Consumption of red and processed meat and breast cancer incidence: A systematic review and meta-analysis of prospective studies

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Abstract

Prior studies on red and processed meat consumption with breast cancer risk have generated inconsistent results. We performed a systematic review and meta-analysis of prospective studies to summarize the evidence regarding the relation of red meat and processed meat consumption with breast cancer incidence. We searched in MEDLINE and EMBASE databases through January 2018 for prospective studies that reported the association between red meat and processed meat consumption with incident breast cancer. The multivariable-adjusted relative risk (RR) was combined comparing the highest with the lowest category of red meat (unprocessed) and

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processed meat consumption using a random-effect meta-analysis. We identified 13 cohort, 3 nested case–control and two clinical trial studies. Comparing the highest to the lowest category, red meat (unprocessed) consumption was associated with a 6% higher breast cancer risk (pooled RR,1.06; 95% confidence intervals (95%CI):0.99–1.14; I^2 = 56.3%), and processed meat consumption was associated with a 9% higher breast cancer risk (pooled RR, 1.09; 95%CI, 1.03–1.16; I^2 = 44.4%). In addition, we identified two nested case–control studies evaluating the association between red meat and breast cancer stratified by *N*-acetyltransferase 2 acetylator genotype. We did not observe any association among those with either fast (per 25 g/day pooled odds ratio (OR), 1.18; 95%CI, 0.93–1.50) or slow *N*-acetyltransferase 2 acetylators (per 25 g/day pooled OR, 0.99; 95%CI, 0.91–1.08). In the prospective observational studies, high processed meat consumption was associated with increased breast cancer risk.

Keywords

red meat; processed meat; breast cancer; *N*-acetyltransferase 2 acetylators; meta-analysis

Introduction

Globally, breast cancer is the most common cancer among women and the second leading cause of cancer death.[1] Given the international variations in breast cancer rates and trends,[2] the importance of identifying modifiable lifestyle risk factors is widely acknowledged as a means to reduce breast cancer. Red meat is hypothesized to be an important dietary risk factor for several cancer sites, and provides a source of animal fat, heme iron and chemical carcinogens that may accumulate during cooking and/or processing. The International Agency for Research on Cancer (IARC) concluded that consumption of red meat (unprocessed) was a probable human carcinogen, whereas processed meat was classified as "carcinogenic to humans."[3] This classification was largely based on the evidence for colorectal, pancreas and prostate cancers for red meat and colorectal cancer for processed meat.[3] Using pooled data from eight cohort studies, Missmer *et al.*[4] observed a null association of red meat and processed meat consumption with breast cancer risk. However, in a recent meta-analysis of 14 studies, Guo *et al.* provided evidence that red meat and processed meat consumption was associated with higher risk of breast cancer.[5] In contrast, Anderson *et al.* reported that only processed meat might increase risk of breast cancer.[6] However, the meta-analysis by Guo *et al.* had several limitations such as including some studies twice in the analysis[4,7–10] as well as including a case–control study.[11]

Epidemiological studies assessing red meat and processed meat intake with risk of breast cancer based on menopausal status are limited and inconsistent, with most of the studies including largely postmenopausal women.[9,10,12–18] In previously meta-analysis, higher processed meat was associated with higher risk of postmenopausal breast cancer, but not breast cancer before menopause.[6] Moreover, breast cancer is a heterogeneous disease, and estrogen receptor positive breast tumors (ER+) are more strongly associated with hormone-related factors than estrogen receptor negative tumors (ER−),[19] therefore, hormone residues of the exogenous hormones used in beef cattle may increase risk of ER+ tumors.[20] However, the association of red meat consumption in relation to tumor hormone receptor status is not

well-established[8,10,18,21,22] and, to our knowledge, no prior meta-analyses have reviewed this association.

Heterocyclic amines (HCAs) are carcinogenic compounds that form in meat when cooking for a long duration at high temperature.[23,24] *N*-acetyltransferase 2 (*NAT2*), an important enzyme in the biotransformation of aromatics and HCAs,[25,26] is a polymorphic enzyme that segregates individuals into biochemical phenotypes, ranging from slow to fast acetylators.[27] It is hypothesized that higher levels of DNA adducts are formed by O-acetylation of HCAs among *NAT2* fast acetylators than among slow acetylators.[28] Therefore, these differences in enzyme activity may modify the carcinogenic effect of red meat. However, regarding the interaction between meat consumption and *NAT2* polymorphisms on risk of breast cancer, evidence in epidemiological studies is sparse and conflicting,[29–31] and it has not been evaluated in published meta-analyses.

In our study, we conducted a meta-analysis on the current evidence for effects of red meat and processed meat intake with risk of breast cancer overall, and according to menopausal, and estrogen and progesterone receptor status. We also examined whether *NAT2* genotype may modify the association between red meat intake and breast cancer risk.

Subjects and Methods

Study strategy

We followed the checklist of the Meta-analysis of Observational Studies in Epidemiology (MOOSE) for background, design, analysis and interpretation.[32] A systematic literature review was conducted in two databases, MEDLINE and EMBASE, related articles and hand-searching of references for all prospective studies describing the association of intake of red meat and processed meat with breast cancer risk until January, 2018. Two authors (M.S.F, E.C.) screened all publications. Only English publications were considered. The search strategy identified 466 unique citations. The definition of red meat and processed meat was based on the IARC Working Group classification.[3] Red meat refers to unprocessed mammalian muscle meat including beef, veal, pork, lamb, mutton, horse, or goat meat. Processed meat refers to meat that has been transformed through salting, curing, fermentation, smoking, or other processes to enhance flavor or improve preservation (e.g., bacon, sausage, salami, hot dog).[3] To minimize the influence of recall and selection bias that occur in case–control studies, we did not include these studies. Only prospective studies were included with multivariable-adjusted risk estimates (relative risk [RR] or hazard ratio [HR]) of red meat, processed meat, or total red meat (red meat + processed meat) consumption as an exposure and breast cancer as an endpoint. Retrospective (historical), case–control, cross-sectional, or ecological studies were excluded; nonoriginal research (reviews, editorials and letters), meeting abstracts and duplicated publications were also excluded. When multiple manuscripts were published from the same study population, the most up-to-date analyses with the largest number of breast cancer cases were considered for this meta-analysis (Fig. 1).

In a previous paper, using data from the Nurses' Health Study II (NHSII),[8] we reported the association between total red meat intake including unprocessed and processed red meat and

risk of breast cancer. For the current meta-analysis, we have updated the previous paper and included the results of red meat and processed meat intake separately.

Data extraction

Information was extracted on study characteristics (first author, publication year, study name, country), duration of follow up (mean, median, or maximum number of follow up), number of participants, number of cases of overall breast cancer, breast cancer before and after menopause, age at baseline (mean, median, or range), dietary assessment method, meat variable definition and covariates in the statistical models. When more than one multivariable model was reported, we extracted the RRs with the greatest number of adjusted variables.

Data synthesis

We conducted separate analyses considering three different variables: "red meat" which included only unprocessed red meat items, "processed meat" which included only processed meats, and "total red meat" which included red meat and processed meats. Because studies reported risk estimates differently (e.g., tertiles, quartiles, or quintiles of intake), we combined the RRs for the highest *vs.* the lowest category of intake. Forest plots were used to visualize the RRs and corresponding 95% confidence intervals (CIs) of the pertinent studies included in the meta-analysis. Potential heterogeneity among the studies was assessed using the I^2 statistic. Random-effects models (DerSimonian and Laird method) were used to calculate the overall RR estimates and 95% CIs. We assessed the possibility of publication bias by visual inspection of a funnel plot and the Begg's test. Potential heterogeneity among studies was assessed using the I^2 statistic, and the heterogeneity was further explored using stratified analysis and the meta-regression method. Sources of heterogeneity included region (North America/other countries), duration of follow-up (<8 years/ ≥8 years of follow-up), adjustment for energy intake, smoking, benign breast disease, family history of breast cancer, and alcohol intake. A two-tailed $p < 0.05$ was considered statistically significant. All statistical analyses were conducted using STATA, version 12, software (STATA Corp, College Station, TX).

Results

Study characteristics

After screening the titles and abstracts, 13 prospective cohort studies met inclusion criteria for red meat and processed meat meta-analyses[6,8–10,12,14,15,17,18,21,22,33,34] (Table 1). In addition, three nested case–control studies[13,35,36] and two clinical trial studies (not testing either red meat or processed meat)[16,37] met inclusion criteria for red/processed meat. Furthermore, two studies met inclusion criteria regarding the interaction between red meat consumption and *NAT2* polymorphisms on risk of breast cancer[29,30] (Table 2).

We conducted separate analyses considering for red meat, processed meat and total red meat. The characteristics of the 18 identified cohort, nested case–control and clinical trial studies are summarized in Table 1. In each study, the number of participants ranged from 493 to 319,826, and they were followed up anywhere from 1.9 to 20 years. A total of

1,133,110 women, including 33,493 cases of breast cancer (13 studies), were included in the red meat and overall breast cancer meta-analysis; a total of 1,254,452 women, including 37,070 cases of breast cancer (15 studies) for processed meat; and a total of 531,722 women, including 21,123 cases of breast cancer (7 studies) for total red meat. Diet was generally assessed by food frequency questionnaire, except two studies (NutriNet Santé and the Supplementation en Vitamines et Mineraux Antioxydants [SU.VI.MAX]) that utilized dietary records.[34,37] Red meat, processed meat and total red meat consumption was reported as gram/day or week, serving/day, or gram/1,000 kcal across studies (Supporting Information Tables S1, S2, S3). From 18 studies (including nested case–control and clinical trial studies), eight studies were from North America,[8,9,12,14,16,18,21,35] nine studies were from Europe[6,10,13,15,17,22,34,36,37] and one study from Japan.[33] In 15 out of 18 studies (CSA, NLCS, NHS, MPCDRF, CNBSS, UKWCS, PLCOCST, SMC, EPIC, BWHS, SU.VI.MAX, NHSII, NIH-AARP, UK Biobank, NutriNet Santé), measures of associations were adjusted for known breast cancer risk factors (Table 1). Seven cohort studies (NHS, CNBSS, UKWCS, EPIC, BWHS, NHSII, NutriNet Santé) reported results for premenopausal breast cancer. Eleven out of 18 studies reported the association between red meat or processed meat intake with breast cancer in postmenopausal women.[6,8,9,13–18,21,34] Three cohort studies (SMC, NHSII, NIH-AARP) reported the association between total red meat intake and breast cancer by estrogen and progesterone receptor status (Table 1). Data on red meat intake and risk of breast cancer stratified by *NAT2* genotypes were available from two nested case–control studies (DCH, NHS) (Table 2).

Publication bias

For overall breast cancer, visual inspection of a funnel plot (Supporting Information Fig. 1) and the Begg's test suggested no evidence of publication bias for red meat ($p = 0.23$) or processed meat ($p = 0.67$).

Red meat, processed meat and total red meat consumption and risk of breast cancer

Across 13 studies that examined the association between red meat and overall breast cancer, red meat consumption was associated with a nonsignificant increased risk of overall breast cancer. The random-effects summary of RRs comparing the highest *vs.* the lowest category of red meat was 1.06 (95% CI: 0.99, 1.14) (Fig. 2), with moderate inconsistency between studies ($I^2 = 56.3\%$).

Among 15 studies that evaluated the association between processed meat and overall breast cancer, the risk estimate comparing the highest *vs.* the lowest category was 1.09 (95% CI: 1.03, 1.16; $I^2 = 44.4\%$) (Fig. 3).

Among seven studies that evaluated the association between total red meat and overall breast cancer, the risk estimate comparing the highest *vs.* the lowest category was 1.09 (95% CI: 0.99, 1.21; $I^2 = 65.3\%$) (Fig. 4).

No individual study had a particularly large influence on the pooled estimate of RR for red meat or processed meat and breast cancer. However, significant association was observed between red meat and breast cancer after excluding SMC (RR = 1.08, 95%CI = 1.01–1.16;

$I^2 = 50.5\%$). In addition, the pooled RRs for red meat and breast cancer was changed to 1.04 (95%CI = 0.98–1.09; $I^2 = 27.8\%$) after excluding NutriNet Santé.

Red meat and processed meat consumption and risk of pre- and post-menopausal breast cancer

Among six cohort studies that examined the association between red meat intake and premenopausal breast cancer, the risk estimate comparing the highest *vs.* the lowest category was 1.07 (95% CI: 0.97, 1.18; $I^2 = 30.9\%$) (Supporting Information Fig. S2–A). Among nine studies that examined the association between red meat intake and postmenopausal breast cancer, the summary of RRs comparing the highest *vs.* the lowest category of red meat was 1.08 (95% CI: 0.99, 1.17; $I^2 = 53.6\%$) (Supporting Information Fig. S2–B). With regard to processed meat, higher intake was not associated with risk of premenopausal breast cancer (highest *vs.* lowest category RR = 1.09; 95%CI = 0.95, 1.25; $I^2 = 50.3\%$) (Supporting Information Fig. S3–A), whereas it was associated with a higher risk of postmenopausal breast cancer (highest *vs.* lowest category RR = 1.10; 95% CI: 1.03, 1.17; $I^2 = 30.8\%$) (Supporting Information Fig. S3–B).

Total red meat consumption, estrogen and progesterone receptor status and risk of breast cancer

Among the three studies with data related to hormone receptor status, total red meat intake was not significantly positively associated with risk of ER+/PR+ tumors (RR: 1.12; 95% CI: 0.92, 1.38) (Supporting Information Fig. S4–A) and ER−/PR− tumors (RR: 1.03; 95% CI: 0.85, 1.24) (Supporting Information Fig. S4–B).

Red meat consumption, *NAT2* acetylator status and risk of breast cancer

Among the two studies with data on *NAT2* genotype status, consumption of red meat was not associated with a higher risk of breast cancer among women with either the fast *NAT2* acetylator genotype (OR: 1.18; 95% CI: 0.93, 1.50 for each 25 g/d increase of red meat) (Fig. 5-A) or the slow *NAT2* acetylator genotype (OR: 0.99; 95% CI: 0.91, 1.08 for each 25 g/d increase of red meat) (Fig. 5-B).

Subgroup analyses

We did not find significant heterogeneity among studies that examined red meat or processed meat in relation to overall breast cancer incidence (Supporting Information Table S4).

Discussion

This systematic review and meta-analysis study reports significant positive associations between processed meat consumption with risk of breast cancer. When considering menopausal status, similar risk estimates were observed for association between processed meat and breast cancer risk before and after menopause, however, this association was not significant among premenopausal women. These associations were independent of traditional breast cancer risk factors. We did not observe significant association between

red meat intake and risk of breast cancer among women with fast or slow *NAT2* acetylator genotype.

Similar to the prior meta-analyses published in 2015 and 2018,[5,6] we found positive association between processed meat intake and breast cancer risk after including several newly published data and excluding duplicate studies. In our meta-analysis, we further expanded the analyses to include the assessment by menopausal and hormone receptor status.

Although high amounts of nitrate and nitrite might link processed meat to increased risk of breast cancer,[38,39] the high content of saturated fat, cholesterol and heme iron found in red meat may also underlie the association with breast cancer.[40,41] A high intake of animal-derived iron was associated with an increased risk of breast cancer in Chinese women.[41] Consistent with these findings, Ferrucci *et al.*[16] reported that intake of red meat, HCA and dietary iron elevated risk of invasive breast cancer. A study of genetic variability in iron-related oxidative stress pathways suggested that women with genotypes resulting in potentially higher levels of iron-related oxidative stress might be at increased risk of breast cancer.[42] However, another study was unable to demonstrate an association of iron or heme iron with breast cancer risk.[14]

Carcinogenic HCAs formed in red meat during high-temperature cooking may play a role in the etiology of breast cancer.[43–45] The carcinogenic effect may depend upon metabolisms of HCAs and related chemicals by *NAT2* genotypes. However, our findings did not support that high intake of red meat might increase risk of breast cancer for women characterized as fast acetylators of *NAT*2 (Fig. 5). The lack of statistical significance might be due to the meta-analysis of two studies that the RR came from red meat in the DCH and the RR came from total red meat in the NHS.

When considering menopausal status, similar risk estimates were observed for association between processed meat and breast cancer risk before and after menopause, however, this association was not significant among premenopausal women. The lack of statistical significance might be due to smaller sample size and lower statistical power among premenopausal women.

Fewer studies evaluated whether the association between total red meat intake and breast cancer varied by hormone receptor status.[8,10,18,21,22] Sex steroid hormones administered to animal for growth promotion might increase risk of hormone receptor positive tumors.[20] In the current analysis, however, the association between high total red meat consumption and breast cancer risk did not differ between ER+/PR+ tumors or ER−/PR− tumors.

Our analysis has several strengths. We limited our analysis to prospective cohort, nested case–control and clinical trial studies to minimize the influence of recall and selection bias that may occur in case–control studies. Also, most prospective studies adjusted for potential breast cancer risk factors. Although we observed wide variations in study population in the cohort studies, low to moderate heterogeneity across studies supported the external validity of pooling results from different studies. Additional strengths included the ability to evaluate the association of red meat intake and breast cancer events in different populations with

different diets, including large variations in red meat intake and to distinguish between unprocessed and processed red meat.

A few limitations of our study should be considered. As in any meta-analysis, publication bias is possible. However, we did not observe significant publication bias for either red meat or processed meat. Although most of the studies adjusted for major breast cancer risk factors, as with most observational studies, we cannot exclude the possibility of residual confounding. In the majority of studies, because diet was assessed using an FFQ, the under- or over-reporting of the amount of food groups could cause measurement error. However, since this equally may affect cases and noncases, likely estimates will be biased toward the null, so actual effect sizes might be larger than we observed here. Moreover, we compared the highest level of intake *vs.* the lowest, but levels of intake do not match sometimes. In some studies, processed poultry was included in processed meat and total red meat. If data for processed red meat were reported, these data were considered in our meta-analysis. Furthermore, at this level of risk subtle biases may be present. In some analyses, especially the one by *NAT2* genotype or by hormone receptor status, sample size was limited. Finally, because the majority of the studies were conducted in North America and Europe, the findings may not be directly generalizable to other racial and ethnic groups.

Conclusion

This systematic review and meta-analysis including prospective cohort studies of red meat and processed meat consumption provides evidence that higher consumption of processed meat is associated with higher risk of breast cancer. However, red meat was not a significant cause of breast cancer. Moreover, we did not find evidence for differing associations according to *NAT2* genotypes. Further studies examining molecular subtypes of breast cancer are needed.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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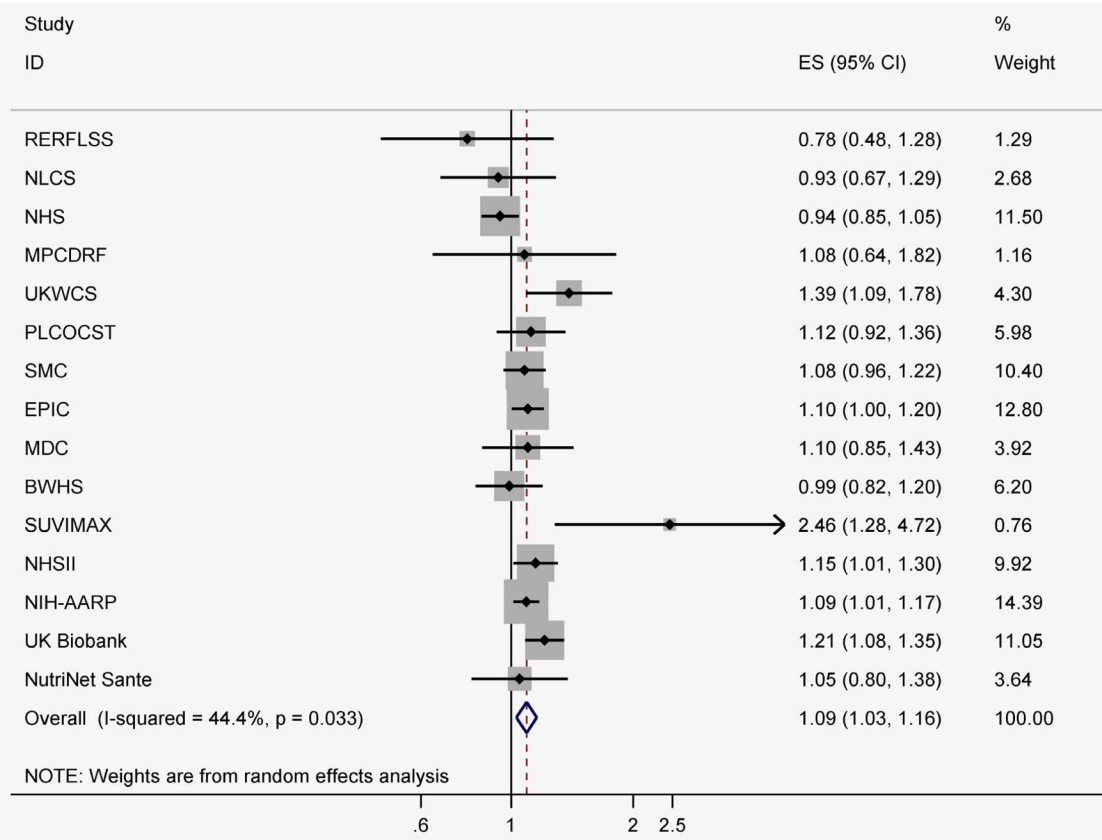
What's new?

The International Agency for Research on Cancer concluded that consumption of red meat is a probable human carcinogen, whereas processed meat was classified as carcinogenic. However, this classification was largely based on the evidence for colorectal, pancreas and prostate cancers. This systematic review and meta-analysis including prospective cohort studies of red meat and processed meat consumption provides evidence that higher consumption of processed meat, but not red meat, is associated with higher risk of breast cancer. These associations were independent of traditional breast cancer risk factors, and no evidence was found for differing associations according to N-acetyltransferase 2 (*NAT2*) genotypes.
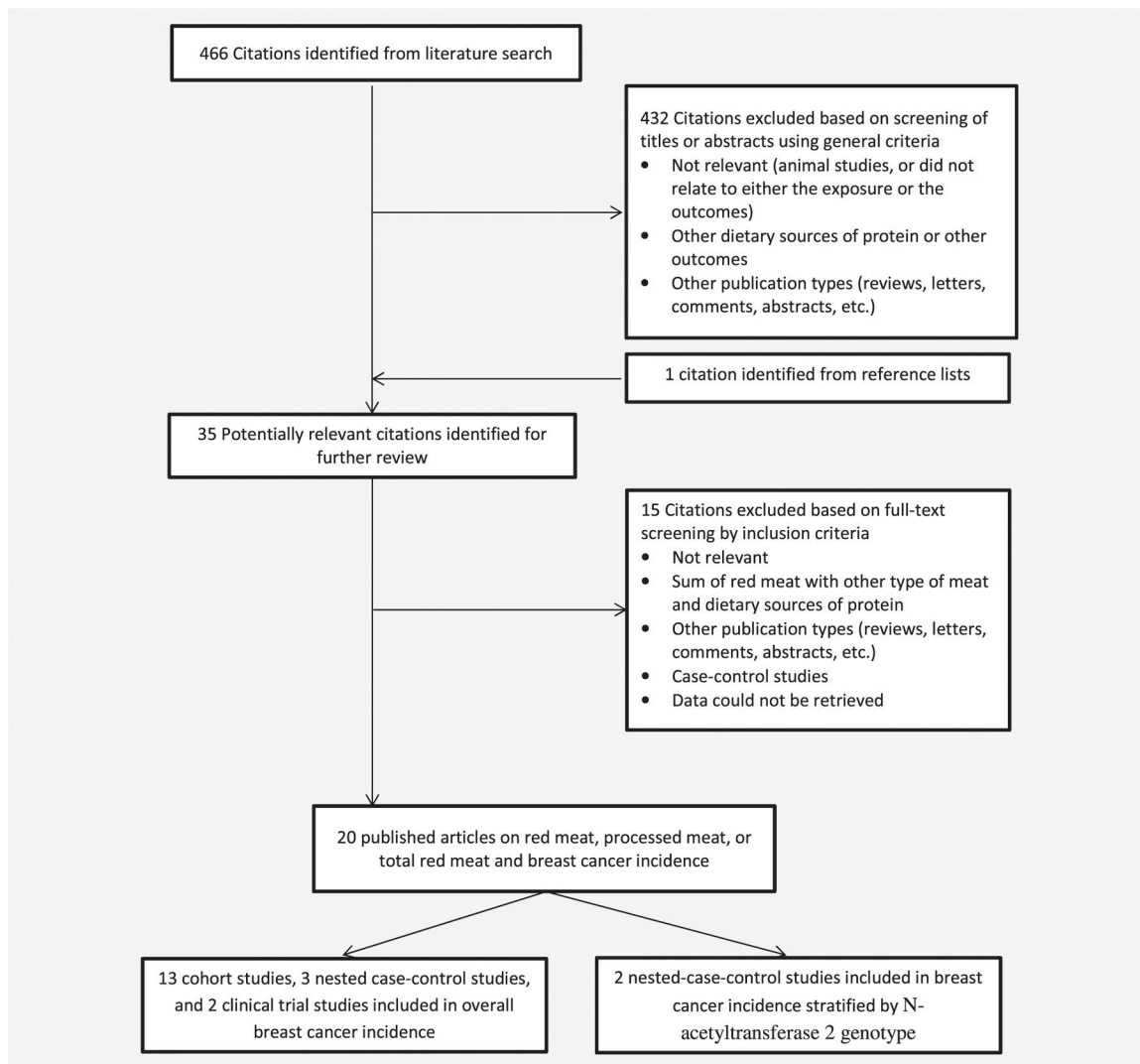
Figure 1.
Search, screening and selection process of prospective cohort studies of red meat and processed meat intake and risk of breast cancer.
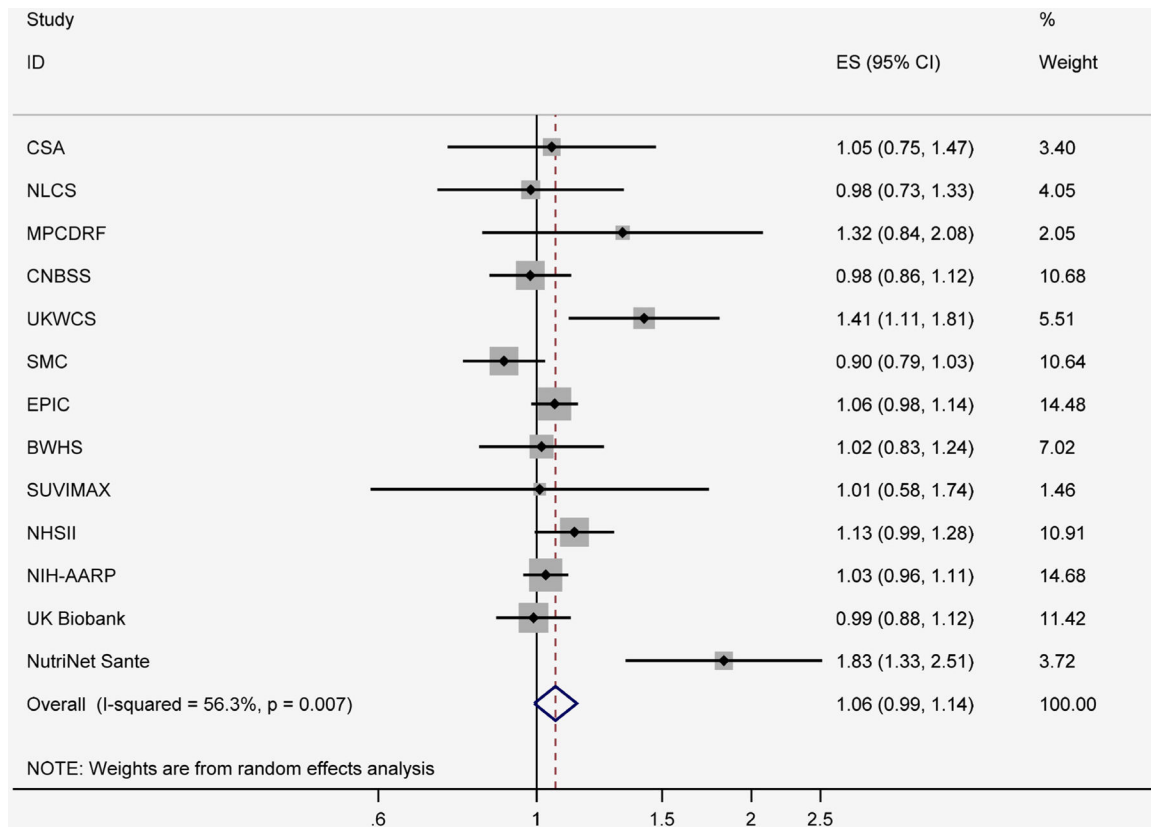
Figure 2.
Red meat intake and relative risks of overall breast cancer (highest category *vs.* lowest category). BWHS, Black Women Health Study; CNBSS, Canadian National Breast Screening Study; CSA, California Seventh-day Adventist; EPIC, European Prospective Investigation into Cancer and Nutrition cohort; MPCDRF, the Monitoring Project on Cardiovascular Disease Risk Factors; NHSII, Nurses' Health Study II; NIH-AARP, National Institute of Health- the American Association of Retired Persons; NLCS, The Netherland Cohort Study; SMC, Swedish Mammography Cohort; SU.VI.MAX, Supplemental en Vitamines et Mineraux Antioxydants; UKWCS, The UK Women's Cohort Study.

Study ID	ES (95% CI)	% Weight
RERFLSS	0.78 (0.48, 1.28)	1.29
NLCS	0.93 (0.67, 1.29)	2.68
NHS	0.94 (0.85, 1.05)	11.50
MPCDRF	1.08 (0.64, 1.82)	1.16
UKWCS	1.39 (1.09, 1.78)	4.30
PLCOCST	1.12 (0.92, 1.36)	5.98
SMC	1.08 (0.96, 1.22)	10.40
EPIC	1.10 (1.00, 1.20)	12.80
MDC	1.10 (0.85, 1.43)	3.92
BWHS	0.99 (0.82, 1.20)	6.20
SUVIMAX	2.46 (1.28, 4.72)	0.76
NHSII	1.15 (1.01, 1.30)	9.92
NIH-AARP	1.09 (1.01, 1.17)	14.39
UK Biobank	1.21 (1.08, 1.35)	11.05
NutriNet Sante	1.05 (0.80, 1.38)	3.64
Overall (I-squared = 44.4%, p = 0.033)	1.09 (1.03, 1.16)	100.00

NOTE: Weights are from random effects analysis

Figure 3.
Processed meat intake and relative risks of overall breast cancer (highest category *vs.* lowest category). BWHS, Black Women Health Study; EPIC, European Prospective Investigation into Cancer and Nutrition cohort; MDC, the Malmö Diet and Cancer; MPCDRF, the Monitoring Project on Cardiovascular Disease Risk Factors; NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; NIH-AARP, National Institute of Health- the American Association of Retired Persons; NLCS, The Netherland Cohort Study; PLCOCST, Prostate Lung Colorectal and Ovarian Cancer Screening Trial; RERFLSS, The Radiation Effects Research Foundation's Life Span Study; SMC, Swedish Mammography Cohort; SU.VI.MAX, Supplemental en Vitamines et Mineraux Antioxydants; UKWCS, The UK Women's Cohort Study.
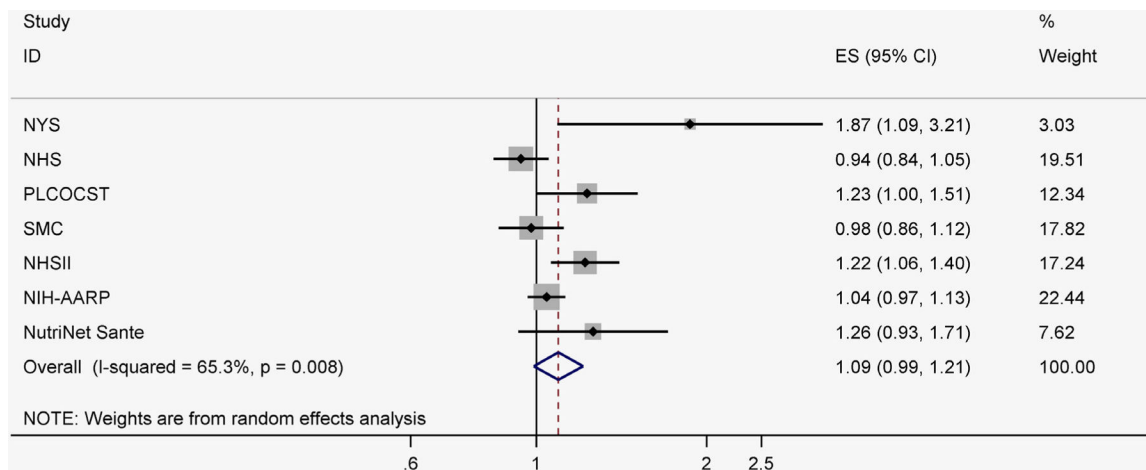
Figure 4.
Total red meat intake and relative risks of overall breast cancer (highest category *vs.* lowest category). NHS, Nurses' Health Study; NHSII, Nurses' Health Study II; NIH-AARP, National Institute of Health- the American Association of Retired Persons; NYS, The New York University Women's Health Study; PLCOCST, Prostate Lung Colorectal and Ovarian Cancer Screening Trial; SMC, Swedish Mammography Cohort.
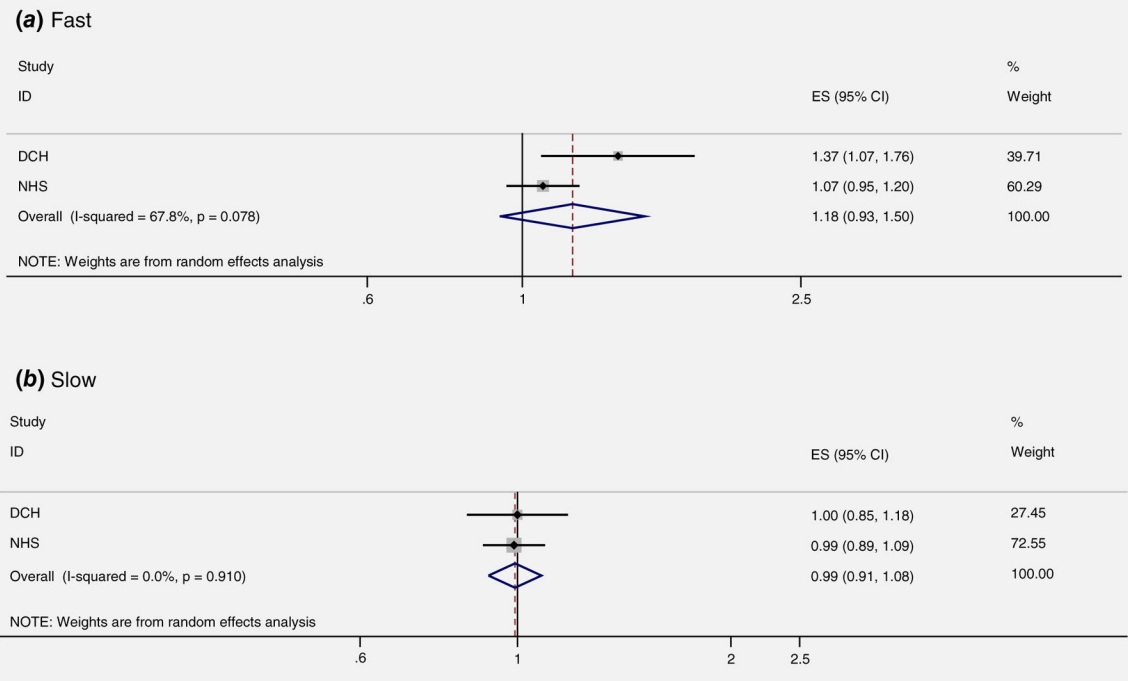
Figure 5.
Red meat intake and risk of breast cancer based on *NAT*2 acetylator genotype (per 25 g/day). DCH, Diet, Cancer, and Health Study; NHS, Nurses' Health Study.

Table 1.

Characteristics of cohort studies that evaluated red meat and processed meat intake and incidence of breast cancer

Author and year	Study name and country	Design of the study	Follow-up (year)	Total No. of participants	Number of breast cancer events	Menopausal status		ER/PR	Baseline age	Red meat variables (method of assessment)	Adjustment
						Pre	Post				
Mills et al.,[12]	CSA/US	Cohort	6	20,341	215	–	–	–	55.4	Red meat (hamburger, steak and other beef or veal) (FFQ)	Age, age at first live birth, age at menarche, menopausal status, history of BBD, maternal history of breast cancer, educational attainment, BMI
Toniolo et al.,[35]	NYS/US	nested case-control	22.2 ± 17.9 months	Control: 829	180	–	–	–	52.1 ± 8.4 for controls 52.2 ± 8.4 for cases	Total red meat (beef, veal, lamb, pork, processed luncheon meats: ham, cold cuts and turkey rolls) (FFQ)	Energy
Key et al.,[33]	RERFLSS/ Japan	Cohort	14	34,759	427	–	–	–		Processed meat (ham, sausages) (FFQ)	Age, city, age at time of bombing, radiation dose
Voorrips et al.,[13]	NLCS/the Netherlands	Case-Cohort design	6.3	Subcohort: 1,598	941	–	941	–	55–69	Red meat Processed meat (FFQ)	Age, history of BBD, maternal breast cancer, breast cancer in one or more sisters, age at menarche, age at menopause, OC use, parity, age at first childbirth, Quetelet index, education, alcohol use, current cigarette smoking, energy intake
Holmes et al.,[9]	NHS/US	Cohort	18	88,647	4,107	854	2,936	–	46.7 ± 7.2	Processed meat (hot dogs, bacon and other processed meat) Total red meat (hamburger, beef, pork or lamb as a main dish, beef, pork or lamb as a sandwich and all processed meat) (FFQ)	Age, total energy intake, alcohol intake, parity and age at first birth, BMI at age 18, weight change since age 18, height, family history of breast cancer, history of BBD, age at menarche, menopausal status, age at menopause HRT, duration of menopause
Van der Hel et al.,[36]	MPCDRF/the Netherland	nested case-control	10	Control: 264	229	–	–	–	47.0 ± 9.1 for controls 47.5 ± 8.0 for cases	Red meat (beef and pork) Processed meat (all processed meat items) (FFQ)	Age, menopausal status, town, energy intake, smoking, alcohol, age at menarche, BMI
Kabat et al.,[14]	CNBSS/ Canada	Cohort	16.4	49,654	2,491	1,171	993	–	40–59	Red meat (FFQ)	Age, BMI, menopausal status, parity, age at menarche, family history of breast cancer in a first degree relative, history of BBD, OC use, HRT, energy intake, alcohol intake, education, study center, randomization group,

Author and year	Study name and country	Design of the study	Follow-up (year)	Total No. of participants	Number of breast cancer events	Menopausal status		ER/PR	Baseline age	Red meat variables (method of assessment)	Adjustment
						Pre	Post				
Taylor et al.,[15]	UKWCS/UK	Cohort	8	33,725	678	283	395	–	52 (35–69)	Red meat (beef, pork, lamb and other red meat included in mixed dishes) Processed meat (bacon, ham, corned beef, spam, luncheon meats, sausages, pies, pasties, sausage rolls, liver pate, salami and meat pizza) (FFQ)	Age, energy intake, menopausal status, BMI, physical activity, smoking status, HRT, OC use, parity, total fruit and vegetable intake
Ferrucci LM et al.,[16]	PLCOCST/US	Clinical Trial	5.5	52,158	1,205	–	1,205	–	55–74	Processed meat (bacon, cold cuts, ham, hot dogs, sausage) Total red meat (bacon, beef, cheeseburgers, cold cuts, ham, hamburgers, hot dogs, liver, pork, sausage, veal, venison, red meat from mixed dishes) (FFQ)	Age, Ethnic group, education, study center, randomization group, family history of breast cancer, age at menarche, age at menopause, age at first birth and number of live births, history of BBD, number of mammograms during 3 years, menopausal HRT, BMI, alcohol use, total fat intake, total energy intake
Larsson et al.,[10]	SMC/Sweden	Cohort	17.4	61,433	2,952	–	–	*	39–76	Red meat (all fresh and minced pork, beef, veal) Processed meat (ham, bacon, sausages, salami, processed meat cuts, liver pate, blood sausages) Total red meat (FFQ)	Age, education, BMI, height, parity and age at first birth, age at menarche, age at menopause, OC use, HRT, family history of breast cancer, total energy intake, alcohol intake
Pala et al.,[17]	EPIC/Europe	Cohort	8.8	319,826	7,119	1,699	3,673	–	50.8 (25–70)	Red meat (fresh, minced and frozen beef, veal, pork, lamb) Processed meat (ham, bacon, sausages, blood sausages, liver pâté, salami, mortadella, tinned meat and others) (FFQ)	Age, center, energy, height, weight, years of schooling, smoking, alcohol intake, menopause
Wirfält et al.,[22]	MDC, Sweden	Cohort	10	15,773	544	–	–	*	45–73	Processed meat (sausages, all types) (mixed methods)	Energy intake, age, method version, season of data collection
Genkinger et al.,[21]	BWHS/US	Cohort	12	52,062	1,268	573	520	*	21–69	Red meat Processed meat (FFQ)	Energy intake, age at menarche, BMI, family history of breast cancer, education, parity and age at first live birth, OC use, menopausal status, age at menopause, HRT, physical activity, smoking status, alcohol intake
Pouchieu et al.,[37]	SU.VI.MAX/France	Randomized clinical trial	11.3	2,367	102	–	–	–	–	Red meat (fresh, minced and frozen beef, veal, pork	Age, number of dietary records, smoking status, educational level,

Author and year	Study name and country	Design of the study	Follow-up (year)	Total No. of participants	Number of breast cancer events	Menopausal status Pre	Menopausal status Post	ER/PR	Baseline age	Red meat variables (method of assessment)	Adjustment
		(placebo group)								and lamb) Processed meat (ham, bacon, sausages, blood sausages, liver pâ té, salami, mortadella, tinned meat and others) (Dietary record)	physical activity, height, BMI, family history of breast cancer, menopausal status at baseline, HRT, number of live births, without-alcohol energy intake, alcohol intake, total lipid intake, mutual adjustment for red meat or processed meat
Farvid et al.,[8]	NHSII/US	Cohort	20	88,803	2,830	1,511	918	*	26–45	Red meat (beef, or lamb as a sandwich, pork, beef, or lamb as a main dish, hamburger) Processed meat (sausage, salami and bologna) Total red meat (red meat and processed meat) (FFQ)	Age, Ethnic group, family history of breast cancer, history of BBD, smoking, height, BMI, age at menarche, parity and age at firth birth, OC use, HRT, age at menopause, menopausal status, alcohol intake, energy intake
Inoue-Choi et al.,[18]	NIH-AARP/US	Cohort	9.4	193,742	9,305	–	9,305	*	62 ± 5.3 (50–71)	Red meat (beef, pork) Processed red meat (ham, bacon, sausages, hot dogs, cold cuts) Total red meat (red meat, processed meat) (FFQ)	Age, Ethnic group, BMI, height, education, cigarette smoking, alcohol intake, physical activity, family history of breast cancer, age at menarche, age at menopause, age at first live birth, number of live births, HRT, OC use, number of previous breast biopsy, total energy intake, total fat intake, fiber intake, intake of other types of meat.
Anderson, et al.,[6]	UK Biobank/UK	Cohort	7	262,195	4,819			–	40–69	Red meat (beef, pork, lamb) Processed meat (FFQ)	Age, deprivation, ethnic group, smoking, alcohol, BMI, physical activity, vegetables, type of bread
Diallo, et al.,[34]	NutriNet Santé/France	Cohort	4.1	45,930	544	169	375		51.7 ± 10.1	Red meat Processed meat Total red meat (red meat and processed meat) 24 h dietary records	Age, energy intake without alcohol, number of 24-h dietary records, smoking, education, physical activity, height, BMI, alcohol, family history of cancers, lipid intake, fruits, vegetables, menopausal status, number of children, mutual adjustment for red meat or processed meat

Table 2.

Characteristics of cohort studies that evaluated red meat intake and incidence of breast cancer by NAT2 acetylator status

Author and year	Study name and country	Design of the study	Follow-up	Total No. of participants	Number of breast cancer events	Baseline age	Red meat variables (method of assessment)	Adjustment
Egeberg et al.,[29]	DCH/Denmark	nested case-control	7	Control:367	367	50–64	Red meat (beef, veal, pork, lamb, offal) Processed meat (bacon, smoked ham, salami, frankfurter, Cumberland sausage, cold cuts, liver pâté, processed fish that is fish prepared by pickling, salting, or smoking) (FFQ)	Parity, age at first birth, education, duration of HRT use, intake of alcohol, BMI
Lee et al,[30]	NHS/US	nested case-control	–	1,560	579		Total red meat (red meat and processed meat) (FFQ)	age, smoking, BMI at 18 yr, weight gain from 18 yr, age at menarche, family history of breast cancer, parity and age at first birth, postmenopausal hormone use, history of benign breast disease, total calorie and alcohol intake.

BMI, Body Mass Index; DCH, Diet, Cancer, and Health Study; HRT, Hormone Replacement Therapy; NHS, Nurses' Health Study.