Systematic Review of the Prospective Cohort Studies on Meat Consumption and Colorectal Cancer Risk: A Meta-Analytical Approach[1]

Manjinder S. Sandhu,[2] Ian R. White, and Klim McPherson

Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Strangeways Research Laboratory, Cambridge, CB1 8RN [M. S. S.]; Medical Research Council Biostatistics Unit, Institute of Public Health, University of Cambridge, Cambridge, CB2 2SR [I. R. W.]; and Cancer and Public Health Unit, London School of Hygiene and Tropical Medicine, London, WC1E 7HT [K. M.], United Kingdom

Abstract

The relation between meat consumption and colorectal cancer risk remains controversial. In this report, we quantitatively reviewed the prospective observational studies that have analyzed the relation between meat consumption and colorectal cancer. We conducted electronic searches of MEDLINE, EMBASE, and CANCERLIT databases through to the end of June 1999 and manual searches of references from retrieved articles. We used both fixed and random-effects meta-analytical techniques to estimate the overall association and to investigate possible sources of heterogeneity among studies. Thirteen studies were eligible for inclusion in the meta-analysis. Pooled results indicate that a daily increase of 100 g of all meat or red meat is associated with a significant 12–17% increased risk of colorectal cancer. The marginally significant between-study heterogeneity for all meat and red meat was explained by a number of study-level covariates. A significant 49% increased risk was found for a daily increase of 25 g of processed meat. The individual study estimates for processed meat showed no detectable heterogeneity. On the basis of this quantitative review of prospective studies, the overall association between meat consumption and risk of colorectal cancer appears to be positive, with marginal heterogeneity between studies. The finding for processed meat and data from experimental studies suggests that it may also be an important predictor of colorectal cancer risk. However, because only a few of the studies reviewed here attempted to examine the independent effect of meat intake on colorectal cancer risk, the possibility that the overall association may be confounded or modified by other factors cannot be excluded.

Introduction

The relation between meat consumption and colorectal cancer risk remains controversial (1–10). Subsequent to the report of the National Academy of Sciences, "Diet and Health" (11), which implicated red meat as a causative factor in the etiology of colorectal cancer, two subsequent reports have reviewed the epidemiological evidence on meat and colorectal cancer risk (4, 7). The report of the WCRF[3] concluded: "The evidence shows that red meat probably increases risk and processed meat possibly increases risk of colorectal cancer" (7). The report from COMA judged that "there is moderately consistent evidence from cohort studies of a positive association between the consumption of red or processed meat and risk of colorectal cancer" (4). A WHO consensus statement reached a similar conclusion, stating that "consumption of red meat is probably associated with increased colorectal cancer risk," but also stated that epidemiological studies on meat and colorectal cancer risk are not consistent (2).

Both the COMA and WCRF reports made dietary recommendations based on their qualitative assessments of the epidemiological literature. The WCRF report recommended limiting "intake of red meat to less than 80 g daily." The COMA report, targeted at the population of the United Kingdom, advised that consumption of red and processed meat for those consuming population average levels (~90 g/day for the United Kingdom population) should not rise. It also recommended that people who are consuming high levels (>140 g cooked weight/day) should consider a reduction.

In contrast, other researchers have noted that "it remains uncertain whether meat is a risk factor for cancer" (12) and that the current prospective evidence on meat and colorectal cancer risk "is now clearly negative for this association" (3). It has also been suggested that any association between high meat consumption and colorectal cancer may be as a result of deficiencies in other protective dietary factors, such as vegetables and fruits (1, 13). References to studies in many of these reports, reviews, and discussion articles are incomplete and limited; therefore, we aimed to review prospective cohort studies that have investigated the relation between meat and colorectal cancer risk. In addition, given that quantitative recommendations—based on qualitative assessments of the literature—have been made, we sought to use quantitative review methods to

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[1] M. S. S. is supported by the United Kingdom Medical Research Council.
[2] To whom requests for reprints should be addressed, at Department of Public Health and Primary Care, Institute of Public Health, University of Cambridge, Strangeways Research Laboratory, Wort's Causeway, Cambridge, CB1 8RN, United Kingdom. Phone: 01223-740168; Fax: 01223-740177; E-mail: manj.sandhu@srl.cam.ac.uk.

[3] The abbreviations used are: WCRF, World Cancer Research Fund; COMA, Chief Medical Officer's Committee on Medical Aspects of Food; OR, odds ratio; HCA, heterocyclic amine.

Table 1 List of studies used in the review and meta-analysis and their selected characteristics

Author, year published	Country	Age at entry; sex	Years of follow-up; % completed follow-up	Start of follow-up	No. of cases; No. in cohort	Dietary assessment;[a] Quantiles[b]	Adjustments
Bjelke *et al.*, 1980 (29)	Norway	45–74; M	5; not stated	1968	41;[c] 12,166	50-item FFQ; Q3	Age
Gaard *et al.*, 1996 (21)	Norway	20–54; M & F	Mean 11.4; 83	1977	143;[c] 55,535	80-item FFQ;[d] Q4	Age; attained age
Giovannucci *et al.*, 1994 (22)	USA	40–75; M	6; 95	1986	205;[c] 47,949	131-item FFQ;[d] Q5	Age; energy intake
Goldbohm *et al.*, 1994 (23)	Netherlands	55–69; M & F	3.3; 95	1986	293;[c] 3,123	150-item FFQ;[d] Q4 & Q5	Age; total calories
Hirayama *et al.*, 1990 (28)	Japan	>40; M & F	17; 80	1965	725; 265,113	9-item FFQ (7 food groups & 2 beverages); Q4	Age
Hsing *et al.*, 1998 (27)	USA	≥35; M	20; 77	1966	145; 13,606	35-item FFQ; Q5	Total calories; age; smoking; alcohol
Kato *et al.*, 1997 (20)	USA	34–65; F	Mean 7.1; (97 in New York State recruits)	1985–1991	100;[c] 14,727	70-item FFQ; Q4	Total calories; age; place of enrollment; education
Knekt *et al.*, 1999 (17)	Finland	15–99; M & F	24; not stated	1967	73;[c] 9,990	1 year dietary history interview; Q4	Age; sex; municipality; smoking; energy intake
Phillips *et al.*, 1985 (26)	USA	>30; M & F	21; not stated	1960	172; 25,439	21-item FFQ; Q3	Age; sex
Sellers *et al.*, 1998 (18)	USA	55–69; F	9; 76	1986	241;[c] 26,937	127-item FFQ;[d] Q3	Age; energy intake
Singh *et al.*, 1998 (19)	USA	25–104; M & F	6; 97	1977	179;[c] 32,051	55-item FFQ;[d] Q3	Age; body mass index; sex; smoking; physical activity; family history; alcohol; aspirin use
Thun *et al.*, 1992 (24)[e]	USA	30–110; M & F	6; 98	1982	1,150; 5,746	42-item FFQ (32 food items & 10 beverages); Q5	None
Willett *et al.*, 1990 (25)	USA	34–59; F	6; 96	1980	150;[c] 88,751	61-item FFQ;[d] Q5	Age; energy intake

[a] Food Frequency Questionnaire.
[b] Quantiles. Q3 = tertiles; Q4 = quartiles; Q5 = quintiles.
[c] Incident cases.
[d] Undertook validation of dietary assessment.
[e] Nested case control.

both confirm the current recommendations and to investigate possible sources of heterogeneity among studies.

Materials and Methods

Inclusion Criteria. We sought to include both published and unpublished prospective cohort studies that contained risk estimates of colorectal cancer associated with meat consumption. A broad definition of "meat" was used, which was taken to include red meat, lamb, beef, pork, and processed meats, such as sausages, meat burgers, ham, bacon and other meat products, but which, where possible, excluded white meat, such as poultry. Eligible outcomes were colon or colorectal cancer incidence or mortality.

Exclusion Criteria. We excluded case-control and ecological studies. Case-control studies, where diet is assessed after the onset of disease, may be subject to information (recall) and selection bias, and inaccurate or biased measurements of dietary exposure attributable to dietary changes as a result of disease (14). Ecological studies, which analyze aggregated data at the level of the population, may be subject to confounding and cannot reliably be extrapolated to the individual level (15). Studies that only classified people as to whether they ate meat or not were also excluded from the analysis, because the level of exposure in the exposed group is not quantified (16).

Search Strategy. We conducted electronic searches of MEDLINE, EMBASE, and CANCERLIT databases through the end of June 1999. A search strategy that included both truncated free-text and exploded MeSH terms was used. MeSH headings included "colorectal," "colon," "bowel," "rectum," "diet," "meat," "cancer," "neoplasm," "prospective," "follow-up," or "cohort" and their variants. All references that matched the inclusion criteria were retrieved and the references of those articles were checked for other relevant publications. References contained in recent reviews of the literature were also consulted (4, 7, 8). Finally, principal investigators responsible for the collated studies and authors of recent reviews were contacted for any unpublished or missed research.

Data Extraction and Classification. Rate ratios, 95% confidence intervals, and various study characteristics were extracted from the original reports and included in the meta-analysis (Table 1). The extracted data for each study were then sent to the original investigator for review and to request any additional data that were required for the meta-analysis.

For each study, the median level of meat consumption (g/day) for each quantile was assigned to each corresponding rate ratio. This was either taken from the report or requested from the investigators (17–26). If the data were unavailable, the median was estimated as the midpoint of each quantile (22, 25, 27, 29), and the amount consumed in g/day was estimated by multiplying the median frequency of consumption by the average portion (serving) size for the cohort population (18, 21, 22, 24–27, 29). If they were unavailable, portion sizes were

estimated using data from another cohort from the same country (18, 24, 26, 27, 29). For the Hirayama study (28), 100 g was used as the average portion size.

Exposure Definition. Because "meat" has no common definition, meat was defined and analyzed in several ways. Risk estimates obtained from the publications were collectively categorized into "All meat." This included meat defined in the individual publications as "all meat," "meat," "other meat," "fatty meat," "fresh meat," "red meat," and "total meat." In addition, meat was also categorized into more specific definitions, *i.e.*, "Red meat" and "Processed meat," Risk estimates categorized as red meat included meat defined in the individual publications as "red meat" or "fatty meat," and for processed meat as "processed meat," "cured meat," "nitrate meat," or "sausages."

Statistical Methods and Analyses. Standard weighted least-squares regression was used to model the log rate ratios for colorectal cancer risk as a linear function of meat intake, adjusting for covariance (30–32). This provided an estimate of the regression coefficient and its SE for each study. Risk estimates for portion sizes were based on approximations for comparison purposes only and on amounts that fitted the data range: 100 g for all meat and red meat, and 25 g for processed meat.

An overall summary estimate of the individual study estimates of β was calculated using both fixed and random-effects meta-analysis (33, 34). Heterogeneity among studies was assessed using the Q statistic (34) and by comparing both random- and fixed-effects estimates (35). To test the appropriateness of a linear model, individual study estimates were grouped into quartiles of exposure (36–38). Because there was no detectable heterogeneity among risk estimates within quartiles ($P > 0.10$), we used standard fixed-effects meta-analysis to estimate the overall relative risk for each quartile of exposure for all meat, red meat and processed meat separately (36). This method gave almost identical results to the full parametric method, suggesting that the linear model was appropriate.

Random-effects meta-regression was used to investigate sources of heterogeneity and to provide an estimate of unexplained or residual heterogeneity, τ^2 (39–41). Only those *a priori* study-level covariates that denoted significant linear dependency are reported here. Study-level covariates included outcome definition (incidence or mortality), cancer definition (colon or colorectal), loss to follow-up, duration of follow-up, magnitude of exposure differential between exposed and unexposed, diet validation, adjustment for energy intake, and the number of confounders included in the analysis. We made no attempt to use a scoring system for study "quality"; instead, the components of study quality were used as covariates in the investigation of heterogeneity (42). Publication bias was assessed using the methods outlined by Egger *et al.* (43).

Results

A total of 17 publications were identified with data that were potentially eligible for inclusion in the review and meta-analysis (17–29, 44, 47). Fifteen of the studies were published in peer-reviewed journals, one as a book (28), and one as part of a congress report (29). Studies were excluded if they classified people only as to whether they ate meat or not (44, 45), if they were pooled analyses of original studies (44), and if the data in the reports were superseded by later publications (46, 47). This left 13 publications. Table 1 lists the studies and selected characteristics. On request, additional information was supplied by authors (17–22, 24–27, 29).

Table 2 "All meat" exposure definitions and risk of colorectal cancer

Author, year; exposure	Published estimate (95% CI)[a]	Derived estimate for 100-g increment in "All meat" consumption[b] (95% CI)[a]
Gaard *et al.*, 1996 (21); total meat		
Females	1.87 (0.77–4.86)	1.57 (0.80–3.06)
Males	0.80 (0.35–1.86)	0.78 (0.42–1.44)
Giovannucci *et al.*, 1994 (22); red meat		
Males	1.71 (1.15–2.55)	1.73 (1.25–2.39)
Goldbohm *et al.*, 1994 (23); fresh meat		
Females	0.88 (0.45–1.69)	0.96 (0.65–1.41)
Males	0.87 (0.43–1.77)	0.87 (0.46–1.64)
Hirayama *et al.*, 1990 (28); meat		
Females	1.05 (0.64–1.75)	1.45 (0.70–2.99)
Males	0.53 (0.23–1.19)	0.55 (0.20–1.55)
Hsing *et al.*, 1998 (27); red meat		
Males	1.80 (0.8–4.4)	1.14 (0.92–1.40)
Kato *et al.*, 1997 (20); red meat		
Females	1.23 (0.68–2.22)	1.56 (0.73–3.34)
Knekt *et al.*, 1999 (17); other meat		
Males and females	1.19 (0.51–2.76)	1.21 (0.76–1.92)
Phillips *et al.*, 1985 (26); meat		
Females	0.7 (0.3–1.4)	0.76 (0.38–1.51)
Males	1.5 (0.7–3.3)	1.51 (0.69–3.32)
Sellers *et al.*, 1998 (18); all meat		
Females	1.13 (0.77–1.64)	1.06 (0.89–1.25)
Singh *et al.*, 1998 (19); total meat		
Males and females	1.85 (1.16–2.87)	1.28 (1.05–1.57)
Thun *et al.*, 1992 (24); fatty meat		
Females	1.05 (0.78–1.41)	1.03 (0.88–1.20)
Males	1.21 (0.92–1.59)	1.07 (0.95–1.21)
Willett *et al.*, 1990 (25); red meat		
Females	1.77 (1.09–2.88)	1.50 (1.09–2.07)

[a] Risk estimate for highest *versus* lowest intake of meat. CI, confidence interval.
[b] Based on data from all quantiles using standard weighted least-squares regression with adjustment for covariance.

All Meat. For all meat, 12 of 17 estimated regression coefficients were positive (Table 2). For a 100-g portion, the estimated rate ratios ranged from 0.55 (0.20–1.55; Ref. 28) to 1.73 (1.25–2.39; Ref. 22). Fig. 1 shows the estimated rate ratios and 95% confidence intervals for each study for an increment of one portion of all meat using a random-effects model. The combined OR for all studies was 1.12 (1.05–1.20) for the fixed-effects model and 1.14 (1.04–1.25) for the random-effects model. A formal test for heterogeneity among studies was not significant [Q 4 statistic (Q) = 22.48; *df*, 16; $P = 0.13$]. However, because of the low power of the test, additional analysis of heterogeneity was warranted. When we fitted a random-effects meta-regression model with no covariates, we estimated the between-study variance as $\tau^2 = 0.0052$. The estimate of τ^2, in comparison to that when the covariate is omitted, allows the proportion of the heterogeneity explained by the covariate to be calculated. Including whether the study outcome was mortality or incidence as a covariate explained all of the between-study variance and was nearly statistically significant ($P = 0.06$). Therefore, for a comparable level of exposure, the summary OR for studies reporting incidence was higher than the summary OR for studies reporting mortality (Table 3). No other explanations of heterogeneity were found.

Processed Meat. For processed meat, 9 of 10 estimated regression coefficients were positive. For a 25-g portion, the estimated rate ratios ranged from 0.88 (0.49–1.57; Ref. 18) to

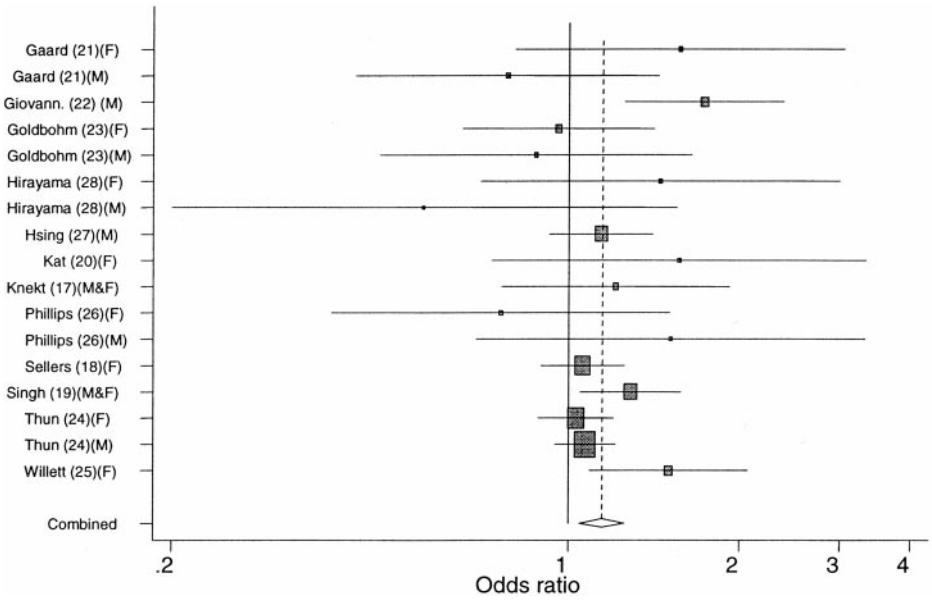

Fig. 1. Random effects meta-analysis of the risk of colorectal cancer for an increase of one portion (100 grams/day) of all meat. *M*, males; *F*, females.

Table 3 Random-effects pooled summaries for all meat and red meat stratified by study-level covariates

Exposure	Pooled summary statistic (Odds ratio and 95% confidence intervals)		Residual heterogeneity	
	Outcome			
	Incidence	Mortality	*P*	τ^2
All meat/100 g/day	1.21 (1.10 to 1.33)	1.07 (0.98 to 1.16)	0.06	0
Red meat/100 g/day	1.30 (1.13 to 1.49)	1.07 (0.98 to 1.16)	0.02	0
	Adjusted for total energy intake			
	Yes	No		
Red meat/100 g/day	1.27 (1.13 to 1.46)	1.07 (0.98 to 1.17)	0.02	0
	Validation of dietary assessment			
	Yes	No		
Red meat/100 g/day	1.29 (1.12 to 1.49)	1.07 (0.98 to 1.17)	0.03	0

2.27 (1.06–4.86; Ref. 21). Fig. 2 shows the estimated rate ratios and 95% confidence intervals for each study for an increment of one portion of processed meat using a random-effects model. The combined OR for all studies was 1.49 (1.22–1.81) for both the random- and fixed-effects models. A formal test for heterogeneity among studies was not significant ($Q = 5.24$; *df*, 9; $P = 0.81$), and we estimated no between-study variance, $\tau^2 = 0$. As expected, no significant explanations of heterogeneity were found.

Red Meat. For red meat, all eight of the estimated regression coefficients were positive. For a 100-g portion, the estimated rate ratios ranged from 1.03 (0.88–1.20; Ref. 24) to 1.73 (1.25–2.39; Ref. 22). Fig. 3 shows the estimated rate ratios and 95% confidence intervals for each study for an increment of one portion of red meat using a random-effects model. The combined OR for all studies was 1.13 (1.05–1.21) for the fixed-effects model and 1.17 (1.05–1.31) for the random-effects model. A formal test for heterogeneity among studies suggested near significance ($Q = 12.6$; *df*, 7; $P = 0.08$). Using a random-effects meta-regression model with no covariates, the between-study variance was estimated as $\tau^2 = 0.0095$. Including whether the study outcome was mortality or incidence as a covariate explained all of the between-study variance ($P = 0.02$). A similar effect was seen when we substituted outcome for a covariate indicating whether a dietary validation study had been undertaken ($P = 0.03$), or whether studies had adjusted for energy intake ($P = 0.02$). Therefore, for a comparable level of exposure, the summary ORs for studies that reported incidence, undertook a diet validation study, or adjusted for total energy intake were significantly higher than the summary ORs for studies that reported mortality or did not undertake a diet validation study or adjust for total energy intake, respectively (Table 2). No other explanations of heterogeneity were found.

Discussion

Summary of Main Findings. In this exploratory meta-analysis, we found a positive association between all meat and red meat consumption and risk of colorectal cancer. Pooled results indicate that a daily increase of 100 g of all meat or red meat is associated with a significant 12–17% increased risk of colorectal cancer. The marginally significant between-study heterogeneity for all meat and red meat was explained by a number of study-level covariates (Table 3). A significant 49% increased risk was found for a daily increase of 25 g of processed meat. The individual study estimates for processed meat, based on

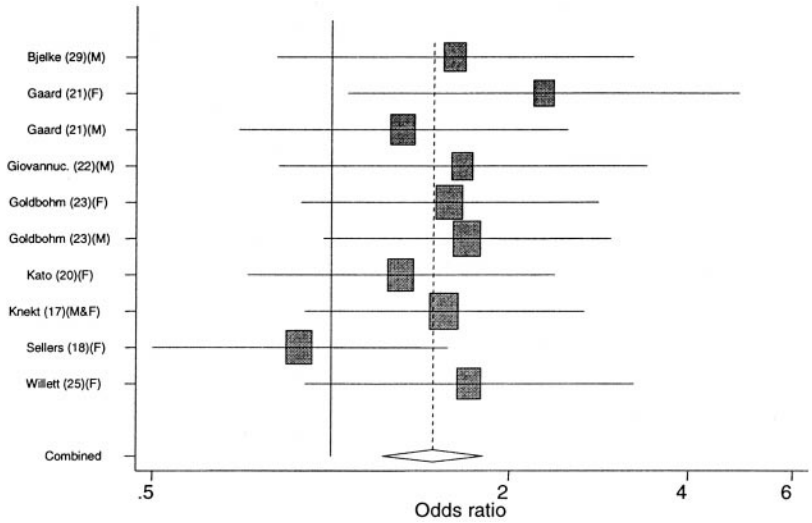

Fig. 2. Random effects meta-analysis of the risk of colorectal cancer for an increase of one portion (25 grams/day) of processed meat. *M*, males; *F*, females.

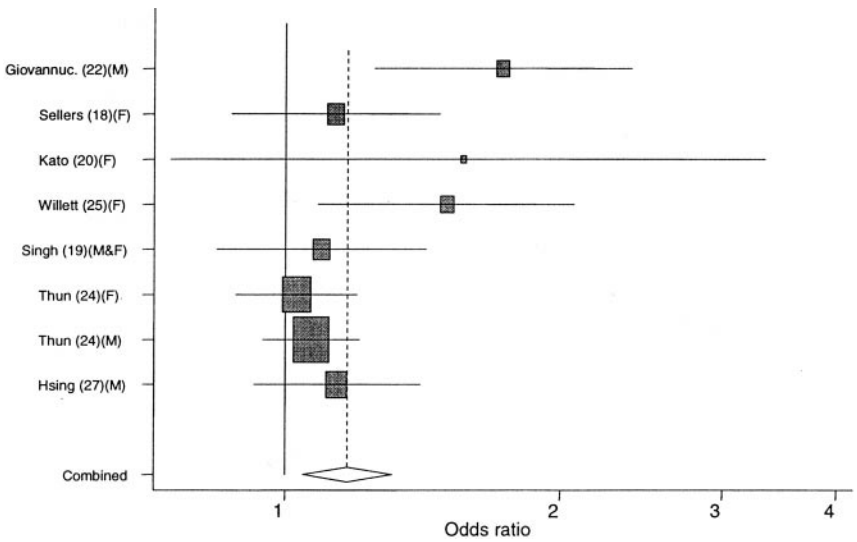

Fig. 3. Random effects meta-analysis of the risk of colorectal cancer for an increase of one portion (100 grams/day) of red meat. *M*, males; *F*, females.

comparable levels of exposure, showed no detectable heterogeneity.

Limitations. The pooled estimates reported here are based on estimates derived from observational prospective cohort studies; therefore, the possibility of residual confounding or bias cannot be excluded (48). Because only 13 studies with 17 risk estimates were included, the power to discriminate among different covariates was limited. Also, as a result of collinearity among study-level covariates and similarities among study characteristics (Table 1), we were unable to determine whether their effects were independent of other study-level covariates. Tests for publication bias have generally low power and, because of the potential for biases and residual confounding, may not be appropriate for observational studies (41). Only studies for red meat showed significant publication bias favoring a positive association ($P = 0.03$). Although we sought to include both published and unpublished studies, a potential for selection bias exists because we did not include non-English language and abstract-only publications, and we may have missed unpublished data.

Interpretation of Heterogeneity. Validity or relative validity studies are used to determine the magnitude of error of an exposure measure and evaluate its effect on the relation under study (49). The effect of random measurement error is to make the observed disease/exposure relation weaker than the true relation. If we take the viewpoint that studies with validated exposure assessments are studies with better measures of exposure and, therefore, less random error in exposure measurement, then higher risk estimates would be expected (Table 2). This attenuation of the estimated risk has led researchers to apply a correction or deattenuation factor based on relative validity studies of exposure assessment. However, rarely is the measure of association between the test and reference measure used in the adjustment of risk estimates (50). Earlier methods to correct for measurement error assumed that the reference measure contains only random within-person errors uncorrelated with errors in the test measure; assumptions which may not be true (49). Recent findings have indicated that failure to account for person-specific biases in the reference and test measures, and correlated errors among measurements, could lead to sig-

nificant distortions in the estimation of the corrected relative risk of disease for a dietary exposure (49, 51). Errors in the measurement of potential confounders may also be a possible source of bias. This bias could result from both the extent of measurement error and from correlation among measurement errors of the exposure and potential confounders (52). The latter could be especially likely in food-frequency questionnaires, because individual perceptions could influence responses to a number of questions. Furthermore, the possibility of residual confounding attributable to unmeasured confounders may also exist.

It is unlikely that there is any real difference among incidence and mortality studies (Table 2). In this analysis, the pooled estimate is lower for mortality studies, implying that meat consumption reduces case-fatality. If meat consumption is a risk factor for etiology and not survival, then we would expect the ratio of disease rates among unexposed and exposed groups to be similar for both incidence and mortality studies. To complicate any additional interpretation, there is also the additional factor of changes in diet as a result of disease. In addition, because studies analyzing incidence were also studies that had, in general, undertaken diet validation studies, collinearity between these two study-level covariates may explain the difference between incidence and mortality studies. These methodological covariates may also be indicative of study "quality." An earlier qualitative comparison of low- and high-quality studies on meat and cancer found that high-quality studies, as defined, found stronger associations than low-quality studies (53).

Total energy intake is positively correlated to consumption of most foods, including meat, and may also be an independent risk factor for colorectal cancer (7). In addition, much of the variation in energy intake relates to factors such as body size and physical activity, which may also independently influence the risk of colorectal cancer (4, 7, 54). This added interindividual variation may produce an additional source of error (14). Therefore, failure to adjust for total energy intake and its correlates may confound the reported associations, and the independent effect of meat consumption would be difficult to determine. However, the effect of this confounding would be dependent upon the relation and strength of association among correlates of energy intake within the individual studies.

Meat and Other Dietary and Associated Factors. The estimation of disease risk associated with a particular dietary factor may be influenced by the presence of other dietary and associated factors. High-meat diets have been negatively associated with food groups rich in antioxidants and fiber (55); components which have been associated with a reduced risk of colorectal cancer (4, 7, 56). Two of the studies included in the review (19, 28) suggested interaction with other dietary and associated factors. Singh *et al.* (19) found that individuals with a high meat intake, a low legume (pulses), intake and high body mass experienced a >3-fold increase in risk relative to other patterns based on these variables. The study by Hirayama (28), in a separate analysis, found an increased risk of colon cancer in men consuming meat daily but rarely eating green-yellow vegetables, and a decreased risk in men consuming both red meat and green-yellow vegetables daily. However, the current prospective epidemiological data show only a weak negative association between vegetables and fruits consumption and risk of colorectal cancer (4, 7). Four recent studies, two randomized trials on adenoma recurrence (57, 58) and two large prospective studies on colorectal cancer (59, 60) found no association among fiber, vegetables, and fruits consumption and risk of colorectal cancer. The two prospective studies based on the Nurses' Health Study (59) and a combined analysis of the Nurses' Heath Study and the Health Professionals' Follow-up Study (60) both adjusted for red meat intake when ascertaining the effect of fiber and vegetables and fruits consumption on colorectal cancer risk, respectively. The multivariate estimates did not materially differ from the unadjusted estimates. Both studies found no association among vegetables and fruits or fiber intake and risk of colorectal cancer. Thus, the effect of meat consumption on the risk of colorectal cancer may be modified or confounded by other dietary and associated lifestyle factors. However, although they may be correlated, it is unlikely that vegetables and fruits consumption may significantly confound this relation.

Biological Mechanisms. The biochemical mechanisms and genetic models by which high consumption of red and processed meat may increase the risk of colorectal cancer have been discussed in numerous reports (9, 61–63). These include the formation from meat products of carcinogenic agents such as *N*-nitroso compounds, polycyclic aromatic hydrocarbons, and HCAs. The finding for processed meat is consistent with a role for *N*-nitroso compounds (64). *N*-nitroso compounds, which are also produced via endogenous synthesis (64), are found almost exclusively in foods containing nitrites or which have been exposed to nitrogen oxides, such as processed meats (65). HCAs, which have been shown to be strong mutagens, are formed on the surface of meat when it is cooked in direct flame or at high temperatures (62). HCAs require metabolic activation to function as mutagens, and genetic polymorphisms for these enzymes have been shown to interact with meat consumption and modify the risk of colorectal cancer (66, 67).

Conclusions. In the context of cancer prevention only, our findings are in general agreement with the conclusions outlined in the COMA and WCRF reports (4, 7). On the basis of this quantitative review of prospective studies, the overall association between meat consumption and risk of colorectal cancer appears to be positive, with marginal heterogeneity among studies. The finding for processed meat and the data from experimental studies suggest that it may also be an important predictor of colorectal cancer. However, whether meat consumption is an independent risk factor for colorectal cancer is uncertain. Colorectal carcinogenesis is a multifactorial and multistep process that may involve several biological pathways and an accumulation of genetic alterations (62, 68), and it is unlikely that determinants of colorectal cancer work in isolation from each other. Indeed, frequent consumption of meat is associated with a number of predictors of colorectal cancer (19, 55). Moreover, because only a few of the studies attempted to examine the independent effect of meat consumption, we cannot exclude the possibility that the association may be confounded or modified by genetic or dietary and associated factors (4, 7, 62, 66).

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