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A review and meta-analysis of red and processed meat consumption and breast cancer

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The relationship between meat consumption and breast cancer has been the focus of several epidemiological investigations, yet there has been no clear scientific consensus as to whether red or processed meat intake increases the risk of breast cancer. We conducted a comprehensive meta-analysis incorporating data from several recently published prospective studies of red or processed meat intake and breast cancer. In the meta-analysis utilising data from the Pooling Project publication (includes data from eight cohorts) combined with data from nine studies published between 2004 and 2009 and one study published in 1996, the fixed-effect summary relative risk estimate (SRRE) for red meat intake (high *v.* low) and breast cancer was 1·02 (95 % CI 0·98, 1·07; *P* value for heterogeneity = 0·001) and the random-effects SRRE was 1·07 (95 % CI 0·98, 1·17). The SRRE for each 100 g increment of red meat was 1·04 (95 % CI 1·00, 1·07), based on a fixed-effects model, and 1·12 (95 % CI 1·03, 1·23) based on a random-effects model. No association was observed for each 100 g increment of red meat among premenopausal women (SRRE 1·01; 95 % CI 0·92, 1·11) but a statistically significant SRRE of 1·22 (95 % CI 1·04, 1·44) was observed among postmenopausal women using a random-effects model. However, the association for postmenopausal women was attenuated and non-significant when using a fixed-effects model (SRRE 1·03; 95 % CI 0·98, 1·08). The fixed- and random-effect SRRE for high (*v.* low) processed meat intake and breast cancer were 1·00 (95 % CI 0·98, 1·01; *P* value for heterogeneity = 0·005) and 1·08 (95 % CI 1·01, 1·16), respectively. The fixed- and random-effect SRRE for each 30 g increment of processed meat were 1·03 (95 % CI 1·00, 1·06) and 1·06 (95 % CI 0·99, 1·14), respectively. Overall, weak positive summary associations were observed across all meta-analysis models, with the majority being non-statistically significant. Heterogeneity was evident in most analyses, summary associations were sensitive to the choice of analytical model (fixed *v.* random effects), and publication bias appeared to have produced slightly elevated summary associations. On the basis of this quantitative assessment, red meat and processed meat intake does not appear to be independently associated with increasing the risk of breast cancer, although further investigations of potential effect modifiers, such as analyses by hormone receptor status, may provide valuable insight to potential patterns of associations.

Breast cancer: Meta-analyses: Diet: Nutrition: Epidemiology

Introduction

Although the association between diet and breast cancer has been investigated extensively, the overall evidence surrounding the potential relationship between dietary factors and breast cancer carcinogenesis has resulted in the identification of very few risk factors. As with most dietary factors, the association between meat consumption and breast cancer has been equivocal[1]. Some early US and international ecological studies reported positive correlations between rates of breast cancer and per capita intake of meat[2–6], and several factors, such as heterocyclic amines, *N*-nitroso compounds, polycyclic aromatic hydrocarbons and haem Fe, have been hypothesised as contributing to breast cancer. However, analytical epidemiological studies that assessed red meat and processed meat as dietary intake variables have not corroborated these findings, as associations across cohort and case–control studies have been variable. In a 1993 meta-analysis of seven

Abbreviations: ER, oestrogen receptor; PR, progesterone receptor; RR, relative risk; SSRE, summary relative risk estimate.

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cohort and case–control studies, Boyd *et al.* [7] reported a statistically significant positive association (summary estimate = 1·54; 95 % CI 1·31, 1·82) between red meat intake and breast cancer. In contrast, slight inverse associations for consumption of red meat (summary relative risk (RR) for each 100 g/d increment = 0·98, 95 % CI 0·93, 1·04) or processed meat (summary RR for each 10 g/d increment = 0·98, 95 % CI 0·96, 1·00) were reported in the comprehensive analysis of the Pooling Project of Prospective Studies of Diet and Cancer published in 2002[8]. In a recent meta-analysis among premenopausal women, a non-significant summary association of 1·11 (95 % CI 0·94, 1·31) was reported across three cohort studies, although data from seven cohorts that were analysed in the Pooling Project publication were not included in the analysis[9].

Since these analyses, several large prospective studies have been published that may provide enhanced clarification to any potential associations between red meat consumption and breast cancer. Specifically, evaluations of the NIH-AARP Diet and Health Study[10,11], Swedish Mammography Cohort[12], European Prospective Investigation into Cancer and Nutrition (EPIC)[13], Prostate, Lung, Colorectal, and Ovarian (PLCO) Cancer Screening Trial[14], Diet Cancer and Health Cohort[15], Shanghai Breast Self Exam Trial[16], UK Women's Cohort Study[17], Monitoring Project on CVD Risk Factors[18] and the Nurses' Health Study (I and II)[19–22] have been published that provided data on red meat consumption and breast cancer. Therefore, to further update the state of the science, we conducted a review and meta-analysis of prospective cohort studies of red meat or processed meat intake and female breast cancer. We performed high *v.* low intake meta-analyses, dose–response examinations, heterogeneity assessments, sensitivity and influence evaluations, and an appraisal of publication bias.

Materials and methods

Literature search and study inclusion

We conducted a MEDLINE literature search using the PubMed interface to identify articles eligible for review. All articles indexed by PubMed that were published up to July 2009 were included. The literature search string included: *breast cancer* OR *breast cancers* OR *breast neoplasm* OR *breast neoplasms* AND (*diet** OR *diet* OR *nutrition* OR *food* OR *meat* OR *beef* OR *pork* OR *lamb*). In addition to the literature search, the bibliographies of review articles pertaining to diet and breast cancer were examined in an effort to identify all available literature that may not have been identified by our database searches. Peer-reviewed publications of prospective cohort studies or nested case–control studies that evaluated red meat or processed meat consumption and female breast cancer were included. Case–control studies, ecological assessments, correlation studies and other publications of aggregate-level analyses were excluded, as were experimental animal studies and mechanistic studies.

Red meat is commonly defined as beef, pork, lamb, or a combination thereof, and processed meat is generally defined as meat made largely from pork, beef or poultry that undergoes methods of preservation, such as curing, smoking or drying[23,24]. Most studies reported associations for categories labelled as 'red meat' or 'processed meat'; however, several studies reported results for individual red (for example, beef, pork) and/or processed (for example, hot dogs, bacon) items. The definitions of red meat and processed meat as a food category varied across studies. While many studies explicitly defined these classifications, other studies reported no description. Studies that reported data for a broad classification of meat, such as 'total meat' categories, which included poultry or fish, were excluded. Studies that reported information pertaining to constituents of red meat, such as fat or protein from animal sources, heterocyclic amine exposure, or cooking practices, were obtained but analysis of these factors was beyond the scope of the present assessment. RR and measures of variability (i.e. 95 % CI) for consumption categories of red or processed meat intake using the lowest category of intake as the reference, or available data for such calculations, were required to be reported in the included articles.

Data extraction

Qualitative information and quantitative data were extracted from each study that met the criteria for inclusion. Specifically, information was extracted pertaining to: the year of the study, the study population (i.e. name and nature of the cohort), geographical location of the study, years of follow-up, methods of dietary exposure ascertainment, red meat and processed meat dietary variables and how these variables were defined, the analytical comparison (i.e. the exposure contrast), the number of exposed cases, the RR estimates and 95 % CI, and the factors that were adjusted or controlled for in the analyses.

A thorough review of each article was conducted to identify cohorts that may have been analysed in multiple publications. If results were reported in multiple publications, the inclusion of data was based on (1) the size of the study population, (2) duration of follow-up with an emphasis on the most recent publication with the longest follow-up, (3) classification and analytical categorisation of red or processed meat, and (4) level of control for potential confounding factors. Data from the Missmer *et al.* [8] publication were used, which was an analysis of the Pooling Project of Prospective Studies of Diet and Cancer[25], in the primary meta-analysis models. Specifically, Missmer *et al.* [8] analysed primary data from eight individual study cohorts from North America and Western Europe, contributing 7379 cases of breast cancer. Data from independent publications of the Nurses' Health Study[22,26], the Seventh Day Adventist Cohort[27] and the Netherlands Cohort Study[28] were not included in the model with Missmer *et al.* [8] because these study populations were analysed in the Pooling Project. Data from these studies were included in a separate meta-analysis model that did not include Missmer *et al.* [8]. Missmer *et al.* [8] evaluated data for 1320 breast cancer cases from the Swedish Mammography Cohort during 10 years of follow-up (1987–1997). In a 2009 update of the Swedish Mammography Cohort, Larsson *et al.* [12] analysed 2952 breast cancer cases during 20 years of follow-up (1987–2007). Thus, data from Larsson *et al.* [12] were included

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in the primary meta-analyses with Missmer *et al.* [8] and data from Larsson *et al.* [12] were removed in the sensitivity analyses. Two publications of the Nurses' Health Study I and II cohorts were identified that analysed diet during pre-school[21] and adolescence[20]. Data from these studies were not included in the meta-analysis models because of likely population overlap with other studies. In addition, these studies differed from the other studies included in this assessment in regards to the methodology of past dietary exposure ascertainment and the analysis of diet during early life-time periods. The characteristics of all cohort and nested case–control studies reviewed in the present paper are summarised in Table 1.

Statistical analyses

Meta-analyses comparing the highest intake category of red meat or processed meat with the lowest (or referent) intake category were conducted. Meta-analysis models were constructed for overall red meat or processed meat groups as well as for individual meat items where applicable (for example, hot dogs, bacon, organ products). In two studies[12,19] that reported data for total red meat (including processed meat items) and red meat only, data were selected specifically for red meat (without processed meat items). Separate meta-analyses were generated among the studies that reported data by menopausal status. Additionally, meta-analyses of dose–response categorical data were conducted using the method proposed by Greenland & Longnecker[29], in which the linear dose–response slope is calculated for each study while accounting for the correlation across intake categories within a study[30]. If the number of cases and person-time data were not available for each intake strata, variance-weighted least squares regression was utilised to estimate the slope coefficient. Different intake units were reported across studies; therefore, we used 80 g as the approximate serving size for red meat and 30 g for processed meat.

Fixed-effects and random-effects models were used to calculate summary RR estimates (SRRE), 95 % CI, and corresponding *P* values for heterogeneity. In the 'one study removed' sensitivity analyses, the relative influence of each study on the model-specific SRRE was examined by generating an SRRE based on all studies in a particular model, followed by the removal of one study at a time in order to compare the overall SRRE with SRRE from models that had one study removed. The presence of publication bias was assessed visually by examining a funnel plot measuring the standard error as a function of effect size, as well as performing Duval and Tweedie's trim and fill method[31]. All statistical analyses were performed using STATA (version 10.0; StataCorp LP, College Station, TX, USA), Comprehensive Meta-Analysis (version 2.2.046; Biostat, Englewood, NJ, USA) and Episheet[32]. The utilisation of independent analytical programs allowed for the validation of calculations.

Results

Red meat

No significant association between the highest category of red meat intake compared with the lowest category of intake and breast cancer was observed in the meta-analysis model that included data from the Pooling Project publication (eight cohorts) combined with data from ten additional studies (SRRE for fixed-effects model = 1·02; 95 % CI 0·98, 1·07; *P* value for heterogeneity = 0·001) (Fig. 1; Table 2). The SRRE for the random-effects model was slightly stronger in magnitude (SRRE 1·07; 95 % CI 0·98, 1·17), primarily because this model provided only 16 % of the relative weight to the pooled analysis of eight cohorts by Missmer *et al.* [8]. Byrne *et al.* [33] reported data only for beef consumption; therefore, this study was removed as part of the sensitivity analysis. This study had less than 1 % of relative weight, so the overall summary estimate remained virtually unchanged with its removal. In the one study removed influence analysis, the removal of any single study did not appreciably alter the overall SRRE by more than 4 %. When Larsson *et al.* [12] was removed (partial overlap with Missmer *et al.* [8]), the fixed- and random-effects summary associations became 1·04 (95 % CI 0·99, 1·08; *P* value for heterogeneity = 0·002) and 1·10 (95 % CI 1·00, 1·21), respectively. Replacing the data from Missmer *et al.* [8] with data from studies that analysed populations included in the Pooling Project (i.e. Holmes *et al.* [22], Mills *et al.* [27] and Voorrips *et al.* [28]) did not markedly modify the overall summary associations (SRRE for fixed-effects model = 1·03; 95 % CI 0·99, 1·08; *P* value for heterogeneity = 0·005; SRRE for random-effects model = 1·06; 95 % CI 0·98, 1·15) nor did this model explain the observed heterogeneity. The summary associations in a sensitivity analysis that included only studies[11–19,22] published after the Pooling Project publication were similar in magnitude to the overall association (fixed-effects SRRE 1·05; 95 % CI 1·00, 1·10; *P* value for heterogeneity = 0·023; random-effects SRRE 1·08; 95 % CI 1·00, 1·17) (Table 2).

The SRRE for the studies that reported data for red meat and breast cancer among premenopausal women was 1·02 (95 % CI 0·92, 1·13; *P* value for heterogeneity = 0·268; fixed-effects model) (Table 2). The fixed-effects SRRE among studies that reported red meat intake data for postmenopausal women was 1·02 (95 % CI 0·98, 1·08; *P* value for heterogeneity = 0·005), while the summary association in the random-effects model was slightly stronger (SRRE 1·11; 95 % CI 0·99, 1·25), largely due to the reduction of relative weight given to the pooled analysis by Missmer *et al.* [8].

In the categorical dose–response meta-analysis, the SRRE for each 100 g increment of red meat intake was 1·04 (95 % CI 1·00, 1·07; *P* value for heterogeneity < 0·0001) in the fixed-effects model and 1·12 (95 % CI 1·03, 1·23) in the random-effects model. Among premenopausal women, the summary association for each 100 g increment of red meat was 1·01 (95 % CI 0·92, 1·11; fixed effects) with a non-significant *P* value for heterogeneity (*P* = 0·316). Among postmenopausal women, the fixed-effects and random-effects SRRE for each 100 g increment of red meat intake were 1·03 (95 % CI 0·98, 1·08; *P* value for heterogeneity < 0·0001) and 1·22 (95 % CI 1·04, 1·44), respectively. Modest differences in summary associations by model were observed among postmenopausal women, largely due to the fact that the random-effects model

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Table 1. Summary of cohort studies of red meat and processed meat and female breast cancer

Author and year	Cohort	Follow-up	Cases in cohort (*n*)	Definition of exposure variable	Analytical comparison	Relative risk estimate*	95 % CI	Statistical adjustment
Pooled analyses: cohort studies								
Missmer *et al.* (2002)[8]	North America and Western Europe	1976–1997	7379	Red meat (bacon, ground beef, roast beef, beef steak, pork, veal, lamb, blood pudding, ham, hot dogs, pâté, beef liver, chicken liver, pork liver, turkey liver, kidney, sausage, processed luncheon meats, white meat, eggs, and total meat products)	Quartiles of intake	0·94†	0·87, 1·02	Age at menarche, interaction between parity and age at first birth, oral contraceptive use, history of benign breast disease, family history of breast cancer, smoking status, education, BMI, height, alcohol intake, total energy intake, menopausal status, interaction of BMI and menopausal status, postmenopausal hormone use
					Per 100 g per d increment in consumption			
	Adventist Health Study	1976–1982	160		All women	0·98	0·93, 1·04	
					Premenopausal women	0·97	0·79, 1·20	
	Canadian National Breast Screening Study	1982–1987	419		Postmenopausal women	0·97	0·91, 1·03	
	Iowa Women's Health Study	1986–1995	1130					
	Netherlands Cohort Study	1986–1992	937					
	NY State Cohort	1980–1986	367					
	NY University Women's Health Study	1985–1994	385					
	Nurses' Health Study (a)	1980–1986	1023					
	Nurses' Health Study (b)	1986–1996	1638					
	Sweden Mammography Cohort	1987–1997	1320					

				Processed meats (bacon, blood pudding, ham, hot dogs sausage, processed luncheon meats)	All women (per 10 g per d increment in consumption)	0·98†	0·96, 1·00	Age at menarche, interaction between parity and age at first birth, oral contraceptive use, history of benign breast disease, family history of breast cancer, menopausal status, BMI, interaction of BMI and menopausal status, postmenopausal hormone use, smoking status, education, height, alcohol intake, total energy intake
				Bacon products	All women (per 10 g per d increment in consumption)	0·99	0·89, 1·09	
				Sausage products (blood pudding, sausage)	All women (per 10 g per d increment in consumption)	0·94	0·83, 1·07	
				Hot dogs	All women (per 100 g/d increment in consumption)	0·75	0·39, 1·44	
Cohort studies								
Byrne *et al.* (1996)[33]	NHANES I/NHEFS Cohort	1982–1987	53	Beef	Frequency of consumption (times/week)			Age
					> 3 *v.* ≤3	0·5†	0·3, 1·1	
Cho *et al.* (2006)[19]	Nurses' Health Study II	1991–2003	1021		Average cumulative intake			Age, calendar year of interview, smoking, height, parity, age at first birth, BMI, age at menarche, family history of breast cancer, history of benign breast disease, oral contraceptive use, alcohol intake, energy intake
				Red meat (beef or lamb as a main dish, pork as a main dish, beef, pork or lamb as a sandwich or mixed dish, hamburger, bacon, hot dogs, other processed meats)	> 1·5 servings/d *v.* ≤3 servings/week (premenopausal)	1·27	0·96, 1·67	
				Beef or lamb as a main dish (processed meat items excluded)	> 1 to ≤3 servings/d *v.* <1 serving/week	1·10†	0·86, 1·39	
				Pork as a main dish	>1 to ≤servings/week *v.* <1 serving/month	1·10	0·81, 1·48	
				Bacon	> 1 servings/week *v.* <1 serving/month (premenopausal)	0·93†‡	0·68, 1·25	

Table 1. *Continued*

Author and year	Cohort	Follow-up	Cases in cohort (*n*)	Definition of exposure variable	Analytical comparison	Relative risk estimate*	95 % CI	Statistical adjustment
				Hot dogs	> 1 servings/week *v.* < 1 serving/month (premenopausal)	1·14†‡	0·83, 1·57	
				Other processed meats (sausage, salami, bologna)	> 3 servings/week *v.* < 1 serving/month (premenopausal)	1·28†‡	0·87, 1·88	
Cross *et al.* (2007)[11]	NIH-AARP Diet and Health Study	1995–2003	5872	Red meat (beef, pork, lamb, bacon, cold cuts, ham, hamburger, hot dogs, liver, pork sausage, steak, meats added to mixed foods such as pizza, chili, lasagna, and stew)	62·7 g/1000 kcal *v.* 9·8	1·02†	0·93, 1·12	Age, sex, education, marital status, family history of cancer, race, BMI, smoking, physical activity, total energy intake, alcohol intake, and fruit and vegetable consumption
				Processed meat (bacon, ham, red and white meat (poultry) versions of: sausage, luncheon meats, cold cuts, hot dogs; meats added to mixed foods such as pizza, chili, lasagna, and stew)	22·6 g/1000 kcal *v.* 1·6	1·03†	0·94, 1·12	
Egeberg *et al.* (2008)[15]§	Diet, Cancer and Health Cohort Study	1993–2000	378		Quartiles of intake (g/d), postmenopausal women			Parity, age at first birth, education, duration of HRT, intake of alcohol, and BMI
				Red meat (beef, veal, pork, lamb and offal)	> 80 *v.* < 50	1·65†	1·09, 2·50	
				Processed meat (processed red meat, including bacon, smoked ham, salami, frankfurter, Cumberland sausage, cold cuts, liver pâté and processed fish prepared by pickling, salting, or smoking)	> 45 *v.* < 20	1·59†	1·02, 2·47	

Ferrucci *et al.* (2009)[14]	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial	1993–2001	1205		Quintiles of intake (g/1000 kcal), postmenopausal women			Age (continuous), race, education, study centre, randomisation group, family history of breast cancer, age at menarche, age at menopause, age at first birth and number of live births, history of benign breast disease, number of mammograms during past 3 years, menopausal hormone therapy use, BMI, alcohol intake, total fat intake, and total energy intake
				Red meat (bacon, beef, cheeseburgers, cold cuts, ham, hamburgers, hot dogs, liver, pork, sausage, veal, venison, and red meat from mixed dishes)	52·8 *v.* 9·4	1·23†	1·00, 1·51	
					ER-positive/PR-positive tumours	1·59	1·03, 2·48	
				Processed meat (bacon, cold cuts, ham, hot dogs, and sausage)	16·9 *v.* 1·4	1·12†	0·92, 1·36	
Frazier *et al.* (2004)[20]	Nurses' Health Study II	1989–1998	361	Red meat (hot dog, bacon processed meat, hamburger, beef, pork or lamb as a sandwich, pork as main dish, beef or lamb as main dish, meatloaf)	Adolescent diet: quintiles of intake (servings/d)			Age, time period, total energy intake, height, parity and age at first birth, BMI at age 18 years, age at menarche, family history of breast cancer, history of benign breast disease, menopausal status, alcohol intake, contraceptive use, weight gain since age 18 years
					5 *v.* 1	1·22	0·82, 1·82	
Gertig *et al.* (1999)[26]§	Nurses' Health Study	1980–1994	455	Red meat (beef, pork, or lamb as a main dish, hamburger, processed meat, bacon, hot dog)	Frequency of consumption (servings/d)			Matched: year of birth, menopausal status, month and time of blood draw, fasting status at blood draw, postmenopausal hormone use. Adjusted: age at menarche, parity, age at first birth, BMI, family history of breast cancer in mother or sister, history of benign breast disease

Table 1. *Continued*

Author and year	Cohort	Follow-up	Cases in cohort (*n*)	Definition of exposure variable	Analytical comparison	Relative risk estimate*	95 % CI	Statistical adjustment
					> 1 *v.* ≤0·5	0·9	0·6, 1·3	
				Processed meat	> 0·50 *v.* ≤0·14	1·0	0·7, 1·5	
				Bacon	> 0·07 *v.* ≤0·07	1·4	1·0, 1·9	
Holmes *et al.* (2003)[22]	Nurses' Health Study	1980–1998	2956		Quintiles of cumulative average intake (servings/d)			Age, 2-year time period, total energy intake, alcohol intake, parity and age at first birth, BMI at age 18 years, weight change since age 18 years, height, family history of breast cancer, history of benign breast disease, age at menarche, menopausal status, age at menopause and HRT use categories, duration of menopause
				Red meat	≥1·32 *v.* ≤0·55 (all women)	0·94	0·84, 1·05	
					≥1·32 *v.* ≤0·55 (premenopausal women)	0·94	0·72, 1·22	
					≥1·32 *v.* ≤0·55 (postmenopausal women)	0·99	0·86, 1·13	
				All processed meat (hot dog, bacon, other processed meat)	≥0·46 *v.* ≤0·10 (all women)	0·94	0·85, 1·05	
					≥0·46 *v.* ≤0·10 (premenopausal women)	0·86	0·67, 1·09	
					≥0·46 *v.* ≤0·10 (postmenopausal women)	1·0	0·88, 1·13	
				Hot dog	≥0·12 *v.* ≤0·01 (all women)	1·04	0·95, 1·15	
					≥0·12 *v.* ≤0·01 (premenopausal women)	1·16	0·94, 1·44	
					≥0·12 *v.* ≤0·01 (postmenopausal women)	1·01	0·90, 1·14	
				Bacon	≥0·14 *v.* 0 (all women)	0·96	0·87, 1·07	
					≥0·14 *v.* 0 (premenopausal women)	0·93	0·73, 1·19	
					≥0·14 *v.* 0 (postmenopausal women)	1·01	0·89, 1·14	
				Other processed meat	≥0·21 *v.* ≤0·02 (all women)	0·89	0·80, 0·98	

					≥0·21 *v.* ≤0·02 (premenopausal women)	0·71	0·57, 0·88	
					≥0·21 *v.* ≤0·02 (postmenopausal women)	0·95	0·85, 1·08	
Kabat *et al.* (2009)[10] (same overall study population as Cross *et al.* (2007)[11])	NIH-AARP Diet and Health Study	1995–2003	3818		Quintiles of intake (g/1000 kcal), postmenopausal women			Age, energy intake, meat groups, age at entry, BMI, age at menarche, age at first live birth, family history of breast cancer, HRT, education, race, saturated fat intake, alcohol intake, physical activity, smoking, age at menopause, number of breast biopsies, and height
				Red meat	> 43·7 *v.* ≤13·0	1·05	0·93, 1·18	
				Processed meat	> 12·5 *v.* ≤2·2	1·00	0·90, 1·12	
Larsson *et al.* (2009)[12]	Swedish Mammography Cohort	1987–2007	2952	Total red meat (sum of fresh red meat and processed meat)	Quintiles of intake ≥ 98 g/d *v.* <46			Stratified by age and year of questionnaire cycle; adjusted for education, BMI, height, parity, age at first birth, age at menarche, age at menopause, use of oral contraceptives, use of postmenopausal hormones, family history of breast cancer, intakes of total energy and alcohol
					Total cases	0·98	0·86, 1·12	
					ER + /PR + tumours	1·10	0·90, 1·34	
					ER + /PR − tumours	0·86	0·60, 1·23	
					ER − /PR − tumours	1·12	0·70, 1·79	
				Fresh red meat (all fresh and minced pork, beef and veal)	Quintiles of intake	0·90†	0·79, 1·03	
				Processed meat (ham, bacon, sausages, salami, processed meat cuts, liver pâté, and blood sausages)	Quintiles of intake	1·08†	0·96, 1·22	
Michels *et al.* (2006)[21]§	Nurses' Health Study, Nurses' Health Study II	1976 (Nurses' Health Study I), 1989 (Nurses' Health Study II)–1993	582		Pre-school diet: per unit increase			Year of birth, age at menarche, parity, age at first birth, family history of breast cancer, adult BMI
				Ground beef	Servings/d (consumed at pre-school age)	1·44	0·81, 2·57	

Table 1. *Continued*

Author and year	Cohort	Follow-up	Cases in cohort (*n*)	Definition of exposure variable	Analytical comparison	Relative risk estimate*	95 % CI	Statistical adjustment
				Liver	Servings/week (consumed at pre-school age)	1·07	0·70, 1·63	
				Hot dogs	Servings/week (consumed at pre-school age)	0·96	0·83, 1·10	
Mills *et al.* (1989)[27]	Seventh Day Adventist Cohort	1976–1982	215		Frequency of consumption			Age at entry, age at first live birth, age at menarche, menopausal status, history of benign breast disease, maternal history of breast cancer, educational, and BMI
				Beef index (hamburger, steak, and other beef or veal)	≥1 times/week *v.* never	1·05	0·75, 1·47	
				Pork	Any *v.* none	0·92	0·43, 1·97	
Pala *et al.* (2009)[13]	European Prospective Investigation into Cancer and Nutrition Cohort	1992–2003	7119		Quintiles of intake (g/d)			Adjusted: energy, height, weight, years of schooling, smoking, and menopause; stratified by centre and age
				Red meat (fresh, minced, and frozen beef, veal, pork, and lamb)	84·6 *v.* 1·4			
					All women	1·06†	0·98, 1·14	
					Premenopausal	0·94	0·80, 1·10	
					Postmenopausal	1·05	0·94, 1·18	
				Processed meat (mostly pork and beef preserved by methods other than freezing, such as salting, smoking, marinating, air-drying, or heating and included ham, bacon, sausages, blood sausages, liver pâté, salami, mortadella, tinned meat, and others)	56·5 *v.* 1·7			
					All women	1·10†	1·00, 1·20	
					Premenopausal	0·99	0·82, 1·19	
					Postmenopausal	1·13	1·00, 1·28	
Shannon *et al.* (2005)[16]§	Shanghai Breast Self-Exam Trial	1989–2000	378		Quartiles of intake (servings/week)			Matched: age, menstrual status, factory/hospital affiliation. Adjusted: age total energy intake, breast-feeding
				Red meat	≥6·1 *v.* ≤3	1·24†	0·77, 1·99	
				Cured meats	≥2·0 *v.* ≤0·5	1·20†	0·82, 1·74	

Taylor *et al.* 2007[17]	UK Women's Cohort Study	1995–2004	678	Red meat (beef, pork, lamb, other red meats included in mixed dishes)	Categories of consumption (g/d)			Age, energy intake, menopausal status, BMI, physical activity, smoking status, HRT use, OCP use, parity, total fruit and vegetable intake
					All women: >57 *v.* 0	1·41†	1·11, 1·81	
					Premenopausal: >57 *v.* 0	1·32	0·93, 1·88	
					Postmenopausal: >57 *v.* 0	1·56	1·09, 2·23	
				Processed meat (bacon, ham, corned beef, spam, luncheon meats, sausages, pies, pasties, sausage rolls, liver pâté, salami, meat pizza)	All women: >20 *v.* 0	1·39†	1·09, 1·78	
					Premenopausal: >20 *v.* 0	1·20	0·85, 1·7	
					Postmenopausal: >20 *v.* 0	1·64	1·14, 2·37	
van der Hel *et al.* (2004)[18]§	Monitoring Project on CVD Risk Factors (Dutch Cohort)	1987–1997	229	Fresh red meat (beef and pork)	Tertiles of intake			Age, menopausal status, town, energy intake
					≥35 g/d *v.* <20			
					All women	1·30†	0·83, 2·02	
					Postmenopausal	1·46	0·76, 2·82	
				Processed meat	All women: ≥45 g/d *v.* <30	1·05†	0·67, 1·64	
Voorrips *et al.* (2002)[28]	Netherlands Cohort Study	1986–1992	783		Quintiles of intake			Age, history of benign breast disease, maternal breast cancer, breast cancer in one or more sisters, age at menarche, age at menopause, oral contraceptive use, parity, age at first childbirth, Quetelet index, education, alcohol use, current cigarette smoking, energy intake
				Beef	Postmenopausal: 5 *v.* 1	1·23	0·92, 1·66	
				Pork	Postmenopausal: 5 *v.* 1	0·80	0·60, 1·08	
				Processed meat	Postmenopausal: 4 *v.* 1	0·93	0·67, 1·29	

NHANES, National Health and Nutrition Examination Survey; NHEFS, NHANES I Epidemiologic Follow-up Study; HRT, hormone replacement therapy; ER, oestrogen receptor; PR, progesterone receptor; OCP, oral contraceptive pill.
* Highest *v.* lowest intake comparison unless otherwise noted.
† Data points are those used in the primary meta-analyses, presented in Figs. 1 and 2.
‡ Risk estimates combined using fixed-effects model before inclusion in primary meta-analysis.
§ Nested case–control study.

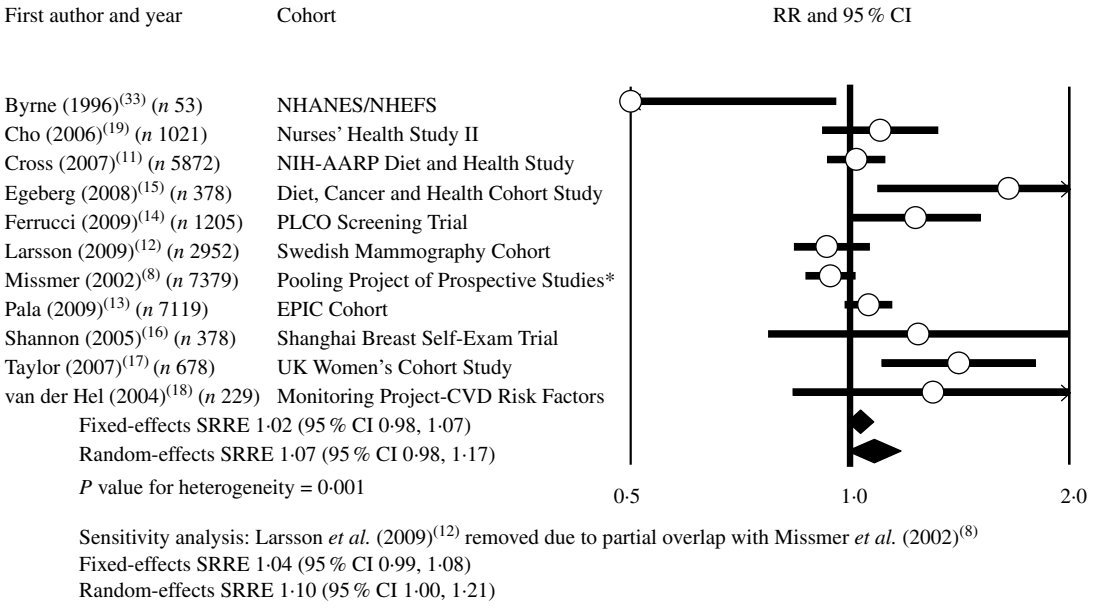

Fig. 1. Meta-analysis of prospective studies of red meat and breast cancer. * Includes data pooled from eight cohorts; partial overlap with Larsson *et al.* (2009)[12]. RR, relative risk; NHANES, National Health and Nutrition Examination Survey; NHEFS, NHANES I Epidemiologic Follow-up Study; PLCO, Prostate, Lung, Colorectal, and Ovarian; EPIC, European Prospective Investigation into Cancer and Nutrition; SRRE, summary relative risk estimate.

provided only 22 % of the total weight to the Pooling Project data from Missmer *et al.* [8] (which included eight cohorts) and 78 % of the relative weight to the five additional studies in this model. The fixed-effects model more appropriately provided 58 % of the relative weight to Missmer *et al.* [8].

Processed meat

No association was observed in the fixed-effects meta-analysis of processed meat intake and breast cancer (SRRE 1·00; 95 % CI 0·98, 1·01; *P* value for heterogeneity = 0·005) (Table 2; Fig. 2). This model provided 85 % of the relative weight to data from the Pooling Project analysis (seven cohorts). In contrast, the random-effects model provided only 23 % of relative weight to this study, resulting in a slightly greater summary association (SRRE 1·08; 95 % CI 1·01, 1·16). The Pooling Project data represented a 10 % increment of processed meat intake rather than a 'high' intake quantile. Removal of data from this study, and inclusion of data from individual publications of the Netherlands Cohort study[28] and the Nurses' Health Study[22], both of which analysed study populations included in the publication by Missmer *et al.* [8], resulted in summary associations of 1·06 (95 % CI 1·01, 1·11) and 1·07 (95 % CI 1·01, 1·14) for fixed- and random-effects models, respectively. Meta-analysis of four studies that reported data for premenopausal women resulted in an SRRE of 1·01 (95 % CI 0·90, 1·13) (same result for fixed and random effects) (Table 2). The summary association was slightly greater among the seven studies that reported data for postmenopausal women (fixed-effects SRRE 1·06; 95 % CI 1·00, 1·13; *P* value for heterogeneity = 0·051; random-effects SRRE 1·09; 95 % CI 0·99, 1·21) (Table 2).

The SRRE for each 30 g increment of processed meat intake was 1·03 (95 % CI 1·00, 1·06; *P* value for heterogeneity < 0·0001) in the fixed-effects model and 1·06 (95 % CI 0·99, 1·14) in the random-effects model. Among premenopausal women, the summary association for each 30 g increment of processed meat was 1·03 (95 % CI 0·98, 1·08; fixed effects) with a non-significant *P* value for heterogeneity ($P = 0·535$). Among postmenopausal women, the fixed-effects and random-effects SRRE for each 30 g increment of processed meat intake were 1·07 (95 % CI 1·02, 1·13; *P* value for heterogeneity < 0·0001) and 1·13 (95 % CI 0·99, 1·28), respectively.

Two studies[19,22] of the Nurses' Health Study I and II cohorts reported categorical intake data for hot dogs, bacon and other processed meat (sausage, salami, bologna), and one study[14] reported data for bacon and sausage. Meta-analysis of the highest *v.* lowest intake of bacon resulted in an SRRE of 1·01 (95 % CI 0·92, 1·12; *P* value for heterogeneity = 0·752), and the SRRE for hot dogs was 1·05 (95 % CI 0·96, 1·15; *P* value for heterogeneity = 0·589) (data not shown). In the meta-analysis of intake of other processed meat, the SRRE was 1·16 (95 % CI 0·98, 1·39). Similarly, non-significant associations were reported for each 10 g/d increment of bacon (pooled RR 0·99; 95 % CI 0·89, 1·09) and sausage (pooled RR 0·94; 95 % CI 0·83, 1·07) in the Pooling Project[8] analysis of seven cohorts. In addition, an inverse association for each 100 g/d increment of hot dogs was observed (pooled RR 0·75; 95 % CI 0·39, 1·44)[8].

Publication bias

In the assessment of prospective studies of red meat intake and breast cancer, the point estimates were skewed slightly

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Table 2. Summary of meta-analysis results of red meat and processed meat and breast cancer

Model	SRRE	95 % CI	Relevant notes
Red meat			
Overall (high intake *v.* low intake) – fixed effects	1·02	0·98, 1·07	Includes data reported in the Pooling Project publication (Missmer *et al.* (2002)[8]) and ten additional prospective studies
Overall (high intake *v.* low intake) – random effects	1·07	0·98, 1·17	Includes data reported in the Pooling Project publication (Missmer *et al.* (2002)[8]) and ten additional prospective studies
Independent publications – fixed effects	1·03	0·99, 1·08	Includes thirteen prospective studies, data from Pooling Project excluded
Independent publications – random effects	1·06	0·98, 1·15	Includes thirteen prospective studies, data from Pooling Project excluded
Studies published between 2003 and 2007 – fixed effects	1·04	1·00, 1·09	Includes ten prospective studies (published after the Pooling Project)
Studies published between 2003 and 2007 – random effects	1·08	0·99, 1·18	Includes ten prospective studies (published after the Pooling Project)
Premenopausal*	1·02	0·92, 1·13	Data from Pala *et al.* (2009)[13], Taylor *et al.* (2007)[17], Cho *et al.* (2006)[19], Missmer *et al.* (2002)[8]
Postmenopausal – fixed effects	1·02	0·98, 1·08	Data from Pala *et al.* (2009)[13], Ferrucci *et al.* (2009)[14], Kabat *et al.* (2009)[10], Egeberg *et al.* (2008)[15], Taylor *et al.* (2007)[17], Missmer *et al.* (2002)[8]
Postmenopausal – random effects	1·11	0·99, 1·25	Data from Pala *et al.* (2009)[13], Ferrucci *et al.* (2009)[14], Kabat *et al.* (2009)[10], Egeberg *et al.* (2008)[15], Taylor *et al.* (2007)[17], Missmer *et al.* (2002)[8]
Dose–response: 100 g increment – fixed effects	1·04	1·00, 1·07	Includes data from the Pooling Project publication and eight additional prospective studies
Dose–response: 100 g increment – random effects	1·12	1·03, 1·23	Includes data from the Pooling Project publication and eight additional prospective studies
Premenopausal*: 100 g/d increment	1·01	0·92, 1·11	Data from Pala *et al.* (2009)[13], Taylor *et al.* (2007)[17], Cho *et al.* (2006)[19], Missmer *et al.* (2002)[8]
Postmenopausal: dose–response 100 g increment – fixed effects	1·03	0·98, 1·08	Data from Pala *et al.* (2009)[13], Kabat *et al.* (2009)[10], Ferrucci *et al.* (2009)[14], Egeberg *et al.* (2008)[15], Taylor *et al.* (2007)[17], Missmer *et al.* (2002)[8]
Postmenopausal: dose–response 100 g increment – random effects	1·22	1·04, 1·44	Data from Pala *et al.* (2009)[13], Kabat *et al.* (2009)[10], Ferrucci *et al.* (2009)[14], Egeberg *et al.* (2008)[15], Taylor *et al.* (2007)[17], Missmer *et al.* (2002)[8]
Processed meat			
Overall (high intake *v.* low intake) – fixed effects	1·00	0·98, 1·01	Includes data reported in the Pooling Project publication and nine additional prospective studies
Overall (high intake *v.* low intake) – random effects	1·08	1·01, 1·16	Includes data reported in the Pooling Project publication and nine additional prospective studies
Independent publications*	1·06	1·01, 1·11	Includes eleven prospective studies, data from Pooling Project excluded
Premenopausal*	1·01	0·90, 1·13	Data from Pala *et al.* (2009)[13], Taylor *et al.* (2007)[17], Cho *et al.* (2006)[19], Holmes *et al.* (2003)[22]
Postmenopausal – fixed effects	1·06	1·00, 1·13	Data from Pala *et al.* (2009)[13], Ferrucci *et al.* (2009)[14], Kabat *et al.* (2009)[10], Egeberg *et al.* (2008)[15], Taylor *et al.* (2007)[17], Holmes *et al.* (2003)[22], Voorrips *et al.* (2002)[28]
Postmenopausal – random effects	1·09	0·99, 1·21	Data from Pala *et al.* (2009)[13], Ferrucci *et al.* (2009)[14], Kabat *et al.* (2009)[10], Egeberg *et al.* (2008)[15], Taylor *et al.* (2007)[17], Holmes *et al.* (2003)[22], Voorrips *et al.* (2002)[28]
Dose–response: 30 g increment – fixed effects	1·03	1·00, 1·06	Includes data from the Pooling Project publication and seven additional prospective studies
Dose–response: 30 g increment – random effects	1·06	0·99, 1·14	Includes data from the Pooling Project publication and seven additional prospective studies
Premenopausal*: 30 g/d increment	1·03	0·98, 1·08	Data from Pala *et al.* (2009)[13], Taylor *et al.* (2007)[17], Cho *et al.* (2006)[19], Holmes *et al.* (2003)[22]
Postmenopausal: dose–response 30 g increment – fixed effects	1·07	1·02, 1·13	Data from Pala *et al.* (2009)[13], Ferrucci *et al.* (2009)[14], Kabat *et al.* (2009)[10], Egeberg *et al.* (2008)[15], Taylor *et al.* (2007)[17], Holmes *et al.* (2003)[22], Voorrips *et al.* (2002)[28]
Postmenopausal: dose–response 30 g increment – random effects	1·13	0·99, 1·28	Data from Pala *et al.* (2009)[13], Ferrucci *et al.* (2009)[14], Kabat *et al.* (2009)[10], Egeberg *et al.* (2008)[15], Taylor *et al.* (2007)[17], Holmes *et al.* (2003)[22], Voorrips *et al.* (2002)[28]

SSRE, summary relative risk estimate.
* Fixed-effects model; results similar for random effects.

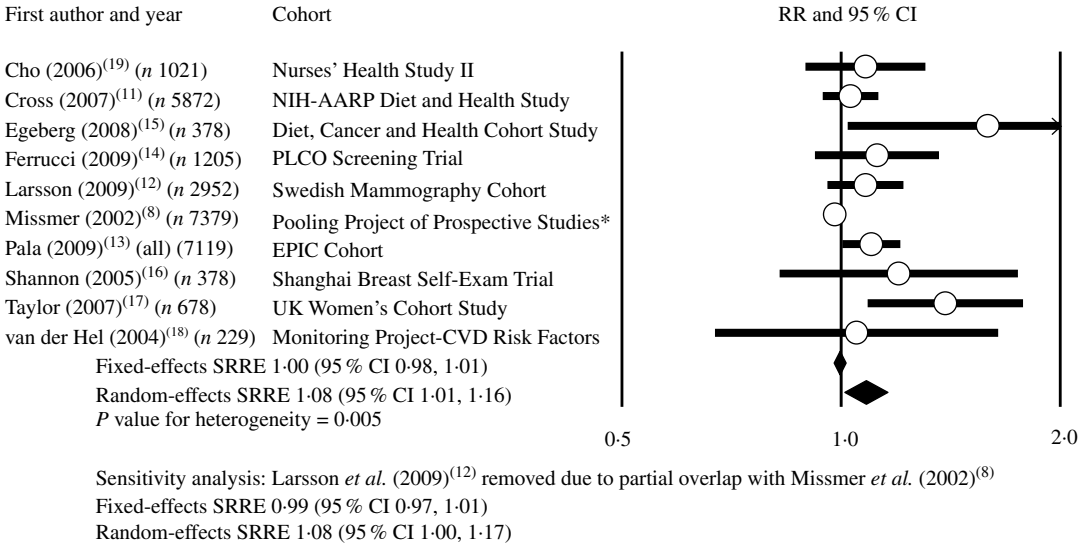

Fig. 2. Meta-analysis of prospective studies of processed meat and breast cancer. * Includes data pooled from seven cohorts; partial overlap with Larsson *et al.* (2009)[12]. RR, relative risk; PLCO, Prostate, Lung, Colorectal, and Ovarian; EPIC, European Prospective Investigation into Cancer and Nutrition; SRRE, summary relative risk estimate.

to the right of the weighted effect size, indicating potential publication bias (Fig. 3). Using Duval and Tweedie's trim and fill method, in which the summary association is recomputed based on the imputation of potentially missing studies, resulted in changing the SRRE from 1·02 to 1·01 and from 1·07 to 1·01 for the fixed- and random-effects models, respectively (based on imputing three studies). Six studies were imputed for the processed meat analysis, resulting in changing the SRRE from 1·08 (95 % CI 1·01, 1·16) to 1·00 (95 % CI 0·94, 1·06) based on the random-effects model (note: the SRRE was virtually unchanged for the fixed-effects model).

Discussion

Since the publication of the Pooling Project analysis of eight cohorts in 2002[8], several large prospective studies have been published that evaluated the relationship between red meat and processed meat consumption and breast cancer. Therefore, the objectives of our quantitative assessment were to synthesise and summarise data across all available prospective studies to update the state of the science, to better clarify any associations, and to identify potential sources of heterogeneity. Overall, most associations across the variety of meta-analysis models were slightly above the null value (i.e. 1·0) and not statistically significant. Significant heterogeneity was evident in most meta-analysis models, and the heterogeneity did not appear to be explained by menopausal status or by year of publication. Moreover, adjusting for publication bias resulted in attenuating summary associations.

In this quantitative assessment, data for red meat intake and breast cancer from ten prospective studies were combined with pooled data reported in the Pooling Project publication[8]. Thus, we were able to meta-analyse data on over 25 000 cases of breast cancer. Among all women, no statistically significant associations were observed in the high *v.* low red meat intake analyses, with SRRE of 1·02 and 1·07 for the fixed- and random-effects models, respectively. Although these summary associations were not indicative of a significant increased risk of breast cancer among consumers of red meat, significant heterogeneity was observed between the effect estimates in this analysis. The heterogeneity did not seem to be explained by selection of cohort data, as removal of data from the Pooling Project study did not modify the summary associations nor did analysing data from studies published after the Pooling Project. Moreover, fixed-effects summary associations were identical (i.e. 1·02) in the analyses of premenopausal women and postmenopausal women. Therefore, the heterogeneity in effect sizes is not probably due to variability in associations by menopausal status.

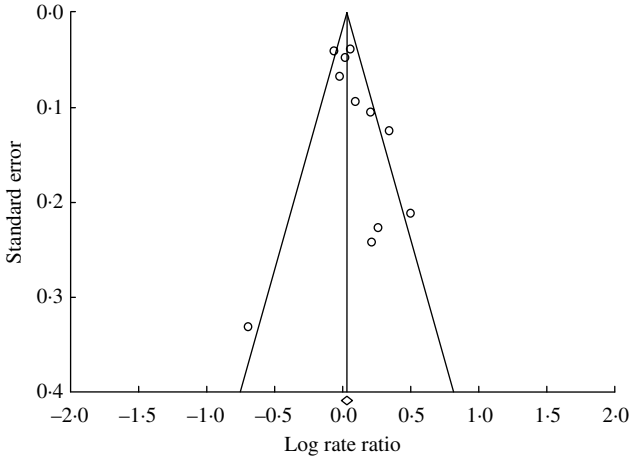

Fig. 3. Funnel plot for prospective studies of red meat and breast cancer. For studies, see Fig. 1.

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High *v.* low intake meta-analysis only takes into account the highest level of intake (compared with the referent group) as reported in a particular study, and the data for the middle intake categories are not typically analysed. In contrast, categorical dose–response regression meta-analysis utilises all available data for each intake strata to produce a summary estimate reflecting risk per incremental level of intake. Although this type of analysis uses all available data, it is assumed that risk increases (or decreases) linearly, and risk may be extrapolated to intake levels considerably higher than what is reported in an individual study. Indeed, we used 100 g increments in the meta-analyses of red meat intake to be consistent with the level reported in the Pooling Project analysis even though this intake level is generally higher than the reported intakes in the majority of cohorts. Similar to the high *v.* low intake analyses, summary associations for each 100 g increment of red meat intake were weakly elevated, but significant heterogeneity was observed (Table 2). Dose–response summary associations by menopausal status were similar for the fixed-effects meta-analyses, but the random-effects summary association was modestly stronger (SRRE = 1·22) among postmenopausal women. This difference was due to less relative weight given to the Pooling Project data of eight cohorts and more weight given to the five other studies. In the Pooling Project analysis, the pooled RR for each 100 g increment of red meat across eight cohorts was 0·97. In contrast, the summary association across five studies of postmenopausal women published after the Pooling Project was 1·13 and 1·34 for the fixed- and random-effects models, respectively, although significant heterogeneity remained (sensitivity analysis data not shown).

Meta-analyses of processed meat intake and breast cancer were similar to the analyses of red meat. Summary associations ranged between 1·00 and 1·13 and most were not statistically significant. Among all women, no association was observed in the fixed-effects analysis of high *v.* low intake, while a summary association of 1·08 was observed in the random-effects model. This difference was largely due to less relative weight provided to the Pooling Project data. When data from the Pooling Project were excluded, the fixed- (i.e. 1·06) and random- (i.e. 1·07) effects models produced similar summary associations, although significant heterogeneity was observed. Summary associations were slightly stronger, albeit weakly elevated, in the analyses of postmenopausal women compared with premenopausal women; however, the CI were largely overlapped. Although data were relatively sparse, analyses of individual processed meat items (for example, bacon, hot dogs) were not supportive of significant associations with breast cancer.

Statistically, based on the available epidemiological data, we were unable to identify significant sources of heterogeneity, although between-study variability was present in most meta-analysis models. From a methodological standpoint, regardless of statistical heterogeneity, variability can be produced by a wide array of factors, such as the type of study population, the methods of dietary assessment and/or measurement, variable definitions (for example, food groups, serving sizes), analytical categorisations (for example, servings per week, g per d), exposure contrasts (analytical cut-points and comparisons of intake levels), and degree of adjustment for potential confounding factors. Despite these sources of potential variability, collectively, the meta-analyses produced relatively consistent results, with most summary associations just above the null value.

Although we were able to conduct a wide variety of meta-analyses for red/processed meat intake and breast cancer, data are relatively sparse for some emerging hypotheses. Indeed, how and/or whether diet early in life may contribute to the development of adult cancer is of increasing scientific interest. Of particular relevance is breast cancer because of increased mammary susceptibility to potential carcinogens during adolescence and early life[34]. In a case–control study nested within the Nurses' Health Study I and II cohorts, Michels *et al.* [21] examined the potential effects of pre-school diet on subsequent breast cancer risk later in life. The mothers of participants in the Nurses' Health Study cohorts were asked about their daughters' perinatal and early childhood dietary habits using a thirty-food item questionnaire. Ground beef was associated with a non-significant 44 % increased risk of breast cancer, while consumption of meat (as a main dish or as a sandwich or mixed dish) or hot dogs were associated inversely, albeit non-significantly, with subsequent breast cancer risk. In a study of the Nurses' Health Study II cohort[20], participants were asked to complete a questionnaire regarding diet during high school, a life period that may be affected by micronutrient intake during adolescent growth. A non-significant positive association between the highest intake of red meat and subsequent risk of breast cancer was reported (RR 1·22; 95 % CI 0·82, 1·82), but no trend based on incremental intake was observed (*P* value for trend = 0·17). Interpretation of these studies should be made with some reservation, as results may be subject to poor recall since study participants (or mothers of cases) are reporting dietary habits that probably occurred 30–40 or more years before ascertainment. Although an intriguing area of research, no conclusions at the present time can be drawn regarding the possible association between pre-school or adolescent meat consumption and adult breast cancer risk because of limited data.

Another area of increasing scientific interest is the potential relationship between dietary factors and breast cancer risk according to tumour hormone receptor status. Although breast tumours differ clinically and biologically by hormone receptor status[19], there is little evidence regarding the potential association between red/processed meat and hormone receptor status cancer. In an analysis of the Nurses' Health Study II, Cho *et al.* [19] evaluated whether the association between red meat or processed meat and breast cancer differed by hormone receptor status among premenopausal women. As reported earlier, the authors found a non-significant positive association between the highest intake quintile of red meat and total breast cancer (RR 1·27; 95 % CI 0·96, 1·67). The positive association, however, was restricted to women with hormone receptor-positive cancer (oestrogen receptor (ER) + /progesterone receptor (PR) +) (RR 1·97; 95 % CI 1·35, 2·88). A non-significant inverse association was reported among women with hormone receptor-negative

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cancer (ER − /PR −) (RR 0·89; 95 % CI 0·43, 1·84). Positive associations were also reported for pork (as a main dish), hamburger, bacon, hot dogs, and other processed meats (for example, sausage, salami, bologna) among women with ER + /PR + cancer, while inverse associations for these same meat groups were observed among women with ER − /PR − cancer. In contrast, in a recent analysis of the Swedish Mammography Cohort[12], stronger associations for red meat intake were found among women with ER − /PR − cancer (RR 1·12; 95 % CI 0·70, 1·79) than ER + /PR + cancer (RR 1·10; 95 % CI 0·90, 1·34). An inverse association for the highest red meat intake category was reported among women with ER + /PR − cancer (RR 0·86; 95 % CI 0·60, 1·23).

It has been hypothesised that mutagenic by-products, such as heterocyclic amines or polycyclic aromatic hydrocarbons, of cooking meat may contribute to mammary carcinogenesis. However, findings from epidemiological studies of heterocyclic amines and polycyclic aromatic hydrocarbons and breast cancer have been variable and limited to few investigations[10,14,35–38]. Some studies[14,39–41] have shown that consumption of well-done meat is associated positively with increasing the risk of breast cancer, but other studies[10,26,38] have found no such effect. In a recent prospective analysis of 3818 postmenopausal breast cancer cases in the NIH-AARP Diet and Health Study cohort, no associations were found for meat cooked at high temperatures, well/very well-done cooked meat, overall mutagenic activity, or specific heterocyclic amines, and the authors concluded that their analysis 'provides no support for a role of meat mutagens in the development of postmenopausal breast cancer'[10]. In another recent analysis of postmenopausal women[14], no significant associations were reported for well/very well-done cooked meat or overall mutagenic activity, but a significant positive association was found for 2-amino-3, 8-dimethylimidazo[4,5-f]quinoxaline (MeIQx). No linear trend was observed for MeIQx, however.

The relationship between meat consumption and breast cancer has been the focus of several epidemiological investigations, yet there has been no clear scientific consensus as to whether red or processed meat intake increases the risk of breast cancer. The current quantitative assessment summarises prospective data on over 25 000 cases of breast cancer, and incorporates data from several recently published cohorts. The results of this meta-analysis do not appear to support an independent association between red meat or processed meat intake and breast cancer. Collectively, all summary associations were weakly elevated, with most ranging between 1·00 and 1·10. Some analyses produced statistically significant associations, although results were sensitive to the choice of model (fixed effects *v.* random effects). Heterogeneity was evident in most meta-analysis models, and this between-study variability could not be explained by analyses of menopausal status, year of publication, or inclusion/exclusion of specific cohorts. In addition, there was modest evidence of publication bias which may have skewed the summary associations slightly in the positive direction. Breast cancer is a heterogeneous disease with differing aetiologies; thus, the potential role that diet may play in the development of breast cancer among subgroups is of great public health importance. Recent studies have suggested that meat consumption may affect breast cancer risk through hormone receptor status, and that diet early in life may influence adult breast cancer. Data for these hypotheses are limited, however, and additional prospective studies are needed before conclusions can be drawn.

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D. D. A. contributed to the writing, analysis, and literature review; L. M. M. contributed to the data extraction and literature review; P. J. M. contributed to the writing, technical and editorial review; C. A. C. contributed to the data extraction, database management, and editorial review.

The authors declare no conflicts of interest.

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