Meta-analysis of prospective studies of red meat consumption and colorectal cancer

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The relationship between red meat consumption and colorectal cancer (CRC) has been the subject of scientific debate. To estimate the summary association between red meat intake and CRC and to examine sources of heterogeneity, a meta-analysis of prospective studies was conducted. Thirty-four prospective studies of red meat and CRC were identified, of which 25 represented independent nonoverlapping study populations. Summary relative risk estimates (SRREs) for high versus low intake and dose–response relationships were calculated. In the high versus low intake meta-analysis, the SRRE was 1.12 (95% CI: 1.04–1.21) with significant heterogeneity (*P*=0.014). Summary associations were modified by tumor site and sex. The SRREs for colon cancer and rectal cancer were 1.11 (95% CI: 1.03–1.19) and 1.19 (95% CI: 0.97–1.46), respectively. The SRREs among men and women were 1.21 (95% CI: 1.04–1.42) and 1.01 (95% CI: 0.87–1.17), respectively. The available epidemiologic data are not sufficient to support an independent and unequivocal positive association between red meat intake and CRC. This conclusion is based on summary associations that are weak in magnitude, heterogeneity across studies, inconsistent patterns of associations across the subgroup analyses, and the likely influence of confounding by other dietary and lifestyle factors. *European Journal of Cancer Prevention* 20:293–307 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.

European Journal of Cancer Prevention 2011, **20**:293–307

Keywords: cancer, diet, epidemiology, meta-analysis, nutrition

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Received 12 November 2010 **Accepted** 12 February 2011

Introduction

The colon and rectum are involved physiologically and anatomically in food digestion, absorption, and elimination. As such, the role of diet as a contributing factor in colorectal cancer (CRC) development has been examined in hundreds of scientific studies. Some researchers have speculated that in western cultures, dietary factors may contribute to up to 50% of new CRC cases (Kune *et al.*, 1992; Willett, 2001); however, there is controversy regarding the specific nutrients, individual foods, or food combinations thought to contribute to CRC. A prominent source of this controversy has been variability in the results of epidemiologic studies examining CRC and a variety of 'exposures', including dietary patterns, broad food groups, individual food items, and micronutrients. Furthermore, tumors arising in the proximal colon, distal colon, and rectum may have variable pathologies, and consequently, dietary factors may influence colorectal neoplasia differently according to anatomic site (Jacobs *et al.*, 2007).

Debates about the potential role of red meat consumption in colorectal carcinogenesis have been especially pronounced [World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR), 1997; Truswell, 2002; Gonzalez and Riboli, 2006; Baghurst, 2007; World Cancer Research Fund (WCRF)/American Institute for Cancer Research, 2007; Boyle *et al.*, 2008; Huxley *et al.*, 2009; Truswell, 2009; McAfee *et al.*, 2010]. For example, the World Cancer Research Fund (WCRF) in collaboration with the American Institute for Cancer Research (AICR) judged that red meat is a convincing cause of CRC in a report published in 2007 [World Cancer Research Fund (WCRF)/ American Institute for Cancer Research, 2007]. This conclusion has been challenged on several scientific and methodological grounds including the lack of consistency in observed associations between red meat consumption and CRC (Boyle *et al.*, 2008; Truswell, 2009; Alexander and Cushing, 2010).

One approach to partially resolving controversies, with issues of consistency at their core, is to perform a meta-analysis, which synthesizes available epidemiologic data across studies and is widely recognized as a way to assess the consistency of associations and sources of heterogeneity (Weed, 2000). Three previous meta-analyses have been conducted which examined red meat consumption and CRC. Each successive publication has contributed additional information, in terms of the volume of data and the diversity of analyses. Two of the meta-analyses (Sandhu *et al.*, 2001; Norat *et al.*, 2002) included data from articles published through 1999, and one included prospective studies published through March, 2006 (Larsson and Wolk, 2006).

0959-8278 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins DOI: 10.1097/CEJ.0b013e328345f985

Since the publication of these meta-analyses, some large prospective studies of red meat and CRC have been published. In addition, several previous studies have been identified that reported data for individual red meat items that were not included in earlier meta-analyses. Therefore, to update the state-of-knowledge on the epidemiology of red meat and CRC, we conducted a meta-analysis of data from all available prospective studies. Our goals were to: (i) estimate summary associations for high red meat intake compared with low intake, (ii) examine potential sources of heterogeneity among subgroups, such as sex or anatomic tumor site, (iii) estimate dose–response associations, (iv) conduct sensitivity analyses based on relevant characteristics, (v) estimate the relative influence of each study, and (vi) examine the potential for publication bias.

Methods

Literature search and study inclusion

We conducted a MEDLINE literature search to identify articles on red meat and CRC published through June 2009 which were eligible for review. In addition, we examined the bibliographies of the WCRF/AICR report on diet and cancer [World Cancer Research Fund (WCRF)/American Institute for Cancer Research, 2007], review articles, and meta-analyses pertaining to red meat consumption and CRC in an effort to identify all available literature that may not have been identified by our database searches. All data considered for inclusion in our meta-analysis originated from peer-reviewed published articles written in English.

Peer-reviewed prospective cohort studies (including nested case–control studies) that reported results for the association between red meat consumption and CRC were included in the meta-analysis. Studies that reported data for a broad classification of meat, such as 'total meat' categories, which included poultry or fish, were excluded. Studies that reported information pertaining to processed meat intake [published previously (Alexander *et al.*, 2010)], constituents of red meat, such as fat or protein from animal sources [published elsewhere (Alexander *et al.*, 2009)], heterocyclic amine exposure, cooking practices, or adenomatous polyps were obtained but these analyses were beyond the scope of the present assessment. A total of 33 (Willett *et al.*, 1990; Thun *et al.*, 1992; Bostick *et al.*, 1994; Giovannucci *et al.*, 1994; Gaard *et al.*, 1996; Kato *et al.*, 1997; Chen *et al.*, 1998; Hsing *et al.*, 1998; Sellers *et al.*, 1998; Singh and Fraser, 1998; Fraser, 1999; Pietinen *et al.*, 1999; Jarvinen *et al.*, 2001; Tiemersma *et al.*, 2002; Chen *et al.*, 2003; Flood *et al.*, 2003; English *et al.*, 2004; Khan *et al.*, 2004; Kojima *et al.*, 2004; Lin *et al.*, 2004; Wei *et al.*, 2004; Wu *et al.*, 2004; Brink *et al.*, 2005; Chan *et al.*, 2005; Chao *et al.*, 2005; Luchtenborg *et al.*, 2005; Norat *et al.*, 2005; Larsson *et al.*, 2005a; Oba *et al.*, 2006; Sato *et al.*, 2006; Cross *et al.*, 2007; Kabat *et al.*, 2007; Lee *et al.*, 2009) cohort studies were included in this assessment (Appendix 1), of which, 23 (Bostick *et al.*, 1994; Kato *et al.*, 1997; Chen *et al.*, 1998; Hsing *et al.*, 1998; Singh and Fraser, 1998; Pietinen *et al.*, 1999; Jarvinen *et al.*, 2001; Tiemersma *et al.*, 2002; Chen *et al.*, 2003; Flood *et al.*, 2003; English *et al.*, 2004; Khan *et al.*, 2004; Kojima *et al.*, 2004; Wei *et al.*, 2004; Brink *et al.*, 2005; Chao *et al.*, 2005; Norat *et al.*, 2005; Oba *et al.*, 2006; Sato *et al.*, 2006; Cross *et al.*, 2007; Kabat *et al.*, 2007; Lee *et al.*, 2009; Nothlings *et al.*, 2009) studies represented independent (nonoverlapping) study populations and reported data that could be analyzed in the quantitative assessment.

Data extraction and statistical analysis

Qualitative information (e.g. location of study, dietary assessment) and quantitative data (e.g. relative risks, exposed cases per strata) were extracted from each study that met the criteria for inclusion. In addition, information for red meat dietary variables and how these variables were defined was extracted. Red meat is commonly defined as beef, pork, lamb, or a combination thereof [Warriss, 2000; World Cancer Research Fund (WCRF)/American Institute for Cancer Research, 2007]. Similarly, in the WCRF/AICR report on diet and cancer, red meat included beef, pork, lamb, and goat from domesticated animals [World Cancer Research Fund (WCRF)/American Institute for Cancer Research, 2007]. However, the definitions of red meat varied across studies; whereas some studies explicitly defined red meat as an intake variable, other studies reported no description. Most studies reported data for variables labeled as 'red meat' and some studies reported data for individual meat items, such as beef or pork. The definitions of red meat in the studies included in this review may have included some processed red meat items.

A thorough review of each article was conducted to identify cohorts that may have been analyzed in multiple publications. For example, Wei *et al.* (2004) analyzed two cohorts, the Nurses' Health Study (women) and the Health Professionals Follow-up Study (men), and data from this publication were used in our overall analyses and sex-specific analyses. Other publications of these cohorts were not used in our primary analyses because they had shorter follow-up (Willett *et al.*, 1990; Giovannucci *et al.*, 1994), analyzed a smaller study population (Chan *et al.*, 2005), or analyzed dietary patterns (Wu *et al.*, 2004). Both Singh and Fraser (1998) and Fraser (1999) analyzed data from the Seventh-Day Adventist Study; however, the number of exposed cases and the statistical adjustments were not reported by Fraser. Thus, results from Singh and Fraser (1998) were used in the meta-analysis. Luchtenborg *et al.* (2005) and Brink *et al.* (2005) analyzed data from the Netherlands Cohort Study and similar results were reported in both publications, although Brink *et al.* (2005) analyzed a slightly larger number of cases and was therefore used in our meta-analysis. Two publications (Bostick *et al.*, 1994; Sellers *et al.*, 1998) of the Iowa

Women's Health Study were identified with study population overlap, thus, we analyzed data from Bostick *et al.* (1994) because the researchers adjusted for a greater number of potential confounding factors and Sellers *et al.* (1998) reported results only for stratified groups based on family history of colon cancer, with no overall results presented. Red meat results from the Cancer Prevention Study II were reported by Thun *et al.* (1992); however, only the direction of the association was reported in the text (e.g. inverse or positive), with no specific values, and thus could not be included in the meta-analysis.

Statistical analyses were based on comparisons of the highest intake category with the lowest intake category (which may include persons who do not consume red meat). In addition, categorical dose–response analyses using the method proposed by Greenland and Longnecker (1992) (Berlin *et al.*, 1993) were conducted to estimate the slopes (β coefficients) from the correlated natural log of the relative risks across intake strata. In the absence of strata-specific information, we used variance-weighted least squares regression to estimate the slope for studies. We did not attempt to rescale consumption data across studies because this may introduce another dimension of measurement error. Thus, we created dose–response meta-analysis models for studies that reported results in grams per day units or times (or servings) per week units. In the study by English *et al.* (2004), the hazard ratio for an increase of one serving of red meat per week was reported, thus we used these data rather than recalculating the dose based on their categorical data. Three studies (Kato *et al.*, 1997; Chen *et al.*, 2003; Khan *et al.*, 2004) did not provide enough information to be included in the dose–response meta-analyses.

Random-effects models were used to calculate summary relative risk estimates (SRREs), 95% confidence intervals (CIs), and corresponding *P* values for heterogeneity. The primary meta-analysis models consisted of data from all cohort studies (men and women combined, colon and rectal cancer outcomes), and separate models by sex and anatomic tumor site, as well as sex stratified by tumor site. Additional models included study location, degree of adjustment for confounders, and publication date. If data for men and women or colon and rectum were reported separately in a study, the point estimates and CIs for each sex or each tumor site were included. The presence of publication bias for studies of red meat and CRC was assessed visually by examining a funnel plot measuring the standard error as a function of effect size, as well as performing Egger's regression method and the Duval and Tweedie imputation method (Rothstein *et al.*, 2005). All statistical analyses were performed by using STATA (version 10.0; StataCorp, College Station, Texas, USA) STATA [10.0] (2008) and Comprehensive Meta-Analysis (version 2.2.046; Biostat, Englewood, New Jersey, USA) (Comprehensive Meta-Analysis).

Results

The characteristics of all studies included in this assessment are reported in Appendix 1.

High versus low intake

The SRRE for all 25 prospective studies of red meat and CRC was 1.12 (95% CI: 1.04–1.21), although the *P* value for heterogeneity was statistically significant (0.014; Table 1, Fig. 1). When restricting the analysis to studies that adjusted simultaneously for at least three factors [out of: total energy, body mass index (BMI), physical activity, alcohol, family history of cancer, education, income (socioeconomic status)], the summary association was attenuated (SRRE = 1.08, 95% CI: 0.99–1.18; *P* heterogeneity = 0.003; Table 1) based on data from 16 studies. The summary association was modified by publication date, as a stronger effect was observed among the studies published before the year 2000 (SRRE = 1.30, 95% CI: 1.06–1.59) compared with studies published after this date (SRRE = 1.12, 95% CI: 1.03–1.22). An SRRE of 1.19 (95% CI: 1.06–1.32) was found in the analysis of studies conducted in North America, whereas nonsignificant summary effect sizes of 1.07, 1.09, and 1.00 were observed in analyses of studies conducted in all other countries, Europe, and Asia, respectively. Removal of data from the study by Khan *et al.* (2004) (red meat variable not explicitly stated) and Chen *et al.* (2003); (univariate value for pork only; yes vs. no intake) attenuated the summary association slightly (SRRE = 1.11, 95% CI: 1.03–1.21; data not tabulated).

Fifteen studies reported data specifically for colon cancer, resulting in an SRRE of 1.11 (95% CI: 1.03–1.19; *P* value for heterogeneity = 0.792; Table 1). Restricting the analysis to the 11 studies that reported results for red meat that were more fully adjusted, the summary effect changed slightly (SRRE = 1.10, 95% CI: 1.03–1.18). Summary associations were modestly stronger in magnitude and more heterogeneous for rectal cancer. The SRRE for the 12 studies that reported data for red meat and rectal cancer was 1.19 (95% CI: 0.97–1.46) with significant heterogeneity (*P* heterogeneity = 0.002). Ten studies adjusted simultaneously for at least three of the aforementioned factors, resulting in an attenuated SRRE of 1.12 (95% CI: 0.91–1.39) for rectal cancer (Table 1).

Summary associations were modified by sex, with stronger effects observed among men compared with women. No association between red meat intake and CRC was observed among women (SRRE = 1.01, 95% CI: 0.87–1.17; *P* heterogeneity = 0.083), based on meta-analysis of 13 prospective studies (Table 1, Fig. 2). When restricting the analysis to the more fully adjusted data, the summary effect became 0.98 (95% CI: 0.82–1.17), based on nine studies (Table 1). Nonsignificant inverse associations were found in the analyses of studies that reported data specifically for colon cancer (SRRE = 0.95,

Table 1 Summary of meta-analysis results for red meat intake and colorectal cancer

Model (number of studies)	SRRE	95% CI	*P* value for heterogeneity	Analytical notes
All studies (*n*=25)	1.12	1.04–1.21	0.014	Includes men and women, colon and rectal tumor sites
Adjusted for three factors (*n*=16)	1.08	0.99–1.18	0.003	Includes only studies that reported adjusting simultaneously for at least three of the following factors: total energy, BMI, physical activity, alcohol, family history of cancer, education, income (SES)
Dose–response: each incremental serving per week (*n*=10)	1.02	1.00–1.04	0.075	Studies that reported data in a servings per week metric
Dose–response: each 70 g increment (*n*=13)	1.05	0.97–1.13	<0.001	Studies that reported data in a grams per day metric
Dose–response: each 70 g increment (*n*=13)	1.09	1.00–1.18	<0.001	Studies that reported data in a grams per day metric (processed meat included with red meat from Pietinen *et al*., 1999)
Colon (*n*=15)	1.11	1.03–1.19	0.792	Includes data reported specifically for colon cancer, men and women included
Colon, adjusted for three factors (*n*=11)	1.10	1.03–1.18	0.625	Includes only studies that reported adjusting simultaneously for at least three of the following factors: total energy, BMI, physical activity, alcohol, family history of cancer, education, income (SES)
Rectal (*n*=12)	1.19	0.97–1.46	0.002	Includes data reported specifically for rectal cancer, men and women included
Rectal, adjusted for three factors (*n*=10)	1.12	0.91–1.39	0.003	Includes only studies that reported adjusting simultaneously for at least three of the following factors: total energy, BMI, physical activity, alcohol, family history of cancer, education, income (SES)
Studies published <2000 (*n*=8)	1.30	1.06–1.59	0.230	Includes only studies published before year 2000 (Willett *et al*., 1990; Giovannucci *et al*., 1994 replaces Wei *et al*., 2004)
Studies published >2000 (*n*=19)	1.12	1.03–1.22	0.009	Includes studies published after 2000
North America (US and Canada; *n*=12)	1.19	1.06–1.32	0.057	Studies conducted among the US or Canadian populations
All other countries (*n*=13)	1.07	0.96–1.19	0.100	Studies conducted in Europe, Japan, China, Australia
Europe (*n*=6)	1.09	0.94–1.27	0.132	Studies conducted in Finland, the Netherlands, Sweden, and other countries (EPIC)
Asia (*n*=6)	1.00	0.86–1.16	0.383	Studies conducted in Japan and China
Men (*n*=9)	1.21	1.04–1.42	0.472	Studies that reported data specifically for men
Men, adjusted for three factors (*n*=5)	1.14	0.96–1.36	0.645	Includes only studies that reported adjusting simultaneously for at least three of the following factors: total energy, BMI, physical activity, alcohol, family history of cancer, education, income (SES)
Men, colon (*n*=4)	1.24	1.00–1.54	0.854	Studies that reported data for colon cancer among men
Men, rectal (*n*=2)	1.16	0.76–1.75	0.586	Studies that reported data for rectal cancer among men
Dose–response: each incremental serving per week (*n*=5)	1.04	1.01–1.06	0.511	Studies that reported data in a servings per week metric
Dose–response: each 70 g increment (*n*=3)	1.01	0.77–1.33	0.021	Studies that reported data in a grams per day metric
Dose–response: each 70 g increment (*n*=3)	1.29	1.04–1.60	0.013	Studies that reported data in a grams per day metric (processed meat included red meat from Pietinen *et al*., 1999)
Women (*n*=13)	1.01	0.87–1.17	0.083	Studies that reported data specifically for women
Women, adjusted for three factors (*n*=9)	0.98	0.82–1.17	0.022	Includes only studies that reported adjusting simultaneously for at least three of the following factors: total energy, BMI, physical activity, alcohol, family history of cancer, education, income (SES)
Women, colon (*n*=7)	0.95	0.81–1.12	0.901	Studies that reported data for colon cancer among women
Women, rectal (*n*=5)	0.95	0.55–1.66	0.008	Studies that reported data for rectal cancer among women
Dose–response: each incremental serving per week (*n*=6)	1.00	0.97–1.03	0.135	Studies that reported data in a servings per week metric
Dose–response: each 70 g increment (*n*=6)	1.00	0.82–1.21	<0.001	Studies that reported data in a grams per day metric

BMI, body mass index; CI, confidence interval; EPIC, European Prospective Investigation into Cancer and Nutrition; SRRE, summary relative risk estimate.

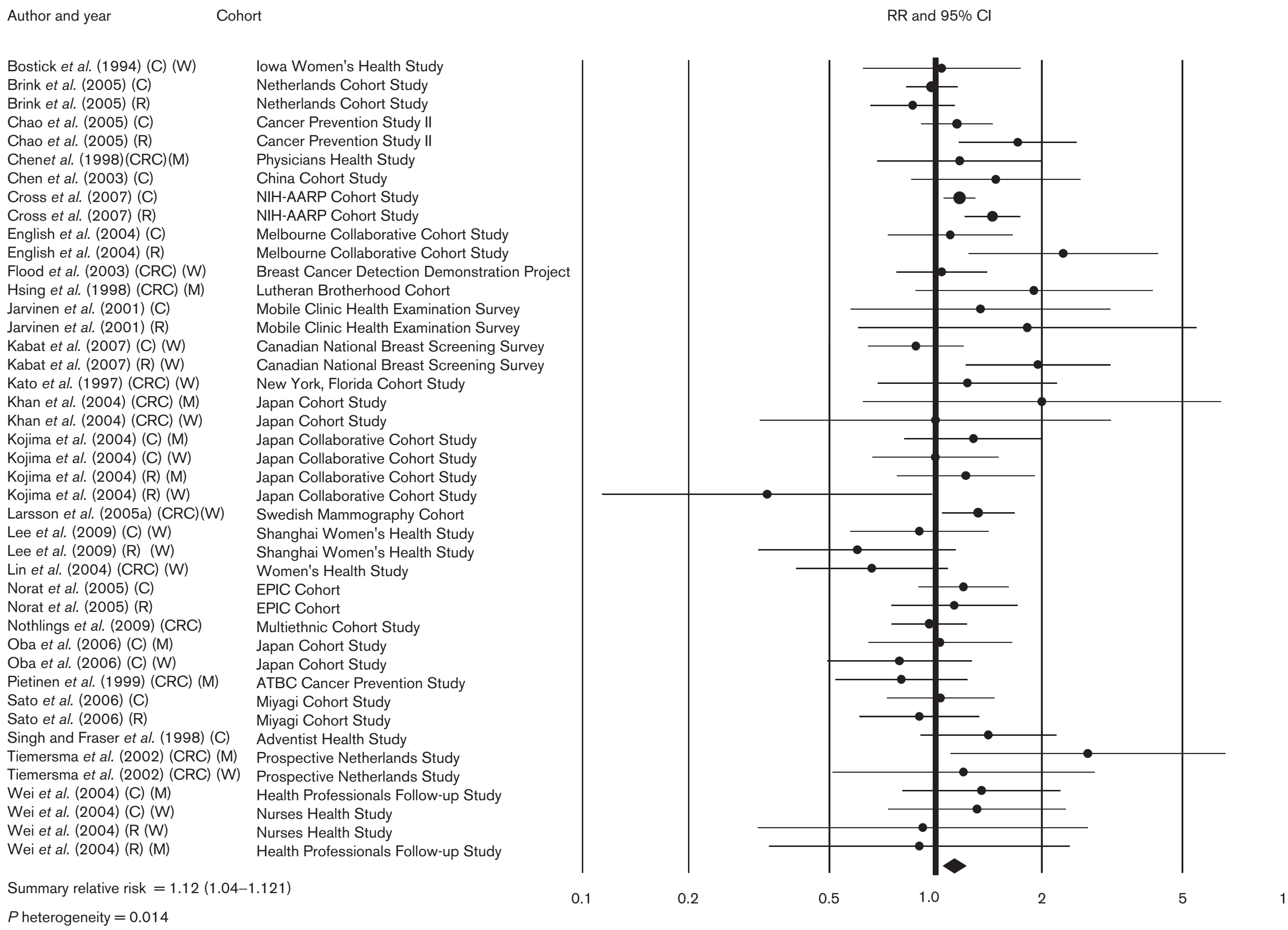
95% CI: 0.81–1.12) or rectal cancer (SRRE = 0.95, 95% CI: 0.55–1.66) among women.

In contrast to the summary results for women, the SRRE for CRC among men was 1.21 (95% CI: 1.04–1.42) and statistically significant, based on data from nine studies (Table 1, Fig. 3). However, after removal of the studies that did not adjust simultaneously for the potential confounding factors referenced above, the SRRE became 1.14 and was no longer statistically significant (95% CI: 0.96–1.36). The summary associations specifically for colon cancer and for rectal cancer among men were 1.24 (95% CI: 1.00–1.54) and 1.16 (95% CI: 0.76–1.75) but were based on data from only four and two studies, respectively.

Dose–response

For the 10 studies that reported red meat intake data in a servings metric, the SRRE for each incremental serving per week was 1.02 (95% CI: 1.00–1.04; *P* heterogeneity = 0.075) among men and women combined (Table 1). For the 13 studies that reported intake data in grams per day format, the SRRE for each 70-g increment of red meat was 1.05 (95% CI: 0.97–1.13) among men and women. No associations for each incremental serving per week (SRRE = 1.00, 95% CI: 0.97–1.03) or for each 70-g increment of red meat (SRRE = 1.00, 95% CI: 0.82–1.21) and CRC were observed in the dose–response analyses among women. For men, the SRRE for each incremental serving of red meat per week was 1.04 (95% CI: 1.01–1.06,

Fig. 1



Meta-analysis of prospective studies of red meat intake and colorectal cancer. C, colon; CRC, colorectal; M, men; R, rectal; W, women.

P heterogeneity = 0.511) in the dose–response analysis of five studies. Three studies reported intake data in grams per day format among men, resulting in an SRRE of 1.01 (95% CI: 0.77–1.33) for each 70-g increment of red meat.

Publication bias

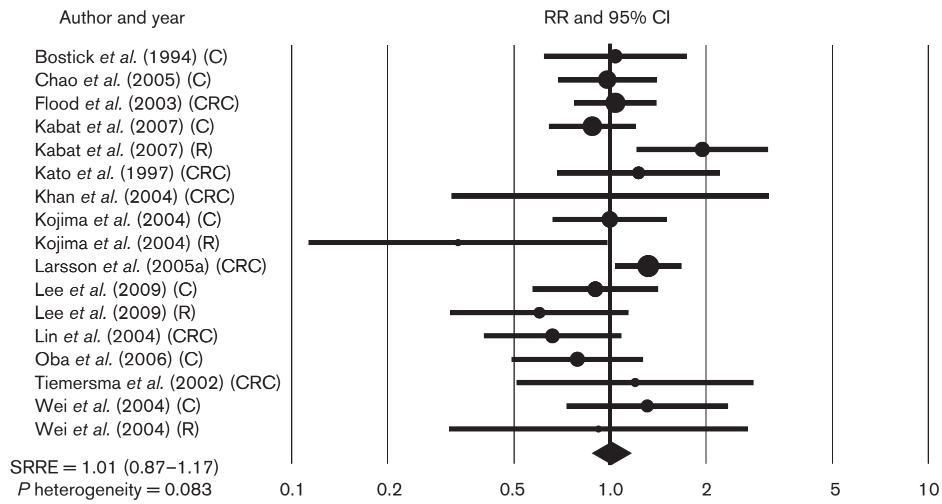
An assessment of the funnel plot of prospective studies of red meat and CRC suggested slight publication bias (Appendix 2). The Duval and Tweedie trim and fill procedure imputed one study to the left of the mean effect, resulting in an adjusted SRRE of 1.11 (95% CI: 1.03–1.21). Egger's regression test was not significant, however ($P = 0.97$; data not tabulated).

Discussion

The basic causal question 'Does dietary intake of red meat have an independent effect on CRC incidence (or mortality)?' is complex, involving biological mechanisms, genetic variation in metabolizing enzymes, food definitions, intake measurement, outcome classifications, statistical testing, colinearity of red meat intake with other food items, and many lifestyle and behavioral characteristics. By itself, meta-analysis can provide important insights into some (but certainly not all) aspects of causation. Prime among these is the capacity of meta-analysis to better characterize the existence and nature of associations summarized across studies. In essence, meta-analysis provides an assessment of the consistency of associations and sources of heterogeneity that may preclude summarization. Meta-analysis also improves the precision of summary estimates of effect, which is especially important when attempting to demonstrate patterns of associations across subgroups.

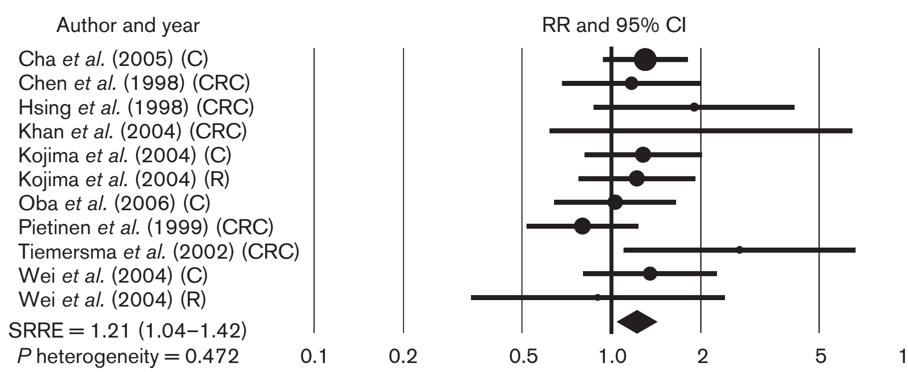
In our analysis, most summary associations were weakly elevated above 1.0, and some were statistically significant, for example among men. Heterogeneity was present in several meta-analysis models, and subgroup analyses were not able to explain all possible sources of between-study variability. Summary associations were modified by sex and by tumor site, with stronger effect sizes for men than women and for colon than rectal tumors. The reason for these differences in summary effects is unclear;

Fig. 2



Meta-analysis of prospective studies of red meat and colorectal cancer among women. C, colon; CRC, colorectal; R, rectal; RR, relative risk; SRRE, summary relative risk estimate.

Fig. 3



Meta-analysis of prospective studies of red meat and colorectal cancer among men. C, colon; CRC, colorectal; R, rectal; RR, relative risk; SRRE, summary relative risk estimate.

however, the disparity in associations by sex does not appear to be the result of higher intake levels among men, nor are there any established biological differences that may have modified associations specifically for red meat intake. However, diet-related effects may differ by sex due to hormonal variation between men and women and by the proclivity of women to develop proximal tumors and men to develop distal and rectal tumors (Jacobs *et al.*, 2007).

As noted above, three earlier meta-analyses of red meat intake and CRC have examined a small subset of similar studies (Sandhu *et al.*, 2001; Norat *et al.*, 2002; Larsson and Wolk, 2006). Two reported summary data for high versus low red meat intake among prospective studies, with similar results. Specifically, Norat *et al.* (2002) reported a summary association of 1.27 (95% CI: 1.11–1.45) in a meta-analysis of nine cohort studies, and Larsson and Wolk (2006) reported a summary association of 1.28 (95% CI: 1.15–1.42) across 14 cohort studies. In both analyses, summary associations were markedly variable by sex and anatomic tumor site, with stronger associations observed among men than women and for colon cancer than rectal cancer. All three studies reported summary associations ranging between 1.13 and 1.28 for each increment of 100–120 g of red meat per day. However, incremental daily intake of 100–120 g/day of red meat is well above the current average daily intake of red meat (i.e. 60–70 g) across the general population [Cotton *et al.*, 2004; US Department of Agriculture (USDA), 2009].

Interpretation of summary associations is complicated by methodological and analytical variation across studies. A universal definition of red meat is not recognized and dietary patterns and food item availability varies across populations. Indeed, summary associations were stronger in magnitude for the studies conducted among North American populations compared with analyses conducted in Europe and Asia (Table 1). The reason(s) for the differences in summary effects are unknown, although variability in dietary practices, lifestyle factors, or behavioral characteristics may be contributory. Red meat as a dietary component and analytical variable may include an array of meat types and disparate distributions of consumption within the construct of the 'red meat' variable. For example, in one study, red meat was defined as beef, pork, or lamb as a main dish (Wei *et al.*, 2004), whereas in another study, beef and pork were included with a variety of processed red meat items (Chao *et al.*, 2005), and in yet another study, red meat was not defined (Jarvinen *et al.*, 2001). In addition, the dietary instruments, (e.g. 33 item Food Frequency Questionnaire, 169 item Food Frequency Questionnaire), the analytical cut-points of intake groups (e.g. 203 + vs. < 80 g/day; 56.6 + vs. < 18.7 g/day), and the types of exposure metrics (e.g. servings per month, times per day, grams per day, unspecified quintiles of intake) are variable across studies. Misclassification of intake may bias the summary associations toward or away from the null value.

Summary associations should be interpreted in light of potential confounding. Indeed, associations for men and women combined, men only, women only, and rectal cancer were attenuated (i.e. closer to the null) after restricting analyses to studies that adjusted simultaneously for at least three potentially important covariates (i.e. total energy, BMI, physical activity, alcohol intake, family history of cancer, and education). Although the subgroup meta-analysis of studies that adjusted for some of these important factors did not have an extreme impact on the overall summary effect, residual confounding or the influence of other unadjusted factors may have affected results. It is well established that the majority of CRCs develop in a stepwise progression from normal epithelium to adenomatous polyps to adenocarcinoma (Willett, 2001), although few studies have adjusted for a history of polyps. Of note, Lin *et al.* (2004) was the only study in the analysis that controlled for a history of polyps (in addition to other important covariates), and the researchers observed a 34% decreased risk of CRC among the highest consumers of red meat. Findings for red meat intake and colorectal adenomas have been inconsistent (Schatzkin *et al.*, 2000; Lanza *et al.*, 2007; Martinez *et al.*, 2007), and a comprehensive evaluation of adenomas is beyond the scope of the current assessment.

Although red meat intake has been associated positively with CRC in many epidemiologic investigations, findings from studies that have evaluated postulated biologically plausible mechanisms (which should be considered when evaluating causation) have been inconsistent in the available scientific literature. It has been hypothesized that cooking meat at high temperatures creates chemical by-products (e.g. heterocyclic amines, polycyclic aromatic hydrocarbons) that may be carcinogenic (Santarelli *et al.*, 2008). Temperature may be considered to be the most important factor in the formation of these chemicals, and high temperature cooking methods, such as frying, may produce heterocyclic amines (HCAs) in the largest quantities. However, an association between cooking methods and specific dietary HCAs and CRC has not been shown consistently in epidemiologic studies. Positive associations with well-cooked meat and fried meat intake reported in some case–control studies (Butler *et al.*, 2003; Lang *et al.*, 1994) have not been substantiated in cohort studies (Gaard *et al.*, 1996; Knekt *et al.*, 1999; Pietinen *et al.*, 1999; Lin *et al.*, 2004). Findings between overall mutagenic activity (i.e. total HCAs) or specific HCAs and CRC are inconsistent, with associations observed above and below 1.0 (Augustsson *et al.*, 1999; Le Marchand *et al.*, 2002; Nowell *et al.*, 2002; Butler *et al.*, 2003; Murtaugh *et al.*, 2004).

Other postulated mechanisms between correlates of red meat intake and CRC involve heme iron, which is found in meat as a natural part of hemoglobin and myoglobin (Sinha *et al.*, 2005), and N-nitroso compounds (mainly in processed meat items), formed from nitrosating agents arising from nitrites under acidic gastric conditions that react with amines or amides [Warriss, 2000; World Cancer Research Fund (WCRF)/American Institute for Cancer Research, 2007; Santarelli *et al.*, 2008]. Although red meat is a primary source of heme iron, very few epidemiologic studies have investigated the potential role that this factor may play in CRC risk, and findings have been variable by tumor location (Lee *et al.*, 2004; Larsson *et al.*, 2005b; Balder *et al.*, 2006; Kabat *et al.*, 2007). Fat intake from animal sources has also been hypothesized to increase the risk of CRC; however, in a 2009 meta-analysis, no statistically significant association was observed between animal fat intake and CRC among prospective studies (SRRE = 1.04, 95% CI: 0.83–1.31 Alexander *et al*, 2009). In addition, recent experimental evidence has suggested that conjugated linoleic acid, a naturally occurring *trans* fat commonly found in ruminant animal foods such as beef, lamb, and dairy products, and stearic acid, a predominant saturated fat in beef, may have anticarcinogenic properties (Bhattacharya *et al.*, 2006; Evans *et al.*, 2009a, 2009b). However, evidence from human studies is limited.

In light of the many issues discussed in this study, it may be helpful to briefly reexamine the WCRF/AICR conclusion on red meat and CRC, recognizing that a complete causal assessment was beyond the scope of this study. Several methodological and analytical issues, such as excluding data from key studies, inconsistencies in data extraction, and misreporting of risk estimates were identified through a review of their dose–response analyses (Alexander, 2009; Truswell, 2009). In an editorial regarding the WCRF/AICR report, doubt was cast on the 'convincing' classification for red meat because of strong previous conclusions for other dietary factors (e.g. fruits and vegetables) and cancer that were not supported by more recently published prospective studies (i.e. they did not substantiate earlier associations; Boyle *et al.*, 2008). The results of our meta-analysis support this critical assessment of the WCRF/AICR analysis. As noted above, the summary effect among studies published in 2000 onward is more than half the magnitude of the summary effect obtained for studies published befor the year 2000 (i.e. SRRE = 1.12 vs. 1.30 for recent vs. older studies). Indeed, the tendency to overstate early findings, which may be stronger in magnitude, increases the likelihood of downplaying inconsistencies within the data or a lack of concordance between subgroups or other sources of evidence (Boffetta *et al.*, 2008). This issue may be especially pronounced in nutritional epidemiology because most associations tend to hover around the null value, making it difficult to parse out modest differences in effects within and between studies.

Summary

Summary associations between red meat consumption and CRC have been in the positive direction when men and women have been analyzed together, but overall, associations have been relatively weak in magnitude, heterogeneity was evident in the majority of models, and most results from individual studies have not been statistically significant. There are some apparent differences in the patterns of associations by sex; in fact, associations from some of the largest and most well-conducted cohort studies have been null or inverse among women. Therefore, based on the currently available data, consumption of red meat does not appear to play a role in the development of CRC among women, although additional research should focus on associations by menopausal status. Patterns of associations have been modestly stronger in magnitude among men; however, the variability in associations by sex has not been explained by level of intake, or biological or hormonal mechanisms. Associations also vary by anatomic tumor site, with associations being slightly stronger for rectal cancer than colon cancer. Variation of methodological and analytical characteristics, such as heterogeneity in meat definitions, dietary measurements used, analytical comparisons in terms of variability in intake cut-points, and the likelihood for residual confounding or bias complicates the interpretation of results across studies. In addition, a dietary pattern characterized by high intake of red meat has been correlated positively with factors that have been associated with increasing the risk of CRC, such as a high BMI, smoking, and alcohol intake, and red meat intake has been correlated inversely with factors suggested as possibly decreasing the risk of CRC, such as physical activity, fruit and vegetable intake, and socioeconomic status. Thus, this colinearity of factors complicates the interpretation of studies of red meat and CRC. As a result of this methodological and analytical variability, the currently available epidemiologic evidence is not sufficient to support an independent positive association between red meat consumption and CRC.

Disentangling the potential effects of dietary factors, such as red meat intake, and risk of CRC is a methodologically challenging undertaking, and there are many unanswered scientific questions. Additional research involving better characterization of meat correlates and by-products from cooking meat, refinement in the methodology to parse out the individual effects of red meat from an overall dietary and lifestyle pattern, and further evaluation of associations among certain subgroups, such as analyses of men and women stratified by tumor location, may help in elucidating the relationship between red meat consumption and CRC.

Acknowledgements

This study was partially funded by the Beef Checkoff, through the National Cattlemen's Beef Association and the National Pork Board; however, National Cattlemen's Beef Association/National Pork Board did not contribute to the writing, analysis, or interpretation of research findings. All data analyzed in this study were extracted from peer-reviewed publications.

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Appendix

Appendix 1 Summary of prospective studies of red meat intake and colorectal cancer

References	Cohort	Analytical category (definition)	Number of exposed cases	Sex	Analytical comparison	Relative risk (95% CI)	Statistical adjustment
Bostick *et al.* (1994)	Iowa Women's Health Study	Red meat	37	Women	Colon: >11.0 vs. <4.0 servings/week	1.04 (0.62–1.76)	Age, total energy intake, alcohol, height, parity, total vitamin E intake, total vitamin E intake by age interaction term, and vitamin A supplement intake
Brink *et al.* (2005)[a]	Netherlands Cohort study				Quartiles of intake (4 vs. 1)		Age, sex, quetelet index, smoking, energy intake, family history of CRC
		Beef	142	Both	Colon	1.28 (0.96–1.72)	
			40	Both	Rectum	0.92 (0.57–1.49)	
		Pork	98	Both	Colon	0.77 (0.57–1.04)	
			34	Both	Rectum	0.70 (0.43–1.13)	
		Minced meat	97	Both	Colon	0.93 (0.68–1.27)	
			35	Both	Rectum	1.01 (0.62–1.67)	
Chan *et al.* (2005)[b] (overlap with Wei *et al.*, 2004)	NHS (US)	Beef, pork, or lamb as a main dish	17	Women	>0.5 vs. ≤ 0.5 servings/day	1.21 (0.85–1.72)	Age, BMI, family history of CRC, postmenopausal hormone use, previous endoscopy, current multivitamin use, regular aspirin use
Chao *et al.* (2005)	CPS II (US)	Red meat (beef, pork, ham, liver, smoked meats, frankfurters, sausage, fried bacon, fried hamburger)			Quintiles of intake (5 vs. 1)		Age, sex, total energy, education, BMI, smoking, recreational physical activity, multivitamin use, aspirin use, alcohol, hormone therapy, fruits, vegetables, high-grain foods
			210	Both	Colon	1.15 (0.90–1.46)	
			96	Both	Rectal	1.71 (1.15–2.52)	
			116	Both	Proximal colon	1.27 (0.91–1.76)	
			64	Both	Distal colon	0.71 (0.47–1.07)	
			124	Men	Colon	1.30 (0.93–1.81)	Age, total energy, education, BMI, smoking, recreational physical activity, multivitamin use, aspirin use, alcohol, hormone therapy, sex, fruits, vegetables, high-grain foods
			86	Women	Colon	0.98 (0.68–1.40)	
Chen *et al.* (2003)[b]	China	Pork	NR	Both	Colon: pork eating, yes vs. no	1.48 (0.85–2.59)	Matched on age, sex, resident location
Chen *et al.* (1998)	Physicians Health Study (US)	Red meat (beef, pork, lamb as a main dish, mixed dish, or sandwich; hot dogs)	43	Men	1+ intake/day vs. ≤ 0.5	1.17 (0.68–2.02)	BMI, physical activity, and alcohol
Cross *et al.* (2007)	NIH-AARP Diet and Health Study (US)	Red meat (beef, pork, and lamb; including bacon, beef, cold cuts, ham, hamburger, hot dogs, liver, pork, sausage, and steak; meats added to mixtures, such as pizza, chili, lasagna, and stew)			Quintiles of intake: 5 vs. 1 62.7 g/1000 kcal vs. 9.8		Age, sex, education, marital status, family history of cancer, race, BMI, smoking, frequency of vigorous physical activity, intake of: total energy, alcohol, fruits and vegetables
			1190	Both	Colorectal	1.24 (1.12–1.36)	
				Both	Colon	1.17 (1.05–1.31)	
				Both	Rectal	1.45 (1.20–1.75)	
English *et al.* (2004)	Melbourne Collaborative Cohort Study (Australia)	Fresh red meat (veal or beef schnitzel, roast beef, veal, steak, meat balls, meatloaf, mixed dishes with beef, roast lamb/chops, pork/chops, rabbit, other game)			Quartiles (4 vs. 1)		Sex, country of birth, energy intake, fat, cereal products
			NR	Both	Colorectal	1.4 (1.0–1.9)	
				Both	Colon	1.1 (0.7–1.6)	
				Both	Rectal	2.3 (1.2–4.2)	
Flood *et al.* (2003)	BCDDP (US)	Red meat (bacon, beef, ham-burger, ham or other lunch meat, hot dogs, liver, pork, sausage; meat components of beef stew, chili, salad, spaghetti, vegetable soup)	NR	Women	Quintile 5 vs. 1: 52.2+ g/1000 kcal vs. ≤ 6.1	1.04 (0.77–1.41)	Energy, total meat (the following factors did not markedly affect the RR, thus, were not in the final model: smoking, education, BMI, alcohol, physical activity, dietary factors, micronutrients, anti-inflammatories)
Fraser (1999) (overlap with Singh and Fraser, 1998)	Seventh Day Adventists Health Study (California)	Red meat	NR	Both	Colon cancer among persons who consumed white meat <1/week: 1+ time/week (red meat) vs. never	1.86 (1.15–3.02)	

Table (*continued*)

References	Cohort	Analytical category (definition)	Number of exposed cases	Sex	Analytical comparison	Relative risk (95% CI)	Statistical adjustment
Gaard *et al.* (1996)[c]	Norway				Colon		Age, attained age
		Meat balls	15	Men	5+/month vs. ≤1	0.61 (0.22–1.69)	
		Meat stews	11	Men	5+/month vs. ≤1	0.74 (0.21–2.64)	
		Meat balls	13	Women	5+/month vs. ≤1	1.08 (0.31–3.79)	
		Meat stews	9	Women	5+/month vs. ≤1	0.58 (0.16–2.13)	
Giovannucci *et al.* (1994) (overlap with Wei *et al.*, 2004]	HPFS (US)	Red meat [beef, pork, or lamb as a main dish, sandwich or mixed dish; hamburger, hot dog, bacon, and preserved meats (e.g. sausage, salami, and bologna)]	55	Men	Colon: 129.5 g/day vs. 18.5	1.71 (1.15–2.55)	Age, total energy intake
		Beef, pork, or lamb as main dish	16	Men	Colon: ≥5 servings/week vs. 0	3.57 (1.58–8.06)	Age
Hsing *et al.* (1998)	Lutheran Brotherhood (US)	Red meat (beef, bacon, fresh pork, smoked ham)			60+ times/month vs. <15		Age, smoking, alcohol, total calories
			14	Men	Colorectal	1.9 (0.9–4.3)	
			13	Men	Colon	1.8 (0.8–4.4)	
Jarvinen *et al.* (2001)	Mobile Clinic Health Exami-nation Survey (Finland)	Red meat			Quartiles of daily intake (4 vs. 1)		Age, sex, BMI, occupation, smoking, geography, energy intake, vegetable and fruit consumption, cereal intake
			NR	Both	Colorectal	1.50 (0.77–2.94)	
				Both	Colon	1.34 (0.57–3.15)	
				Both	Rectal	1.82 (0.60–5.52)	
Kabat *et al.* (2007)	NBSS (Canada)	Red meat (ascertained from 22 meat items including beef, pork, ham, bacon, pork-based lunch meats, veal)			40.3 g/day vs. <14.25		Age, BMI, menopausal status, oral contraception, hormone replacement use, diet (fat, fiber, folic acid, total calories), smoking, alcohol, education, physical activity
			NR	Women	Colorectal	1.12 (0.86–1.46)	
				Women	Colon	0.88 (0.64–1.21)	
				Women	Rectal	1.95 (1.21–3.16)	
Kato *et al.* (1997)	New York, Florida	Red meat	NR	Women	Quartiles of intake (4 vs. 1)	1.23 (0.68–2.22)	Age, total calorie intake, education, enrollment place
Khan *et al.* (2004)	Japan	Meat, except chicken (pork, beef, mutton, liver, ham, sausages)	NR	Men	Several times/week; everyday vs. never; several times/year; several times/month	2.0 (0.6–6.3)	Age, smoking
			NR	Women	Several times/week; everyday vs. never; several times/year; several times/month	1.0 (0.3–3.0)	Age, health status, health education, health screening and smoking
Kojima *et al.* (2004)	Collaborative Cohort Study (Japan)				3–7/week vs. 0–2/month		Age, family history of CRC, BMI, alcohol, smoking, walking per day, education, regions of enrollment
		Beef	11	Men	Colon	1.46 (0.74–2.86)	
			10	Men	Rectal	1.38 (0.68–2.78)	
		Pork	17	Men	Colon	1.14 (0.61–2.14)	
			20	Men	Rectal	1.11 (0.61–2.03)	
		Beef	11	Women	Colon	1.11 (0.57–2.14)	
			1	Women	Rectal	0.37 (0.05–2.84)	
		Pork	20	Women	Colon	0.93 (0.54–1.60)	
			3	Women	Rectal	0.32 (0.09–1.15)	
Larsson *et al.* (2005a)	Swedish Mammo-graphy Cohort	Red meat (whole beef, chopped meat, minced meat, bacon, hot dogs, ham or other lunch meat, blood pudding, kidney or liver, liver pate)		Women	94+ g/day vs. <50		Age, BMI, education, energy intake, alcohol, saturated fat, calcium, folate, fruits, vegetables, whole grain foods
			NR	Women	Colorectal	1.32 (1.03–1.68)	
				Women	Rectal	1.28 (0.83–1.98)	
				Women	Proximal colon	1.03 (0.67–1.60)	
				Women	Distal colon	2.22 (1.34–3.68)	
		Beef and pork (whole beef, minced meat, chopped beef)		Women	4+ servings/week vs. <2		
			NR	Women	Colorectal	1.22 (0.98–1.53)	
				Women	Rectal	1.08 (0.72–1.62)	
				Women	Proximal colon	1.10 (0.74–1.64)	
				Women	Distal colon	1.99 (1.26–3.14)	

Lee *et al.* (2009)	Shanghai Women's Health Study (China)	Red meat			67+ g/day vs. <24		Age, education, income, survey season, tea consumption, NSAID use, energy intake, and fiber intake
			62	Women	Colorectal	0.8 (0.6–1.1)	
			41	Women	Colon	0.9 (0.6–1.5)	
			21	Women	Rectal	0.6 (0.3–1.1)	
Lin *et al.* (2004)	Women's Health Study (US)	Red meat (beef or lamb as main dish, beef, pork, or lamb in a sandwich, hot dogs, bacon, processed meats, hamburgers)	30	Women	1.42+ servings/day vs. ≤ 0.13	0.66 (0.40–1.09)	Age, random treatment assignment, BMI, family history of CRC, history of polyps, physical activity, smoking, alcohol, postmenopausal hormone therapy, total energy
Luchtenborg *et al.* (2005) [same population as Brink *et al.* (2005)]	NLCS (Netherlands)				Quartiles of intake (4 vs. 1)		Age, sex, family history of CRC, smoking, BMI, energy intake
		Beef	134	Both	Colon	1.29 (0.96–1.73)	
			38	Both	Rectal	0.95 (0.59–1.54)	
		Pork	92	Both	Colon	0.77 (0.57–1.04)	
			31	Both	Rectal	0.70 (0.44–1.13)	
		Minced meat	93	Both	Colon	0.93 (0.68–1.27)	
			33	Both	Rectal	1.01 (0.61–1.66)	
Norat *et al.* (2005)	EPIC (Europe)	Red meat (fresh, minced, and frozen beef, veal, pork, lamb)			≥ 80 g/day vs. <10		Age, sex, energy, height, weight, occupational physical activity, smoking, alcohol intake, dietary fiber, center
			250	Both	Colorectal	1.17 (0.92–1.49)	
			NR	Both	Colon	1.20 (0.88–1.61)	
				Both	Rectal	1.13 (0.74–1.71)	
				Both	Proximal (right) colon	1.18 (0.73–1.91)	
				Both	Distal (left) colon	1.24 (0.80–1.94)	
Nothlings *et al.* (2009)	Multiethnic Cohort Study (Hawaii, Los Angeles County)	Red meat	240	Both	26.0+ g/1000 kcal/day vs. 0–<10.4	0.96 (0.74–1.23)	Age at blood draw, sex, ethnicity, family history of CRC, BMI, physical activity, smoking, intake of dietary fiber, calcium, vitamin D, folic acid, and ethanol
Oba *et al.* (2006)	Japan	Red meat (beef, pork)	32	Men	Colon: 56.6+ g vs. ≤ 18.7	1.03 (0.64–1.66)	Age, height, BMI, smoking, alcohol, physical activity
			27	Women	Colon: 42.3+ g vs. ≤ 10.7	0.79 (0.49–1.28)	
Pietinen *et al.* (1999)	ATBC Study (Finland)	Beef, pork, lamb	45	Men	99+ g vs. <36	0.8 (0.5–1.2)	Age, supplement group, smoking, BMI, alcohol, education, physical activity at work, calcium intake
		Total red meat	45	Men	203 g vs. <80	1.1 (0.7–1.7)	
Sato *et al.* (2006) (Japan)	Miyagi Cohort Study	Beef			1–2/week vs. almost never		Age, sex, smoking, alcohol, BMI, education, family history of cancer, walking, consumption of fat, calcium, fiber
			46	Both	Colorectal	0.93 (0.67–1.30)	
			25	Both	Colon	0.84 (0.54–1.32)	
			21	Both	Rectal	1.01 (0.62–1.67)	
			16	Both	Proximal colon	0.97 (0.55–1.70)	
			8	Both	Distal colon	1.06 (0.46–2.43)	
		Pork (excluding ham or sausage)			3–4/week vs. almost never		
			73	Both	Colorectal	1.13 (0.79–1.74)	
			48	Both	Colon	1.46 (0.81–2.62)	
			26	Both	Rectal	0.74 (0.39–1.42)	
			24	Both	Proximal colon	1.05 (0.50–2.22)	
			16	Both	Distal colon	1.90 (0.63–5.74)	
Sellers *et al.* (1998) (overlap with Bostick *et al.*, 1994)	Iowa Women's Health Study	Red meat (beef, beef stew, hamburger, liver, venison)			Colon >7 servings/week vs. <3.5		Age, energy intake, history of polyps
			16	Women	Family history of colon cancer	1.0 (0.5–2.1)	
			53	Women	No family history of colon cancer	1.3 (0.8–2.0)	
Singh and Fraser (1998)	Adventist Health Study (California)	Red meat (current intake of beef or pork)	45	Both	Colon: 1+/week vs. never	1.41 (0.90–2.21)	Age, sex, BMI, physical activity, smoking, alcohol, aspirin use, parental history of colon cancer
Thun *et al.* (1992)	CPS II (US)	Red meat	NR	Men	Colon	No association (data NR)	Matched on age, race, and sex. Adjusted for total fat, exercise, BMI, family history of colon cancer, aspirin use, intake of vegetables, fruits, and grains
		Beef		Men		Inverse association (data NR)	Matched on age, race, and sex

Table (*continued*)

References	Cohort	Analytical category (definition)	Number of exposed cases	Sex	Analytical comparison	Relative risk (95% CI)	Statistical adjustment
		Pork		Men		Positive association (data NR)	
		Red meat	NR	Women	Colon	No association (data NR)	
		Beef		Women		Inverse association (data NR)	
		Pork		Women		Positive association (data NR)	
Tiemersma *et al.* (2002)[b]	Netherlands	Fresh red meat (beef, pork)	45	Both	5 + /week vs. 0–3/week	1.6 (0.9–2.9)	Age, sex, center, total energy intake, alcohol, body height
			30	Men	5 + /week vs. 0–3/week	2.7 (1.1–6.7)	
			15	Women	5 + /week vs. 0–3/week	1.2 (0.5–2.8)	
Wei *et al.* (2004)	NHS; HPFS (US)	Beef, pork, lamb as a main dish			5 + /week vs. 0		Age, family history, BMI, physical activity, processed meat, alcohol, calcium, folate, height, smoking before the age of 30 years, history of endoscopy, and sex
			155	Both	Colon	1.43 (1.00–2.05)	
			31	Both	Rectum	0.90 (0.47–1.75)	
	HPFS		32	Men	Colon	1.35 (0.80–2.27)	Age, family history, BMI, physical activity, alcohol, calcium, folate, height, smoking before the age of 30 years, history of endoscopy
			7	Men	Rectum	0.90 (0.34–2.45)	
	NHS		123	Women	Colon	1.31 (0.73–2.36)	
			24	Women	Rectum	0.92 (0.31–2.71)	
Willett *et al.* (1990) (overlap with Wei *et al.*, 2004)	NHS (US)	Red meat (beef, pork or lamb as a main dish			134 + g/day vs. <59		
			44	Women	Colon	1.77 (1.09–2.88)	Age and total energy intake
		sandwich or mixed dish, hamburger, hotdogs, preserved meats, and bacon)	44	Women	Colon	1.61 (1.03–2.53)	Age, total energy intake, and chicken and fish consumption
Wu *et al.* (2004) (overlap with Wei *et al.*, 2004)	HPFS (US)	Red meat	NR	Men	Colon: high vs. low	1.40 (0.92–2.13)	Multivariate (not explicitly stated for this analysis)
		Red meat dish (beef, pork lamb as main dish)		Men	Colon: high vs. low	1.68 (1.21–2.33)	

Outcome is colorectal cancer, unless otherwise noted.

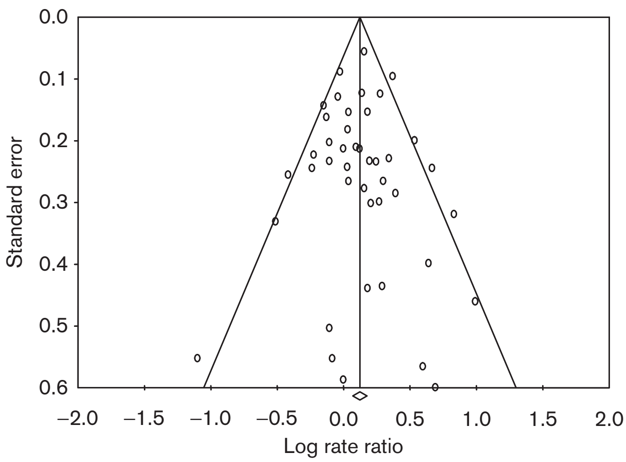
ATBC, α-tocopherol, β-carotene cancer prevention; BCDDP, breast cancer detection demonstration project; BMI, body mass index; CRC, colorectal cancer; CPS II, Cancer Prevention Study II; EPIC, European Prospective Investigation into Cancer and Nutrition; HPFS, Health Professionals Follow-up Study; NBSS, National Breast Screening Study; NIH-AARP, National Institutes of Health-AARP (formerly the American Association for Retired Persons); NHS, Nurses' Health Study; NLCS, Netherlands Cohort Study; NR, not reported.

[a]Case–cohort study.

[b]Nested case–control.

[c]Study not included in meta-analysis because red meat item is not explicitly defined.

Appendix 2



Funnel plot of prospective studies of red meat and colorectal cancer.