covered by the dietary assessment and diagnosis of the disease is usually 1 year (recent diet) in case-control studies although it can be as large as 10–20 years (current diet at the time of subject recruitment) in cohort studies.

Additional methodological issues concern the dietary measurement methods and their validation. We did not attempt to stratify studies by type of questionnaire or by results of their validity studies, because the information given in the papers was very often insufficient to do so. The imprecision of dietary assessment methods causes random measurement errors, which lead to underestimation of the magnitude of the relationship between dietary intake and cancer risk. It has been estimated that, for typical degrees of measurement error, the underestimation is roughly 2-fold ,[103] but this may be larger if dietary intake was not assessed during the period of exposure most relevant to cancer etiology, which is not known with any precision. We decided not to apply formal corrections for measurement error, which would have increased the pooled relative risk estimates because, with very few exceptions, no data from dietary questionnaire validation studies were available for the different types of questionnaire used and for the specific underlying study population.

There is the theoretical possibility that the association between red meat and processed meat and colorectal cancer risk could be due to uncontrolled confounding factors. Known or suspected risk factors were controlled for in many of the studies. It is the opinion of the authors that the diversity of the populations where the studies were carried out argues against the hypothesis that unknown confounders can entirely explain the association.

We found that relative risks for total and red meat were more elevated in studies that included processed meat in the definition of these 2 meat groups than in studies that evaluated fresh meat and fresh red meat (Fig. 4), that could be a support for an increased effect of processed meat. These results should be taken with caution for different reasons: these subgroups were set up *a posteriori*, after the data had been seen, and the finding could be spurious; besides, the definition of meat groups is not always clear in the publications. Nevertheless, this finding is in agreement with the summary relative risk per gram of intake estimated from the dose-response relationship, which was higher for processed meat than for red meat consumption.

The calculation of population attributable risks for diet has specific methodological limitations, particularly due to the fact that the population distribution by exposure level is not precisely known and the association with cancer risk is measured with some approximations. We estimated the prevalence of red meat consumption using data that do not refer to individuals, but to populations. In order to estimate the attributable risk fraction, we used the overall slope estimated in the dose-response analysis instead of slopes estimated for subgroups of different geographical areas, sex or cancer sub-sites. Our decision was mainly due to the fact that most of the studies were carried out in the USA and in Western Europe, and there were not enough studies to obtain meaningful estimates for specific geographical areas of the world. The overall slope had the advantage of being the result of the largest number of available studies. The coefficient of variation applied for the estimation of quartile distribution of red meat intake was the value found in the preliminary analysis of EPIC data. The application of a lower coefficient of variation will not change the estimates substantially, but if the variability is much higher than the hypothetical value used, our estimates of attributable risk and preventable proportion would be an overestimation of the real unknown corresponding values. For North America, for example, if a coefficient of variation of an extreme value such as 200% is applied, instead of 85% as we did, the attributable risk fraction in men will be 9% instead of 14% and the preventable fraction 8% instead of 12 %. The decrease is more important if the average intake level is high than if it is low.

Estimates of cancer risks attributable to diet have been published in the past. Doll and Peto, in their widely quoted 1981 paper[104] estimated that 35% of all US cancer deaths and even 90% of colon cancer deaths were attributable to diet. These figures now appear questionable because epidemiological evidence suggests quite strongly that physical activity accounts for an important percentage of avoidable colon cancer. More recently, Willett[105] estimated that 50–80% of colorectal cancer deaths could be avoidable by dietary change. In the Health Professionals Follow-Up Study,[106] it was estimated that about a third to a half of colon cancer risk might be avoidable if exposure to 6 risk factors (overweight, physical activity, supplementation with folic acid, alcohol consumption, smoking and red meat intake) were modified to become equal to that of the men in the approximate bottom 20% or bottom 5% of a risk score distribution. In a case-control study, La Vecchia *et al.*[107] estimated that 56% of colon cancer risk would have been avoided if all subjects were moved to the lowest exposure levels of 6 risk factors considered together. The attributable risk for individual factors was 12% for high education, 14% for low physical activity, 14% for high energy intake, 22% for low vegetable intake, 7% for high eating frequency, and 8% for a family history of colorectal cancer. In a case-control study in Northern Italy,[90] the proportion of risk of colorectal cancer attributable to red meat consumption was estimated as 16% for males and 17% for females. In our study, the estimates of colorectal cancer risk attributable to current red meat consumption were 9.7% and 7.3% for Southern European men and women. The highest estimates of the attributable fraction correspond to the areas of highest per caput red meat consumption, Argentina, Uruguay and Paraguay, followed by Australia and New Zealand and by North America.

We computed the reduction in cancer risk that could potentially be achieved with a hypothetical dietary reduction of average red meat consumption from current levels to an average of 70 g/week. In simulating a change, we chose as goal the intake of this small portion size once a week because at this level there is no evidence of excess risk compared to no consumption. Therefore, this assumption does not require complete avoidance of red meat. Such a reduction could potentially lead to a decrease in colorectal cancer risk in men as high as 17.9% in Australia and 12.1% in North America. According to the estimated preventable proportions, approximately 22,000 incident cases could be avoided in North America, 21,000 in Europe, 7,000 in Asia and 6,000 in South America.

In calculating attributable and preventable fractions, we assumed that the association between red meat consumption and colorectal cancer is causal and free from bias. Our estimates refer only to a single risk factor, but individual dietary factors may not contribute independently. Other dietary and non-dietary factors, such as vegetable and fruit intake, smoking habits, reproductive history, physical activity and infectious agents, may also contribute to risk differences. The isolated change of a single dietary factor represents a simplification and it may well be that interventions addressing the totality of diet-related risk factors could remove a larger proportion of excess risk. Based on the available data, it is not possible to determine to what extent reducing exposure to modifiable risk factors at various ages, after exposure at varying levels for varying duration, will prevent colorectal cancer. Neither is it possible to estimate the latency between a reduction in average red meat consumption occurring in a given population and the expected reduction in colorectal cancer incidence.

Our results do not imply that meat consumption should be completely avoided as part of a balanced diet. Nevertheless, they support previous recommendations[3] to adopt a diet characterized by low intake of red and processed meat.

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APPENDIX I – CORRECTION FACTORS BY GEOGRAPHICAL AREA AND PER CAPUT ENERGY INTAKE[1]

Geographical area	Survey		FAO energy (kcal/day)	Correction factor	
	Energy (kcal/day)	Year		Males	Females
North America				0.73	0.49
USA Females	1742		3562		
USA Males	2593		3562		
South America					
Brazil	2262	1974/75	2488	1.06	0.77
Caribbean				1.23	0.89
St Lucia	1881	1974	2067		
Trinidad Tobago	2948	1970	2481		
Europe (EPIC)				0.81	0.60
Eastern Europe				0.86	0.66
Poland males	2579	1982–85	3351		
Poland females	1886		3351		
Novosibirsk males	2907		3385		
Novosibirsk females	2028		3385		
Kaunas males	3232		3385		
Kaunas females	2792		3385		
High Income Asia				0.82	0.60
Japan	2034	1993	2893		
Middle Income Asia				0.96	0.70
Philippines	1769	1978	2149		
Low Income Asia				1.11	0.80
Bangladesh	1773	1973/74	1912		
Indonesia	1859	1987	2475		
Pakistan	2390	1984/85	2161		
Sri Lanka	2281	1981/82	2263		
Middle East Asia				0.75	0.54
Turkey	2105	1981/82	3285		
China	2467	1990	2668	1.08	0.79
India	2719	1971/72	2022	1.57	1.14
North Africa				1.04	0.76
Morocco	2466	1970/71	2442		
Tunisia	2275	1985	2935		
Sub-Saharian Africa				1.06	0.77
Cote d'Ivoire	2104	1979	2799		
Rwanda Rural	2444	1982/83	2279		
Togo	2026	1988/89	2235		
Average correction factor				1.17	0.85

[1]kcal/day, from surveys[60,61] and Food Balance Sheets (F.A.O.).

APPENDIX II – TOTAL MEAT, RED MEAT AND PROCESSED MEAT INTAKE AND COLORECTAL CANCER CASE-CONTROL STUDIES

Author, location	Design	Type of meat and partition	OR (95% CI)		Adjustment
Haenzsel *et al.*, 1973[68]	Hawaiian-Japanese	Meat, total (times/month)			
Hawaii	Colorectal 179 Control 357	≤20	1		
	Recruitment 1966–1970	20–39	2.2		
	FFQ[2]	≥40	2.4[5]		
		Sausage and other processed pork (times/month)			
		>6	1		
		6–11	1.27		
		12–23	1.35		
		≥24	2.3[5]		
Dales *et al.*, 1978[69]	Colorectum 77	All meat (times/month)	Unadjusted: 1.54 (0.90–2.66)		Age, gender,
USA	Controls 215	>66 *vs.* ≤66	Adjusted: 1.67		other foods,
	American Blacks	Nitrite-treated meats	Unadjusted: 1.48 (0.87–2.51)		parity,
	Recruitment: 1973–1976	(times/month)			smoking,
	FFQ (89)[2]	>32 *vs.* ≤32	Adjusted: 1.22		others
Graham *et al.*, 1978[70]	White males	Meats, including fish			
USA	Colon 256 Controls 783	(times/month)	Colon	Rectum	
	Rectum 330 Controls 628	0.–20	1	1	
	Recruitment: 1959–1965[3]	21–30	0.65	1.01	
		31–40	0.59	1.42	
		41–50	0.70	1.45	
		50+	0.30	1.77	
		Bacon: Not associated			
Haenszel *et al.*, 1980[71]	Colorectum 588 Controls 588[2]	Meat, total (times/month)	0.87 NS		Age, gender,
Japan		≥12 *vs.* <12			prefecture
Manousos *et al.*, 1983[72]	Colorectum 100 Controls 100	Meat, fish, eggs, novel protein			
	Recruitment: 1979–1980	Highest *vs.* lowest quartile: not reported.			
Greece	FFQ (80)[2]	$p = 0.01$			

APPENDIX II – TOTAL MEAT, RED MEAT AND PROCESSED MEAT INTAKE AND COLORECTAL CANCER CASE-CONTROL STUDIES (CONTINUED)

Author, location	Design	Type of meat and partition		OR (95% CI)		Adjustment	
Miller *et al.,* 1983[73] Canada	348 colon (171 male and 177 female)	Sausages, cold cuts, luncheon meats and animal organs servings/week				Age, gender, other foods, saturated fat	
	194 rectum (114 male and 80 female)						
	542 hospital and 535 population controls			Males		Females	
	1976–1978	Males	Females	Colon	Rectum	Colon	Rectum
		<10.1	<5.1	1	1	1	1
		<29.1	<17	0.8	1.1	0.9	0.9
		≥29.1	≥17	1.0	1.3	1.0	1.2
Pickle *et al.,* 1984[74] USA	Colon 58 Rectum 28	Meat, total (serving/week)		Colon: 1.71		Age, gender, ethnic group, others	
	Controls 176			Rectum: 1.06			
	Recruitment: 1970–1977	≥12.6 *vs.* <12.6		Colon: 1.09			
	Mean age: 74 FFQ (57)	Beef, pork, lamb, mutton, wild game (serving/week)		Rectum: 1.25			
	Rural area[2]			Colon: 1.16			
		≥6 *vs.* <6		Rectum: 1.37			
		Bacon, sausage, lunch meat, corned beef (serving/week)					
		≥3 *vs.* <3					
Tajima and Tominaga, 1985[75] Japan	Colon 42 Rectum 51	Ham and sausage		Colon	Rectum	Gender, age	
	Controls 186	Low		1	1		
	Age 40–74	Medium		2.19	0.60		
	Recruitment: 1981–1983 FFQ[2]	High		2.87[4]	0.60		
Macquart-Moulin *et al.,* 1986[76] France	Colorectal 399 Control 399	Fresh meat Quartiles		1		Age, gender, total energy, weight	
	Recruitment: 1979–1984	Reference: lowest		1.32			
	Mean age = 65 FFQ (158)[2]			1.40			
				0.89			
		“Charcuterie” Quartiles		1			
		Reference: lowest		1.31			
				0.88			
				0.89			
Kune *et al.,* 1987[77] Australia	Colon 392 Rectum 323	Meat (g/week)				Age, gender	
	Controls 727	Males	Females	Males	Females		
	Recruitment: 1980–1981	<830	<602	1	1		
	Dietary history (+300)[3]	<1011	<757	0.69	0.98		
		<1270	<890	0.65	0.77		
		<1600	<1080	0.80	0.66		
		<1600	>1080	1.13	0.76		
Vlajinac *et al.,* 1987[78] Belgrade	Colon 81 Controls 162 Hospital and neighbourhood controls age 24–85	Meat (times/month)		*vs.* Hospital	*vs.* Neighbours		
		<24		1	1		
		24–42		1.25	0.63		
	Recruitment: 1984–1986	43–63		1.34	1.26		
	FFQ (49)	64+		2.34	9.20		
		Nitrite-treated meats over and above the median		Hospital:1.10 Neighbours: 0.81			
La Vecchia *et al.,* 1988[79] Italy	Colon 339 Rectum 236	Highest *vs.* lowest tertile		Colon	Rectum	Age, gender, education, area, other foods	
	Controls 778			1.01	1.05		
	Age < 75	Raw ham		1.04	0.73		
	Recruitment: 1985–1987	Ham		1.05	0.73		
	FFQ (29)[2]	Salami and sausages					
Young *et al.,* 1988[37] USA	Colon 353 Controls: 618 white Americans	Any meat-based meal		No differences between cases and controls			
		Diet over 35 years		1.85 (1.33–2.58)			
	Age 35–89	20 *vs.* 1/month		OR not reported, $p < 0.15$			
	Recruitment: 1981–1982	Bacon, ham, lunchmeat					
	FFQ (25)[3]	Sausage, hot dogs, processed lunch meat					
Tuyns *et al.,* 1988[80] Belgium	Colon 453 Rectum: 365	Fresh meat, smoked meat.		Colon	Rectum	Age, gender, province	
	Controls: 3669	<705		1	1		
	Recruitment: 1978–1982	−906		1.00	1.00		
	Age: 35–75	−1175		0.98	0.67		
	FFQ (extensive list)[3]	+1175 g/w		0.82	0.75[4]		
		Meat, except poultry and rabbit		Colon	Rectum		
		<575		1	1		
		−767		0.90	0.78		
		−1015		0.89	0.74		
		+1015 g/w		0.89	0.57[5]		
		Charcuterie g/w		Colon	Rectum		
		0		1	1		
		<50		1.16	1.38		
		50–125		0.83	0.94		
		>125		0.90	0.98		
Lee *et al.,* 1989[81] Singapore	Colorectum 203:426	Red meat and poultry excluding fish and liver (g/day)				Age, gender, dialect, education	
	Males 121:239						
	Females 82:187						
	Chinese origin	Males	Females	Colorectum	Colon	Rectum	
	Colon 77 males 55 females	<59.8	<30.3	1	1	1	
	Rectum 44 males 27 females	<112.2	<73.3	1.17 (0.75–1.80)	1.13 (0.67–1.89)	1.17 (0.61–2.23)	
	Recruitment: 1985–1987	>112.2	>73.37	1.18 (0.76–1.83)	1.30 (0.78–2.17)	0.91 (0.46–1.81)	
	FFQ (116)[2]						

APPENDIX II – TOTAL MEAT, RED MEAT AND PROCESSED MEAT INTAKE AND COLORECTAL CANCER CASE-CONTROL STUDIES (CONTINUED)

Author, location	Design	Type of meat and partition		OR (95% CI)		Adjustment
		Pork, beef, mutton (g/day)				
		Males	Females	Colorectum	Colon	Rectum
		<43.9	<19.9	1	1	1
		<79	<47.5	1.18 (0.77–1.81)	1.01 (0.60–1.70)	1.43 (0.75–2.74)
		>79	>47.5	1.29 (0.84–1.97)	1.41 (0.87–2.31)	0.97 (0.48–1.92)
				Cured or smoked luncheon meat		
		>1 time/wk *vs.* less		2.9 (1.2–7.1) $p = 0.03$		
Wohlebb *et al.,* 1990[82]	Colorectum 43 Controls 41	Cured or smoked bacon		5.0 (0.99–25)		
USA	Males	>1 time/wk *vs.* less				
	Age 45–75 FFQ (55)[2]	Fresh meat times/month		Colorectum		
		<16		1		
		<25		2.30		
		26–32		2.11		
		≥32		2.52[5]		
Benito *et al.,* 1990[83]	Colon: 144	Processed meat				Age, gender,
Spain	Males 72 Females 72	times/month	Colorectum	Colon	Rectum	weight 10
	Rectum 130	0	1	1	1	years prior,
	Males 74 Females 56	<11	1.35	1.97	1.98	education,
	Population controls 295	11–22	1.42	1.99	2.05	occupation,
	Age < 80	≥22	1.36	2.87[5]	2.42	physical
	Recruitment: 1984–1988					activity, other
	FFQ (99)					foods
Hu *et al.,* 1991[84]	Colon 111 Rectum 225	Meat intake before 1985			Meat intake before 1966	
China	Controls 336	≥5 kg/year *vs.* none			≥2 kg/year *vs.* <2	
	Recruitment: 1985–1988	Colon males not significant			Colon not significant	
	FFQ (25)[2]	Colon females not significant			Male rectum not significant	
		Rectum Male 3.38 (1.65–6.95)			Females rectum 2.06 (1.13–3.75)	
		Rectum Females not significant				
Gerhardsson *et al.,*	Colon 452 Rectum 268	Beef, pork, ham, bacon,				Age, gender,
1991[41]	Controls: 624	sausages				protein, boiled
Sweden	Recruitment: 1986–1988	serving/year		Colon	Rect.	and fried meat
	FFQ (55)[3]	<85		1	1	intake
		<167		1.1	1.6	
		<215		1.3	1.3	
		≥215		1.3	1.7	
				1.4	2.4[4]	
		Bacon/smoked ham		Colon	Rectum	
		More seldom		1	1	
		1–3 ts/month		0.9 (0.7–1.3)	1.5 (1.0–2.2)	
		>once/week		1.3 (0.8–1.9)	1.7 (1.1–2.8)[4]	
		Sausage fried		Colon	Rectum	
		More seldom		1	1	
		1–3 times/month		0.9 (0.7–1.3)	1.5 (1.0–2.2)	
		>once/week		1.3 (0.8–1.9)	1.7 (1.1–2.8)[4]	
		Sausage oven-roasted		Colon	Rectum	
		More seldom		1	1	
		1–3 ts/month		1.0 (0.7–1.3)	1.0 (0.7–1.6) 1.5	
		>once/week		1.0 (0.6–1.4)	(0.9–2.3)	
		Sausage boiled		Colon	Rectum	
		More seldom		1	1	
		1–3 ts/month >once/week		1.2 (0.8–1.7)	1.3 (0.9–2.0)	
				1.2 (0.5–2.8)	2.1 (0.9–4.9)[4]	
Bidoli *et al.,* 1992[85]	Colon 123 Rectum 125	Beef and pork		Colon	Rectum	Age, gender,
Italy	Controls 699	Lowest tertile		1	1	social status
	Mean age: Controls 56.4	Second tertile		1.5	1.5	
	Colon 57 Rectum 62	Highest tertile		1.6	2.0[5]	
	Recruitment:					
	1986–1990	Highest *vs.* lowest tertile		Colon	Rectum	
	FFQ[2]					
		Cured ham		1.4 NS	1.6 NS	
		Boiled ham		1.3 NS	1.2 NS	
		Salami and sausages		1.8[4]	1.9[4]	
Peters *et al.,* 1992[39]	White men and women 746	Beef, pork or lamb as		Both genders:		Age, gender,
USA	colon cancer (327 females,	sandwuich, mixed or main		1.04 (0.92–1.19)		social-class
	419 males) 746 hospital-	dish)		Males: 1.18[4]		strata,
	based controls	RR per 10 servings/month		Females: 1.14[5]		macronutrients,
	Incidence: 1983–86	Bacon, hot dogs, salami,		Both genders: 0.99 (0.93–1.06)		alcohol,
	FFQ (116)	bologna, etc.		Males: 1.05		calcium,
		RR per 10 servings/month		Females: 1.12[5]		physical
						activity,
						weight, family
						history,
						pregnancy
						history
Iscovich *et al.,* 1992[86]	Colon 110	Fresh meat (times/year)				Age, gender,
Argentina	Controls: 220	<269		1		residence,
	Recruitment: 1985–1987	269–381		0.93 (0.42–2.03)		other foods
	Age: 35–80 FFQ (140)[3]	382–392		0.30 (0.11–0.80)		
		>392		0.41 (0.19–0.91)[5]		

APPENDIX II – TOTAL MEAT, RED MEAT AND PROCESSED MEAT INTAKE AND COLORECTAL CANCER CASE-CONTROL STUDIES (CONTINUED)

Author, location	Design	Type of meat and partition		OR (95% CI)		Adjustment
		Red Meat (times/year)				
		<176		1		
		176–315		2.29 (1.03–5.08)		
		>315		0.82 (0.39–1.70)		
		Processed (times/year)				
		<16		1		
		16–76		0.83 (0.41–1.69)		
		76–198		0.86 (0.42–1.79)		
		>198		0.43 (0.21–0.89)[4]		
Steinmetz *et al.,* 1993[87] Australia	Colon	Red meat, processed meat (servings/week)				Age, gender, occcupation, Quetelet index, alcohol intake
	Males 121 cases, 241 controls	Males	Females	Males	Females	
	Females 99 cases, 197 controls	≤7.4	≤6.1	1	1	
	Recruitment: 1979–1980	7.5–10.9	6.2–8.1	0.53 (0.27–1.04)	0.57 (0.27–1.20)	
	Age: 30–74	11–14.4	8.2–11.2	0.71 (0.37–1.33)	1.17 (0.57–2.40)	
	FFQ (165)[3]	≥14.5	≥11.3	1.18 (0.62–2.25)	0.95 (0.45–1.99)	
		Red meat (servings/week)				
		Males	Females	Males	Females	
		≤3.9	≤3.4	1	1	
		4.0–5.5	3.5–5.0	1.80 (0.92–3.52)	1.44 (0.70–2.93)	
		5.6–8.2	5.1–7.1	1.64 (0.82–3.27)	1.15 (0.57–2.32)	
		≥8.3	≥7.2	1.59 (0.81–3.13)	1.48 (0.73–3.01)	
		Processed meat (servings/week)				
		Males	Females	Males	Females	
		≤2.2	≤1.4	1	1	
		2.3–4.3	1.5–2.8	0.69 (0.35–1.37)	0.54(0.25–1.23)	
		4.4–7.6	2.9–4.3	0.68 (0.35–1.34)	0.81 (0.37–1.77)	
		≥7.7	≥4.4	1.03 (0.55–1.95)	0.77 (0.35–1.68)	
Centonze *et al.,* 1994[88] Italy	Colorectum 119 Controls 121	Meat, fish, eggs (g/day)				Age, gender, smoking, education, changes in diet
	Rural Area	<149		1		
	Median age: 67	150–199		0.8 (0.41–1.54)		
	Recruitment: 1987–1989	+199		0.74 (0.38–1.44)		
	FFQ (70)[3]	Fresh Meat (g/day)				
		<87		1		
		88–131		1.16 (0.62–2.19)		
		>131		0.74 (0.37–1.45)		
		Processed (g/day)				
		2		1		
		≥3		1.01 (0.57–1.69)		
Kampman *et al.,* 1995[89] Netherlands	232: 259	Red meat (g/d)		Both genders		Age, gender, total energy, alcohol intake family history, others
	Males 130:136	<52		1		
	Females 102:123	52–72		0.80 (0.47–1.38)		
	Age < 75	73–94		0.91 (0.54–1.55)		
	Recruitment: 1989–1993	>94		1.11 (0.65–1.90)		
	FFQ (289)[3]	Males	Females	Males	Females	
		<60	<38	1	1	
		60–83	38–59	0.80 (0.39–1.61)	1.82 (0.75–4.46)	
		84–102	60–83	0.57 (0.27–1.30)	2.71 (1.15–6.38)	
		>102	>83	0.89 (0.43–1.81)	2.35 (0.97–5.56)	
				$p = 0.62$	$p = 0.04$	
La Vecchia *et al.,* 1996[90] Italy	Colon 828 Rectum 498	Red meat		Colorectum: 1.6 (1.4–1.9)		Age, gender, education, area, other foods, energy, family history
	Controls: 2024 Hospital based	More than 4 times/week *vs.* less		Colon: 1.6 (1.3–1.9)		
	Age: 20–74			Rectum: 1.6 (1.3–2.0)		
	Recruitment: 1985–1992					
	FFQ (29)					
	Colon	Total meat (including fish) serving/day				Age, gender, total energy
	Males 238:224	Males	Females	Males	Females	
	Females 186:190	0.–1.5	0.–1.17	1	1	
	Age: 30–62	1.5–1.9	1.18–1.53	0.79 (0.44–1.41)	0.67 (0.36–1.24)	
	Recruitment: 1985–1989	2–2.6	1.54–2.08	1.18 (0.68–2.05)	0.76 (0.40–1.45)	
	FFQ (71)[3]	>2.6	>2.08	1.52 (0.84–2.77)	0.78 (0.39–1.55)	
Shannon *et al.,* 1996[91] USA	Colon Males 238:224	Red meat serving/day				
	Females 186:190	Males	Females	Males	Females	
	Age 30–62	0.–0.78	0.–0.49	1	1	
	Recruitment 1985–1989	>0.78–1.2	>0.49–0.79	1 (0.58–1.74)	0.90 (0.50–1.64)	
	FFQ (71)[3]	>1.2–1.7	>0.79–1.2	1.05 (0.61–1.83)	1.03 (0.55–1.90)	
		>1.7	>1.2	1.48 (0.82–2.66)	0.72 (0.37–1.38)	
Franceschi *et al.,* 1997[92] Italy	Colon 1225 Rectum 728	Red meat serving/wk		Colorectum		Age, gender, education, total energy, physical activity, others
	Controls 4154	<2.3		1		
	Age: 19–74	<3.5		0.98 (0.83–1.17)		
	Recruitment: 1992–1996	<4.8		1.12 (0.94–1.34)		
	FFQ (79)[3]	<6.3		1.0 (0.83–1.21)		
		>6.3		1.14 (0.93–1.39)		
		OR per 1 serving/day		Colorectum 1.09 (0.90–1.31)		
				Colon 1.06 (0.85–1.32)		
				Rectum 1.16 (0.88–1.52)		
		Processed meat serving/wk		Colorectum		
		<1		1		
		<2		1.21 (1.03–1.42)		

APPENDIX II – TOTAL MEAT, RED MEAT AND PROCESSED MEAT INTAKE AND COLORECTAL CANCER CASE-CONTROL STUDIES (CONTINUED)

Author, location	Design	Type of meat and partition		OR (95% CI)		Adjustment
		<3		1.06 (0.89–1.26)		
		<4		1.24 (1.02–1.49)		
		>4		1.02 (0.84–1.24)		
		OR per 1 serving/day		Colorectum 0.97 (0.79–1.18)		
				Colon: 1.08 (0.87–1.36)		
				Rectum: 0.78 (0.57–1.06)		
Le Marchand *et al.*, 1997[54] Hawaii	Prevalent and incidents Colorectum (Males 698 Females 494)	Red meat		Males	Females	Age, gender, ethnicity, family history, alcohol, tobacco, BMI, total energy, others
		Colorectum (quartiles, reference: lowest)		1-1.2-1.5-1.6 (1.0–2.5)	1-0.8-0.7-0.7 (0.4–1.2)	
		Tertiles (reference: lowest)				
	Right colon (Males 197 Females 164)	Right colon		1-1.5-2.3[4]	1-1.2-0.8	
	Left colon (Males 270 Females 194)	Left colon		1-0.9-1.1	1-0.8-0.8	
	Rectum (Males 221 Females 129)	Rectum		1-1.2-1.3	1-0.90.7	
	Controls 1192	Processed meat (quartiles)		1-1.7-2.2 2.3 (1.5–3.4)[5]	1-0.8-1.1 1.2 (0.8–2.0)	
	Multiethnic	Right colon		1-1.1-1.6	1-1.2-1.0	
	Recruitment: 1987–1989	Left colon		1-1.6-1.4	1-0.8-1.1	
	FFQ (>280)[3]	Rectum		1-1.1-2.2	1-0.8-0.8	
Augustsson *et al.*, 1999[43] Sweden	Colon 521 Rectum 249	Total meat and fish intake		Colon	Rectum	Age, gender, energy
	Controls 553	Quintiles. Reference category: lowest		1.4 (0.9–2.2)	1.4 (0.9–2.3)	
	Age: 51–77			1.4 (0.9–2.1)	1.4 (0.8–2.3)	
	Recruitment: 1992–1994			1.7 (1.1–2.6)	1.4 (0.9–2.4)	
	FFQ (188)[3]			0.9 (0.5–1.4)	1.0 (0.6–1.6)	
Murata *et al.*, 1999[93] Japan	Colon 265 Rectum 164 Controls 794 Recruitment: 1989–1997 FFQ[2]	Total meat excluding fish. Every day *vs.* rare		Colon: 1.41 (1.13–1.77)[5] Rectum: 1.33 (1.01–1.77)[4]		Age, alcohol, tobacco, gender, eating attitude other foods
Kampman *et al.*, 1999[47] USA	Colon	Red meat: beef and ham (servings/week)				Age, gender, total energy, BMI, dietary fiber, tobacco, other
	1542 cases/1860 controls	Males	Females	Males	Females	
	Age: 30–79	≤2.2	≤1.5	1	1	
	Males 868/989	2.3–3.7	1.6–2.5	0.8 (0.6–1.0)	1.1 (0.8–1.5)	
	Females 674/871	3.8–5.6	2.6–4.0	1.1 (0.8–1.0)	1.3 (0.9–1.8)	
	Recruitment: 1992–1995	5.7–8.8	4.1–6.2	1.0 (0.7–1.4)	1.3 (0.9–1.8)	
	FFQ (800)[3]	>8.8	>6.2	0.9 (0.7–1.3)	1.0 (0.7–1.5)	
		Processed meat: bacon, sausages, cold cuts				
		Males	Females	Males	Females	
		≤0.5	1	≤0.2	1	
		0.6–1.0	1.1 (0.8–1.6)	0.3–0.5	1.3 (1.0–1.9)	
		1.1–1.8	1.2 (0.9–1.8)	0.6–0.9	1.2 (0.9–1.7)	
		1.9–3.1	1.3 (1.0–1.8)	1.0–1.7	1.3 (0.9–1.8)	
		>3.1	1.4 (1.0–1.9)	>1.7	1.1 (0.8–1.6)	
Levi *et al.*, 1999[94] Switzerland	Colon 119 Rectum 104	Red meat (serving/week)		Colorectum		Education, tobacco, alcohol, BMI, vegetables, total energy, physical activity
	Control 491					
	Mean age: 63	<2.25		1		
	Recruitment: 1992–1997	2.25–3.75		1.27 (0.81–2.02)		
	FFQ (70)[2]	>3.75		2.06 (1.29–3.30)[5]		
		OR for 1 serving/day		Colorectum 1.54 (1.28–1.85)		
				Colon 1.63 (1.30–2.04)		
				Rectum 1.50 (1.2–1.88)		
		Pork and processed meat (serving/week)		Colorectum		
		>2.25		1		
		2.25–3.75		1.12 (0.68–1.85)		
		>3.75		2.33 (1.42–3.830)[5]		
		OR for 1 serving/day		Colorectum 1.27 (1.13–1.43)		
				Colon 1.34 (1.17–1.53)		
				Rectum 1.18 (1.02–1.37)		
Boutron-Ruault *et al.*, 1999[95] France	Right colon: 43	Fresh meat g/d				Age, gender, total energy
	Left colon: 63	Males	Females	Both genders		
	Rectum: 65	82.1	56.5	1		
	Controls: 309	<105.0	<81.4	1.2 (0.7–2.0)		
	Age 30–79	<127.1	<102.6	1.0 (0.6–1.8)		
	Recruitment: 1985–1990	>127.1	>102.6	1.2 (0.6–2.1)		
	Dietary history[3]					
		Delicatessen (g/day)				
		Males	Females	Both genders		
		<19.2	<11.2	1		
		<34.7	<21.2	1.6 (0.9–2.9)		
		<55.3	<33.3	1.2 (0.6–2.2)		
		>55.3	>33.3	2.4 (1.3–4.5)[5]		

[1]FFQ, food frequency questionnaire. Number of items between parentheses.–[2]Hospital-based.–[3]Population-based.–[4]$p < 0.05$.–[5]$p < 0.01$.

APPENDIX III – COHORT STUDIES

Author, location	Design	Type of meat and partition		OR (95% CI)		Adjustment
Phillips and Snowdon, 1985[96]	Colorectum Cancer	Meat (times/week)				Age, gender
Seventh-day Adventist,	Mortality					
USA	Colon 147 Rectum 35	<1		1		
	Cohort: 25493 subjects	1–3		1.4 (1.0–1.9)		
	Age > 35					
	Recruitment: 1960–1980	≥4		0.9 (0.6–1.5)		
	Follow-up 20 years FFQ (21)					
Hirayama, 1990[97] Japan	Colorectal Cancer	Meat		Males		
	Mortality	Daily		Intestine	Rectum	
	Age 40 or older	Occasional		1	1	
	Intestine: 256 men, 318	Rare		1.86 (1.17–2.97)	1.50 (1.01–2.22)	
	women	None		1.52 (0.90–2.57)	1.47 (0.95–2.28)	
	Rectum: 316 men, 247			1.89 (0.84–2.47)	1.54 (0.74–3.20)	
	women					
	Cohort: 265118 subjects			Females		
	Follow-up: 1966–1982			Intestine	Rectum	
		Daily		1	1	
		Occasional		0.83 (0.59–1.18)	1.20 (0.76–1.91)	
		Rare		0.74 (0.50–1.10)	1.08 (0.65–1.79)	
		None		0.95 (0.57–1.56)	1.41 (0.77–2.60)	
Thun *et al.,* 1992[98]	Colon Cancer Mortality	Meat excluding fish and poultry		Males	Females	
Cancer Prevention Study,	Deaths: 2757 Subjects	Quintiles		1	1	
USA	1185124	References: lowest		1.12	0.92	
	Mean age: 57	Red meat (g/day)		1.08	1.06	
	Recruitment: 1982			1.01	0.91	
	Follow-up: 2 years			1.21	1.05	
	FFQ (42)					
Willett *et al.,* 1990[99]	Colon: 150 cases					Age, energy
The Nurses Health Cohort Study,	Cohort: 8875 women	<59		1		
USA	Age: 34–59	59–83		1.16 (0.67–1.99)		
	(512 488 person/years)	84–105		0.25 (0.73–2.13)		
	Recruitment: 1980–1986	106–133		1.13 (0.65–1.97)		
	FFQ (61)	≥134		1.77 (1.09–2.88)[2]		
		Processed meat				
		<1/month		1		
		1–3/month		1.09 (0.70–1.69)		
		1/w		1.45 (0.91–2.31)		
		2–4/w		1.86 (1.16–2.98)		
		≥4/w		1.21 (0.53–2.72)[2]		
Giovannucci *et al.,* 1994[19] Health	Colon: 205 cases	Red meat (g/day)		1		Age, obesity, total energy,
Professionals Follow-up Study,	Cohort: 47949 men	18.5		0.97 (0.62–1.54)		family history, alcohol,
USA	(737910 person/years)	42.9		0.98 (0.62–1.56)		tobacco, physical
	Age: 40–75	64.1		1.21 (0.77–1.88)		activity, others
	Recruitment: 1986	88.5		1.71 (1.15–2.55)[2]		
	Follow-up 6 years	129.5				
		Processed meat				
		None		1		
		1–3/month		1.25 (0.87–1.80)		
		1/w		1.40 (0.92–2.13)		
		2–4/w		1.67 (1.06–2.61)		
		≥5/w		1.16 (0.44–3.04)		
Goldbohm *et al.,* 1994[40]	Case-cohort	Fresh red meat and poultry				Age, gender, total energy,
Netherlands	Males Colon 157	Men, Women	Men	Women	Both genders	other types of meat
	Cohort: 58279	g/day				
	Females Colon 155	53,43	1	1	1	
	Cohort: 62573	84/72	1.09 (0.58–2.04)	0.83 (0.44–1.56)	0.92 (0.59–1.44)	
	Age 55–69	101,91	1.62 (0.89–2.93)	1.03 (0.58–1.84)	1.24 (0.81–1.90)	
	Recruitment: 1986–1990	123,107	0.98 (0.51–1.91)	1.05 (0.57–1.93)	0.98 (0.62–1.55)	
	Follow-up 3.3 years	158,145	0.87 (0.43–1.77)	0.88 (0.45–1.69)	0.84 (1.51–1.37)	
	FFQ (150)					
		Both genders: OR per 5 g/day: 0.98 (0.93–1.03)				
				Processed meat		
				Processed Meat		
		g/day	Men	Women	Both genders	
		0.–10	1.25 (0.59–2.70)	1.22 (0.66–2.26)	1.23 (0.76–1.98)	
		10–20	1.45 (0.67–3.12)	1.48 (0.77–2.87)	1.43 (0.87–2.35)	
		>20	1.84 (0.85–3.95)	1.66 (0.82–3.35)	1.72 (1.03–2.87)[2]	
Bostick *et al.,* 1994[100]	Colon: 212	Total eggs and meat (serving/week)				Age, gender, total energy,
Iowa Women Health's Study,	Cohort: 35215	<9		1		other foods, others
USA	Women	9–11		0.83 (0.54–1.26)		
	(167447 person/years)	11.5–14		1.02 (0.69–1.52)		
	Age: 55–69	14.5–18		0.71 (0.44–1.13)		
	Recruitment: 1986–1990	>18		0.88 (0.52–1.49)		
	FFQ (127)	Red meat (serving/week)				
		<4		1		
		4–6		1.13 (0.76–1.69)		
		6.5–8		1.20 (0.77–1.87)		
		8.5–11		0.88 (0.54–1.42)		
		>11		1.04 (0.62–1.76)		
		Processed meat (serving/week)				
		0		1		
		0.5		1.0 (0.73–1.38)		
		1		1.07 (0.71–1.61)		
		2–3		0.81 (0.46–1.44)		
		>3		1.51 (0.72–3.17)		

APPENDIX III – COHORT STUDIES (CONTINUED)

Author, location	Design	Type of meat and partition	OR (95% CI)		Adjustment
Gaard *et al.,* 1996[48] Norway	Colon: 143 cases 19% (48) Cohort 570842 person/years Age 20–53 Recruitment: 1977–1983 Mean follow-up 11.4 FFQ (80)	Excluding fish (meals/week) ≤2 3 4 ≥5	Males 1 1.33 1.44 0.80	Females 1 1.33 1.40 1.87	Age
Kato *et al.,* 1997[101] New York University Women's Health Study, USA	Colorectal Cohort: 15785 women (105044 person-years) Recruitment: 1985–1991 Age: 34–65 FFQ (70)	Red meat Quartiles Reference: lowest category Ham, sausages Quartiles Reference: lowest category	1 1.28 (0.72–2.28) 1.27 (0.71–2.28) 1.23 (0.68–2.22) 1 1.39 (0.81–2.38) 1.38 (0.79–2.42) 1.09 (0.59–2.02)		Age, total energy, education, others
Chen *et al.,* 1998[57] Physicians Health Study, USA	Nested case-control Males Colorectum 212:221 Age: 40–84 Recruitment: 1982 13 years follow-up	Red meat (srving/day) ≤5 >0.5–1 >1	 1 0.98 (0.64–1.52) 1.17 (0.68–2.02)		
Hsing *et al.,* 1998[44] Lutheran Brotherhood Cohort, USA	Colorectum Cancer Mortality in white males Colon: 120 Rectum: 25 286731 person-years Recruitment: 1966 20 y follow-up FFQ (35)	Red meat (time/month) <15 15–19 20–29 30–59 ≥60	 1 1.2 (0.6–2.2) 1.5 (0.9–2.5) 1.4 (0.8–2.5) 1.9 (0.9–4.3) p trend = 0.1		Age, smoking status, alcohol intake, total energy
Singh and Fraser, 1998[42] Adventist Health Study, USA	Colorectum: 157 (135 colon 22 recto-sigmoidal junction) Cohort: 32051 Age > 25 Recruitment: 1976–1982 FFQ (51)	Meat Never ≥1 time/wk ≥1 time/wk Red meat Never <1 time/wk ≥1 time/wk	 1 1.50 (0.92–2.45) 1.85 (1.16–2.87)[2] 1 1.58 (1.01–2.45) 1.41 (0.9–2.21)		BMI, physical activity, parental history of colon cancer, tobacco alcohol,
Knekt *et al.,* 1999[102] Finland	Colorectum 73 Cohort: 9985 subjects Recruitment: 1966–1972 Follow-up until 1990 (21 years) Dietary history	Meat and meat-products (cured) Quartiles. Reference: lowest	1 1.48 (0.77–2.84) 1.28 (0.63–2.57) 1.84 (0.98–3.47)		
Pietinen *et al.,* 1999[50] ATBC Prevention Study, Finland	Cases: 185 Cohort: 27111 Male smokers Age: 50–69 Recruitment: 1988 (Follow up 8 years) FFQ (276)	Red meat (g/day) 79 114 143 203 Processed meat (g/day) 26 50 73 122	 1 1.1 (0.8–1.7) 1.0 (0.7–1.6) 1.1 (0.7–1.7) 1 1.5 (1.0–2.2) 1.2 (0.7–1.8) 1.2 (0.7–1.8)		Age, tobacco years, BMI, alcohol, education, physical activity, others

[1]FFQ, Food frequency questionnaire. Number of items between parentheses.–[2]$p < 0.05$.–3$p < 0.01$.–[4]$p < 0.05$.–[5]$p < 0.01$.