

Processed meat and colorectal cancer: a quantitative review of prospective epidemiologic studies

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A tremendous amount of scientific interest has been generated regarding processed meat consumption and cancer risk. Therefore, to estimate the association between processed meat intake and colorectal cancer (CRC), a meta-analysis of prospective studies was conducted. Twenty-eight prospective studies of processed meat and CRC were identified, of which 20 represented independent nonoverlapping study populations. Summary relative risk estimates (SRREs) for high versus low intake and dose-response relationships were calculated. The SRRE for high (vs. low) processed meat intake and CRC was 1.16 [95% confidence interval (CI): 1.10–1.23] for all studies. Summary associations were modified considerably by sex; the SRRE for men was 1.23 (95% CI: 1.07–1.42) and the SRRE for women was 1.05 (95% CI: 0.94–1.16), based on nine and 13 studies, respectively. Sensitivity analyses did not indicate appreciable statistical variation by tumor site, processed meat groups, or study location. The SRRE for each 30-gram increment of processed meat and CRC was 1.10 (95% CI: 1.05–1.15) based on nine studies, and the SRRE for each incremental serving of processed meat per week was 1.03 (95% CI: 1.01–1.05) based on six studies.

Introduction

The possible association between meat consumption and risk of cancer, particularly colorectal cancer, has generated interest among health professionals and the general public. It was estimated that dietary factors may contribute to more than 50% of all colorectal cases in Western cultures (Kune *et al.*, 1992; Willett, 2001). However, if this estimate is accurate, evidence for specific dietary nutrients or contaminants, individual foods, or food combinations has not been elucidated. Recently, it has been suggested that between 10 and 12% of new colorectal cancer cases in the United Kingdom and the United States (US) may be attributable to intake of processed meat, although this estimate was based on data from one multicenter cohort study (World Cancer Research Fund/American Institute for Cancer Research, 2009). In 2007, the World Cancer Research Fund (WCRF) in collaboration with the American Institute for Cancer Research (AICR) judged that processed meat is a convincing cause of colorectal cancer [World Cancer Research Fund (WCRF), 2007]. However, their report stated that, 'There is no generally agreed definition of 'processed meat'. The term is used inconsistently in epidemiological studies. Judgements

Overall, summary associations were weak in magnitude (i.e. most less than 1.20), processed meat definitions and analytical comparisons were highly variable across studies, and isolating the independent effects of processed meat intake is difficult, given the likely influence of confounding by other dietary and lifestyle factors. Therefore, the currently available epidemiologic evidence is not sufficient to support a clear and unequivocal independent positive association between processed meat consumption and CRC. *European Journal of Cancer Prevention* 00:000–000 © 2010 Wolters Kluwer Health | Lippincott Williams & Wilkins.

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and recommendations are therefore less clear than they could be' (pg. 117, WCRF/AICR 2007).

There is immense variability in how processed meat is defined, measured, and analyzed across epidemiologic studies. Meat processing may be defined as any mechanical, chemical, microbiological, or enzymatic treatment of meat that alters the form in which it originally occurs, and processed meat is often classified as meat that is preserved by methods other than refrigeration and freezing, and that undergoes treatment to alter the flavor, improve the quality, or enhance preservation (Romans *et al.*, 2000; Warriss, 2000; Santarelli *et al.*, 2008). As a scientific variable, processed meat commonly includes cured ham, raw and cooked sausages, bacon, finely comminuted sausages (e.g. hot dogs, bologna), luncheon meats, and fermented and/or dried items. However, definitions and consumption patterns vary by study and geographic/cultural differences. Pork and beef represent the primary muscle foods used as the basis for processed meat, and ham and sausage may provide the greatest dietary contributions to processed meat as a food group. However, other processed meat sources include poultry and fish. Since the

1990s, mechanically separated chicken and turkey have become very important components of many sausages traditionally made from pork and beef (Borchert, 2004; United States Department of Agriculture, 2006). In fact, most hot dogs and bologna that are currently sold have significant portions (often over 50%) of chicken and turkey as ingredients (Borchert, 2004; United States Department of Agriculture, 2006), which further complicates the classification. Particle size reduction and blending procedures fall within the definition of processing; hence, some studies include hamburger or minced beef in their processed meat category, even though there may be no other differences from raw meat. Salt, sugar, nitrate or nitrite, phosphate, and spices or essential oils may be added ingredients for meat curing. Furthermore, processed meat may be exposed to liquid or wood-generated smoke (Warriss, 2000; Santarelli *et al.*, 2008). Epidemiologically, isolating and estimating intake of specific processed meats from dietary measurement instruments may be difficult because of the potential overlap with broad meat groups or differences in how processed meat is defined and interpreted on a food frequency questionnaire. Despite these methodological challenges, investigators have evaluated processed meat intake and cancer outcomes in numerous epidemiologic studies.

Several hypotheses have been generated regarding the possible role that processed meat intake may play in carcinogenesis. Mechanistically, high fat content from sources such as processed meat may influence colorectal cancer risk by stimulating bile acid secretion, and heme iron in red meat has been postulated to promote carcinogenesis by cellular proliferation in the colonic mucosa [Norat *et al.*, 2002; World Cancer Research Fund (WCRF), 2007; Santarelli *et al.*, 2008]. Cooking meat using high temperature methods, such as boiling, pan-frying, and grilling, may facilitate the formation of dietary mutagens, namely heterocyclic amines. However, most ready-to-eat processed meats are cooked at low temperatures, often below the thresholds needed to form these compounds so they are likely to contain a lower level of these mutagens compared with fresh meats, such as poultry (Santarelli *et al.*, 2008) that may be cooked at higher temperatures. Exposing either fresh or processed muscle foods to an open flame or wood smoke may deposit polycyclic aromatic hydrocarbons, such as benzo[a]pyrene, on the meat surface. Perhaps the most commonly suggested mechanism involving processed meats and cancer risk pertains to nitrate, nitrite, or N-nitroso compounds, which have been shown to be carcinogenic in some laboratory animal studies (World Cancer Research Fund (WCRF), 2007; Santarelli *et al.*, 2008). However, the majority of dietary nitrate is from vegetable sources, and a proportion of nitrate is converted to nitrite endogenously. Furthermore, exogenous exposure to N-nitroso compounds is not specific to processed meat (e.g. grilled bacon, smoked fish), as these compounds may be found in other dietary

sources, such as certain cheeses or malted alcoholic beverages, such as beer and some distilled whiskey (Lijinsky, 1999; Santarelli *et al.*, 2008). Despite these proposed mechanisms, the available epidemiologic evidence from human studies is limited and inconsistent.

Three previously published meta-analyses examined processed meat consumption and colorectal cancer; summary associations across the available epidemiologic studies seem to be getting weaker in magnitude with each successive published meta-analysis. The first, published in 2001, analyzed prospective studies through 1999, for which a summary association of 1.49 [95% confidence interval (CI): 1.22–1.81] for each 25 g/day increment of processed meat was reported (Sandhu *et al.*, 2001). The second meta-analysis, published in 2002, yielded a summary association of 1.39 (95% CI: 1.09–1.76) for the highest versus lowest intake level of processed meat, based on data from seven prospective studies (Norat *et al.*, 2002). In the third meta-analysis, published in 2006, the summary association between processed meat (high vs. low intake) and colorectal cancer was 1.20 (95% CI: 1.11–1.31) based on data from 13 prospective studies (Larsson and Wolk, 2006). Notably, associations between processed meat and colorectal cancer among men were stronger in magnitude than among women, as a statistically significant summary relative risk estimate (SRRE) of 1.27 (95% CI: 1.06–1.52) was reported for men, but a nonsignificant SRRE of 1.07 (95% CI: 0.94–1.23) was observed for women. In their dose–response analysis, a summary association of 1.09 (95% CI: 1.05–1.13) was observed for every 30-gram increment of processed meat (Larsson and Wolk, 2006).

Since the publication of these meta-analyses, some large prospective studies of processed meat and colorectal cancer have been published. In addition, some previous studies were identified as reporting data for individual processed meat items that were not included in prior meta-analyses. Therefore, to update the state of knowledge on the epidemiology of processed meat and colorectal cancer, a meta-analysis of data from all available prospective studies was conducted. Specific goals were to (i) estimate summary associations for high processed meat intake compared with low intake, (ii) examine potential sources of heterogeneity among subgroups, such as gender 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

A MEDLINE literature search using the PubMed interface was conducted to identify relevant articles published through July 2009. Unqualified keywords, searched as text words in the title, abstract, and full journal article,

were used in a search string for a variety of colorectal cancer terms (e.g. colon cancer, rectal cancer, colorectal carcinoma). The dietary search string component included searching on a broad category of meat, which was then focused on processed meat (e.g. processed, preserved, cured) and individual processed meat items (e.g. ham, sausage) as an analytical variable used in epidemiologic studies. In addition, the bibliographies of the WCRF/AICR report on diet and cancer [World Cancer Research Fund (WCRF), 2007], review articles, and meta-analyses pertaining to meat consumption and colorectal cancer were examined in an effort to identify all available literature that may not have been identified by the database searches. All data considered for inclusion in the meta-analysis originated from peer-reviewed published articles of prospective epidemiologic studies written in English.

The scope of this meta-analysis was processed meat consumption, classified as meat, predominantly red meat (although poultry and fish are sometimes included as well) that undergoes preservation methods other than freezing. A quantitative assessment specific to red meat is beyond the scope of this review and has been submitted elsewhere. Studies were excluded that did not report data specifically for either colorectal cancer, colon cancer, or rectal cancer (i.e. studies of the digestive tract, without specific anatomic identification, were excluded). Studies that evaluated adenomatous polyps were not evaluated. To be included, studies were required to report point estimates (i.e. relative risks) and measures of variability (i.e. 95% CI) for a high category of processed meat intake compared with the lowest category of intake, or data were required to be available for such calculations. A total of 28 cohort studies (Willett *et al.*, 1990; Thun *et al.*, 1992; Bostick *et al.*, 1994; Giovannucci *et al.*, 1994; Goldbohm *et al.*, 1994; Gaard *et al.*, 1996; Kato *et al.*, 1997; Sellers *et al.*, 1998; Knekt *et al.*, 1999; Pietinen *et al.*, 1999; Tiemersma *et al.*, 2002; 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; Chao *et al.*, 2005; Larsson *et al.*, 2005; Luchtenborg *et al.*, 2005; Norat *et al.*, 2005; Balder *et al.*, 2006; Oba *et al.*, 2006; Sato *et al.*, 2006; Cross *et al.*, 2007; Nothlings *et al.*, 2009) were included in this assessment (Table 1), of which 20 studies (Gaard *et al.*, 1996; Kato *et al.*, 1997; Sellers *et al.*, 1998; Knekt *et al.*, 1999; Pietinen *et al.*, 1999; Tiemersma *et al.*, 2002; Flood *et al.*, 2003; English *et al.*, 2004; Khan *et al.*, 2004; Kojima *et al.*, 2004; Lin *et al.*, 2004; Wei *et al.*, 2004; Chao *et al.*, 2005; Larsson *et al.*, 2005; Norat *et al.*, 2005; Balder *et al.*, 2006; Oba *et al.*, 2006; Sato *et al.*, 2006; Cross *et al.*, 2007; Nothlings *et al.*, 2009) represented independent (nonoverlapping) study populations and reported data that could be included in the meta-analysis.

Data extraction and statistical analysis

Qualitative information and quantitative data were extracted from each study that met the criteria for

inclusion. Specifically, information was extracted pertaining to the following: (i) the year of the study, (ii) the name and nature of the cohort, (iii) geographic location of the study, (iv) methods of dietary exposure ascertainment, (v) the definition of processed meat, (vi) the intake metric comparison, (vii) the number of exposed cases per intake strata, (viii) the relative risk estimate and 95% CI for each sex and anatomic tumor location (i.e. colorectal, colon, rectal) where applicable, and (ix) the factors that were adjusted or controlled for in the analysis.

Each article was reviewed to identify cohorts that may have been analyzed in multiple publications. In these situations, the inclusion of data was based on (i) the size of the study population, (ii) duration of follow-up with an emphasis on the most recent publication with the longest follow-up, (iii) classification and analytical categorization of processed meat, and (iv) level of control for potential confounding factors. Four articles were identified that reported overlapping analyses of the Netherlands Cohort Study (Goldbohm *et al.*, 1994; Brink *et al.*, 2005; Luchtenborg *et al.*, 2005; Balder *et al.*, 2006); thus, data were extracted from the most recent publication (Balder *et al.*, 2006), which analyzed the most cases with the longest follow-up, and controlled for the most potential confounding factors. Two studies of the Iowa Women's Health cohort were identified (Bostick *et al.*, 1994; Sellers *et al.*, 1998); thus, data were selected from the study (Sellers *et al.*, 1998) with longer follow-up that analyzed more cases although fewer variables were included in their multivariate analyses. 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 the overall analyses and sex-specific analyses. Other publications of these cohorts were not used in the primary analyses because they had shorter follow-up, analyzed a smaller study population, or did not explicitly state the type of multivariate analysis (Willett *et al.*, 1990; Giovannucci *et al.*, 1994; Wu *et al.*, 2004). The study by Gaard *et al.* (1996) was removed as part of the sensitivity analyses because this study evaluated a very limited exposure source (poached/fried sausages) and adjusted for age only. Cumulative meta-analyses, based on 5-year publication date increments, were conducted to determine whether the strength of association changed over time. In these analyses, data from Goldbohm *et al.* (1994) [replaced by Balder *et al.* (2006) in overall analysis] and data from Giovannucci *et al.* (1994) and Willett *et al.* (1990) [replaced by Wei *et al.* (2004) in overall analysis] were used for the early time periods.

Statistical analyses were based on comparisons of the highest intake category with the lowest intake category (which may include persons who do not consume processed meat). In addition, categorical dose-response analyses were conducted using the method proposed by

Table 1 Summary of prospective cohort studies of processed meat consumption and colorectal cancer

Author and year	Cohort (total number in study)	Exposure ascertainment	Analytical category (definition)	Number of exposed cases	Sex	Analytical comparison	Relative risk (95% CI)	Statistical adjustment
Balder <i>et al.</i> (2006) ^a	NLCS (Netherlands) (120 852 total cohort; 1535 cases; 5000 subcohort members)	FFQ (150 item, 14 meat items)	Processed meat [preservation (i.e., smoking, fermentation, nitrate/nitrite salt, curing)]	275	Men	Quartiles (4 vs. 1)	1.18 (0.84–1.64)	Age, BMI, family hx of CRC, smoking, nonoccupational physical activity, total energy intake, alcohol, total vegetable consumption
				NR	Men	Colorectal	1.33 (0.89–1.99)	
				NR	Men	Rectal	0.96 (0.60–1.53)	
				115	Women	Colorectal	1.05 (0.74–1.48)	
				NR	Women	Colon	1.07 (0.73–1.57)	
				NR	Women	Rectal	1.01 (0.54–1.90)	
Bostick <i>et al.</i> (1994)	Iowa Women's Health Study (35 215)	FFQ (127 item)	Processed meats [bacon, hot dogs, other processed meats (sausage, salami, bologna, etc.)]	8	Women	Colon: >3 vs. <0 servings/week	1.51 (0.72–3.17)	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 <i>et al.</i> (2005) ^a [overlap with Balder <i>et al.</i> (2006); Goldbohm <i>et al.</i> (1994); Luchtenborg <i>et al.</i> (2005)]	NLCS (Netherlands) (120 852 total cohort; 608 cases; 2948 subcohort members)	FFQ (150 item)	Meat products [meat items that have undergone some form of preservation (mostly cured, sometimes also smoked or fermented)]	123	Both	Colon: quartiles of intake (4 vs. 1)	1.17 (0.86–1.59)	Age, sex, quetelet index, smoking, energy intake, family hx of CRC
				47	Both	Rectum: tertile of intake (3 vs. 1)	1.04 (0.64–1.68)	
Chao <i>et al.</i> (2005)	CPS II (US) (148 610)	FFQ (68 item)	Processed meat [ham, smoked meats, frankfurters/sausage, fried bacon]	261	Both	Quintiles of intake (5 vs. 1)	1.13 (0.91–1.41)	Age, sex, total energy, education, BMI, smoking, recreational physical activity, multivitamin use, aspirin use, alcohol, hormone therapy, fruits, vegetables, high-grain foods
				94	Both	Colon	1.26 (0.86–1.83)	
				133	Both	Rectal	0.97 (0.72–1.29)	
				97	Both	Proximal colon	1.39 (0.94–2.05)	
				143	Men	Distal colon	1.11 (0.80–1.54)	
				118	Women	Colon	1.16 (0.85–1.57)	
Cross <i>et al.</i> (2007)	NIH-AARP Diet and Health Study (US) (494 036)	FFQ (124 item)	Processed meat (bacon, red meat sausage, poultry sausage, luncheon meats, cold cuts, ham, hot dogs, meats added to mixtures, such as pizza, chili, lasagna, and stew)	1183	Both	Quintiles of intake (5 vs. 1) 22.6 g/1000 kcal vs. 1.6	1.20 (1.09–1.32)	Age, sex, education, marital status, family hx of cancer, race, BMI, smoking, frequency of vigorous physical activity, total energy intake, alcohol intake, and fruit and vegetable consumption
					Both	Colorectal	1.18 (1.06–1.32)	
					Both	Colon	1.24 (1.03–1.49)	
					Both	Rectal	1.24 (1.03–1.49)	
English <i>et al.</i> (2004)	Melbourne Collaborative Cohort Study (Australia) (37 112)	FFQ (121 item)	Processed meat (salami, sausages, frankfurters, bacon, ham, corned beef, lunch meats)	NR	Both	Quartiles (4 vs. 1)	1.5 (1.1–2.0)	Sex, country of birth, energy intake, fat, cereal products
Flood <i>et al.</i> (2003)	BCDDP (US) (45 496)	FFQ (62 item)	Processed meat (bacon, ham or other lunch meat, hot dogs, sausage)	NR	Women	Quintiles (5 vs. 1) 22.2 + g/1000 kcal vs. ≤ 0.02 g/1000 kcal	0.97 (0.73–1.28)	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)

Gaard <i>et al.</i> (1996)	Norway (50 535)	FFQ	Poached or fried sausages	4	Women	Colon: 5 + /week vs. <1	3.50 (1.02–11.9)	Age, attained age
Giovannucci <i>et al.</i> (1994) [overlap with Wei <i>et al.</i> (2004)]	HPFS (US) (47 949)	FFQ (131 item)	Processed meats	6	Men	Colon: 5 + /week vs. <1	1.98 (0.70–5.58)	Age
				7	Men	Colon: ≥ 5 vs. 0 servings/week	1.16 (0.44–3.04)	
Goldbohm <i>et al.</i> (1994) ^a [overlap with Balder <i>et al.</i> (2006); Brink <i>et al.</i> (2005); Luchtenborg <i>et al.</i> (2005)]	NLCS (Netherlands) (120 852 total cohort; 312 cases; 3500 subcohort members)	FFQ (150 item)	Processed meat (raw and cooked, cured meat products and sausages)	59	Both	Colon: >20 vs. 0 g/day	1.72 (1.03–2.87)	Age and energy (continuous variables); sex and dietary fiber intake
				37	Men	Colon: >20 vs. 0 g/day	1.84 (0.85–3.95)	Age and energy (continuous variables)
				22	Women	Colon: >20 vs. 0 g/day	1.66 (0.82–3.35)	
Kato <i>et al.</i> (1997)	New York, Florida (14 727)	Questionnaire	Ham, sausages	NR	Women	Quartiles of intake (4 vs. 1)	1.09 (0.59–2.02)	Age, total calorie intake, education, enrollment place
Khan <i>et al.</i> (2004)	Japan (3158)	Baseline survey	Ham, sausage	NR	Men	Several times/week; everyday vs. never;	0.5 (0.1–2.2)	Age, smoking
				NR	Women	several times/yr; several times/month	1.4 (0.4–4.5)	Age, health status, health education, health screening and smoking
Knekt <i>et al.</i> (1999)	Mobile Clinic Health Examination Survey (Finland) (9985)	FFQ	Cured meat	NR	Both	Quartiles (4 vs. 1)	1.84 (0.98–3.47)	Age, sex, smoking, energy intake, municipality
Kojima <i>et al.</i> (2004)	Collaborative Cohort Study (Japan) (107 824)	FFQ (33 item)	Ham and sausage	28	Men	3–7/week vs. 0–2/month	1.44 (0.90–2.31)	Age, family hx of CRC, BMI, alcohol, smoking, walking per day, education, regions of enrollment
				16	Men	Colon	1.00 (0.56–1.78)	
				15	Women	Colon	0.94 (0.53–1.66)	
				9	Women	Rectal	1.56 (0.69–3.53)	
Larsson <i>et al.</i> (2005)	Swedish Mammography Cohort (61 433)	FFQ (67 item)	Processed meat (bacon, hot dogs, ham or other lunch, blood pudding)	NR	Women	32+ g/day vs. <12	1.07 (0.85–1.33)	Age, BMI, education, energy intake, alcohol, saturated fat, calcium, folate, fruits, vegetables, whole grain foods
					Women	Colorectal	0.90 (0.60–1.34)	
					Women	Rectal	1.02 (0.69–1.52)	
					Women	Proximal colon	1.39 (0.86–2.24)	
Lin <i>et al.</i> (2004)	Women's Health Study (US) (37 547)	FFQ (131 item)	Processed meat (hot dogs, processed meats, bacon)	32	Women	Distal colon	0.85 (0.53–1.35)	Age, random treatment assignment, BMI, family hx of CRC, hx of polyps, physical activity, smoking, alcohol, postmenopausal hormone therapy, total energy
					Women	0.50+ servings/day vs. none	0.85 (0.53–1.35)	
						Quartiles of intake g/day (4 vs. 1)		
						Colon	1.17 (0.86–1.59)	
Luchtenborg <i>et al.</i> (2005) ^a [overlap with Balder <i>et al.</i> (2006); Brink <i>et al.</i> (2005); Goldbohm <i>et al.</i> (1994)]	NLCS (Netherlands) (120 852 total cohort; 588 cases; 2,948 subcohort members)	FFQ (150 item, 14 meat items)	Meat products (meat items that have undergone preservation)	120	Both	Colon	1.17 (0.86–1.59)	Age, sex, family history of CRC, smoking, BMI, energy intake
				45	Both	Rectal	1.04 (0.64–1.68)	
Norat <i>et al.</i> (2005)	EPIC (Europe) (478 040)	FFQ (88–266 items)	Processed meat [preserved pork and beef (salting, smoking, marinating, air drying, heating); i.e., ham, bacon, sausages, salami, bologna, tinned meat, and lunch meat]	121	Both	80 g/day vs. <10	1.42 (1.09–1.86)	Age, sex, energy, height, weight, occupational physical activity, smoking, alcohol intake, dietary fiber, center
				NR	Both	Colorectal	1.30 (0.92–1.84)	
					Both	Colon	1.62 (1.04–2.50)	
					Both	Rectal	1.19 (0.70–2.10)	
					Both	Proximal (right) colon	1.48 (0.87–2.53)	
						Distal (left) colon	1.48 (0.87–2.53)	
Nothings <i>et al.</i> (2009) ^a	Multiethnic Cohort Study (Hawaii, Los Angeles County) (215 000; 1009 cases; 1522 controls)	FFQ (> 180 item)	Processed meat	263	Both	11.0+ g/1000 kcal/day vs. 0–3.5	1.08 (0.83–1.39)	Sex, age at blood draw, ethnicity, family hx of CRC, BMI, fiber, calcium, vitamin D, folic acid, ethanol, physical activity, smoking

Table 1 (continued)

Author and year	Cohort (total number in study)	Exposure ascertainment	Analytical category (definition)	Number of exposed cases	Sex	Analytical comparison	Relative risk (95% CI)	Statistical adjustment	
Oba <i>et al.</i> (2006)	Japan (30 221)	FFQ (169 item)	Processed meat (Chinese style roasted pork)	44	Men	Colon: 20.3+ g vs. ≤ 3.9	1.98 (1.24–3.16)	Age, height, BMI, smoking, alcohol, physical activity	
				23	Women	Colon: 16.3+ g vs. ≤ 3.0	0.85 (0.50–1.43)		
Pietinen <i>et al.</i> (1999)	ATBC Study (Finland) (27 111)	Dietary history questionnaire	Processed meat	42	Men	122+ g vs. <27 g	1.2 (0.7–1.8)	Age, supplement group, smoking, BMI, alcohol, education, physical activity at work, calcium intake	
Sato <i>et al.</i> (2006)	Miyagi Cohort Study (Japan) (47 605)	FFQ (40 item)	Ham or sausage	37	Both	3–4/week vs. almost never	0.91 (0.61–1.35)	Age, sex, smoking, alcohol, BMI, education, family hx of cancer, walking, consumption of fat, calcium, fiber	
				20	Both	Colorectal	0.75 (0.45–1.27)		
				17	Both	Rectal	1.10 (0.60–2.03)		
				9	Both	Proximal colon	0.69 (0.32–1.51)		
				7	Both	Distal colon	0.65 (0.28–1.55)		
Sellers <i>et al.</i> (1998) [overlap with Bostick <i>et al.</i> (1994)]	Iowa Women's Health Study (35 216)	FFQ (127 item)	Nitrate meats (bacon, hot dogs, processed meat)	17	Women	Colon > 1.5 servings/week vs. ≤ 0.5	0.8 (0.4–1.6)	Age, energy intake, hx of polyps	
				62	Women	Family hx of colon cancer vs. No family hx of colon cancer			1.0 (0.7–1.4)
Thun <i>et al.</i> (1992)	CPS II (US) (764 343)	FFQ (32 item)	Processed meat	NR	Men	Colon	Positive association (data not reported)		
			Ham	NR	Men	Colon	Positive association (data not reported)		
Tiemersma <i>et al.</i> (2002) ^a	Monitoring Project on Cardiovascular Disease Risk Factors (Netherlands) (>36 000; 102 cases; 537 controls)	FFQ	Processed meat	NR	Women	Colon	Positive association (data not reported)	Age, sex, center, total energy intake, alcohol, body height	
			Ham	NR	Women	Colon	Positive association (data not reported)		
			Sausage (as a snack)	51	Both	Yes vs. No	0.9 (0.6–1.3)		
Wei <i>et al.</i> (2004)	NHS; HPFS (US) (134 365) HPFS (46 632) NHS (87 733)	FFQ	Processed meat	81	Both	5+ times/week vs. 0	1.33 (1.04–1.70)	Age, family hx, BMI, physical activity, beef, pork, lamb as main dish, alcohol, calcium, folate, height, smoking before age 30 years, hx of endoscopy, sex	
			Processed meat	15	Both	Colon			0.90 (0.52–1.57)
			Processed meat	37	Men	Rectum			1.27 (0.87–1.85)
				8	Men	Rectal			1.06 (0.48–2.33)
Willet <i>et al.</i> (1990) [overlap with Wei <i>et al.</i> (2004)]	NHS (US) (88 751)	FFQ (61 item)	Processed meat (hot dogs, preserved meat and bacon)	44	Women	Colon	1.32 (0.95–1.83)	Age	
				7	Women	Rectal	0.73 (0.33–1.59)		
				7	Women	Colon: 5+ servings/week vs. > 1 servings/month	1.21 (0.53–2.72)		
Wu <i>et al.</i> (2004) [overlap with Wei <i>et al.</i> (2004)]	HPFS (US) (47 311)	FFQ (131 item)	Processed meat	NR	Men	Colon: high vs. low	1.25 (0.95–1.65)	Multivariate (not explicitly stated for this analysis)	

Outcome is colorectal cancer, unless otherwise noted.

^aNested case-control or case-cohort.

ATBC, alpha-tocopherol; BCCP, beta-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; hx, history; 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.

Greenland and colleagues (Greenland and Longnecker, 1992; Berlin *et al.*, 1993) to estimate the slopes (coefficients) from the correlated natural log of the relative risks across intake strata. This method requires that the number of cases/strata, person-time/strata, the relative risk and associated variance is known for a minimum of three intake categories. For studies that did not report all necessary information for the aforementioned method, the slope was estimated using variance-weighted least squares regression methods. Consumption data were not rescaled across studies because this may introduce another dimension of measurement error. Therefore, dose-response meta-analysis models were generated for studies that reported results in grams per day units or times (or servings) per week units. The median level of consumption for each category of processed meat intake was assigned to each risk estimate when calculating the individual study coefficients. If the median intake value was not provided, the midpoint of each category was used. For an open-ended upper category of intake, the intake level was estimated based on the difference between the median or midpoint of the penultimate category and the lower bound of the highest category of intake (i.e. assuming the same amplitude as the earlier category). Five studies (Gaard *et al.*, 1996; Kato *et al.*, 1997; Knekt *et al.*, 1999; Tiemersma *et al.*, 2002; 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 SRREs, 95% CIs, and corresponding *P* values for heterogeneity. The estimates of the individual studies were weighted based on the inverse of the variance, which is related to the sizes of the study populations. 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, publication date, and specific meat items. If data for men and women or colon and rectum were reported separately in a study, the point estimates and CI for each sex or tumor site were included. The presence of publication bias for studies of processed meat and colorectal cancer 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 Duval and Tweedie's imputation method (Rothstein *et al.*, 2005). All statistical analyses were performed by using STATA (version 10.0; StataCorp, College Station, Texas, USA) (STATA, 2008) and Comprehensive Meta-Analysis (version 2.2.046; Biostat, Englewood, New Jersey, USA) (Comprehensive Meta-Analysis, 2007).

Results

Characteristics of all studies included in this assessment are reported in Table 1. Most studies reported data for processed meat as a food group, comprising several

individual food items (e.g. ham, lunch meats, hot dogs), although some studies evaluated single food items such as ham or sausage, and processed meat was not defined in some studies. Analytical metrics (e.g. servings per week, grams per day) and unit comparisons (e.g. 5 times per week vs. < 1, > 32 g per day vs. < 12) were highly variable across studies. Men and women were analyzed together in many studies; however, several studies reported sex-specific data, and many studies restricted their cohorts to men only or women only. Similarly, colorectal cancer was reported as a combined outcome in many studies, but colon cancer and rectal cancer were reported separately in numerous studies as well. Of the 42 point estimates reflecting data from 20 individual studies, only six associations (from five studies) were statistically significant.

High versus low intake

In the meta-analysis of all 20 independent studies, the summary association between processed meat and colorectal cancer was 1.16 (95% CI: 1.10–1.23, *p*-heterogeneity = 0.556), which included data for men and women combined (Table 2, Fig. 1). Summary associations were not modified by tumor site, as the SRRE for colon cancer was 1.19 (95% CI: 1.10–1.28) and the SRRE for rectal cancer was 1.18 (95% CI: 1.03–1.36) among 12 and eight studies, respectively (Table 2). Summary associations were markedly stronger among men than women. The SRRE for the nine studies that reported data specifically for men was 1.23 (95% CI: 1.07–1.42) whereas the SRRE among the 13 studies that reported data for women was 1.05 (95% CI: 0.94–1.16). Although data that were both sex-specific and tumor site-specific were limited to relatively few studies, summary associations were in the positive direction for colon cancer among men (SRRE = 1.35, 95% CI: 1.13–1.61) and women (SRRE = 1.11, 95% CI: 0.97–1.27), and summary associations were null or slightly inverse for rectal cancer among men (SRRE = 0.99, 95% CI: 0.71–1.38) and women (SRRE = 0.96, 95% CI: 0.72–1.29) (Table 2).

In addition to the above analyses, numerous sensitivity analyses were conducted for a variety of study characteristics where applicable, such as the geographic location of the study, publication date, level of statistical adjustment, and processed meat categories. There was slight variability in summary associations by study location (Table 2). The SRRE for the eight studies conducted in the US was 1.15 (95% CI: 1.07–1.23, *p*-heterogeneity = 0.871), whereas the SRRE for the non-US studies was slightly stronger in magnitude and more heterogeneous (SRRE = 1.20, 95% CI: 1.08–1.34, *p*-heterogeneity = 0.260). The summary association was weaker in more recent studies published after the year 2000 (SRRE = 1.16, 95% CI: 1.10–1.23) compared with studies published before the year 2000 (SRRE = 1.24, 95% CI: 1.03–1.50). More specifically, in our cumulative meta-analysis, the SRRE

Table 2 Summary of processed meat and results of colorectal cancer meta-analysis

Model (number of studies)	SRRE	95% CI	P value for heterogeneity	Analytical notes
All studies (n=20)	1.16	1.10–1.23	0.556	Includes men and women, colon and rectal tumor sites, single meat items where applicable
Studies conducted in the US (n=8)	1.15	1.07–1.23	0.871	Includes data from studies conducted among participants in the US
Studies conducted outside the US (n=12)	1.20	1.08–1.34	0.260	Includes data from non-US study populations
Studies conducted in Europe (n=7)	1.19	1.05–1.35	0.437	Includes data from studies conducted in Europe (Netherlands, Norway, Finland, Sweden, EPIC cohort)
Studies conducted in Asia (n=4)	1.13	0.90–1.43	0.191	Includes data from studies conducted in Japan and China
Studies published prior to year 2000 (n=8)	1.24	1.03–1.50	0.448	Includes data from Goldbohm 1994, Giovannucci 1994, and Willett 1990 that are not in overall model
Studies published between 2000 and 2009 (n=15)	1.16	1.10–1.23	0.612	Includes data from updated cohorts for Balder 2006 and Wei 2004
Processed meat food group variable (n=13)	1.17	1.10–1.24	0.745	Includes data for a processed meat food group variable
Individual processed meat items (n=7)	1.14	0.94–1.38	0.202	Includes data for ham/sausage, poached/fried sausage, Chinese style roasted pork
Colon (n=12)	1.19	1.10–1.28	0.436	Includes data reported specifically for colon cancer, men and women included
Rectal (n=8)	1.18	1.03–1.36	0.384	Includes data reported specifically for rectal cancer, men and women included
Men (n=9)	1.23	1.07–1.42	0.608	Studies that reported data specifically for men
Men, colon (n=6)	1.35	1.13–1.61	0.460	Studies that reported data for colon cancer among men
Men, rectal (n=3)	0.99	0.71–1.38	0.977	Studies that reported data for rectal cancer among men
Women (n=13)	1.05	0.94–1.16	0.786	Studies that reported data specifically for women
Women, colon (n=8)	1.11	0.97–1.27	0.525	Studies that reported data for colon cancer among women
Women, rectal (n=4)	0.96	0.72–1.29	0.583	Studies that reported data for rectal cancer among women
Dose–response for each 30-g increment of processed meat (n=9)	1.10	1.05–1.15	0.273	SRRE for each 30-g increment of processed meat; includes data from studies that reported intake in grams per day units
Dose–response for each incremental serving per week (n=6)	1.03	1.01–1.05	0.683	SRRE for each incremental serving of processed meat per week; includes data from studies that reported intake in servings/times per week units
Men, dose–response for each 30-g increment of processed meat (n=4)	1.14	0.96–1.37	0.050	SRRE for each 30-g increment of processed meat; includes data from studies that reported intake in grams per day units
Men, dose–response for each incremental serving per week (n=2)	1.03	0.99–1.06	0.824	SRRE for each incremental serving of processed meat per week; includes data from studies that reported intake in servings/times per week units
Women, dose–response for each 30-g increment of processed meat (n=5)	1.00	0.91–1.10	0.819	SRRE for each 30-g increment of processed meat; includes data from studies that reported intake in grams per day units
Women, dose–response for each incremental serving per week (n=4)	1.03	1.00–1.06	0.786	SRRE for each incremental serving of processed meat per week; includes data from studies that reported intake in servings/times per week units

CI, confidence interval; SRRE, summary relative risk estimate.

was 1.49 (95% CI: 1.00–2.22) for three studies published between 1990 and 1995, 1.24 (95% CI: 1.03–1.50) for eight studies published through 1999, 1.17 (95% CI: 1.05–1.30) for 13 studies published through 2004, and 1.16 (95% CI: 1.10–1.23) for 20 studies published through 2009 (Fig. 3).

The overall meta-analysis was generally robust to the exclusion of studies that did not adjust for several important factors associated with colorectal cancer, such as physical activity, body mass index, and alcohol intake (data not tabulated). In the meta-analysis of 13 studies that analyzed processed meat as a food group, the SRRE was 1.17 (95% CI: 1.10–1.24) (Table 2). Meta-analysis of the studies that reported data for ham/sausage, poached/fried sausage, or Chinese style roasted pork resulted in an SRRE of 1.14 (95% CI: 0.94–1.38). Removal of Gaard *et al.* (1996) (outlier study that evaluated poached/fried sausage only) in this model resulted in an SRRE of 1.10 (95% CI: 0.91–1.32).

Dose–response

As mentioned, dose–response meta-analysis models were generated for studies that reported results in grams per day units or times (or servings) per week units. In the meta-analysis of nine studies that reported data in times per day units, the SRRE for each increment of 30 g of processed meat was 1.10 (95% CI: 1.05–1.15) (Table 2).

Summary associations were modified by sex; the SRRE for each 30-g increment of processed meat was 1.14 (95% CI: 0.96–1.37) among men (based on data from four studies) and no association between each 30-g increment of processed meat intake and colorectal cancer was observed among women (SRRE = 1.00, 95% CI: 0.91–1.10), based on data from five studies (Table 2). Among men and women, the SRRE for each one serving increment of processed meat per week was 1.03 (95% CI: 1.01–1.05), based on data from six studies (Table 2).

Publication bias

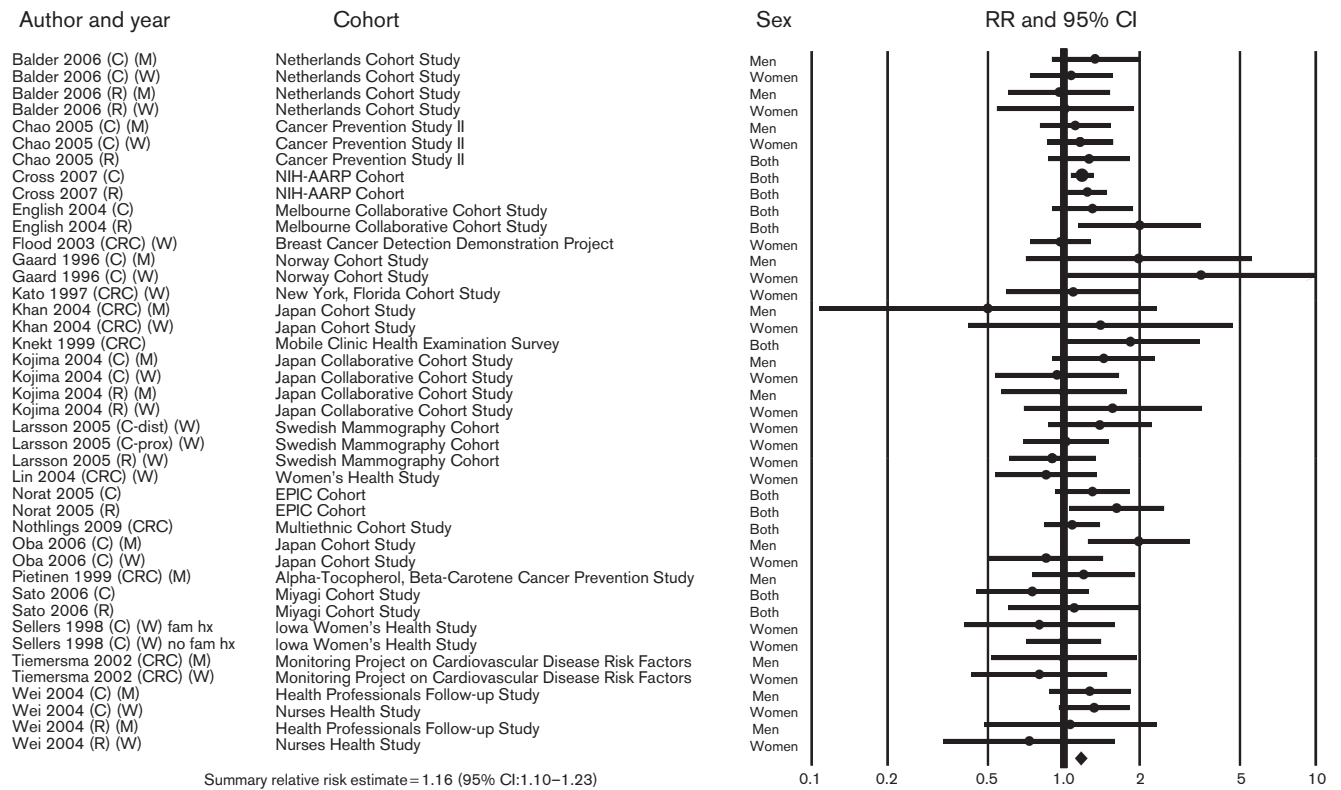
An assessment of the funnel plot of prospective studies of red meat and colorectal cancer suggested slight publication bias (Fig. 2), although statistically testing using Duval and Tweedie's trim and fill procedure and Egger's regression test was not supportive of significant publication bias.

Discussion

Processed meat and postulated mechanisms

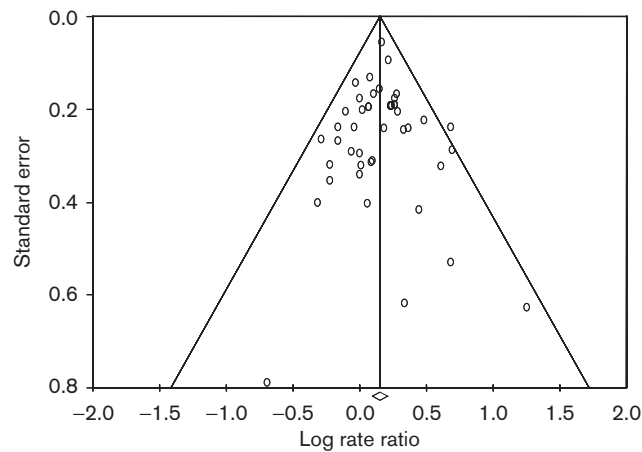
Processed meat comprises a heterogeneous array of meat products, which are made using a wide variety of muscle foods, nonmeat ingredients, and processing methods. From an epidemiologic perspective, there is no discrete characterization of 'processed meat,' as it is commonly

Fig. 1



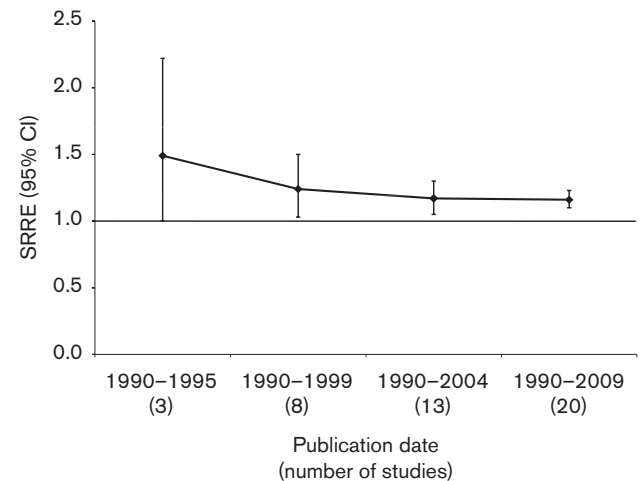
Meta-analysis of prospective studies of processed meat intake and colorectal cancer. Analysis based on high versus low intake comparisons. C, colon; CI, confidence interval; CRC, colorectal cancer; M, men; R, rectal; W, women.

Fig. 2



Funnel plot of prospective studies of processed meat intake and colorectal cancer.

Fig. 3



Cumulative meta-analysis of prospective studies of processed meat intake and colorectal cancer. CI, confidence interval; SRRE, summary relative risk estimates.

evaluated either as a broad food group or as individual meat items. Processed meat is typically defined as meat that is preserved by methods other than freezing, which undergoes treatment to alter the flavor, improve the

quality, or enhance preservation (Santarelli *et al.*, 2008). This food group commonly includes products (e.g. bacon, ham, sausage) that are cured, smoked, comminuted,

canned, or ground, and that are made from beef or pork, but may include other sources of meat, such as poultry or fish. The processing of meat serves numerous functions, including food safety, shelf-life extension, tenderization (by mechanical, enzymatic, chemical, or other means), manipulation and control of macronutrient composition (protein, fat, and moisture content), portion control (size, weight, and shape), color enhancement, flavor, and consumer convenience (Romans *et al.*, 2000; Warriss, 2000). There are a variety of methods used to preserve meat, and two methods in particular, curing and smoking, have generated scientific interest regarding potential health concerns (Santarelli *et al.*, 2008).

Curing meat involves the addition of sugar, salt, nitrite, or nitrate to meat to prevent bacterial growth or spore germination, extend shelf-life, improve meat flavor or texture, and to enhance meat color (Warriss, 2000; Honikel, 2008; Santarelli *et al.*, 2008). Nitrite and nitrate are environmentally ubiquitous chemicals and are naturally occurring ions that are part of the global nitrogen cycle [International Agency for Research on Cancer (IARC) and IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2006]. Although exposure to these compounds may occur through ingestion of cured meat, exposure occurs more frequently through consumption of vegetables and baked and processed cereal products [Dich *et al.*, 1996; International Agency for Research on Cancer (IARC) and IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2006]. Moreover, exposure to nitrite may also occur endogenously when ingested nitrate is excreted in the saliva and reduced to nitrite by oral bacteria, which is then re-ingested (Grosse *et al.*, 2006; Honikel, 2008).

Nitrosating agents arising from nitrite under acidic gastric conditions may react with amines or amides to form N-nitroso compounds (NOCs), especially nitrosamines, some of which have been shown to be carcinogenic in laboratory animals [International Agency for Research on Cancer (IARC) and IARC Monographs on the Evaluation of Carcinogenic Risks to Humans, 2006; Grosse *et al.*, 2006; Santarelli *et al.*, 2008]. Exposure to exogenous NOCs is not limited to processed meat, as exposure may occur through consumption of certain cheeses or beer (Dich *et al.*, 1996; Lijinsky, 1999; Santarelli *et al.*, 2008). Nitrosamines may also be formed endogenously when high amine-containing foods, such as fish, and nitrate or nitrite-containing foods, such as spinach, are consumed together and exposed to gastric acidity. Relatively few prospective studies have analytically isolated these chemicals in terms of colorectal cancer risk. It is unclear whether or how these chemicals may play a role in colorectal carcinogenesis through the processed meat pathway since the exposure is not specific to processed meat intake. Furthermore, if nitrates, nitrites, or NOCs were definitively associated with colorectal cancer, it would be expected that patterns of associations for

processed meat would be considerably stronger in magnitude (i.e. further from 1.0 in the positive direction) than red meat, as they are known sources of nitrogen compounds. Collectively, associations between processed meat and colorectal cancer are indeed stronger than for red meat; however, the difference in magnitude of risk estimates is negligible.

Another postulated carcinogenic mechanism involves exposure to polycyclic aromatic hydrocarbons (PAHs), which are produced from the incomplete combustion of organic compounds. PAHs are considered dietary mutagens and animal carcinogens (Santarelli *et al.*, 2008; Agency for Toxic Substances and Disease Registry, 1995). More than 100 PAHs exist, with benzo[a]pyrene (BaP) being the most extensively studied (Cross and Sinha, 2004). Environmentally, exposure may occur from cigarette smoke, from cooking meat over a direct flame (Cross and Sinha, 2004), breathing vehicle exhaust, or any source of wood burning (Agency for Toxic Substances and Disease Registry, 1995). Occupational exposures may occur among coke oven workers, or in other industries involved in asphalt, roofing tar, crude oil, coal, and creosote (Agency for Toxic Substances and Disease Registry, 1995). Open grilling, barbecuing, and smoking meat may produce PAHs. Grilling and barbecuing processed meat is not as common a cooking method as with other types of meat. However, smoking is a common type of meat preservation method, which may involve exposing meat to smoke from incomplete wood pyrolysis, which, in turn, may generate PAHs (Santarelli *et al.*, 2008). Although exposure to PAHs has been hypothesized as contributing to colorectal carcinogenesis, epidemiologic data are inconsistent and the potential for risk remains uncertain because of difficulties in quantifying individual intake (Cross and Sinha, 2004).

As with PAHs, heterocyclic amines (HCAs) are mutagenic by-products produced from cooking meat, predominantly at high temperature. HCAs are formed when amino acids and creatine (a phosphate storage chemical found in vertebrate muscle) react with sugars during cooking meat, including poultry and fish, at high temperatures. To date, over 17 different HCAs resulting from the cooking of muscle foods have been identified (Cross and Sinha, 2004; National Cancer Institute, 2007). The formation of HCAs has been suggested to be influenced by four factors as follows: type of food (especially creatine levels), cooking method, temperature, and cooking time (National Cancer Institute, 2007). Temperature is considered to be the most important factor in the formation of these compounds, and frying, broiling, and grilling meats likely produce HCAs in the largest quantities because of high-temperature cooking methods (National Cancer Institute, 2007). Processed meat, however, is generally not associated with considerable HCA formation. In fact, cooking other types of meat, such as poultry, fish, or pan-fried beef, produces abundantly

more HCAs than processed meat (Sinha *et al.*, 1998; Santarelli *et al.*, 2008). As a result, it has been suggested that HCAs are not a significant determinant of colorectal cancer (Santarelli *et al.*, 2008).

Dietary fat intake has been hypothesized as being a link in the relationship between processed meat intake and colorectal cancer risk; however, no statistically significant association was observed between animal fat intake and colorectal cancer in a recent meta-analysis of prospective studies (SRRE = 1.04, 95% CI: 0.83–1.31) (Alexander *et al.*, 2009). Heme iron, which is found primarily in meat as hemoglobin and myoglobin (Sinha *et al.*, 2005), has also been postulated as contributing to colorectal cancer risk. However, available epidemiologic data for heme iron and colorectal cancer are limited, and processed meat as a food group contains less heme iron than red meat as food group.

Quantitative summary of epidemiologic data

As mentioned above, three meta-analyses of processed meat consumption and colorectal cancer have been published earlier (Sandhu *et al.*, 2001; Norat *et al.*, 2002; Larsson and Wolk, 2006), and each successive publication observed weaker summary associations, with this publication continuing that trend. In the most recent of these publications (Larsson and Wolk, 2006), the authors reported a summary association of 1.20 (95% CI: 1.11–1.31) in their high versus low intake analysis of 13 prospective studies published through 2005. Comparatively, we identified four studies (Oba *et al.*, 2006; Sato *et al.*, 2006; Cross *et al.*, 2007; Nothlings *et al.*, 2009) published after the most recent meta-analysis, three studies (Tiemersma *et al.*, 2002; Khan *et al.*, 2004; Lin *et al.*, 2004) not included in the earlier meta-analysis but published during their literature search period, and we replaced two studies with updated data from two publications (Bostick *et al.*, 1994; Balder *et al.*, 2006). Meta-analysis of data not included in prior meta-analysis publications resulted in an SRRE of 1.13 (95% CI: 1.05–1.22), which was influenced heavily by Cross *et al.* (2007) (SRRE with this study removed = 1.04, 95% CI: 0.93–1.18). Overall, in our high versus low meta-analysis, we observed a summary association of 1.16 (95% CI: 1.10–1.23), based on analysis of data from 20 prospective studies. Similarly, we observed no appreciable difference in summary risk estimates by tumor site (colon vs. rectal), but marked differences in sex were apparent. Larsson and Wolk (2006) reported summary associations of 1.27 (95% CI: 1.06–1.52) among men ($n = 5$ studies) and 1.07 (95% CI: 0.94–1.23) among women ($n = 8$ studies). In our evaluation, we observed an SRRE of 1.23 (95% CI: 1.07–1.42) among nine studies for men and an SRRE of 1.05 (95% CI: 0.94–1.16) among 13 studies for women. It appears that associations between processed meat intake and colorectal cancer observed in epidemiologic prospective studies may be getting weaker over time; the

summary associations in meta-analyses published in 2001 (Sandhu *et al.*, 2001) and 2002 (Norat *et al.*, 2002) (which both evaluated studies published prior to year 2000) were markedly stronger in magnitude compared with the summary associations reported in the 2006 meta-analysis (Larsson and Wolk, 2006) and the present assessment. Indeed, in our sensitivity analyses, the SRRE for the studies published before the year 2000 was 1.24 (95% CI: 1.03–1.50) and the SRRE for the studies published between 2000 and 2009 was 1.16 (95% CI: 1.10–1.23). In addition to the published meta-analyses, an evaluation of meat intake and colorectal cancer based on data from the Pooling Project of Prospective Studies of Diet and Cancer was published as an abstract at the Proceedings of the American Association for Cancer Research (Cho and Smith-Warner, 2004). The authors pooled data across 14 prospective cohorts and evaluated almost 8000 incident cases of colorectal cancer, resulting in a nonsignificant RR (relative risk) of 1.05 (95% CI: 0.96–1.15) for each 30 g/day increase of processed meat (Cho and Smith-Warner, 2004). This analysis, however, was not published as a full manuscript. Although the summary associations between processed meat intake and colorectal cancer have become gradually weaker in magnitude over time (Fig. 3), they remain elevated and likely always will, because processed meat intake is correlated to several adverse factors that are associated with increasing the risk of colorectal cancer.

Despite the apparent attenuation of epidemiologic associations over time, the relatively weak magnitude of associations, and the extensive variability in how processed meat is defined and analyzed across studies, WCRF/AICR's judgment on processed (or cured) meat and colorectal cancer changed from 'possible' in 1997 to 'convincing' in 2007. In fact, they suggest that no amount of processed meat can be shown with confidence to not increase the risk of colorectal cancer. In our assessment, however, summary associations were suggestive of only slightly elevated risks and no appreciable relationship was observed among the studies of women. Over the past decade, numerous epidemiologic studies of processed meat and colorectal cancer have been published; however, the scientific evidence does not appear to be clearer today than it was a decade ago. Furthermore, hypothesized mechanisms have been refined although the available human data remain limited and inconsistent.

Methodological challenges

Processed meat has been shown to be correlated with unhealthy dietary characteristics in studies of dietary patterns (e.g. high refined sugar intake, smoking, alcohol, low fruit and vegetable intake), and positive associations between these 'Western' lifestyles and colorectal cancer has been reported in several epidemiologic studies (Slattery *et al.*, 1998, 2000; Fung *et al.*, 2003; Reedy *et al.*, 2010), although not all studies that evaluated dietary patterns

characterized by high intake of meat observed positive associations (Terry *et al.*, 2001; Dixon *et al.*, 2004; Key *et al.*, 2009; Nothlings *et al.*, 2009). Indeed, evaluating the relationship between processed meat consumption and cancer poses more methodological challenges than most dietary factors; processed meat is composed of a variety of sources of meat (e.g. pork, beef, poultry, smoked fish) and types or cuts (e.g. upper quarter) of meat within sources; meat processing methods vary (e.g. curing, drying, smoking); cooking and consumption practices are heterogeneous (e.g. ready-to-eat luncheon meats, pan-fried bacon), geographic and/or cultural differences may result in variable intake patterns (e.g. greater proportion of salted pork or fish in many Asian countries, higher intake of ham and bacon in many westernized nations), and accurately and precisely measuring processed meat intake in observational studies may be difficult because of the way processed meat is defined and interpreted in food frequency questionnaires. Despite these sources of between-study variability, most tests for statistical heterogeneity in the meta-analysis models reported herein were not significant. Testing for heterogeneity only indicates statistical variation between the effect sizes of the studies; heterogeneity testing does not indicate sources of variation by specific study characteristics. Therefore, subgroups for certain characteristics, such as sex and tumor site, were generated in an effort to discern any possible patterns of associations.

The subgroup analyses were not indicative of differing patterns of associations by tumor site or level of statistical adjustment, but they did reveal marked differences by sex and publication date. Although associations between dietary factors and cancer may be modified by hormonal factors (Jacobs *et al.*, 2007), there is no clear evidence as to how or why the relationship between processed meat intake and colorectal cancer may be modified by sex. On average, men consume a greater amount of meat and total calories than women, although most studies control for the effects of total energy intake. Furthermore, the dose-response analyses were held constant at 30-g increments for both men and women, although summary effects were considerably different. Thus, other dietary or lifestyle characteristics, such as fiber intake, vitamin D, or physical activity, may have impacted summary associations between sexes. As discussed earlier, summary associations become gradually weaker over time. The reason(s) for this discrepancy is unclear, although possible reasons may be that more recently conducted studies have refined methods to more accurately measure processed meat intake and some important confounding factors, longer follow-up in some cohorts has attenuated associations over time, constituents of processed meat have changed over time, or the differences may be the result of statistical variation.

When synthesizing quantitative data across observational studies, some important methodological caveats should be considered. For example, confounding by other dietary

factors or lifestyle characteristics may impact results. In our sensitivity analyses, there were no remarkable differences between the overall models and the models that included only the most well-adjusted studies. However, studies varied in the number and type of covariates for which they adjusted in their analyses, and residual confounding or confounding by uncontrolled factors may have impacted results. In addition, co-linearity among study-level covariates compromises the analytical power to discriminate among different dietary factors, limiting the ability to isolate the independent effects of specific food groups or food items. For example, in a recent study of dietary and lifestyle risk factors for colorectal cancer, the authors reported a summary association between high versus low intake of processed meat similar to what we observed, and they concluded that 'the potential for residual confounding to explain wholly, or in part, the observed relationships cannot be ruled out' (Huxley *et al.*, 2009). Further, they state, 'given the frequent co-occurrence of smoking, alcohol, physical inactivity and diets that are high in meat (both processed and nonprocessed meat), it is impossible to disentangle the individual effects that each of these variables may have on risk' (Huxley *et al.*, 2009). In the presence of weak associations, the distorting influences of bias, confounding, and chance may be enhanced further (Boffetta *et al.*, 2008).

The dietary instruments [e.g. 33-item FFQ (Food Frequency Questionnaire), 169-item FFQ], the analytical cut-points of intake groups (e.g. > 122 vs. 27 g/day as in Pietinen *et al.*, 1999; > 32 vs. < 12 g/day as in Larsson *et al.*, 2005), 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. Finally, publication bias may impact summary associations in any quantitative assessment of the epidemiologic literature. Although there was not a strong indication of publication bias based on statistical testing in the studies examined herein, tests for publication bias generally have low power. Thus, identification of unpublished data would be required to fully examine this potential bias.

Summary

In light of many issues discussed above, causal claims regarding processed meat and colorectal cancer should be treated with caution. The currently available epidemiologic evidence is insufficient to support a clear and unequivocal independent positive association between processed meat consumption and colorectal cancer. Although most meta-analyses resulted in statistically significant positive summary associations with little statistical heterogeneity, overall associations were weak in magnitude (most less than 1.20) and individual studies varied by processed meat definitions and types of meat items. Furthermore, summary associations seem to be weakening over time, and most summary associations

between processed meat and colorectal cancer among women are null. At the individual study level, the vast majority of associations are not statistically significant, and there is extensive variability in processed meat consumption patterns. Several carcinogenic mechanisms involving processed meat intake have been postulated; however, the available data are inconsistent and have not shown clear mechanistic relationships between processed meat and colorectal cancer. Additional research in this area that focuses on well-characterized chemical exposures and specific types of meat and cooking methods may facilitate a more complete interpretation. It is difficult to analytically isolate the effects of processed meat, as co-linearity with other types of food exists and consumption of processed meat has been shown to be correlated with some unhealthy dietary and lifestyle characteristics in studies of dietary patterns. The epidemiologic studies published to date are not adequate to disentangle any independent effects of processed meat or specific processed meat items and colorectal cancer risk.

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