Other Reviews

Red meat and colorectal cancer: a critical summary of prospective epidemiologic studies

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Summary

Meat consumption and cancer has been evaluated in hundreds of epidemiologic studies over the past three decades; however, the possible role of this food group on carcinogenesis is equivocal. In this comprehensive review, the currently available epidemiologic prospective studies of red meat intake and colorectal cancer are summarized to provide a greater understanding of any potential relationships. Specifically, salient demographic, methodological and analytical information is synthesized across 35 prospective studies. Collectively, associations between red meat consumption and colorectal cancer are generally weak in magnitude, with most relative risks below 1.50 and not statistically significant, and there is a lack of a clear dose–response trend. Results are variable by anatomic tumour site (colon vs. rectum) and by gender, as the epidemiologic data are not indicative of a positive association among women while most associations are weakly elevated among men. Colinearity between red meat intake and other dietary factors (e.g. Western lifestyle, high intake of refined sugars and alcohol, low intake of fruits, vegetables and fibre) and behavioural factors (e.g. low physical activity, high smoking prevalence, high body mass index) limit the ability to analytically isolate the independent effects of red meat consumption. Because of these factors, the currently available epidemiologic evidence is not sufficient to support an independent positive association between red meat consumption and colorectal cancer.

Keywords: Colorectal cancer, diet, epidemiology, nutrition.

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Introduction

In a 1979 edition of the American Journal of Epidemiology, Graham and Mettlin (1) reported that the 'animal fat hypothesis' was introduced by Ernst Wynder at a 1965 symposium on the aetiology of cancer in the gastrointestinal tract. During the symposium, country-specific age-adjusted mortality rates for colon cancer were shown to increase with increasing per capita animal fat consumption, based on international data (1). Subsequently, the animal fat hypothesis evolved into the hypothesis that meat intake may be associated with increasing the risk of certain types of cancer, although analytical epidemiologic evidence was lacking. In a 1975 ecologic study by Armstrong and Doll (2), published in the International Journal of Cancer, worldwide per capita animal protein consumption rates were strongly correlated with incidence and mortality rates of colon cancer and rectal cancer among men and women. However, in another early ecologic study, no correlation between beef consumption (prior to 1970) and age-adjusted colorectal cancer incidence and mortality rates

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were observed based on data from the US Department of Agriculture (3). The early hypothesis-generating studies gave way to more advanced and scientifically rigorous designs, such as analytical epidemiologic case–control and prospective cohort studies. To date, despite more than 50 epidemiologic studies of red meat and colorectal cancer over the past few decades, including over 30 prospective studies published in the past 20 years, the potential relationship between red meat consumption and colorectal cancer is equivocal.

Several postulated mechanisms regarding meat consumption and cancer have been examined, although findings from human studies have been relatively inconsistent. Mechanisms involving dietary mutagens (e.g. heterocyclic amines, polycyclic aromatic hydrocarbons), chemical compounds that are not naturally present in foods but may develop during cooking, have been the most heavily studied, but associations from epidemiologic analyses have been variable across several specific compounds (4–8). Other mechanisms involve the potential role of nitrate and nitrite, commonly used in processed meats for preservation agents, and N-nitroso compounds, which have been shown to be carcinogenic in some laboratory animal studies (9). However, exposure is not specific to meat intake, as greater exposure may occur through consumption of other dietary sources such as vegetables or cereal products. Finally, some researchers have suggested that iron, particularly haem iron, may play a role in cancer development (4,10). Red meat is a primary source of haem iron, which is found naturally in meat as part of haemoglobin and myoglobin, although relatively few studies have evaluated the potential role that this factor may play in cancer risk (11).

In 2007, the World Cancer Research Fund (WCRF), in collaboration with the American Institute for Cancer Research (AICR), released a summary report entitled, 'Food, Nutrition, Physical Activity, and the Prevention of Cancer: a Global Perspective' (12). This second report (the first was issued in 1997 (13)), evaluated the scientific evidence pertaining to numerous dietary factors and their relation with 17 different types of cancer. Twenty-two panellists formalized conclusions and recommendations based on the scientific literature that was assembled, synthesized and disseminated by independent international working groups. The WCRF/AICR panel judged that consumption of red meat is a 'convincing' cause of colorectal cancer (12), although there were numerous limitations to the available data. Specifically, the epidemiologic associations across the consortium of studies are relatively weak in magnitude (i.e. relative risk [RR] < 1.5), most individual studies have not observed statistically significant associations, there is no clear evidence of dose–response, and patterns of associations vary by study characteristics. Moreover, red meat is defined and analysed heterogeneously across studies. Despite their judgment, WCRF/AICR does not suggest that people exclude red meat from their diet; instead, they recommend that individuals who eat red meat should consume less than 500 g (18 oz) per week, and that the population average consumption of red meat should be no more than 300 g (11 oz) per week (12). This recommendation is generally consistent with the current red meat consumption levels based on national survey data (14,15).

While acknowledging that WCRF/AICR embarked on a comprehensive, ambitious and arduous foray into the epidemiology surrounding red meat and colorectal cancer (in addition to numerous other dietary factors and cancer endpoints), the judgments and conclusions from a public health perspective have not been met with scientific consensus. In an editorial by researchers at the International Agency for Research on Cancer, the scientific and methodological grounds for WCRF/AICR's 'convincing' classification for red meat and colorectal cancer were questioned due to 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 prior associations) (16). Furthermore, International Agency for Research on Cancer raised questions about their evaluation process and classification system (16). Another commentary by Truswell suggested that the evidence supporting a change in conclusion from probable to convincing was incomplete and inaccurate because of some errors and omissions (17).

The purpose of this review is to synthesize and summarize the available epidemiologic studies of red meat intake and colorectal cancer, and to provide a scientific overview of the methodological and analytical complexity of evaluating this topic.

Literature search and data extraction

Literature searches using MEDLINE® were performed to identify articles eligible for review. The search string utilized for this review is as follows: colon cancer OR colon neoplasm OR colon carcinoma OR rectal cancer OR rectal neoplasm OR rectal carcinoma OR colorectal cancer OR colorectal neoplasm OR colorectal carcinoma AND (diet* OR diet OR food OR nutrition OR meat OR lamb OR pork OR beef). This search yielded approximately 10 000 articles, and abstracts of all articles were reviewed and relevant studies were obtained. In addition, the reference sections of review articles, meta-analyses, and the WCRF/AICR report were reviewed to identify articles that may not have been found by our database searches. Epidemiologic prospective studies (i.e. cohort, nested case–control) published in English that specifically reported data for the association between red meat intake and colorectal cancer (combined outcome), colon cancer or rectal cancer were included. Case–control studies were obtained but not reviewed herein. Studies that evaluated total meat intake or fish or poultry intake only were excluded. Data for correlates of red meat intake, such as processed meat or animal fat consumption, were examined but not summarized in this review. A total of 35 prospective studies, published prior to 1 January 2010, met the aforementioned criteria and were included herein (Table 1).

Salient study design, methodological and analytical information was extracted from each study. Specifically, the following information was extracted on a study-by-study basis: author and year of study, geographic location of where the study was conducted, the name and nature of the cohort (e.g. Nurses' Health Study, Japan Collaborative Cohort Study), gender and age of study population, sample size, years of follow-up, method of intake ascertainment, red meat variable name and definition, intake metric units, analytical comparison of intake values, number of exposed cases, RR estimates and 95% confidence intervals, the variables that were statistically adjusted for or were matched on for each respective RR estimate (Table 2). In addition, the potential impact of bias and/or confounding on the interpretation of each study was critically examined.

Summary of epidemiologic studies of red meat intake and colorectal cancer

Studies conducted in North America

Among the largest cohort studies of red meat consumption and cancer risk, Cross *et al.* (18) analysed approximately 500 000 individuals in the National Institutes of Health-AARP (formerly the American Association for Retired Persons) Diet and Health Study. The analysis focused upon red and processed meat intake and several cancer types, including colorectal cancer. The authors reported a statistically significant rate ratio of 1.24 (95% CI: 1.12–1.36) for the highest quintile of red meat consumption and colorectal cancer among men and women analysed together. A significant test for trend was also reported; however, significant positive associations were observed only in the fourth (42.9 g 1000 $kcal^{-1}$) and fifth ($\geq$62.7 g 1000 $kcal^{-1}$) quintiles of intake. Associations were modified by tumour site; the RR for colon cancer was 1.17 (95% CI: 1.05–1.31), while the RR for rectal cancer was 1.45 (95% CI: 1.20–1.75). Gender-specific associations were not reported. Although their analyses were adjusted for numerous factors, it is noteworthy that the highest consumers (i.e. persons in the highest quintile of intake) of red meat also had the highest body mass index, were more likely to smoke cigarettes, less likely to engage in physical activity, less likely to be a college graduate, consumed lower amounts of fruits and vegetables and had a higher daily caloric intake. Thus, residual confounding by any or some of these factors may have contributed to the statistically significant positive associations observed in this study, especially considering the fairly weak magnitudes of association.

Chao *et al.* (19) conducted an evaluation of red meat consumption and colorectal cancer among 148 610 participants residing in 21 states who were enrolled in the US Cancer Prevention Study II Nutrition Cohort. A weak, non-significant association was reported for the highest (vs. lowest) quintile of red meat consumption and colorectal cancer among men and women combined (RR = 1.15; 95% CI: 0.90–1.46). Interestingly, associations varied considerably by tumour site and by gender. Positive associations were reported for rectal cancer (RR = 1.71; 95% CI: 1.15–2.52) and proximal colon cancer (RR = 1.27; 95% CI: 0.91–1.76), respectively, while an inverse association was observed for distal colon cancer (RR = 0.71; 95% CI: 0.47–1.07). A non-significant positive association was reported among men (RR = 1.30; 95% CI: 0.93–1.81) but a non-significant inverse association was observed among women (RR = 0.98; 95% CI: 0.68–1.40). Positive confounding was evident as associations that were adjusted only for age and total energy were markedly stronger in magnitude than associations that were adjusted for several dietary and lifestyle factors. In a previous analysis of 764 343 participants enrolled in this cohort (baseline questionnaire in 1982), the authors indicated that no associations between red meat and colon cancer mortality were found; however, data were not provided in their publication (Thun *et al.* (20)).

In an analysis that combined data from the US Nurses' Health Study cohort (87 733 women) and the Health Professionals Follow-up Study (46 632 men), Wei *et al.* (21) reported a marginally significant positive association between beef, pork or lamb as a main dish and colon cancer (RR = 1.43; 95% CI: 1.00–2.05), but a non-significant inverse association was observed for rectal cancer (RR = 0.90; 95% CI: 0.47–1.75). Similar patterns of associations were reported by gender, with RRs of 1.31 and 1.35 for colon cancer among women and men, respectively, and RRs of 0.92 and 0.90 for rectal cancer among women and men, respectively. This trend is in contrast with many other studies for which stronger associations above 1.0 were observed for rectal cancer compared with colon cancer. No monotonic patterns of associations or significant tests for trend were observed. The comparison group (reference category) included participants who do not consume red meat, which is important because greater variability in other dietary and non-dietary factors likely exist between meat consumers and non-meat consumers. The second quintile of intake (<3 servings per month), which equates to less than one serving of red meat per week, was associated with stronger positive associations among men and women than was the fifth quintile of intake (5 or more servings per week). Therefore, if the reference group included participants who consumed less than one

Table 1 Characteristics of prospective studies of red meat and colorectal cancer

Author and year	Cohort	Number of study participants	Age of participants	Follow-up years
Bostick *et al.* 1994 (33)	Iowa Women's Health Study	35 215 women	55–69	1986–1990
Brink *et al.* 2005 (37)*	Netherlands Cohort Study	2 948	55–69	1989–1994
Chan *et al.* 2005 (23)† [overlap with Wei *et al.* 2004 (21)]	Nurses' Health Study (US)	32 826 women	30–55	1989–2000
Chao *et al.* 2005 (19)	Cancer Prevention Study II (US)	86 404 men; 97 786 women	50–74	1992–2001
Chen *et al.* 2003 (49)†	China	64 693	30–80+	1990–1998
Chen *et al.* 1998 (29)	Physicians Health Study (US)	22 071 men‡	40–84	1982–1994
Cross *et al.* 2007 (18)	National Institutes of Health-AARP Diet and Health Study (US)	294 724 men; 199 312 women	50–71	1995–2003
English *et al.* 2004 (50)	Melbourne Collaborative Cohort Study (Australia)	37 112	27–75	1990–2002
Flood *et al.* 2003 (32)	Breast Cancer Detection Demonstration Project (US)	45 496 women	40–93	1987–1998
Fraser 1999 (27) [overlap with Singh and Fraser 1998 (26)]	7th Day Adventists Health Study (California)	34 192	>25	1976–1982
Gaard *et al.* 1996 (43)§	Norway	50 535	20–53	1977–1991
Giovannucci *et al.* 1994 (24) [overlap with Wei *et al.* 2004 (21)]	Health Professionals Follow-Up Study (US)	47 949 men	40–75	1986–1992
Hsing *et al.* 1998 (28)	Lutheran Brotherhood (US)	17 633 men	>35	1966–1986
Jarvinen *et al.* 2001 (41)	Mobile Clinic Health Examination Survey (Finland)	9 959	15–99	1966–1999
Kabat *et al.* 2007 (31)	National Breast Screening Study (Canada)	49 654 women	40–59	1982–2000
Kato *et al.* 1997 (35)	New York, Florida	14 727 women	34–65	1985–1994
Khan *et al.* 2004 (46)	Japan	3 158	>40	1984–2002
Kojima *et al.* 2004 (45)	Collaborative Cohort Study (Japan)	45 181 men; 62 643 women	40–79	1988–1999
Larsson *et al.* 2005 (42)	Swedish Mammography Cohort	61 433 women	40–75	1987–2003
Lee *et al.* 2009 (48)	Shanghai Women's Health Study (China)	73 224 women	40–70	1997–2005
Lin *et al.* 2004 (30)	Women's Health Study (US)	39 876 women	>45	1993–2003
Luchtenborg *et al.* 2005 (38) [same population as Brink *et al.* 2005 (37)]	Netherlands Cohort Study	2 948	55–69	1989–1994
Norat *et al.* 2005 (36)	European Prospective Investigation into Cancer and Nutrition (Europe)	478 040	21–83	1992–2002
Nothlings *et al.* 2009 (5)	Multiethnic Cohort Study (Hawaii, Los Angeles County)	215 000	45–75	1993–NR
Oba *et al.* 2006 (47)	Japan	13 894 men; 16 327 women	35+	1992–2000
Pietinen *et al.* 1999 (40)	Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (Finland)	27 111 men	50–69	1988–1995
Sato *et al.* 2006 (44)	Miyagi Cohort Study (Japan)	47 605	40–64	1990–2001
Sellers *et al.* 1998 (34) [overlap with Bostick *et al.* 1994 (33)]	Iowa Women's Health Study	35 216 women	55–69	1986–1995
Singh and Fraser 1998 (26)	Adventist Health Study (California)	32 051	>25	1976–1982
Thun *et al.* 1992 (20)	Cancer Prevention Study II (US)	764 343	>30	1982–1988
Tiemersma *et al.* 2002 (39)†	Netherlands	~30 000	20–59	1987–1998
Wei *et al.* 2004 (21)	Health Professionals Follow-Up Study (US)	46 632 men	40–75	1986–2000
	Nurses' Health Study (US)	87 733 women	30–55	1980–2000
Willett *et al.* 1990 (22) [overlap with Wei *et al.* 2004 (21)]	Nurses' Health Study (US)	88 751 women	34–59	1980–1986
Wu *et al.* 2004 (25) [overlap with Wei *et al.* 2004 (21)]	Health Professionals Follow-Up Study (US)	47 311 men	40–75	1986–2000

*Case-cohort study.
†Nested case–control.
‡Baseline blood samples drawn from 212 cases and 221 controls. §Red meat not analyzed explicitly; meat balls and meat stews evaluated.

Table 2 Results from prospective studies of red meat and colorectal cancer

Author and year	Analytical category (definition)	Gender	Number of exposed cases	Analytical comparison, high vs. low intake	Relative risk (95% CI)	Statistical adjustment
Bostick *et al.* 1994 (33)	Red meat	Women	37	Colon: >11.0 vs. <4.0 servings per 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 (37)*				Quartiles of intake (4 vs. 1)		Age, sex, Quetelet index, smoking, energy intake, family hx of CRC
	Beef	Both	142	Colon	1.28 (0.96–1.72)	
		Both	40	Rectum	0.92 (0.57–1.49)	
	Pork	Both	98	Colon	0.77 (0.57–1.04)	
		Both	34	Rectum	0.70 (0.43–1.13)	
	Minced meat	Both	97	Colon	0.93 (0.68–1.27)	
		Both	35	Rectum	1.01 (0.62–1.67)	
Chan *et al.* 2005 (23)[†] [overlap with Wei *et al.* 2004 (21)]	Beef, pork or lamb as a main dish	Women	17	>0.5 vs. ≤0.5 servings per day	1.21 (0.85–1.72)	Age, BMI, family hx of CRC, post-menopausal hormone use, previous endoscopy, current multi-vitamin use, regular aspirin use
Chao *et al.* 2005 (19)	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, multi-vitamin use, aspirin use, alcohol, hormone therapy, fruits, vegetables, high-grain foods
		Both	210	Colon	1.15 (0.90–1.46)	
		Both	96	Rectal	1.71 (1.15–2.52)	
		Both	116	Proximal colon	1.27 (0.91–1.76)	
		Both	64	Distal colon	0.71 (0.47–1.07)	
		Men	124	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
		Women	86	Colon	0.98 (0.68–1.40)	
Chen *et al.* 2003 (49)[†]	Pork	Both	NR	Colon: Pork eating, yes vs. no	1.48 (0.85–2.59)	Matched on age, gender, resident location
Chen *et al.* 1998 (29)	Red meat (beef, pork, lamb as a main dish, mixed dish, or sandwich; hot dogs)	Men	43	1+ intake per day vs. ≤0.5	1.17 (0.68–2.02)	BMI, physical activity and alcohol

Table 2 *Continued*

Author and year	Analytical category (definition)	Gender	Number of exposed cases	Analytical comparison, high vs. low intake	Relative risk (95% CI)	Statistical adjustment
Cross *et al.* 2007 (18)	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, chilli, lasagna and stew)			Quintiles of intake: 5 vs. 1 62.7 g 1000 $kcal^{-1}$ vs. 9.8		Age, sex, education, marital status, family hx of cancer, race, BMI, smoking, frequency of vigorous physical activity, intake of: total energy, alcohol, fruits and vegetables
		Both	1190	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 (50)	Fresh red meat (veal or beef schnitzel, roast beef, veal, steak, meat balls, meat loaf, 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
		Both	NR	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 (32)	Red meat (bacon, beef, hamburger, ham or other lunch meat, hot dogs, liver, pork, sausage; meat components of beef stew, chilli, salad, spaghetti, vegetable soup)	Women	NR	Quintile 5 vs. 1: 52.2+ g 1000 $kcal^{-1}$ 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 (27) [overlap with Singh and Fraser 1998 (26)]	Red meat	Both	NR	Colon cancer among persons who consumed white meat <1 per week: 1+ time per week (red meat) vs. never	1.86 (1.15–3.02)	
Gaard *et al.* 1996 (43)‡				Colon		Age, attained age
	Meat balls	Men	15	5+ per month vs. ≤1	0.61 (0.22–1.69)	
	Meat stews	Men	11	5+ per month vs. ≤1	0.74 (0.21–2.64)	
	Meat balls	Women	13	5+ per month vs. ≤1	1.08 (0.31–3.79)	
	Meat stews	Women	9	5+ per month vs. ≤1	0.58 (0.16–2.13)	
Giovannucci *et al.* 1994 (24) [overlap with Wei *et al.* 2004 (21)]	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])	Men	55	Colon: 129.5 g d^{-1} vs. 18.5	1.71 (1.15–2.55)	Age, total energy intake
	Beef, pork or lamb as main dish	Men	16	Colon: ≥5 servings per week vs. 0	3.57 (1.58–8.06)	Age

Table 2 *Continued*

Author and year	Analytical category (definition)	Gender	Number of exposed cases	Analytical comparison, high vs. low intake	Relative risk (95% CI)	Statistical adjustment
Hsing *et al.* 1998 (28)	Red meat (beef, bacon, fresh pork, smoked ham)			60+ times per month vs. <15		Age, smoking, alcohol, total calories
		Men	14	Colorectal	1.9 (0.9–4.3)	
		Men	13	Colon	1.8 (0.8–4.4)	
Jarvinen *et al.* 2001 (41)	Red meat			Quartiles of daily intake (4 vs. 1)		Age, sex, BMI, occupation, smoking, geography, energy intake, vegetable and fruit consumption, cereal intake
		Both	NR	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 (31)	Red meat (ascertained from 22 meat items including beef, pork, ham, bacon, pork-based lunch meats, veal)			40.3 g d^{-1} vs. <14.25		Age, BMI, menopausal status, oral contraception, hormone replacement use, diet (fat, fibre, folic acid, total calories), smoking, alcohol, education, physical activity
		Women	NR	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 (35)	Red meat	Women	NR	Quartiles of intake (4 vs. 1)	1.23 (0.68–2.22)	Age, total calorie intake, education, enrolment place
Khan *et al.* 2004 (46)	Meat, except chicken (pork, beef, mutton, liver, ham, sausages)	Men	NR	Several times per week; everyday vs. never; several times per year; several times per month	2.0 (0.6–6.3)	Age, smoking
		Women	NR	Several times per week; everyday vs. never; several times per year; several times per month	1.0 (0.3–3.0)	Age, health status, health education, health screening and smoking
Kojima *et al.* 2004 (45)				3–7 per week vs. 0–2 per month		Age, family hx of CRC, BMI, alcohol, smoking, walking per day, education, regions of enrolment
	Beef	Men	11	Colon	1.46 (0.74–2.86)	
		Men	10	Rectal	1.38 (0.68–2.78)	
	Pork	Men	17	Colon	1.14 (0.61–2.14)	
		Men	20	Rectal	1.11 (0.61–2.03)	
	Beef	Women	11	Colon	1.11 (0.57–2.14)	
		Women	1	Rectal	0.37 (0.05–2.84)	
	Pork	Women	20	Colon	0.93 (0.54–1.60)	
		Women	3	Rectal	0.32 (0.09–1.15)	

Table 2 *Continued*

Author and year	Analytical category (definition)	Gender	Number of exposed cases	Analytical comparison, high vs. low intake	Relative risk (95% CI)	Statistical adjustment
Larsson *et al*. 2005 (42)	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 d^{-1} vs. <50		Age, BMI, education, energy intake, alcohol, saturated fat, calcium, folate, fruits, vegetables, whole grain foods
		Women	NR	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 per week vs. <2		
		Women	NR	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 (48)	Red meat			67+ g d^{-1} vs. <24		Age, education, income, survey season, tea consumption, NSAID use, energy intake and fibre intake
		Women	62	Colorectal	0.8 (0.6–1.1)	
		Women	41	Colon	0.9 (0.6–1.5)	
		Women	21	Rectal	0.6 (0.3–1.1)	
Lin *et al*. 2004 (30)	Red meat (beef or lamb as main dish, beef, pork or lamb in a sandwich, hot dogs, bacon, processed meats, hamburgers)	Women	30	1.42+ servings per day vs. ≤0.13	0.66 (0.40–1.09)	Age, random treatment assignment, BMI, family hx of CRC, hx of polyps, physical activity, smoking, alcohol, post-menopausal hormone therapy, total energy
Luchtenborg *et al*. 2005 (38) [same population as Brink *et al*. 2005 (37)]				Quartiles of intake (4 vs. 1)		Age, sex, family hx of CRC, smoking, BMI, energy intake
	Beef	Both	134	Colon	1.29 (0.96–1.73)	
		Both	38	Rectal	0.95 (0.59–1.54)	
	Pork	Both	92	Colon	0.77 (0.57–1.04)	
		Both	31	Rectal	0.70 (0.44–1.13)	
	Minced meat	Both	93	Colon	0.93 (0.68–1.27)	
		Both	33	Rectal	1.01 (0.61–1.66)	
Norat *et al*. 2005 (36)	Red meat (fresh, minced and frozen beef, veal, pork, lamb)			≥ 80 g d^{-1} vs. <10		Age, sex, energy, height, weight, occupational physical activity, smoking, alcohol intake, dietary fibre, centre
		Both	250	Colorectal	1.17 (0.92–1.49)	
		Both	NR	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 (5)	Red meat	Both	240	26.0+ g 1000 $kcal^{-1}$ per day vs. 0 to <10.4	0.96 (0.74–1.23)	Age at blood draw, sex, ethnicity, family hx of CRC, BMI, physical activity, smoking, intake of dietary fibre, calcium, vitamin D, folic acid and ethanol
Oba *et al*. 2006 (47)	Red meat (beef, pork)	Men	32	Colon: 56.6+ g vs. ≤18.7	1.03 (0.64–1.66)	Age, height, BMI, smoking, alcohol, physical activity
		Women	27	Colon: 42.3+ g vs. ≤10.7	0.79 (0.49–1.28)	

Table 2 *Continued*

Author and year	Analytical category (definition)	Gender	Number of exposed cases	Analytical comparison, high vs. low intake	Relative risk (95% CI)	Statistical adjustment
Pietinen *et al.* 1999 (40)	Beef, pork, lamb	Men	45	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	Men	45	203 g vs. <80	1.1 (0.7–1.7)	
Sato *et al.* 2006 (44)	Beef			1–2 per week vs. almost never		Age, sex, smoking, alcohol, BMI, education, family hx of cancer, walking, consumption of fat, calcium, fibre
		Both	46	Colorectal	0.93 (0.67–1.30)	
		Both	25	Colon	0.84 (0.54–1.32)	
		Both	21	Rectal	1.01 (0.62–1.67)	
		Both	16	Proximal colon	0.97 (0.55–1.70)	
		Both	8	Distal colon	1.06 (0.46–2.43)	
	Pork (excluding ham or sausage)			3–4 per week vs. almost never		
		Both	73	Colorectal	1.13 (0.79–1.74)	
		Both	48	Colon	1.46 (0.81–2.62)	
		Both	26	Rectal	0.74 (0.39–1.42)	
		Both	24	Proximal colon	1.05 (0.50–2.22)	
		Both	16	Distal colon	1.90 (0.63–5.74)	
Sellers *et al.* 1998 (34) [overlap with Bostick *et al.* 1994 (33)]	Red meat (beef, beef stew, hamburger, liver, venison)			Colon: >7 servings per week vs. <3.5		Age, energy intake, hx of polyps
		Women	16	Family hx of colon cancer	1.0 (0.5–2.1)	
		Women	53	No family hx of colon cancer	1.3 (0.8–2.0)	
Singh and Fraser 1998 (26)	Red meat (current intake of beef or pork)	Both	45	Colon: 1+ per week vs. never	1.41 (0.90–2.21)	Age, sex, BMI, physical activity, smoking, alcohol, aspirin use, parental hx of colon cancer
Thun *et al.* 1992 (20)	Red meat	Men	NR	Colon	No association (data NR)	Matched on age, race and sex. Adjusted for total fat, exercise, BMI, family hx of colon cancer, aspirin use, intake of vegetables, fruits and grains
	Beef	Men			Inverse association (data NR)	Matched on age, race and sex
	Pork	Men			Positive association (data NR)	
	Red meat	Women	NR	Colon	No association (data NR)	
	Beef	Women			Inverse association (data NR)	
	Pork	Women			Positive association (data NR)	

Table 2 *Continued*

Author and year	Analytical category (definition)	Gender	Number of exposed cases	Analytical comparison, high vs. low intake	Relative risk (95% CI)	Statistical adjustment
Tiemersma *et al.* 2002† (39)	Fresh red meat (beef, pork)	Both	45	5+ per week vs. 0–3 per week	1.6 (0.9–2.9)	Age, sex, centre, total energy intake, alcohol, body height
		Men	30	5+ per week vs. 0–3 per week	2.7 (1.1–6.7)	
		Women	15	5+ per week vs. 0–3 per week	1.2 (0.5–2.8)	
Wei *et al.* 2004 (21)	Beef, pork, lamb as a main dish			5+ per week vs. 0		Age, family hx, BMI, physical activity, processed meat, alcohol, calcium, folate, height, smoking before age 30 years, hx of endoscopy and gender
		Both	155	Colon	1.43 (1.00–2.05)	
		Both	31	Rectum	0.90 (0.47–1.75)	
		Men	32	Colon	1.35 (0.80–2.27)	Age, family hx, BMI, physical activity, alcohol, calcium, folate, height, smoking before age 30 years, hx of endoscopy
		Men	7	Rectum	0.90 (0.34–2.45)	
		Women	123	Colon	1.31 (0.73–2.36)	
		Women	24	Rectum	0.92 (0.31–2.71)	
Willett *et al.* 1990 (22) [overlap with Wei *et al.* 2004 (21)]	Red meat (beef, pork or lamb as a main dish sandwich or mixed dish, hamburger, hotdogs, preserved meats and bacon)			134+ g day^{-1} vs. <59		
		Women	44	Colon	1.77 (1.09–2.88)	Age and total energy intake
		Women	44	Colon	1.61 (1.03–2.53)	Age, total energy intake, and chicken and fish consumption
	Beef, pork or lamb as a main dish	Women	16	Colon: 1+ serving per day vs. <1 serving per month	2.49 (1.24–5.03)	Age
Wu *et al.* 2004 (25) [overlap with Wei *et al.* 2004 (21)]	Red meat	Men	NR	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.
*Case-cohort study.
†Nested case–control.
‡Red meat item not explicitly defined.
BMI, body mass index; CRC, colorectal cancer; hx, history; NR, not reported.

serving of red meat per week, the association for the highest quintile of consumption may be null or close to null for colon cancer, with the association for rectal cancer remaining inverse. In an earlier analysis of the Nurses' Health Study cohort, Willett *et al.* (22) reported significantly elevated associations between red meat intake (RR = 1.77; 95% CI: 1.09–2.88) and beef, pork and lamb as a main dish (RR = 2.49; 95% CI: 1.24–5.03) and colon cancer. However, these associations were based on only 6 years of follow-up, compared with 20 years of follow-up in the study by Wei *et al.* In addition, the authors adjusted for fewer covariates. Consequently, the associations observed in the analysis by Wei *et al.* were markedly attenuated and not statistically significant. In a subgroup analysis of the Nurses' Health Study, Chan *et al.* (23) dichotomized red meat intake (>0.5 servings per day vs. ≤0.5 servings per day), and observed a weakly elevated non-significant association (RR = 1.21; 95% CI: 0.85–1.72).

In a previous analysis of the Health Professionals Follow-up Study, Giovannucci *et al.* (24) reported statistically significant positive associations between red meat (RR = 1.71; 95% CI: 1.15–2.55) or intake of beef, pork or lamb as a main dish (RR = 3.57; 95% CI: 1.58–8.06) and colon cancer. However, their analysis did not control for as many important confounding factors as Wei *et al.* and their follow-up time was 8 years shorter. In another analysis of this cohort, Wu *et al.* (25) evaluated dietary patterns and colon cancer and adenoma formation, although they reported positive associations between red meat and colon cancer in the text of their publication. They did not tabulate their data so it is unclear what, if any, factors were included in their regression models.

Nothlings *et al.* (5) evaluated meat intake, heterocyclic amines, and polymorphic enzymes and colorectal cancer in the Multiethnic Cohort Study, which included African–Americans, Japanese–Americans, Latinos, Native Hawaiians and Caucasians in Los Angeles county and Hawaii. The authors utilized a nested case–control study design and analysed approximately 1000 cases of colorectal cancer. A non-significant inverse association between 26+ g of red meat (per 1000 kcal d^{-1}) and colorectal cancer was reported (OR = 0.96, 95% CI: 0.74–1.23) after adjustment for numerous factors, including body mass index, family history of colorectal cancer, smoking, physical activity, vitamin D and dietary fibre. No significant associations were observed for red meat and colorectal cancer among the acetylator genotypes.

In a 6-year prospective study examining the relation between dietary factors and incident colon cancer among non-Hispanic white cohort members of the California 7th Day Adventist Health Study, a non-significant positive association between one or more servings of red meat and colon cancer was reported (RR = 1.41; 95% CI: 0.90–2.21) (Singh and Fraser) (26). Of note, the association was stronger in magnitude (RR = 1.58) and statistically significant for the 0 to <1 per week consumption category, and the associations for white meat were stronger than for red meat. In another analysis of this population, Fraser *et al.* (27) reported that among persons who consume white meat less than once per week, the association between one or more servings of red meat per week (versus never) was significantly elevated (RR = 1.86; 95% CI: 1.15–3.02). However, the authors indicated that the positive association between red meat intake and colon cancer risk was observed only among persons who consumed legumes infrequently (RR = 2.68; 95% CI: 1.24–5.78). Furthermore, associations were stronger among the highest consumers of white meat than red meat.

In a US cohort of white male policy holders of the Lutheran Brotherhood Insurance Society who completed a mail questionnaire in 1966 that ascertained a variety of factors, including diet, a non-significant positive association between red meat intake and colorectal cancer was reported (RR = 1.9; 95% CI: 0.9–4.3), although the analysis was adjusted for few factors (i.e. age, smoking, alcohol and total calories) (Hsing *et al.*) (28). Of note, a pattern of positive associations, similar to that seen for red meat intake, was observed for fruit consumption; a food group that is not suggested to increase the risk of colorectal cancer. Although the follow-up of this study was extensive (20 years), dietary information was collected only once, at baseline in 1966. Thus, dietary choices and/or lifestyle factors may have changed throughout the follow-up period.

In a study of N-acetyltransferase [NAT] genotype (metabolic enzymes involved in the metabolism of potentially carcinogenic heterocyclic amines), red meat intake and colorectal cancer among male members of the US Physicians Health Study cohort, a weak positive non-significant association for >1 serving of red meat per day (vs. ≤0.5 per day) was reported among all men (RR = 1.17; 95% CI: 0.68–2.02) (Chen *et al.*) (29). A stronger positive association between red meat and colorectal cancer was observed among rapid NAT1/NAT2 acetylators (RR = 2.35; 95% CI: 0.77–7.12), although the association was imprecise and was based on only 11 exposed cases.

In addition to some of the studies summarized above, other studies conducted in North America evaluated women specifically, and of these studies, no evidence of independent positive associations between red meat and colorectal cancer has been observed. The Women's Health Study is an ongoing randomized, double-blind, placebo-controlled trial designed to evaluate the use of low-dose aspirin and Vitamin E for the primary prevention of cancer and cardiovascular disease among US women. However, data from this study have been used in a variety of epidemiologic investigations. Indeed, Lin *et al.* (30) examined the association between red meat consumption and risk of colorectal cancer among women followed from 1993 to 2003. The authors reported a statistically significant inverse trend; decreasing risks of colorectal cancer were observed with increasing quintiles of red meat intake. The highest level of intake (1.42 servings per day vs. 0.13 servings per day) was associated inversely with colorectal cancer (RR = 0.66; 95% CI: 0.40–1.09). This association was adjusted for several important factors, including a history of polyps. Of importance, this study was not included in the 2007 WCRF/AICR report for red meat intake, even though this was a well-conducted study that evaluated a high intake level of red meat. In another evaluation of participants enrolled in a clinical trial, Kabat *et al.* (31) analysed data from the Canadian National Breast Screening Study, a randomized controlled trial of screening for breast cancer, to examine the association between red meat consumption and colorectal cancer. Stark differences in associations were observed by tumour site; inverse associations were reported in the third, fourth and fifth quintiles of red meat intake for colon cancer while positive associations were reported for all intake quintiles for rectal cancer. Overall, a non-significant weakly elevated association between red meat consumption and colorectal cancer was reported (RR = 1.12; 95% CI: 0.86–1.46). Flood *et al.* (32), in a cohort study of women enrolled in the Breast Cancer Detection Demonstration Project, reported no association between the highest quintile of red meat intake (>52.2 g 1000 $kcal^{-1}$ vs. <6.1 g 1000 $kcal^{-1}$) and colorectal cancer (RR = 1.04; 95% CI: 0.77–1.41). Similarly, non-significant associations of 0.95 were observed in the third and fourth quintiles of red meat intake.

Bostick *et al.* (33), in an analysis of over 30 000 participants in the Iowa Women's Health Study, reported no association between greater than 11 servings of red meat per week (vs. <4 servings) and risk of colon cancer (RR = 1.04; 95% CI: 0.62–1.76) in their multivariate analysis. Furthermore, no dose–response relationship was observed (*P*-trend = 0.78). In a more recent publication of this cohort, Sellers *et al.* (34) examined the association between red meat consumption (>7 servings per week vs. <3.5 servings per week) and colon cancer while stratifying by positive or negative family history of colon cancer. A non-significant positive association was reported among women with no family history of colon cancer (RR = 1.3; 95% CI: 0.8–2.0) and no association was observed among women with a positive family history (RR = 1.0; 95% CI: 0.5–2.1), after adjusting for age at baseline, total energy intake, and history of colorectal polyps.

In a study of women enrolled at mammographic screening clinics in New York and Florida, a non-significant RR of 1.23 (95% CI: 0.68–2.22) for the highest quartile of red meat intake and colorectal cancer was reported, and no significant trend was observed (*P*-trend = 0.545) (35). Neither the intake units nor the comparison metrics were reported, and the specific definition of red meat was not provided.

Studies conducted in Europe

The European Prospective Investigation into Cancer and Nutrition study (the EPIC cohort), consists of approximately half a million men and women from 10 European countries who are followed for cancer incidence. In an evaluation of meat consumption among participants in the EPIC cohort, Norat *et al.* (36) reported weak non-significant positive associations between red meat intake and colon (RR = 1.20; 95% CI: 0.88–1.61) and rectal (RR = 1.13; 95% CI: 0.74–1.71) cancer. Associations were not modified appreciably by anatomic site within the colon, and no significant trend tests were reported for red meat. Associations for each 100 g intake of red meat were positive, but not statistically significant for colon cancer and rectal cancer separately, but a significant positive association of 1.22 (95% CI: 1.02–1.43) was reported for colorectal cancer. Among the red meat consumers, the strongest associations were observed among persons who also consumed the lowest amounts of fish and fibre. Although 1329 incident colorectal cancers were ascertained in this study, mean follow-up was relatively short (4.8 years).

In a case-cohort analysis of the Netherlands Cohort Study, Brink *et al.* (37) observed no significant associations between intake of red meat (beef, pork and minced meat) and colon and rectal cancer. Specifically, the colon cancer RRs (high vs. low intake) were 0.77 (95% CI: 0.57–1.04) for pork intake, 1.28 (95% CI: 0.96–1.72) for beef intake and 0.93 (95% CI: 0.68–1.27) for minced meat intake. For rectal cancer, the RRs were 0.70 (95% CI: 0.43–1.13) for pork intake, 0.92 (95% CI: 0.57–1.49) for beef intake, and 1.01 (95% CI: 0.62–1.67) for minced meat intake. Virtually, the same associations were reported in another analysis of the same study population (Luchtenborg *et al.*) (38). In a previous analysis conducted in the Netherlands, Tiemersma *et al.* (39) reported a non-significant positive RR of 1.6 between fresh beef and pork intake and colorectal cancer. This association was modified markedly by gender (RR for men = 2.7; 95% CI: 1.1–6.7; RR for women = 1.2; 95% CI: 0.5–2.8).

In a study conducted in Finland, Pietinen *et al.* (40) analysed data among 27 111 male smokers from the Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study. An inverse association was observed for beef, pork or lamb consumption (RR = 0.8; 95% CI: 0.5–1.2) and a non-significant positive association close to the null value was reported for total red meat consumption (RR = 1.1; 95% CI: 0.7–1.7), which included processed meat food items. No significant positive trends were observed, and associations for all intake quartiles were below 1.0 for beef, pork or lamb consumption. In another study conducted in

Finland, Jarvinen *et al*. (41) analysed data for red meat and colorectal cancer from the Finnish Mobile Clinic Health Examination Survey. Compared with other investigations, the intake categories of this study were extremely high (e.g. >206 g day^{-1} for the highest red meat quartile among men). In fact, the intake values of the reference category were higher than the highest intake category of many other studies. None of the associations between any of the red meat intake categories and colorectal, colon or rectal cancer were statistically significant, but most RRs were in the positive direction. No monotonic patterns of risk were observed for any of the associations, and the RRs attenuated with increasing categories of consumption for rectal cancer.

Larsson *et al*. (42) reported a statistically significant positive association between 94 or more grams of red meat per day (vs. <50 g day^{-1}) and colorectal cancer (RR = 1.32; 95% CI: 1.03–1.68) among women in the Swedish Mammography Cohort. Associations increased monotonically with increasing categories of red meat consumption. Their findings were modified by tumour location; the strongest and statistically significant association was observed for distal colon cancer (RR = 2.22; 95% CI: 1.34–3.68), while no association was reported for proximal colon cancer (RR = 1.03; 95% CI: 0.67–1.60) and a non-significant positive association was reported for rectal cancer (RR = 1.28; 95% CI: 0.83–1.98). An evaluation of four or more servings of beef/pork per week (vs. <2 per week) resulted in weak non-significant associations ranging between 1.08 and 1.22 for colorectal, proximal and rectal cancer, while the association was statistically significant for distal colon cancer (RR = 1.99; 95% CI: 1.26–3.14).

In a prospective analysis conducted by the Norwegian Health Screening Service, Gaard *et al*. (43) reported no significant associations between consumption of meat balls or meat stews and risk of colon cancer, as associations ranged between 0.58 and 1.08 among men and women.

Studies conducted in Asia

Among the individual studies conducted in Japan and China, associations between red meat intake and colorectal cancer are generally closer to the null value compared with associations from studies conducted in other geographic locations. In a Japanese study of almost 50 000 participants (the Miyagi Cohort), dedicated to investigating meat consumption and colorectal cancer, associations between beef (1–2 servings per week vs. almost never) and colorectal, colon and rectal cancer were approximately 1.0 or below among men and women, after adjustment for several important factors (Sato *et al*.) (44). Results for pork were more variable; the RR for colon cancer was 1.46 while the RR for rectal cancer was 0.74, but these associations were not statistically significant. Of interest, the RRs for beef and proximal and distal tumours were close to 1.0, and the RR for pork and proximal tumours was 1.05, but the RR for distal tumours was 1.90, albeit not significant. No *P*-values for trend were statistically significant across any of the analyses.

Associations have been modified by gender in other cohort studies conducted in Japan. Among men, RRs ranging between 1.03 and 2.0 were reported for consumption of red meat, beef and pork across colon and rectum tumour sites, but none of the associations were statistically significant and analyses were based on a small to moderate number of exposed cases (Kojima *et al*. (45); Khan *et al*. (46); Oba *et al*. (47)). The strongest association (i.e. RR = 2.0) was reported in an analysis that adjusted only for age and smoking (46), while the weakest association (i.e. RR = 1.03) was observed after adjustment for age, height, BMI, smoking, alcohol and physical activity in a larger study (47), suggesting the importance of controlling for the potential effects of confounding.

In the same three studies, associations between red meat, beef and pork across colon and rectal tumour sites among women ranged between 0.32 and 1.11, and none were statistically significant (45–47). Similarly, in a recent analysis of the Shanghai Women's Health Study, Lee *et al*. (48) observed non-significant associations ranging between 0.6 and 1.0 across all intake quintiles of red meat for colon and rectal cancer. Specifically, RRs for the highest intake quintiles were 0.9 (0.6–1.5) for colon cancer and 0.6 (0.3–1.1) for rectal cancer. In a Chinese nested case–control study, Chen *et al*. (49) reported a non-significant association of 1.48 (0.85–2.59) for pork intake among men and women; however, this result was based on only a dichotomized (yes or no) intake classification and was not fully adjusted.

Studies conducted in other locations

In an analysis of the Melbourne Collaborative Cohort Study conducted in Australia (English *et al*.) (50), fresh red meat was defined as a broad category of items, including veal or beef schnitzel, roast beef, veal, steak, meat balls, meat loaf, mixed dishes with beef, roast lamb/chops, pork/chops, rabbit and other game. A statistically significant positive association was reported for rectal cancer (RR = 2.3; 95% CI: 1.2–4.2), but no association was observed for colon cancer (RR = 1.1; 95% CI: 0.7–1.6). In addition, the authors conducted analyses for each incremental serving of red meat per week. The RR for each increase of one serving of red meat was 1.08 (0.99–1.16) for rectal cancer, but no association was observed for colon cancer 1.00 (0.94–1.07).

Discussion

Overall, the majority of associations between red meat consumption and colorectal cancer across the prospective epidemiologic studies are above 1.0, although most are weakly elevated (i.e. RR < 1.5) and not statistically significant. Additionally, a clear dose–response relationship is lacking and patterns of associations vary by certain study characteristics, such as anatomic tumour site (colon vs. rectum) and gender (Figs 1–3). Results across studies are generally stronger for rectal cancer than colon cancer, although associations are highly inconsistent. Findings from studies that reported associations between red meat and proximal (i.e. right-sided colon) or distal (i.e. left-sided colon) colon cancer have been variable, as associations appear to be stronger for distal colon cancer than for proximal colon cancer. However, interpretation of results by anatomic site within the colon is limited by relatively sparse data across studies. Furthermore, there are no established biological mechanisms explaining any differences in associations between red meat and risk of proximal colon cancer, distal colon cancer or rectal cancer.

Perhaps the most intriguing differences in associations between red meat and colorectal cancer are those observed between men and women. The currently available epidemiologic data are not indicative of a positive association between red meat consumption and colorectal cancer among women, based on results from over a dozen prospective studies. In fact, associations for red meat intake among women in some of the largest cohort studies range between 0.66 and 1.04 (i.e. Iowa Women's Health Study, American Cancer Society's Cancer Prevention Study-II, Women's Health Study, the National Cancer Institute's Breast Cancer Detection Demonstration Project, the Shanghai Women's Health Study) (19,30,32,33,48). Associations among men are typically 10% to 30% stronger in magnitude, but the disparity in associations by gender do not appear to be the result of higher intake levels among men. As with associations by anatomic tumour site, there are no established biological differences that may modify associations specifically for red meat intake. However, one hypothesis is that diet-related effects may differ by gender due to hormonal variation between men and women and by the proclivity of women to develop proximal tumours and men to develop distal and rectal tumours (51).

Although red meat intake has been associated with colorectal cancer in many epidemiologic investigations, relatively few studies have evaluated postulated mechanisms. Cooking meat at high temperatures, such as frying or grilling, may create heterocyclic amines or polycyclic aromatic hydrocarbons that are potentially carcinogenic chemical by-products (4,9). Results for overall mutagenic activity (i.e. total heterocyclic amines) or specific heterocyclic amine compounds and colorectal cancer are inconsistent; associations are observed above and below 1.0 (5–8,52,53). In a recent analysis of the National Institutes of Health-AARP cohort, the heterocyclic amines, 2-amino-3,8-dimethylimidazo[4,5-f]quinoxaline (MeIQx) and 2-amino-3,4,8-trimethylimidazo[4,5-f]quinoxaline (DiMeIQx) and overall mutagenic activity were significantly associated with colon cancer risk but null associations were observed for rectal cancer (4). Null associations for colon and rectal cancer were observed for 2-amino-1-methyl-6-phenylimidazo[4,5-b] pyridine (PhIP) and the polycyclic aromatic hydrocarbon benzo(a)pyrene [B(a)P] (4). Well-done cooked meat and fried meat intake has been associated positively with colorectal cancer in some case–control studies (7,54), although cohort studies have not substantiated these findings (5,30,40,43,55). Haem iron, for which red meat is a prominent source, has been postulated to increase the risk of colorectal cancer because of positive associations reported for red meat and colorectal cancer in some studies and generally null associations for poultry and fish (which are not major sources of haem iron). However, few epidemiologic studies have investigated the potential role that this factor may play in colorectal cancer risk, and findings have been variable by tumour location as well as the methodology utilized to estimate haem iron as a percentage of total iron from meat intake (4,31,42,56–58). Other postulated mechanisms include N-nitroso compounds (mainly in processed meat items), which are formed from nitrosating agents arising from nitrites under acidic gastric conditions that react with amines or amides (9,12,59). Other possible mechanisms have been investigated through several genetic epidemiologic studies of the modifying effect of polymorphisms involved in the metabolism of potentially carcinogenic mutagens produced from high-temperature cooking (5,60). However, most associations are imprecise because of limited statistical power to assess gene–environment interactions. Animal fat intake has also been hypothesized to increase the risk of colorectal cancer, but no association was observed in a meta-analysis of prospective studies (61). Recent experimental evidence has indicated 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 predominate saturated fat in beef, may have anti-carcinogenic properties (62–64); however, evidence from human studies is limited.

As with most dietary factors and chronic disease outcomes, particularly those that are heavily intertwined with other dietary and lifestyle choices such as red meat, several methodological and analytical considerations (or limitations) warrant mention. The instruments and methods used to estimate individual dietary exposures are one of the most important considerations when interpreting findings from epidemiologic studies. All studies reviewed herein utilized a food frequency questionnaire (FFQ) to ascertain self-reported dietary information. An FFQ is a generally reliable and efficient method of dietary ascertainment that may be reasonably accurate in ranking individuals by their frequency of consumption and in determining patterns of

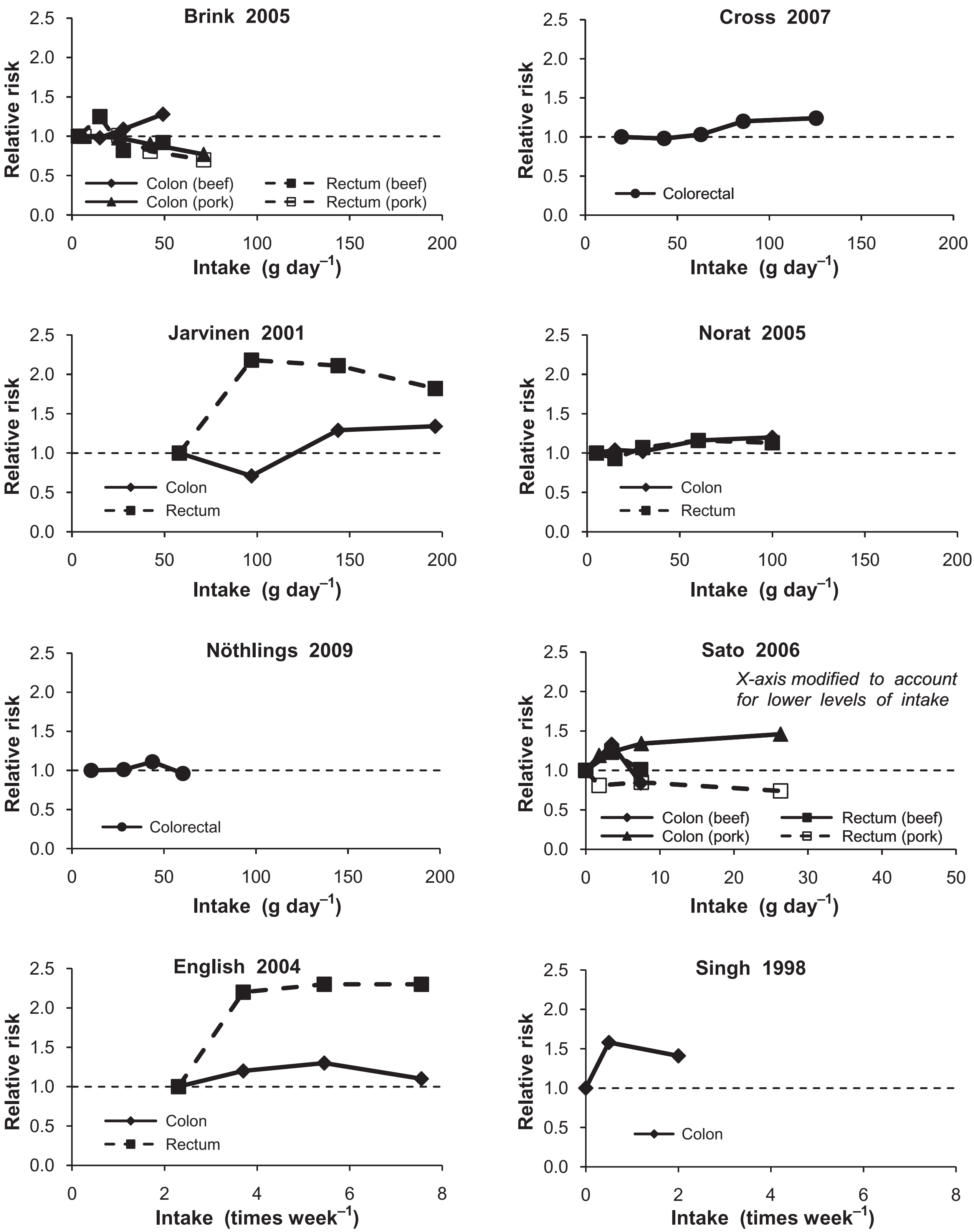

Figure 1 Red meat intake and colorectal cancer among men and women combined.

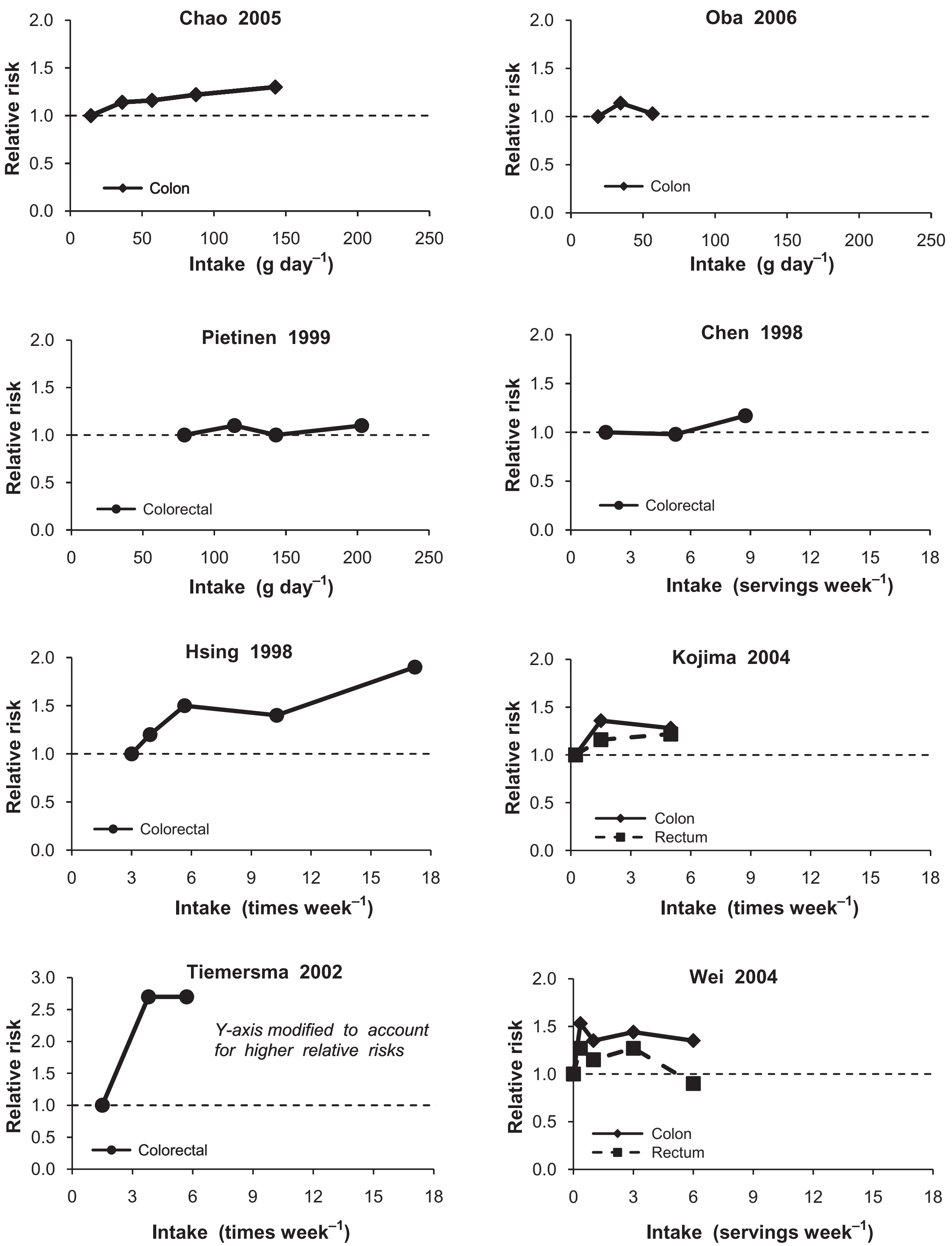

Figure 2 Red meat intake and colorectal cancer among men.

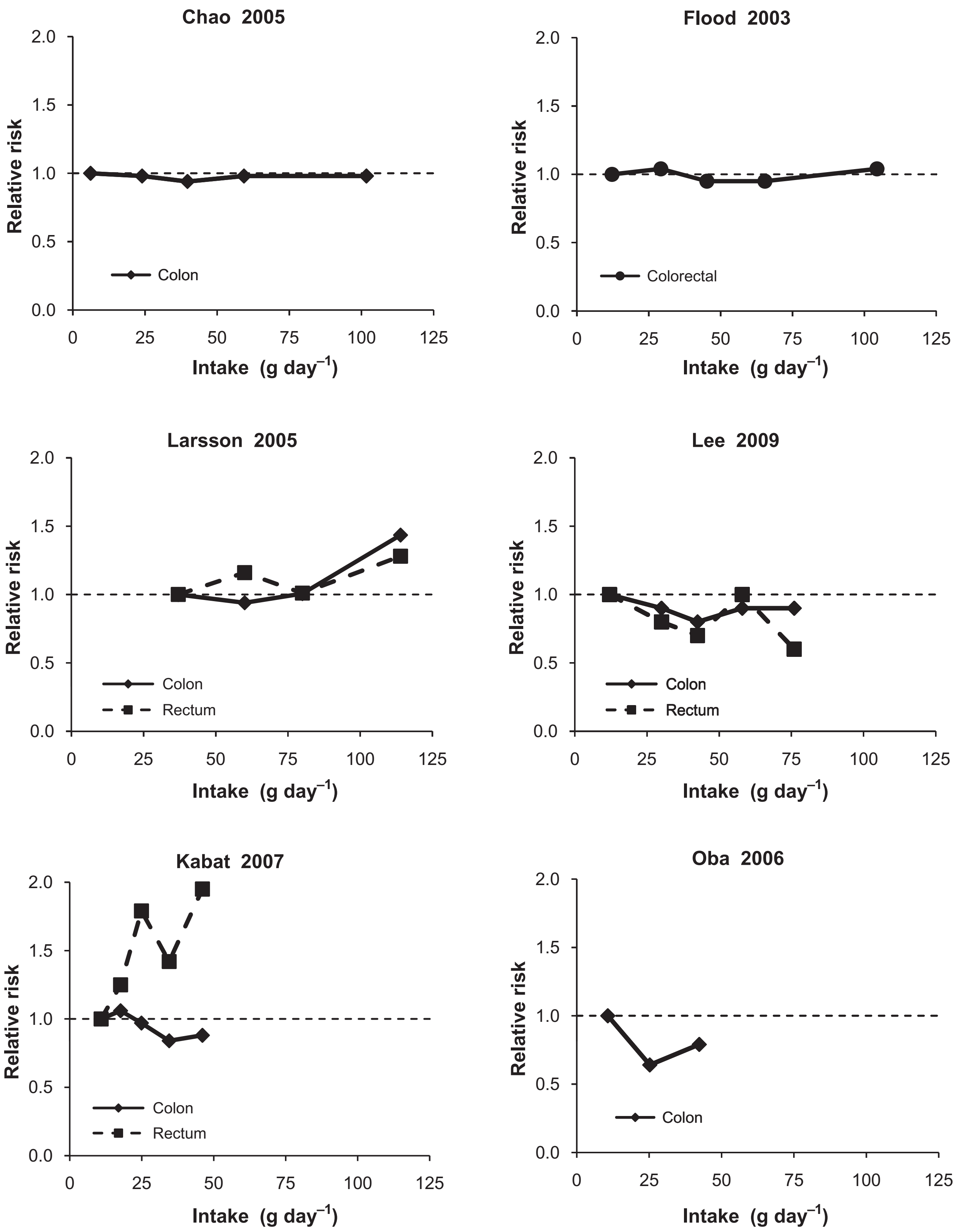

Figure 3 Red meat intake and colorectal cancer among women.

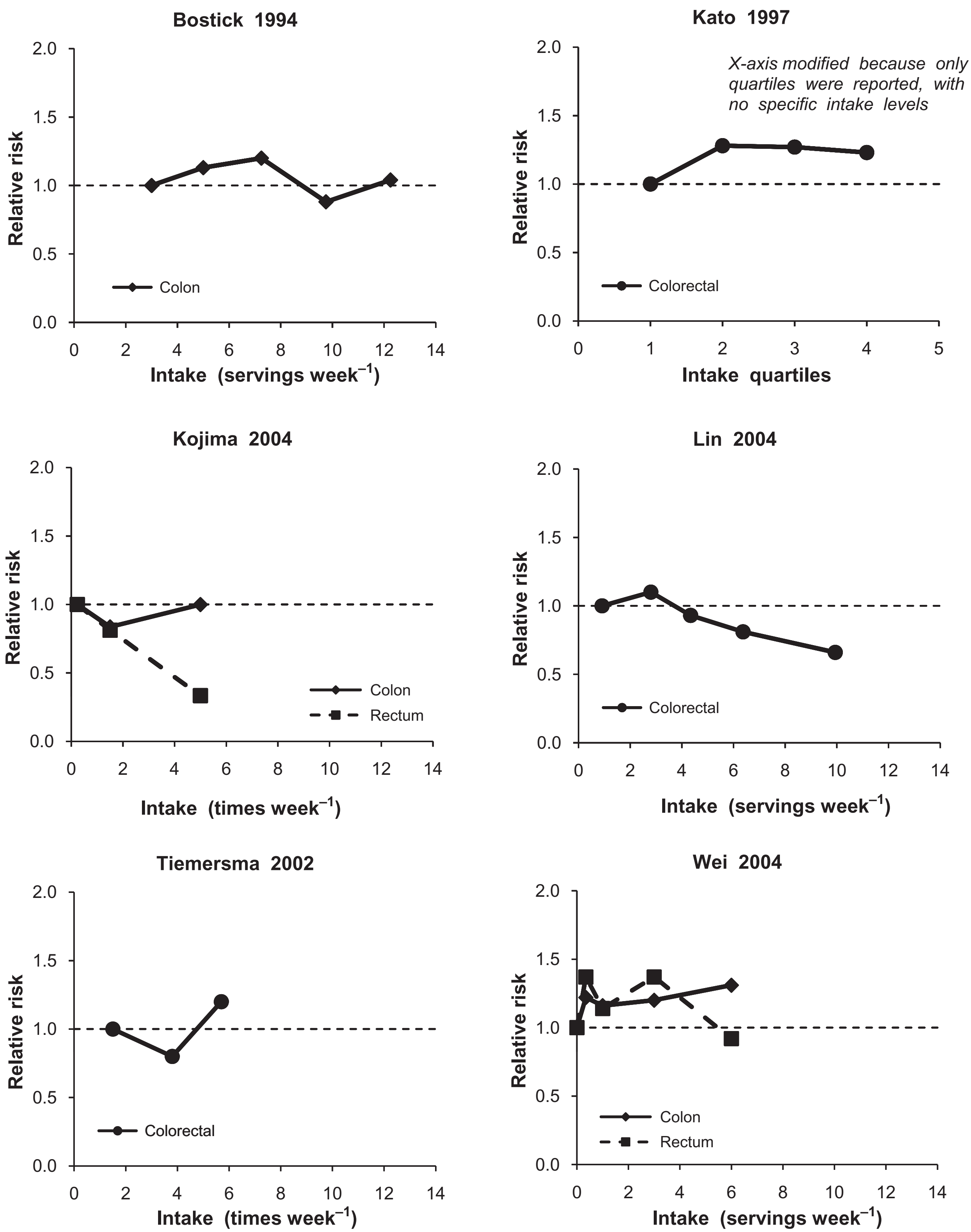

Figure 3 *Continued.*

intake among populations (65). However, a FFQ may be affected by random error (i.e. chance) and/or systematic error (i.e. bias), and may not be overly accurate in estimating the actual amount of intake.

Other important caveats to consider when interpreting a collection of literature include heterogeneity by type or definition of dietary exposure, level of exposure, analytical cut-points of exposure, or the method by which exposure categories are analysed. A universally accepted definition of 'red meat' is not available, and this food group includes a variety of types of meat. These meat items may reflect the geographical and cultural characteristics of the study population, but variability may also exist within the same geographic location or population. For example, many of the studies conducted among the US populations include a mixture of beef, pork or lamb items in their 'red meat' variable, with or without processed meat items included. Some studies conducted in Asia, Scandinavian countries or other locations commonly evaluated specific red meats (e.g. beef, pork or minced meat). Finally, in some studies red meat is not defined in the article. The amount of red meat intake is highly variable across studies and the cut-points of exposure categories differ considerably across studies (e.g. >80 g day^{-1} vs. <10 g day^{-1}; >94 g day^{-1} vs. <52 g day^{-1}, etc.) as do the types of exposure metrics (e.g. >2 servings per month vs. <2 servings per month; 3–4 servings per week vs. almost never; 4th quartile of intake vs. 1st quartile of intake [undefined], etc.) (Figs 1–3). Rarely will exposure be defined and/or ascertained in exactly the same fashion across epidemiologic studies, particularly those of dietary factors and cancer. Consequently, interpreting data such as intake–response trends is complicated by the variability of exposure units and intake comparisons within and across studies.

Interpretation of epidemiologic studies of red meat and colorectal cancer should be done in light of potential confounding. Red meat intake has been shown to be highly correlated with dietary and lifestyle factors that may confound or modify associations with colorectal cancer. For example, Cross *et al.* (4,18) showed that persons in the highest intake quintile of red meat (compared with the lowest quintile) consumed more total daily calories, were more likely to smoke, had a higher body mass index, consumed lower amounts of fruits, vegetables, fibre and calcium, engaged less frequently in physical activity, and were less educated. Even if these factors are adjusted for using statistical methods, residual confounding, as well as uncontrolled confounding, is a prominent concern when attempting to evaluate the independent effects of red meat intake. Moreover, a dietary pattern (i.e. 'Western' lifestyle) characterized by high consumption of red meat has been correlated positively with deleterious factors (e.g. high body mass index, smoking, alcohol intake), and has been correlated inversely with salubrious factors (e.g. physical activity, fruit and vegetable intake). In several studies of persons who regularly adhere to a Western dietary pattern, positive associations with colorectal cancer have been reported (66–68), although null associations have been observed in some large studies of patterns characterized by high intake of red meat (5,69–71). In a recent evaluation of dietary and lifestyle factors and colorectal cancer risk, moderate consumption of red meat was suggested, although the authors stated that, 'given the frequent co-occurrence of smoking, alcohol, physical inactivity and diets that are high in meat (both processed and non-processed meat), it is impossible to disentangle the individual effects that each of these variables may have on risk' (72).

The possible role that red meat consumption may play in colorectal carcinogenesis, if any at all, is unclear. No mechanisms involving red meat intake, independent of other food items, has been clearly established as contributing to colorectal cancer risk. As summarized herein, the currently available epidemiologic studies of red meat intake and colorectal cancer generally show weakly elevated associations, along with some null and inverse associations, with the large majority being non-statistically significant. In addition, there is a lack of a clear dose–response relationship as many associations in the lower quantiles of intake are stronger than the associations in the highest quantiles of intake. Collectively, associations are variable by anatomic tumour site, with no clear pattern of associations for colon tumours or rectal tumours. Associations also vary by gender, and overall, the epidemiologic data are not indicative of a positive association among women. Findings among men are slightly stronger in magnitude, although the potential reasons for this observed disparity between genders is unclear. Bias and confounding are likely explanations for many of the positive associations reported across the epidemiologic literature – there may be a greater propensity to report positive associations for red meat than to report null associations. Furthermore, colinearity between red meat intake and other dietary factors (e.g. Western lifestyle, high intake of refined sugars and alcohol, low intake of fruits, vegetables and fibre) and behavioural factors (e.g. low physical activity, high smoking prevalence, high body mass index) limits the ability to analytically isolate the independent effects of red meat consumption. In conclusion, the currently available epidemiologic evidence is not sufficient to support a clear and unequivocal independent positive association between red meat intake and colorectal cancer.

Conflict of Interest Statement

No conflict of interest was declared.

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