

# Intake of Various Food Groups and Risk of Breast Cancer: A Systematic Review and Dose-Response Meta-Analysis of Prospective Studies

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## ABSTRACT

Despite increasing evidence for the association of food-based dietary patterns with breast cancer risk, knowledge about the shape of the relationship and the quality of meta-evidence are insufficient. We aimed to summarize the associations between food groups and risks of breast cancer. We performed a systematic literature search of the PubMed and Embase databases up to March 2020. We included cohort, case-cohort, nested case-control studies, and follow-up studies of randomized controlled trials that investigated the relationship between breast cancer risk and at least 1 of the following food groups: red meat, processed meat, fish, poultry, egg, vegetables, fruit, dairy product (overall, milk, yogurt, and cheese), grains/cereals, nuts, legumes, soy, and sugar-sweetened beverages. Summary risk ratios (RRs) and 95% CIs were estimated using a random-effects model for linear and nonlinear relationships. Inverse linear associations were observed for vegetables (RR per 100 g/d, 0.97; 95% CI, 0.95–0.99), fruit (RR per 100 g/d, 0.97; 95% CI, 0.95–0.99), cheese (RR per 30 g/d, 0.95; 95% CI, 0.91–1.00), and soy (RR per 30 g/d, 0.96; 95% CI, 0.94–0.99), while positive associations were observed for red (RR per 100 g/d, 1.10; 95% CI, 1.03–1.18) and processed meat (RR per 50 g/d, 1.18; 95% CI, 1.04–1.33). None of the other food groups were significantly associated with breast cancer risk. A nonlinear association was observed only for milk, such that the intake of >450 g/d increased the risk, while no association was observed for lower intake amounts. High intakes of vegetables, fruit, cheese, and soy products and low intakes of red and processed meat were associated with lower risks of breast cancer. However, causality cannot be inferred from these statistical correlations. *Adv Nutr* 2021;12:809–849.

**Keywords:** breast cancer, hormone receptor-positive, ER/PR-positive, refined grain, whole grain

## Introduction

Breast cancer is the most commonly diagnosed cancer among females and the leading cause of cancer-related death in women. In 2018, 2.1 million new breast cancer cases were estimated, accounting for approximately 11.6% of all cancers in the world (1), whilst in the same time-period, an estimated 600 000 deaths occurred worldwide in 2018, accounting for 6.6% of deaths from all cancer types (2).

Knowledge of the etiology of breast cancer is still limited (2), but a variety of modifiable and nonmodifiable risk factors have been identified. Indeed, race, ethnicity, family history of cancer, and genetic traits have been identified as important nonmodifiable risk factors in epidemiologic studies. However, modifiable risk factors have also been identified, such as increased alcohol consumption, physical inactivity, exogenous hormone uses, and certain female reproductive factors, such as pregnancy and age at first birth (3). Importantly, the potential role of diet on the risk of breast cancer has been examined in a large volume of epidemiologic studies; however, the specific associations between numerous specific food groups and breast cancer risks are relatively unclear.

Indeed, multiple systematic reviews and meta-analyses have evaluated the association of single food groups with breast cancer risks, and most of the prior meta-analyses

This study was supported by Vice Chancellor of Research, Shiraz University of Medical Sciences (grant number 99-01-106-23236).

Author disclosures: The authors report no conflicts of interest.

Supplemental Tables 1 and 2 and Supplemental Figures 1–19 are available from the “Supplementary data” link in the online posting of the article and from the same link in the online table of contents at <https://academic.oup.com/advances/>.

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Abbreviations used: IGF-I, insulin-like growth factor I; RCTs, randomized controlled trial; RR, risk ratio; SSB, sugar-sweetened beverages.

have only compared breast cancer risks in the highest versus lowest intakes of selected food groups. Moreover, multiple systematic reviews have examined dietary patterns (i.e., multiple food groups in combination) and breast cancer risks, finding moderate evidence to indicate that dietary patterns rich in vegetables, fruits, and whole grains and lower in animal-source foods and refined carbohydrates are correlated with decreased risks of postmenopausal breast cancer. The data pertaining to these dietary patterns and premenopausal breast cancer risks follow the same direction, but the evidence remains insufficient since few studies include premenopausal breast cancer (4, 5). However, the present study seeks to strengthen the field by taking a novel approach to examining individual foods/food groups. Thus, the objective of our comprehensive meta-analysis was to assess the shape of the diet/breast cancer relationship by performing linear and nonlinear dose-response analyses. We estimated the summary associations between intake of 13 food groups [as defined by the Schwingshackl et al. methodology (6)] and breast cancer risks.

## Methods

The protocol of this meta-analysis has been registered in the International Prospective Register of Systematic Reviews (PROSPERO; [www.crd.york.ac.uk/prospero/index.asp](http://www.crd.york.ac.uk/prospero/index.asp); identifier CRD42019144956). This systematic review was developed based on the standards of the Meta-Analysis of Observational Studies in Epidemiology guidelines (7).

### Study selection

To be eligible for inclusion, studies were required to: 1) be of cohort, case-cohort, or nested case-control design, including follow-up studies of randomized controlled trials (RCTs); 2) provide data on the association between the risk of breast cancer and at least 1 of the following 13 food groups: grains/cereals, vegetables, fruit, eggs, dairy products (overall or milk, yogurt, and cheese), fish, poultry, red meat, processed meat, nuts, legumes, soy product, sugar-sweetened beverages (SSB); 3) include participants aged  $\geq 18$  y; and 4) assess dietary intake at the beginning of the study. When dietary intake was assessed during adolescence or early adulthood, the study was not included in our meta-analysis. If  $\geq 2$  studies were published on the same exposure-outcome pair, we included only the most recent study with the longest follow-up, and thus the greatest number of events. Moreover, studies that only investigated the highest versus lowest categories were excluded. We also excluded studies conducted on micro- and macronutrients (i.e., soy fiber or phytoestrogen), and focused our evaluation on dietary groups. Studies that only assessed cancer recurrence or survivorship as the outcome were excluded, and studies with case-control and cross-sectional designs and RCTs and non-RCTs were excluded. We imposed no limitation or restriction on the geographical location and health status of participants.

### Search strategy

Articles published through March 2020 and indexed in PubMed and Embase were searched for prospective studies, based on the above inclusion criteria, with no language restriction. The search terms used as keywords in the search strategy are listed in **Supplemental Table 1**. In addition, the bibliographies of all relevant prior reviews and primary studies identified by the electronic search strategy were scanned for relevant papers.

### Data extraction

Our 2 reviewers independently extracted the following information: name of first author, year of publication, country, cohort name, age at entry, menopause status, sample size, total cases, dietary assessment, outcome, outcome assessment, type and quantity of food group, adjustment factors, duration of study, and risk estimate [risk ratios (RRs), HRs, or ORs with their corresponding 95% CIs]. Results for the fully adjusted model were extracted as the preferential data for our analyses. When a study did not report sufficient information for data extraction, we contacted the corresponding author by e-mail at least 2 times, 1 week apart; accordingly, we attained additional data for 2 papers using this method (8, 9). For the linear dose-response relationship, no studies were excluded because of incomplete data. But for the nonlinear analysis, 9 studies did not report the number of cases in each category and 1 study did not provide data on the amount of dietary intake in each category. Since we could not obtain required data after contacting the corresponding authors, we excluded these studies from the nonlinear analysis.

### Risk of bias assessment and quality of evidence

We used the Newcastle-Ottawa Scale to assess the methodological quality of included studies (10). We examined 3 main domains—selection, comparability, and outcome—to rate the quality of studies. In the selection domain, 4 items were assessed: representativeness of the exposed cohort, selection of the nonexposed cohort, ascertainment of exposure, and demonstration that the outcomes were not present at the start of the study. In the comparability domain, the control of confounders in the design or analysis of the studies was checked. Finally, in the outcome domain, the outcomes ascertainment, duration of follow-up, and adequacy of follow-up of cohorts were considered. If a study received 3–4 stars in the selection domain, 1–2 stars in the comparability domain, and 2–3 stars in the outcome domain, the quality was rated as good. If a study received 2 stars in the selection domain, 1–2 stars in the comparability domain, and 2–3 stars in the outcome domain, the quality was rated as fair. If a study received 0–1 star in the selection domain, 0 stars in the comparability domain, or 0–1 star in the outcome domain, the quality was rated as poor.

The overall quality of the studies included in this meta-analysis was also evaluated by the use of the NutriGrade scoring system (11), which comprises the following items: 1) risk of bias, study quality, and study limitations (0–2 points); 2) precision (0–1 point); 3) heterogeneity (0–1 point); 4)

directness (0–1 point); 5) publication bias (0–1 point); 6) funding bias (0–1 point); 7) effect size (+2 points); and 8) dose response (+1 point). This scoring system recommends 4 categories to define the meta-evidence as high ( $\geq 8$  points), moderate (6–7.99 points), low (4–5.99 points), or very low (0–3.99 points).

### Statistical analysis

We used HRs and 95% CIs as the effect sizes for all analyses. The reported RRs or ORs in the primary studies were considered to be equal to HRs. The dose-response meta-analysis was performed using the method proposed by Greenland and Longnecker (12) and Orsini et al. (13) and consists of 2 parts: linear analysis and nonlinear analysis. Using a random-effects model, we performed a linear dose-response meta-analysis by pooling the HRs for each increment of 100 grams of meat, poultry, fish, fruit, and vegetable intake; 50 grams of processed meat, egg, fruit juice, and legume intake; 200 grams of dairy (as a whole), milk, and yogurt intake; 30 grams of cheese and soy intake; 20 grams of cereals intake; and 28 grams of nut intake.

To assess the nonlinear dose-response relationship, a 2-stage hierarchical regression model was used, in which the difference between category-specific and reference-specific doses, expressed in quadratic terms, was calculated. Then, the dose-response association, considering within- and between-study variances, was estimated through the use of spline transformations. This method requires the distribution of cases and noncases across  $>3$  categories of food groups, using the median value and the adjusted RRs with their 95% CIs for each category of exposure. For the estimation quantity of food consumption, the median intake of each food group was used. If a study reported both the mean and median of the group, we used the median. Only mean intakes were reported in 11 papers, so for these studies the mean intake was used. In instances where the amount of food intake in each category was reported in the closed interval, consumption was considered as the midpoint of the interval. For the open-ended exposure categories, we considered the length of the open-ended interval to be the same as that of the adjacent interval. We set 2-sided statistical significance a priori at  $P < 0.05$ .

The Q test and the  $I^2$  statistic (with a value of  $I^2 > 50\%$  considered to represent potentially important statistical heterogeneity) was used to explore heterogeneity between studies. To discern the source of heterogeneity, we performed subgroup analyses of potential influencing factors, including menopause status, presence of estrogen receptor, follow-up duration, geographical location, number of cases, and characteristics of the food items (e.g., high- vs. low-fat content or whole vs. refined grain). However, it was not possible to perform subgroup analyses by all of these factors for all of food groups, because in some cases fewer than 2 studies were in a subgroup or the primary studies did not report the results appropriately; for example, for milk, some primary studies reported data separately according to the fat content (low- vs. high-fat intake) for dairy, yogurt, cheese,

and meat, while some studies did not report results according to the fat content.

If at least 10 studies were available, we explored potential small-study effects, such as publication bias, by using Egger's test and funnel plots. Stata version 13 software was used to conduct all statistical analyses.

### Results

As detailed in **Figure 1**, 7635 records were obtained following the literature search. Of these, 210 articles were potentially relevant for inclusion in the meta-analysis because they reported  $\geq 1$  of the 13 food groups and breast cancer risk in the title or abstract. Finally, the number of studies included in the meta-analysis for each food group were as follows: total meat: 13; red meat: 20; processed meat: 17; poultry: 13; fish: 17; egg: 11; fruit: 15; vegetable: 14; dairy: 10; milk: 13; yogurt: 6; cheese: 10; total cereals (both whole and refined): 14; soy and soy products: 7; nuts: 6; and legumes: 4. The number of studies on SSB was not adequate. The included studies were performed in Asia, Europe, North America, and Australia (1 study), and characteristics of all studies are presented in **Table 1**.

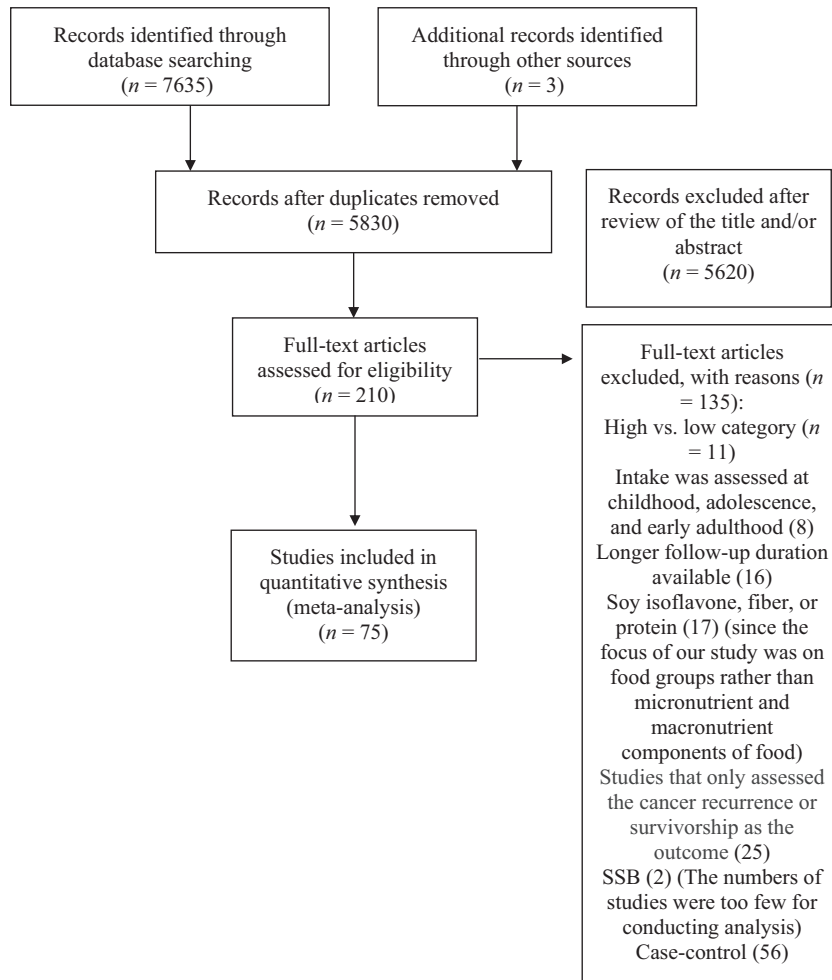
#### Total meat

From 14 studies, we investigated the association of total meat consumption with breast cancer, where 1 study was excluded (14) due to an identical publication with a longer duration being available. Therefore, 13 studies, with 48 590 breast cancer cases, were included in the linear dose-response meta-analysis (15–28). Each additional 100-g/d increase of total meat was associated with a small increase in the risk of breast cancer (RR, 1.07; 95% CI, 1.01–1.13;  $I^2$ , 75.5%;  $P$ -heterogeneity  $< 0.001$ ; **Supplemental Figure 1**). A subgroup analysis by duration, number of cases, and location indicated that this association persisted only in studies with a duration of  $< 10$  y, case numbers of  $\geq 1000$ , and studies conducted in Europe; while in studies with a duration of  $\geq 10$  y, case numbers of  $< 1000$ , and studies conducted in the United States, no association was observed (**Table 2**). Moreover, the difference between premenopausal and postmenopausal status was nonsignificant (**Table 2**).

We found no evidence of a nonlinear dose-response association ( $P$ -nonlinearity, 0.21;  $n = 11$  studies; **Figure 2A**).

#### Red meat

The association of red meat with breast cancer was investigated by 26 articles. We excluded 6 papers because other papers on the same cohort with longer durations were published (14, 29–33); thus, only the most recent studies with the longest follow-ups were included. These 20 studies (15, 16, 18–22, 24, 34–43), with 78 267 breast cancer cases, were included in the linear dose-response meta-analysis. Each 100-g/d increase of red meat was associated with a small increase in the risk of breast cancer (RR, 1.10; 95% CI, 1.03–1.18); however, statistically significant heterogeneity was observed in this model ( $I^2$ , 60.2%;  $P$ -heterogeneity  $< 0.001$ ; **Supplemental Figure 2**). The observed positive



**FIGURE 1** Flowchart of study selection.

associations persisted in additional analyses, stratified by follow-up duration, geographic location, number of cases, and menopausal status (Table 2). The subgroup differences were not statistically significant, with the exception of follow-up duration, which showed a stronger inverse association for studies with a duration of <10 y.

There was no evidence of a nonlinear dose-response association ( $P$ -nonlinearity, 0.24;  $n = 14$  studies). The risk of breast cancer increased by approximately 10% with increasing intake of red meat, up to 150 g/d (Figure 2B).

### Processed meat

From 20 papers that investigated the relationship between processed meat and breast cancer, 3 articles (14, 32, 33) were excluded because the same exposure-outcome pair with a longer duration was published. There were 17 studies, with 34 414 breast cancer cases, included in the linear dose-response meta-analysis (15, 16, 18–20, 22, 23, 25, 27, 34, 37, 39–41, 44, 45). A positive association was observed for each additional 50-g/d increase of processed meat (RR, 1.18; 95% CI, 1.04–1.33;  $I^2$ , 63.5%;  $P$ -heterogeneity < 0.001; Supplemental Figure 3). Subgroup analyses by menopause

status and follow-up duration indicated no significant association (Table 2). However, subgroup analyses by number of cases and geographic location revealed a stronger positive association for studies with case numbers of <1000 and studies conducted in Europe (Table 2).

No evidence of a nonlinear dose-response association was detected ( $P$ -nonlinearity = 0.10;  $n = 15$  studies). The risk of breast cancer increased by approximately 10% with an increasing intake of processed meat, up to 50 g/d (Figure 2C).

### Poultry

From 14 studies that investigated the association of poultry with breast cancer, 1 study was excluded (32) because a paper on the same cohort with a longer duration was published. Therefore, 13 studies, with 27 445 breast cancer cases, were included in a linear dose-response meta-analysis (15, 16, 19, 22–26, 36, 37, 39, 40, 46). No association was observed for each 100-g/d increase of poultry (RR, 0.97; 95% CI, 0.91–1.03;  $I^2$ , 22.9%;  $P$ -heterogeneity, 0.21; Supplemental Figure 4). Subgroup analyses by menopause status, follow-up duration, and geographic location indicated no significant association in the subgroups (Table 2). A subgroup analysis by

**TABLE 1** General study characteristics of the included studies investigating the association between various food groups and risk of breast cancer

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Adebamowo et al., 2005 (47)	Prospective cohort (8)	Nurses' Health Study (NHS) II, USA	90 638	57.8	90	710	Bean and lentil	Validated FFQ (130)	Cancer registration system	Age, study area, family history of breast cancer, age at menopause, age at first birth, parity, use of exogenous female hormone, smoking, consumption of green leafy vegetables, walking time, BMI, and total EI
Anderson et al., 2018 (34)	Prospective cohort (7)	UK Biobank	258 922	40–69	NM	9701	Red meat, processed meat	Not validated FFQ (NM)	Linkage to 3 routine administrative databases	Age, deprivation and ethnic group, smoking, alcohol, BMI and physical activity, consumption of cooked and raw vegetables, and type of bread
Boggs et al., 2010 (48)	Prospective cohort (12)	Black Women's Health Study (BWHHS), USA	51 928	38.9	85	1597	Total fruit and vegetable, yellow orange	Validated FFQ (85)	Medical record or cancer registry data	Age, energy intake, age at menarche, BMI at age 18 y, family history of breast cancer, education, geographic region, parity, age at first birth, OCP use, menopausal status, age at menopause, menopausal hormone use, vigorous activity, smoking status, alcohol intake, and multivitamin use

(Continued)

**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Butler et al., 2010 (49)	Prospective cohort (10,7)	Singapore Chinese Health Study (SCHS), Singapore	34,028 Post	55	NM	629	Vegetable, soy food	Validated FFQ (165)	Cancer registry	Age at interview, dialect group, interview year, education, parity, BMI, first-degree relative with diagnosis of breast cancer, EI
Cho et al., 2006 (29)	Prospective cohort (12)	NHS II, USA	349 573 Pre	36	>90	10 722	Red meat	Validated FFQ (130)	Self-reported	Age at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for smoking, height, parity and age at first birth, BMI, age at menarche, family history of breast cancer, history of benign breast disease, OCP use, alcohol intake, EI
Couto et al., 2013 (35)	Prospective cohort (16)	Women's Lifestyle and Health (WLH), Sweden	44 840 (40 031 Pre and 27 509 Post)	30–49	93	1278	Cereals, fruits and nuts, vegetable, dairy products, red meat, fish	Validated FFQ (80)	National cancer register	History of breast cancer in mother and/or sister(s), personal history of benign breast disease, smoking status, BMI, height, age at first birth and number of children, educational level, age at menarche, total energy intake, and consumption of beverages, potatoes, sweets, and eggs

(Continued)



**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Daniel et al., 2011 (46)	Prospective cohort (9)	National Institute of Health-American Association of Retired Persons (NIH-AARP), USA	184 488 Post	> 18	90	7181	Fish	Validated FFQ (124)	Linking cohort members to state cancer registries and to the US National Death Index	EI, age at entry, BMI, age at first menstrual period, age at first live birth, family history of breast cancer, HRT, education, race, intake, physical activity, smoking, age at menopause, number of breast biopsies, height
Dunneram et al., 2019 (15)	Prospective cohort (18)	UK Women's Cohort	29 183	53.2	NM	1625	Red meat, processed meat, fish, poultry, egg	Validated FFQ (217)	National Health Service Central Register	Age, ethanol intake, duration of breastfeeding, physical activity, smoking, social class, menopausal status
Diallo et al., 2018 (50)	Prospective cohort (4.1)	NutriNet-Sante, France	590 742	51.7	87	13 010	Red meat, processed meat	Validated web based 24-hr dietary records	Medical records	Age, energy intake without alcohol, number of 24-hour dietary records, smoking, educational level, physical activity, height, BMI, alcohol intake, family history of cancers, lipids intake, fruits, vegetables, hormone replacement therapy, number of children, contraception, red meat intake, and processed meat intake
Egeberg et al., 2008 (16)	Nested case-control (4.2)	Diet, Cancer and Health (DCH), Denmark	1134 Post	57	NM	378	Total meat, red meat, poultry, processed meat, fish	Validated FFQ (192)	Danish Cancer Registry	Parity, age at first birth, education, duration of HRT use, intake of alcohol, and BMI
Egeberg et al., 2009 (51)	Prospective cohort (9.6)	DCH, Denmark	25 278 Post	56	100	978	Whole-grain product,	Validated FFQ (192)	Danish Cancer Registry	Parity, age at first birth, education, duration of HRT use, use of HRT, intake of alcohol, and BMI

(Continued)

**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Emaus et al., 2016 (52)	Prospective cohort (11.5)	European Prospective Investigation into Cancer and Nutrition (EPIC), European countries	335 054	50.8	100	10 197	Fruit, vegetable	Validated FFQ (260), UK and Sweden (FFQ and a 7-day record)	Record linkage and cancer registries	Stratified by age and center and adjusted for energy intake divided into energy from fat and energy from nonfat sources, saturated fat intake, age at menarche, oral contraceptive use, age at first full-term pregnancy, menopausal status, hormone replacement therapy use, BMI, BMI at menopause, physical activity, smoking status and intensity, alcohol user (yes or no), alcohol consumption, educational level
Engeset et al., 2006 (53)	Prospective cohort (6.4)	EPIC, European countries	1 932 107	> 18	NM	4776	Fish	Validated FFQ (260), UK and Sweden (FFQ and a 7-day record)	Health insurance and cancer and pathology registries	Stratified by center, adjusted for time of follow-up, energy intake from fat, EI from CHO and protein, alcohol intake, height, weight, age at menarche, number of full-term pregnancies and age at first FTP, current use of hormone replacement therapy, current use of OCP, and menopausal status

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**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Farvid et al., 2014 (86)	Prospective cohort (20)	NHS II, USA	88 803	36.4	95	2826	Egg, total red meat (unprocessed and processed), poultry (chicken and turkey), fish, nut	Validated FFQ (130)	Self-reported + review of pathology reports	Age at start of follow-up and calendar year of current questionnaire cycle and was simultaneously adjusted for race, family history of breast cancer in mother or sisters, history of benign breast disease, smoking, BMI at menarche, parity and age at first birth, OCP use, alcohol intake, and energy. In Post women, we additionally adjusted for postmenopausal hormone use and age at menopause
Farvid et al., 2016 (54)	Prospective cohort (11.5)	NHS II, USA	90 476	27–44	98	6459	Fruit, vegetable, whole-grain, total refined-grain food intake	Validated FFQ (130)	Self-report	Race, family history of breast cancer in mother or sisters, history of benign breast disease, smoking, height, BMI at age 18, weight change since age 18, age at menarche, parity and age at first birth, OCP use, alcohol intake, and energy. In postmenopausal women, additionally adjusted for hormone use, age at menopause, hormone use and menopausal status, and age at menopause

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**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Farvid et al., 2018 (55)	Prospective cohort (22)	NHS II, USA	90 503 (56 231 Pre and 34 272 Post)	36.5	96	3191 (1706 Pre- and 1134 Post-menopausal)	Dairy	Validated FFQ (130)	Self-report	Smoking, race, parity and age at first birth, height, BMI at age 18 y, weight change since age 18, age at menarche, family history of breast cancer, history of benign breast disease, OCP use, adolescent alcohol intake, adult alcohol intake, physical activity, adolescent energy intake. In postmenopausal women, additional adjustment for hormone use and age at menopause. Among all women, additionally adjusted for hormone use and menopausal status and age at menopause
Farvid et al., 2019 (56)	Prospective cohort (23.7)	NHS I and NHS II, USA	93 844	36	96	3300	Fruits, fruit juice, vegetable	NHS II: Validated FFQ (130), NHS I: Validated FFQ (61)	Hospital records and pathology reports	Family history of breast cancer, history of benign breast disease, height, BMI at age 18 y, weight change since age 18, smoking, physical activity, OCP, alcohol intake, total EI, age at menarche, parity and age at first birth, and menopausal status, age at menopause, and MHT

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**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Ferrucci et al., 2009 (37)	Prospective cohort (5.5)	Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO), USA	52 158	65.2	NM	6464	Red meat, white meat, poultry, processed meat	Validated FFQ (124)	Self-report and physician reports	Age, race, education, study center, randomization group, family history of breast cancer, age at menarche and menopause, age at first birth and number of live births, history of benign breast disease, number of mammograms during past 3 y, menopausal hormone therapy, BMI, alcohol, total fat, and EI
Folsom and Demissie, 2004 (57)	Prospective cohort (14)	Iowa Women's Health Study (IWHIS), USA	3 377 526 Post	55–69	NM	10 147	Fish	Validated FFQ (127)	Linkage of cohort identifiers to Iowa State-wide cancer incidence and death records	Age, EI, educational level, physical activity level, alcohol consumption, smoking, pack-years of cigarette smoking, age at first live birth, estrogen use, vitamin use, BMI, waist/hip ratio, diabetes, hypertension, and intake of whole grains, fruit and vegetables, red meat, cholesterol, and saturated fat
Fung et al., 2011 (58)	Prospective cohort (26)	NHS I, USA	75 929	38–63	>90	792	Total fruit and vegetable, fruit juice, whole grain, nut	Validated FFQ (61)	Self-report	Age, energy intake, smoking, alcohol, weight change since age 18, height, postmenopausal hormone use, physical activity, BMI at age 18, family history of benign breast disease, modified Alternate Mediterranean Diet score

(Continued)

**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Gaard et al., 1995 (17)	Prospective cohort (6)	Norwegian Women Study,	24 897	43	100	248	Total meat, egg, milk	Validated FFQ (50)	Linkage to cancer registry	Age
Genkinger et al., 2013 (18)	Prospective cohort (12)	Norway BWHHS, USA	52 062	38.8	85	1516	Total meat, red meat, white meat, processed meat, fish, milk, cheese	Validated FFQ (85)	Medical record or cancer registry data	Energy intake, age at menarche, BMI, family history of breast cancer, education, parity and age at first live birth, OCP use, menopausal status, age at menopause, menopausal hormone use, vigorous physical activity, smoking status, and alcohol intake
George et al., 2009 (59)	Prospective cohort (8)	NIH-AARP Diet and Health STUDY	195 229 Post	61.5	90	5815	Fruit and vegetable	Validated FFQ, 124 food items	Cancer registry	Age, smoking, energy intake, BMI, alcohol, physical activity, education, race, marital status, family history of cancer, menopausal HRT, mutual adjustment between fruit and vegetables
Giles et al., 2006 (60)	Prospective cohort (9.1)	Melbourne Collaborative Cohort Study (MCCS), Australia	12 273 Post	40–69	100	245	All cereal products, rice	Validated FFQ (122)	Cancer registry and medical records	Age at attendance, country of birth, total energy intake, and HRT
Haraldsdottir et al., 2017 (61)	Prospective cohort (27.3)	Reykjavik Study, Iceland	9340	40–50	100	744	Fish	Validated FFQ (NM)	Cancer registry	Age, education, family history of breast cancer, BMI in midlife, age at first child, age at menarche, and intake of milk, rye, meat, fish liver oil, fish, salted/smoked fish, alcohol

(Continued)

**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Harris et al., 2015 (30)	Prospective cohort (15)	Swedish Mammography Cohort (SMC), Sweden	37 004	61.8	100	1603	Red meat	Validated FFQ (96)	Linkage of the study cohort with Swedish cancer register	Age, energy intake, height, BMI, education, OCP use, HRT, age at menarche, age at menopause, family history of breast cancer, history of benign breast disease, smoking status, physical activity, and alcohol intake
Hirvonen et al., 2006 (62)	Prospective cohort (6.6)	Supplementation in Vitamins and Mineral Antioxidants (SUVIMAX), France	91 016	49.9	NM	5294	Fruit juice	24-hour dietary record every 2 months	Self-report	Age, smoking, number of children, use of OCP, family history of breast cancer, and menopausal status
Hjartåker et al., 2010 (63)	Prospective cohort (8.6)	Norwegian Women and Cancer Study (NOWAC), Norway	64 903 (36 605 Pre and 28 298 Post)	51	100	947 (151 Pre and 796 Post)	Dairy, milk, yogurt, cheese	Validated FFQ (NM)	Cancer registry	Age, energy intake, alcohol intake, height, weight, increase since age 18, level of physical activity, years of education, maternal history of breast cancer, mammography practice, and use of OCP
Holmes et al., 2003 (19)	Prospective cohort (18)	NHS I, USA	88 647	46.7	98	4107	Total meat, red meat, white meat, processed meat, egg, fish	Validated FFQ (61)	Self-report	Age, 2-y time period; total Et; alcohol intake; parity and age at first birth categories; BMI at age 18 in kg/m <sup>2</sup> ; weight change since age 18 in kg; height in inches; family history of breast cancer; history of benign breast disease; age at menarche in years, menopausal status, age at menopause, HRT use categories, and duration of menopause

(Continued)

**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Inoue-Choi et al., 2016 (20)	Prospective cohort (9.4)	NIH-AARP, USA	38 748 Post	62	90	15 230	Total meat, red meat, processed meat	Validated FFQ (124)	Linkage to cancer registries	Age, race, BMI, height, education level, alcohol intake, physical activity, familial history of breast cancer, age at menarche, age at menopause, age at first live birth, number of live births, hormone use, OCP use, numbers of previous breast biopsies, total calorie intake, total fat intake, fiber intake, and intake of other types of meat (white, red, processed, processed red, processed white, unprocessed)
Kabat et al., 2009 (14)	Prospective cohort (8)	NIH-AARP, USA	120 755 Post	62	90	38 748	Total meat, red meat, white meat, processed meat	Validated FFQ (124)	Linking to state cancer registries and to the US National Death Index	Energy intake, age at entry, BMI, age at first menstrual period, age at first live birth, family history of breast cancer, HRT, education, race, total EI, saturated fat, alcohol intake, physical activity, smoking, age at menopause, number of breast biopsies, height

(Continued)

**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Kesse-Guyot et al., 2007 (64)	Prospective cohort (7.7)	SUVIMAX, France	3627	49	>99	82	Dairy, milk, yogurt, cheese	24-hour record every 2 months	Self-report and validated pathological report	Educational level, parity, group of treatment, smoking status, overall physical activity, marital status, energy from fat, energy from other sources, alcohol intake, BMI, family history of breast cancer in first degree, menopausal status, and HRT use at baseline for the whole population, HRT use for menopausal women, dietary energy-adjusted calcium intake
Key et al., 1999 (44)	Prospective cohort (12)	Life Span Study (LSS), Japan	11 067	>18	NM	400	Processed meat, egg, fish, fruit, rice, low fiber bread, soy product (miso paste, tofu)	Food and drink questionnaire (19)	Cancer registries	None
Key et al., 2018 (21)	Prospective cohort (11.9)	Million Women Study (MWS), UK	691 571	59.9	90	27 863	Fruits, vegetable, milk, yogurt, egg, total meat, processed meat, cheese	Validated FFQ (130)	Record linkage to the UK NHS databases	Socioeconomic status, BMI, height, smoking, current use of MHT, dietary EI, and alcohol consumption
Kiyabu et al., 2015 (65)	Prospective cohort (14.1)	Japan Public Health Center-based Prospective Study (JPHCPS), Japan	38 234	57.3	100	556	Fish	Validated FFQ (138)	Cancer registry	Age, BMI, age at menarche, age at first birth, parity, menopausal age, menopausal status at baseline, use of exogenous female hormones that

(Continued)



**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Larsson et al., 2009 (38)	Prospective cohort (17.4)	SMC, Sweden	61 433	60	100	2952	Red meat	Validated FFQ (96)	National and regional Swedish cancer registers	include OCP and MHT, leisure-time physical activity, smoking status, alcohol intake, and total energy-adjusted intake of isoflavones Stratified by age in months at the start of each follow-up period and calendar year of the questionnaire cycle education, BMI, height, parity and age at first birth, age at menarche, age at menopause, use of OCP, use of postmenopausal hormones, family history of breast cancer, and intakes of total energy and alcohol
Lin et al., 2007 (66)	Prospective cohort (10)	Women's Health Study (WHS), USA	31 487 (10 578 pre and 20 909 Post)	55.18	NM	1019 (276 Pre and 743 Post)	Dairy	Validated FFQ (131)	Either self-report or vital record	Age, BMI, physical activity, family history of breast cancer in a first-degree relative, history of benign breast disease, age at menarche, parity, age at first birth, multivitamin, smoking status, alcohol consumption, total EI, age at menopause, and baseline MHT

(Continued)

**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Lo et al., 2019 (22)	Prospective cohort (7.6)	Sister Study, USA	275 921	55.3	NM	1536	Red meat, processed meat, poultry	Validated FFQ (110 items)	Medical records	Age; ethnicity; household income; education; baseline menopausal status; BMI; interaction term between baseline menopausal status and BMI; waist-to-hip ratio; total EI; consumption of vegetables, fruit, dairy, and other meat categories, including organ meat; percent calories from fat; number of relatives diagnosed with breast cancer before the age of 50; lifetime duration of breastfeeding; hormone therapy; parity; use of OCP; alcohol; physical activity; smoking
Marcondes et al., 2019 (39)	Prospective cohort (17)	Rotterdam Study (RS), Netherlands	3209 Post	67	100	199	Red meat, processed meat, egg, fish, poultry, dairy, milk, cheese, yogurt	Validated FFQ (170)	Medical records and histopathological data	Age, physical activity, smoking status, history of breast cancer in first-degree relatives, MHT, parity, breast-feeding history and age of menopause, education, alcohol intake, iron intake did not alter the HR with more than 10%

(Continued)

TABLE 1 (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Masala et al., 2012 (67)	Prospective cohort (11,25)	EPIc, Italy	31 510	50	NM	1072	Fruit juice, citrus fruit, nut and seeds	Validated FFQ (188)	Linkages with hospital discharge system	Weight, height, education, number of children, age at menarche, menopausal status, EI (except alcohol), alcohol intake, current use of HR, smoking status, physical activity
McCullough et al., 2005 (68)	Prospective cohort (16)	Cancer Prevention Study (CPS) II , USA	140 725 Post	62.4	91	3976	Dairy, milk	Validated FFQ (68)	Medical record reports and cancer registries	Age, energy, history of breast cyst, family history of breast cancer, height, weight gain since age 18, alcohol use, race, age at menopause, age at first birth and number of live births, education, mammography history, and HRT use
Mills et al., 1989 (23)	Prospective cohort (6)	Seventh Day Adventist, USA	20 341	55.4	99	199	Total meat, processed meat, egg, fish, poultry, milk, cheese	Validated FFQ with five 24-hour dietary recalls	Self-report and diagnosis by senior medical personnel	Age at entry, age at first live birth, age at menarche, menopausal status, history of benign breast disease, maternal history of breast cancer, educational attainment, and BMI

(Continued)

**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Narita et al., 2017 (69)	Prospective cohort (14)	JPHCPS, Japan	44 444	58	100	681	Rice, soy	Validated FFQ (138)	Cancer registry	Age, area, BMI at 5-y follow-up, age at menarche, age at first birth, parity, age at menopause, use of exogenous female hormones, smoking status, leisure-time physical activity, alcohol intake, and total energy-adjusted intakes of fat, isoflavones, vitamin C, and carbohydrate
Nicodemus et al., 2001 (70)	Prospective cohort (9)	IWHS, USA	29 119 Post	61.3	NM	977	Whole grain, refined grain	Validated FFQ (NM)	National Cancer Institute's surveillance	Age, energy intake, estrogen use, personal history of benign breast disease, family history of breast cancer, mammography, status, age at first live births, number of live births, current weight, waist-to-hip ratio, vitamin use, educational attainment, and vitamin A and refined grain intake
Nilsson et al., 2020 (8)	Prospective cohort (11.2)	Northern Sweden Diet Database (NSDD), Sweden	185 987	> 18	NM	5907	Milk, yogurt, cheese	Validated FFQ (84)	Linkage to the Swedish cancer register	Age, screening year, dairy product category, BMI, civil status, education level, physical activity in leisure time, smoking status, recruitment cohort, and quintiles of fruit and vegetables, alcohol, and EI

(Continued)

**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Nishio et al., 2007 (71)	Prospective cohort (8)	JACC, Japan	20 129	57.7	NM	237	Soy product (miso paste, tofu)	Validated FFQ (NM)	Cancer registration system	Age, study area, family history of breast cancer, age at menopause, age at first birth, parity, use of HRT, smoking, consumption of green leafy vegetables, walking time, BMI, and total EI
Olsen et al., 2003 (72)	Prospective cohort (4.7)	DCH, Denmark	23 798 Post	57	100	819	Fruit, vegetable	Validated FFQ (192)	Danish cancer registry	Age, duration, baseline values of parity, previous benign breast tumor surgery, education, use of HRT, duration of HRT, intake of alcohol, and BMI
Pala et al., 2009 (40)	Prospective cohort (8.6)	EPIC, European countries	3 19 826	51	NM	7119	Milk, egg, red meat, poultry, processed meat, milk, cheese	Validated FFQ (260), UK and Sweden (FFQ and a 7-day record)	Cancer registry	Age, EI, alcohol intake, height, weight, increase since age 18, level of physical activity, years of education, maternal history of breast cancer, mammography practice, and use of OCP
Park et al., 2009 (73)	Prospective cohort (7)	NIH-AARP, USA	1 98 903	50–71	90	5856	Dairy	Validated FFQ (124)	Linking cohort members to state cancer registries and to the US National Death Index	Race/ethnicity, education; marital status; BMI; family history of cancer; vigorous physical activity; MHT; alcohol consumption; intakes of red meat and total energy; smoking; combined age at first birth and number of children; age at menopause; and intake of fat

(Continued)

**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Pouchieu et al., 2014 (41)	Prospective cohort (11.3)	SUVIMAX, France	2367	47	84	102	Red meat, processed meat	24-h dietary records	Medical data and validated pathological reports	Age, intervention group, number of dietary records, smoking status, educational level, physical activity, height, BMI, family history of breast cancer, menopausal status at baseline, MHT at baseline, number of live births, without-alcohol EI, alcohol intake, total lipid intake. In addition, the red meat model is adjusted for processed meat intake, and the processed meat intake model is adjusted for red meat (mutual adjustment)
Rohan et al., 1993 (74)	Nested case-control (5)	Canadian National Breast Screening Study (CNBSS), Canada	1700	40–59	NM	518	Cereals, bread	Dietary history questionnaire	Medical records	Age, age at menarche, surgical menopause, age at first live birth, years of education, family history of breast cancer, history of benign breast disease, and other contributors to total food intake
Shannon et al., 2005 (24)	Nested case control (10)	Breast self-exam trial, China	1070	–	100	Total meat, red meat, processed meat, poultry, fish, egg, fruit, vegetable, dairy, soy, cereals	Validated FFQ (117)	Evaluated by medical workers	Age and total energy intake	
Shibata et al., 1992 (75)	Prospective cohort (8)	Leisure World Cohort study, USA	7200 post	73.8	100	Fruit and vegetable	FFQ (59)	Local hospitals records	Age, smoking	

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**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Shin et al., 2002 (76)	Prospective cohort (16)	NHS I, USA	67 956 (42 990 pre and 24 966 Post)	46.7	>90	3172 (827 Pre and 2345 Post)	Dairy	Validated FFQ (61)	Either self-report or vital record	Age, time period, physical activity, history of benign breast disease, family history of breast cancer, height, weight change since age 18, BMI at age 18, age at menarche, parity, age at first birth, alcohol intake, total energy intake, total fat intake, glycemic index, B-carotene intake, vitamin E and D intake; for postmenopausal women, age at menopause and MHT were added
Shin et al., 2019 (77)	Prospective cohort (6.3)	Health Examinees-Gem, South Korea	78 320	40–69	NM	359	Milk	Validated FFQ (106)	Cancer Registry	BMI, total EI, educational level, parity, age at first birth, age at menarche, OCP use, regular exercise, alcohol consumption, and the presence of a family history of breast cancer
Sonestedt et al., 2008 (78)	Prospective cohort (10.3)	Malmö Diet and Cancer (MDC), Sweden	15 773	> 18	NM	544	Total fruit and vegetable, fruit juice, cereals, low-fiber bread, nut	Validated FFQ (168)	Cancer registries	Season of data collection, diet interviewer, method version, age, total energy, weight, height, educational status, smoking habits, leisure time physical activity, hours of household activities, alcohol consumption, age at menopause, parity, and current use of MHT

(Continued)



**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Stolzenberg-Solomon et al., 2006 (79)	Prospective cohort (10)	PLCO, USA	25 400 Post	62.9	NM	91	Orange, grapefruit juice, or both	Validated FFQ (137)	Cancer registries, death certificates, physician reports	Energy, education, use of HRT, birth control pill use, mammography screening history, history of benign breast disease, family history of breast cancer, age at menarche, age at menopause, age at first birth, and number of live births
Stripp et al., 2003 (80)	Prospective cohort (4.8)	DCH, Denmark	23 693 Post	57	90	394	Fish	Validated FFQ (192)	Record linkage to cancer register	Baseline values of parity, previous benign breast tumor surgery, school education, use of HRT, duration of HRT use, intake of alcohol, and BMI
Suzuki et al., 2013 (81)	Prospective cohort (10.2)	JPHCPS, Japan	47 289	56	77	22 397	Total fruit and vegetable	Validated FFQ (138)	Linkage to population-based registries	Age time-scales, area, height, recent BMI, BMI at age 20 y, age at menarche, age at first birth, parity, menopausal status, use of exogenous female hormones, smoking status, leisure-time physical activity, alcohol intake, total energy-adjusted intake of isoflavones, vitamin C supplement and combination variables, recent BMI, and menopausal status
Taylor et al., 2007 (25)	Prospective cohort (8)	UK Women's Cohort Study (UKWCS), UK	34 403	52	NM	678	Total meat, red meat, processed meat, poultry	Validated FFQ (217)	Central register	Age, energy intake, menopausal status, BMI, physical activity, smoking status, HRT use, OCP use, parity, and total fruit and vegetable intake

(Continued)

**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Toniolo et al., 1994 (26)	Nested case-control (6)	New York University Women's Health Study, USA	829	52.2	NM	180	Total meat, fish, poultry, dairy	Validated FFQ (71)	Self-report	Height, BMI, age at menarche, age at first full-term pregnancy, number of full-term pregnancies, first-degree family history of breast cancer, history of benign breast conditions, race, religion, EI
Trichopoulos et al., 2010 (31)	Prospective cohort (9.8)	EPIC, Greece	14 807	> 18	91.5	240	Cereals, fruit, vegetable, dairy, meat, and meat product	Validated FFQ (150)	Medical records and death certificates	Age, smoking, education, BMI, EI, age of menarche, age at first delivery, menopausal status, age at menopause, HRT, metabolic equivalents of task
van den Brandt et al., 2018 (82)	Case-cohort (20.3)	Netherlands Cohort Study (NLCS), Netherlands	62 573 Post	62	100	2321	Nut	Validated FFQ (150)	Medical records and pathology reports	Age at baseline, cigarette use duration, BMI, nonoccupational physical activity, education, family history of breast cancer, history of benign breast disease, age at menarche, parity, age at first birth, age at menopause, OCP use, postmenopausal HRT, EI, alcohol, and alternate
Van Der Hel et al., 2004 (27)	Nested case-control (10)	Dutch prospective cohort, Netherlands	261	47.5	100	228	Total meat, processed meat	Short validated FFQ (90)	Linkage to cancer registry	Mediterranean Diet Score, excluding alcohol and nuts

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**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Vatten et al., 1990 (28)	Prospective cohort (12)	Norwegian Women Study, Norway	14 500	35–51	95	152	Total meat	Validated FFQ (60)	Cancer registry	Age
Verhoeven et al., 1997 (83)	Prospective cohort (4.3)	NLCS, Netherlands	1812 post	55–69	96	519	Fruit and vegetable	Validated FFQ (150)	Linkage to cancer registries and national database of pathology reports	Age, energy intake, alcohol intake, benign breast disease, maternal breast cancer, breast cancer in sister(s), age at menarche, age at menopause, age at first birth, parity
Voorrips et al., 2002 (45)	Prospective cohort (6.3)	NLCS, Netherlands	62 573 Post	55–69	96	2368	Processed meat, milk and milk product, cheese	Validated FFQ (150)	Linkage to regional cancer registries and national database of pathology reports	Age, history of benign breast disease, maternal breast cancer, breast cancer in 1 or more sisters, age at menarche and menopause, OCP use, parity, age at first childbirth, BMI, education, alcohol use, cigarette smoking, and energy intake
Wada et al., 2013 (84)	Prospective cohort (15)	Takayama study, Japan	15 607	52.2	NM	172	Soy	Validated FFQ (169)	Cancer registries	Area, age, age at menarche, number of pregnancies, menopausal status, age at first pregnancy, smoking, alcohol consumption, leisure-time physical activity, educational level, total energy, and meat, fish, vegetable, and fruit consumption

(Continued)

**TABLE 1** (Continued)

Author, year	Study design (n follow-ups)	Cohort name	Participants, n	Age, y <sup>1</sup>	Follow-up rate, % <sup>2</sup>	Cases, n	Interested exposure	Exposure assessment (n items)	Outcome assessment	Adjusted covariate
Wilson et al., 2009 (85)	Prospective cohort (14)	NHS II, USA	90 628 Pre	36	>90	1697	Bread/ starches	Validated FFQ (130)	Self-report	Age in months and calendar year and adjusted for the following: BMI, height, OCP use, parity and age at first birth, age at menarche, family history of breast cancer, history of benign breast disease, smoking, physical activity, animal fat, glycemic load, alcohol intake, and total energy intake
Wirfalt et al., 2011 (42)	Prospective cohort (10.3)	MDC, Sweden	15 773	45–73	100	544	Milk, yogurt, egg, red meat, fish, cheese	Modified diet history, 7 days	Patients' medical records and an immunohistochemistry methodology	MHT, height, weight, alcohol habits, household activity, leisure-time physical activity, work activity
Wu et al., 2019 (86)	Case-cohort (5.3)	DCH, Denmark	1347	61	NM	414	Whole-grain rye and whole-grain wheat	Validated FFQ (192)	Linkage to the Danish Cancer Registry	BMI, education, parity, HRT, age at first birth, age at menopause, age at first period, exercise, smoking status, waist-hip ratio, menopause status, and alcohol intake
Zhang et al., 2016 (9)	Prospective cohort (22)	NHS I and NHS II, USA	143 206	50.4	>90	5714	Total rice intake (white and brown)	NHS II: Validated FFQ (130), NHS I: Validated FFQ (61)	Medical records and pathological reports	Age, ethnicity, BMI, smoking, physical activity, family history of cancer, multivitamin supplementation, total EI, MHT, and intake of alcohol, fruit, vegetables, red meat, fish, nuts, whole grains, and sugar-sweetened beverage

CHO, carbohydrate; EI, energy intake; FTP, full-term pregnancy; HRT, hormone replacement therapy; JACC, Japan Collaborative Cohort; MHT, menopausal hormone therapy; NM, not mentioned; OCP, oral contraceptive pill.

<sup>1</sup>Values are means or ranges.

<sup>2</sup>The percentage of participants who completed the study.

**TABLE 2** Subgroup analysis of studies investigated the association of various food groups with risk of breast cancer

Subgroup factors	n of studies	RR (95% CI)	I <sup>2</sup> , %
Red meat, 100 grams/day			
Menopause status			
Premenopause	9	1.02 (0.94–1.12)	17.1
Postmenopause	11	1.09 (0.99–1.20)	63.0
P between-group heterogeneity	0.34		
Estrogen-progesterone receptor			
Er+Pr+	4	1.21 (0.93–1.58)	75.6
Er+Pr–	2	0.97 (0.81–1.15)	0.0
Er–Pr–	3	1.22 (0.91–1.64)	30.3
P between-group heterogeneity	0.17		
Follow-up			
<10 y	8	1.22 (1.09–1.37)	44.1
≥10 y	12	1.03 (0.96–1.11)	47.4
P between-group heterogeneity	<0.001		
Geographic location			
Europe	12	1.12 (1.02–1.22)	51
North America	7	1.09 (0.98–1.21)	71.6
P between-group heterogeneity	0.12		
Number of cases			
<1000	6	1.14 (0.95–1.36)	44.4
≥1000	14	1.09 (1.02–1.17)	63.1
P between-group heterogeneity	0.06		
Poultry, 100 grams/day			
Menopause status			
Premenopause	5	1.01 (0.98–1.05)	27.6
Postmenopause	8	0.99 (0.96–1.02)	59.3
P between-group heterogeneity	0.27		
Follow-up			
<10 y	8	0.97 (0.87–1.07)	38.1
≥10 y	5	0.96 (0.88–1.06)	5.8
P between-group heterogeneity	0.94		
Geographic location			
Europe	5	1.07 (0.96–1.20)	0.0
USA	7	0.93 (0.86–1.01)	38.0
P between-group heterogeneity	0.12		
Number of cases			
<1000	6	1.08 (0.97–1.19)	40
≥1000	7	0.99 (0.98–1.0)	35.9
P between-group heterogeneity	0.04		
Fish, 100 grams/day			
Menopause status			
Premenopause	6	1.02 (0.92–1.14)	0.0
Postmenopause	9	0.99 (0.93–1.04)	0.0
P between-group heterogeneity	0.52		
Follow-up			
<10 y	5	1.05 (0.87–1.26)	64.7
≥10 y	12	0.98 (0.91–1.07)	0.0
P between-group heterogeneity	0.87		
Geographic location			
Europe	9	0.99 (0.88–1.12)	20.6
USA	6	1.01 (0.87–1.16)	52.2
Asia	3	1.12 (0.85–1.47)	0.0
P between-group heterogeneity	0.63		
Number of cases			
<1000	9	1.15 (0.82–1.60)	49.1
≥1000	8	0.98 (0.93–1.03)	0.0
P between-group heterogeneity	0.24		
Egg, 50 grams/day			
Menopause status			
Premenopause	4	1.06 (0.91–1.23)	39.5
Postmenopause	4	1.01 (0.94–1.09)	0.0
P between-group heterogeneity	0.71		

(Continued)

**TABLE 2** (Continued)

Subgroup factors	n of studies	RR (95% CI)	I <sup>2</sup> , %
Follow-up			
<10 y	3	1.0 (0.95–1.06)	0.0
≥10 y	8	1.04 (0.93–1.16)	61.7
P between-group heterogeneity	0.32		
Geographic location			
Europe	5	1.03 (0.98–1.08)	68.5
USA	3	1.02 (0.93–1.12)	0.0
Asia	2	0.87 (0.70–1.08)	75
P between-group heterogeneity	0.34		
Number of cases			
<1000	6	1.11 (0.82–1.50)	70.3
≥1000	5	1.01 (0.97–1.06)	0.0
P between-group heterogeneity	0.34		
Total meat, 100 grams/day			
Menopause status			
Pre-menopause	4	1.04 (0.93–1.16)	48.3
Postmenopause	7	1.04 (0.98–1.10)	83.9
P between-group heterogeneity	0.66		
Follow-up			
<10 y	7	1.13 (1.03–1.23)	73.1
≥10 y	7	1.02 (0.96–1.08)	55.2
P between-group heterogeneity	<0.001		
Geographic location			
Europe	7	1.06 (1.02–1.10)	73.4
USA	6	1.0 (0.98–1.02)	78.9
P between-group heterogeneity	0.03		
Number of cases			
<1000	8	1.29 (1.10–1.51)	59.7
≥1000	6	1.01 (0.97–1.06)	72.7
P between-group heterogeneity	<0.001		
Processed meat, 50 grams/day			
Menopause status			
Pre-menopause	6	1.03 (0.92–1.16)	0.0
Postmenopause	11	1.11 (1.01–1.22)	32.2
P between-group heterogeneity	0.49		
Follow-up			
<10 y	8	1.19 (1.03–1.38)	35.6
≥10 y	7	1.17 (0.94–1.46)	76.9
P between-group heterogeneity	0.29		
Geographic location			
Europe	10	1.37 (1.16–1.62)	46.1
USA	6	1.005 (0.93–1.08)	0.0
P between-group heterogeneity	0.001		
Number of cases			
<1000	9	1.29 (1.01–1.64)	60.0
≥1000	8	1.07 (0.96–1.20)	45.8
P between-group heterogeneity	0.001		
Dairy, 200 grams/day			
Menopause status			
Pre-menopause	7	0.96 (0.90–1.02)	54.8
Postmenopause	7	0.99 (0.96–1.02)	27.1
P between-group heterogeneity	0.39		
Follow-up			
<10 y	4	0.96 (0.95–0.97)	0.0
≥10 y	6	0.99 (0.97–1.01)	50.3
P between-group heterogeneity	0.004		
Geographic location			
Europe	4	0.96 (0.85–1.09)	42.5
USA	5	0.97 (0.94–0.997)	58.3
P between-group heterogeneity	0.02		
Number of cases			
<1000	4	0.91 (0.82–1.02)	0.0
≥1000	6	0.97 (0.96–0.98)	72.4
P between-group heterogeneity	0.34		

(Continued)

**TABLE 2** (Continued)

Subgroup factors	n of studies	RR (95% CI)	I <sup>2</sup> , %
Milk, 200 grams/day			
Menopause status			
Premenopause	4	1.0 (0.92–1.09)	0.0
Postmenopause	8	1.0 (0.96–1.03)	33.0
<i>P</i> between-group heterogeneity	0.89		
Type of milk			
Low fat	5	1.01 (0.97–1.06)	57.3
Whole milk	6	1.03 (0.99–1.08)	0.0
<i>P</i> between-group heterogeneity	0.35		
Follow-up			
<10 y	6	0.98 (0.92–1.05)	49.8
≥10 y	7	0.99 (0.96–1.03)	60.5
<i>P</i> between-group heterogeneity	0.97		
Geographic location			
Europe	8	0.99 (0.95–1.03)	63.1
USA	4	0.98 (0.95–1.01)	0.0
<i>P</i> between-group heterogeneity	0.10		
Number of cases			
<1000	8	0.95 (0.88–1.03)	67.1
≥1000	5	1.0 (0.98–1.01)	0.0
<i>P</i> between-group heterogeneity	0.37		
Cheese, 30 grams/day			
Menopause status			
Premenopause	4	0.93 (0.70–1.25)	53.7
Postmenopause	7	0.90 (0.82–0.99)	76.3
<i>P</i> between-group heterogeneity	0.29		
Follow-up			
<10 y	5	0.96 (0.87–1.06)	60.4
≥10 y	5	0.94 (0.87–1.01)	75.1
<i>P</i> between-group heterogeneity	0.37		
Geographic location			
Europe	8	0.95 (0.91–0.99)	77.9
USA	2	1.04 (0.49–2.19)	76.1
<i>P</i> between-group heterogeneity	0.63		
Number of cases			
<1000	5	0.95 (0.81–1.12)	81
≥1000	5	0.98 (0.95–1.01)	60.1
<i>P</i> between-group heterogeneity	0.025		
Fruit, 100 grams/day			
Menopause status			
Premenopause	3	0.97 (0.93–1.0)	0.0
Postmenopause	10	0.98 (0.96–1.0)	62
<i>P</i> between-group heterogeneity	0.50		
Estrogen-progesterone receptor			
Er+Pr+	4	0.97 (0.96–0.99)	0.0
Er–Pr–	4	0.98 (0.94–1.02)	0.0
Er+Pr–	5	0.99 (0.94–1.04)	43.6
<i>P</i> between-group heterogeneity	0.65		
Geographic location			
Europe	6	0.967 (0.94–0.99)	68.6
North America	5	0.98 (0.97–0.99)	0.0
Asia	4	0.87 (0.73–1.05)	86.1
<i>P</i> between-group heterogeneity	0.70		
Number of cases			
<1000	9	0.96 (0.92–0.998)	70.8
≥1000	6	0.97 (0.95–0.99)	64.1
<i>P</i> between-group heterogeneity	0.51		
Vegetable, 100 grams/day			
Menopause status			
Premenopause	4	1.01 (0.96–1.06)	0.0
Postmenopause	10	1.01 (0.995–1.022)	0.0
<i>P</i> between-group heterogeneity	0.98		

(Continued)



**TABLE 2** (Continued)

Subgroup factors	n of studies	RR (95% CI)	I <sup>2</sup> , %
Estrogen receptor			
Er+	4	0.99 (0.96–1.01)	1.1
Er–	4	0.94 (0.90–0.997)	52.7
P between-group heterogeneity	0.11		
Geographic location			
Europe	6	0.97 (0.95–0.99)	0.0
USA	5	0.99 (0.95–1.02)	63.3
Asia	3	0.92 (0.84–1.01)	45.4
P between-group heterogeneity	0.004		
Number of cases			
<1000	10	0.97 (0.94–1.001)	62.4
≥1000	4	0.97 (0.95–1.0)	0.0
P between-group heterogeneity	0.10		
Fruit and vegetable, 100 grams/day			
Geographic location			
Europe	3	0.99 (0.98–1.0)	0.0
USA	3	0.98 (0.97–0.99)	0.0
Asia	2	0.94 (0.78–1.12)	90.2
P between-group heterogeneity	0.22		
Number of cases			
<1000	3	0.95 (0.89–1.01)	67.8
≥1000	5	0.99 (0.97–1.0)	46.9
P between-group heterogeneity	0.19		
Total cereals, 20 grams/day			
Menopause status			
Premenopause	5	1.0 (0.99–1.01)	0.0
Postmenopause	7	1.0 (0.99–1.01)	22.3
P between-group heterogeneity	0.40		
Grain, 20 grams/day			
Whole/refined			
Whole grain	5	1.0 (0.99–1.01)	30.8
Refined grain	7	1.0 (0.99–1.01)	0.0
P between-group heterogeneity	0.025		
Follow-up			
<10 y	6	1.0 (0.99–1.01)	31.7
≥10 y	8	0.99 (0.98–1.01)	0.0
P between-group heterogeneity	0.15		
Geographic location			
Europe	6	1.0 (0.99–1.01)	0.0
North America	4	0.99 (0.95–1.02)	75.7
Asia	3	1.0 (0.98–1.02)	0.0
P between-group heterogeneity	0.76		
Number of cases			
<1000	9	1.0 (0.99–1.01)	15.4
≥1000	5	1.0 (0.99–1.01)	32.7
P between-group heterogeneity	0.83		

+, positive/present; –, negative/not present; Er, estrogen receptor; Pr, progesterone receptor; RR, risk ratio.

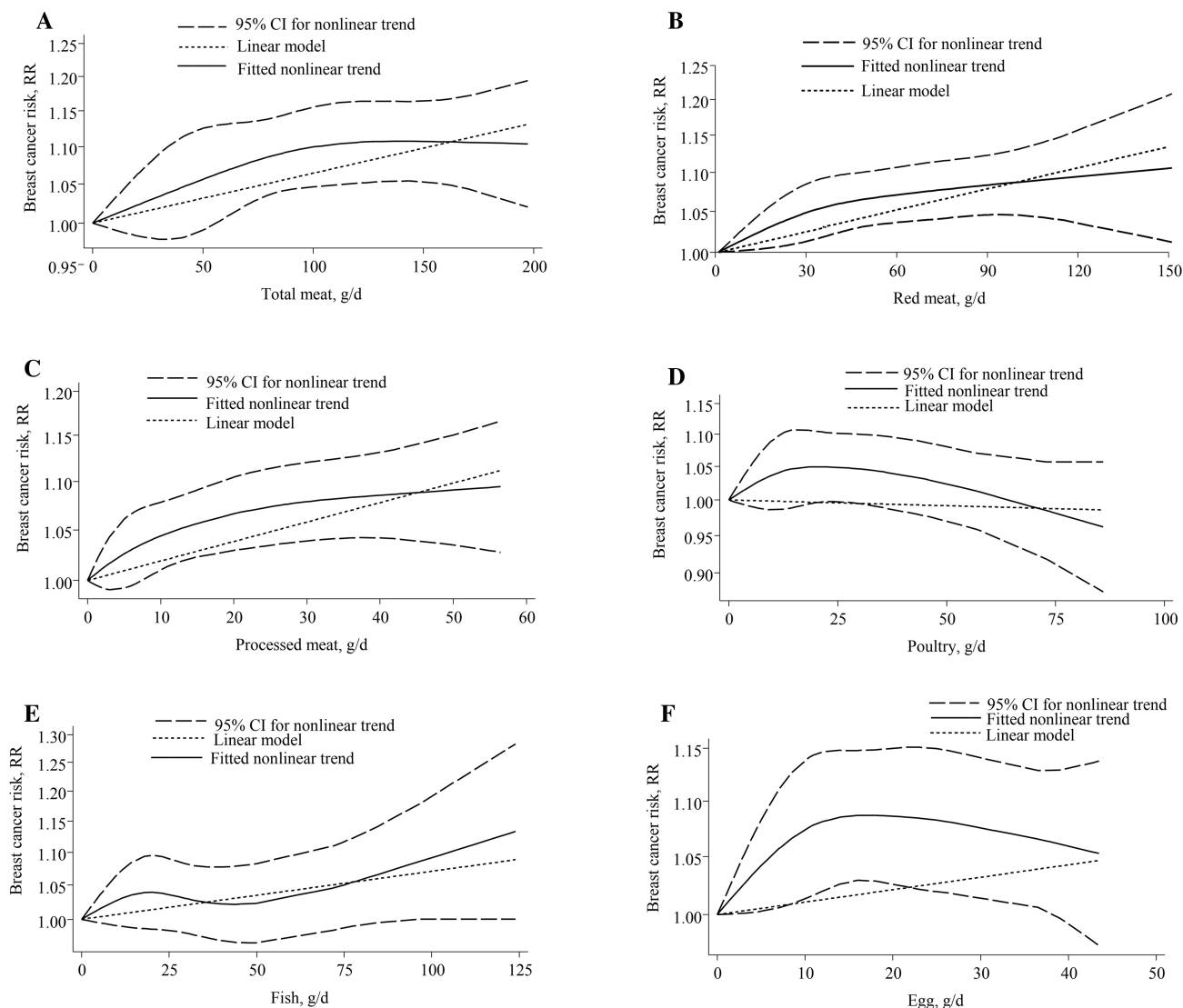
number of cases revealed a stronger positive association for studies with case numbers of <1000. There was no evidence of a nonlinear dose-response association (*P*-nonlinearity = 0.08; *n* = 10 studies; [Figure 2D](#)).

### Fish

From 18 studies that investigated the association of fish with breast cancer, 1 study was excluded ([32](#)) because a study on the same cohort with a longer duration was published. Thus, 17 studies, with 28 818 breast cancer cases, were included in a linear dose-response meta-analysis ([15](#), [16](#), [18](#), [19](#), [23](#),

[24](#), [26](#), [35](#), [36](#), [39](#), [42](#), [44](#), [46](#), [53](#), [57](#), [65](#), [80](#)). No association was observed for each additional 100-g/d increase of fish (RR, 1.0; 95% CI, 0.93–1.08; *I*<sup>2</sup>, 22.6%; *P*-heterogeneity, 0.19; **Supplemental Figure 5**). Subgroup analyses by menopause status, follow-up duration, number of cases, and geographic location indicated no significant association in the subgroups ([Table 2](#)).

There was no evidence of a nonlinear dose-response association (*P*-nonlinearity, 0.39; *n* = 11 studies). The risk of breast cancer increased by approximately 10% with increasing intake of fish, up to 110 g/d ([Figure 2E](#)).



**FIGURE 2** Nonlinear dose-response relationship between daily intakes of (A) total meat, (B) red meat, (C) processed meat, (D) poultry, (E) fish, and (F) egg and risk of breast cancer. RR = risk ratio.

### Egg

There were 11 studies, with 53 310 breast cancer cases, included in the linear dose-response meta-analysis of the association between egg intake and breast cancer risk (15, 17, 19, 21, 23, 24, 36, 39, 40, 42, 44). No association was found for each additional 50-g/d increase of egg (RR, 1.03; 95% CI, 0.96–1.12;  $I^2$ , 48.8%;  $P$ -heterogeneity, 0.03; **Supplemental Figure 6**). Subgroup analyses by menopause status, follow-up duration, geographic location, and number of cases indicated no significant difference between the subgroups (Table 2).

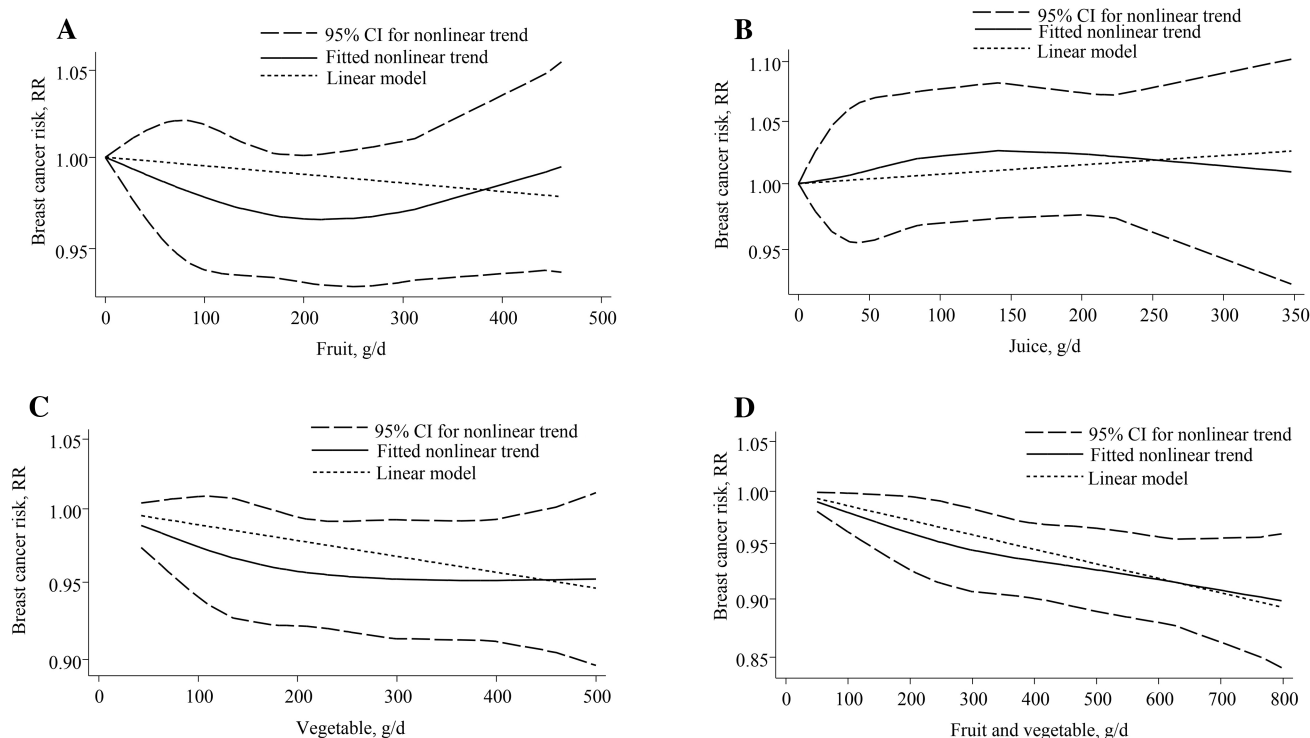
Although a nonlinear dose-response association was detected, the shape of the curve did not provide any valuable information ( $P$ -nonlinearity, 0.03;  $n = 7$  studies; **Figure 2F**).

### Fruit

Only 1 study assessed the association between combined fruit and vegetable intake and breast cancer, so it was not included in the analyses (87).

From 21 papers that investigated the relationship between fruit and breast cancer, 6 were excluded because papers on the same cohorts with longer durations were published (31, 72, 88–91). However, 4 of these studies were included in the subgroup analyses according to menopause status (31, 72) and presence of estrogen receptor (89, 90), since the updated papers on the same studies did not report the results according to these factors (52, 56).

There were 15 studies, with 7071 breast cancer cases, included in the linear dose-response meta-analysis (15, 21, 24, 29, 35, 44, 48, 49, 52, 56, 59, 74, 75, 78, 81, 83). A small, inverse association was observed for each additional 100-g/d increase of fruit (RR, 0.97; 95% CI, 0.95–0.99;  $I^2$ , 66.5%;  $P$ -heterogeneity < 0.001; **Supplemental Figure 7**). Also, in subgroup analyses by geographic location, number of cases, menopause status, and presence of estrogen progesterone receptor, no significant difference was found between the subgroups (Table 2).



**FIGURE 3** Nonlinear dose-response relationship between daily intakes of (A) fruit, (B) juice, (C) vegetables, and (D) fruits and vegetables and risk of breast cancer. RR = risk ratio.

There was no evidence of a nonlinear dose-response association detected ( $P$ -nonlinearity, 0.20;  $n = 7$  studies; [Figure 3A](#)).

#### Fruit juice

There were 6 studies, with 4463 breast cancer cases, included in the linear dose-response meta-analysis of fruit juice intake and breast cancer risk ([15, 56, 58, 62, 67, 78](#)). No significant association was observed for each additional 50-g/d increase of fruit juice (RR, 1.0; 95% CI, 0.99–1.01;  $I^2$ , 26.7%;  $P$ -heterogeneity, 0.23; [Supplemental Figure 8](#)).

There was no evidence of a nonlinear dose-response association ( $P$ -nonlinearity, 0.78;  $n = 5$  studies; [Figure 3B](#)).

#### Vegetable

From 18 papers that investigated the relationship between vegetable intake and breast cancer, 4 were excluded because papers on the same cohorts with longer durations were published ([31, 72, 88, 91](#)); however, 1 of these 4 studies ([72](#)) was included in a subgroup analysis since the updated paper on the same cohort ([52](#)) did not report the results according to menopause status.

There were 14 studies, with 54 845 breast cancer cases, included in the linear dose-response meta-analysis ([15, 21, 24, 29, 48, 49, 52, 56, 59, 74, 75, 78, 81, 83](#)). A small, inverse association was observed for each additional 100-g/d increase of vegetable intake (RR, 0.97; 95% CI, 0.953–0.995;  $I^2$ , 55.8%;  $P$ -heterogeneity, 0.006; [Supplemental Figure](#)

[9](#)). Subgroup analyses by menopause status, presence of estrogen receptor, geographical location, and number of cases indicated no significant difference in the effect sizes between the subgroups ([Table 2](#)). The follow-up durations of all studies, except 1, were longer than 10 y.

There was no evidence of a nonlinear dose-response association ( $P$ -nonlinearity, 0.37;  $n = 6$ , studies; [Figure 3C](#)).

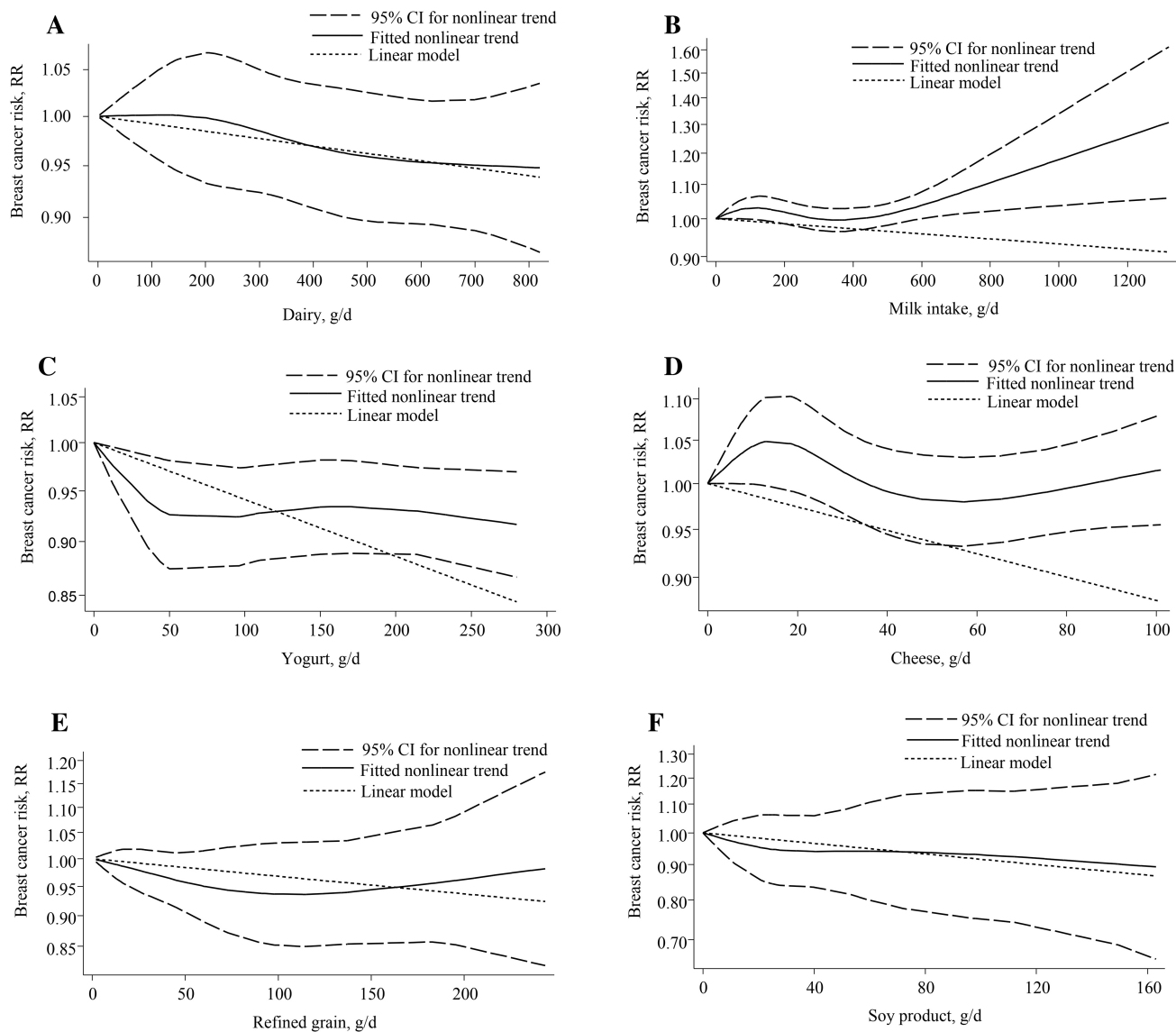
#### Fruit and vegetable

There were 8 studies with breast cancer cases included in the linear dose-response meta-analysis of fruit and vegetable intake ([24, 48, 52, 56, 58, 78, 81, 87](#)). A small, inverse association was observed for each additional 100-g/d increase of fruit and vegetable intake (RR, 0.98; 95% CI, 0.97–0.996;  $I^2$ , 54.7%;  $P$ -heterogeneity, 0.03; [Supplemental Figure 10](#)). Subgroup analyses by geographical location and number of cases indicated no significant difference between the subgroups ([Table 2](#)). Follow up durations of all studies, except 1, were longer than 10 y.

There was no evidence of a nonlinear dose-response association ( $P$ -nonlinearity, 0.67;  $n = 8$  studies; [Figure 3D](#)).

#### Dairy

There were 10 studies, with 16 175 breast cancer cases ([15, 24, 26, 31, 35, 55, 63, 66, 73, 76](#)), that reported the association of dairy intake as a whole with breast cancer risk. Studies that assessed dairy products separately were not included in this category. A linear dose-response meta-analysis indicated no



**FIGURE 4** Nonlinear dose-response relationship between daily intakes of (A) dairy, (B) milk, (C) yogurt, (D) cheese, (E) refined grains, and (F) soy product and risk of breast cancer. RR = risk ratio.

significant association for each additional 200-g/d increase of dairy intake (RR, 0.97; 95% CI, 0.95–1.003;  $I^2$ , 55.6%;  $P$ -heterogeneity, 0.02; **Supplemental Figure 11**). Subgroup analyses by menopause status and number of cases indicated no significant difference between the subgroups (**Table 2**). Geographic location and follow-up duration were the sources of heterogeneity (**Table 2**).

There was no evidence of a nonlinear dose-response association ( $P$ -nonlinearity, 0.83;  $n = 8$  studies; **Figure 4A**).

### Milk

There were 13 studies, with 47 729 breast cancer cases, included in the linear dose-response meta-analysis of milk intake and breast cancer risk (8, 17, 18, 21, 23, 39, 40, 42, 45, 63, 64, 68, 77). No significant association was observed for each additional 200-g/d increase of milk intake (RR,

0.99; 95% CI, 0.96–1.02;  $I^2$ , 52.3%;  $P$ -heterogeneity, 0.01; **Supplemental Figure 12**). Subgroup analyses by menopause status, follow-up duration, geographical location, type of milk, and number of cases indicated no significant difference between the subgroups (**Table 2**).

We found evidence of a nonlinear dose-response association ( $P$ -nonlinearity, 0.04;  $n = 12$  studies). The association of milk intake with breast cancer risk was not significant for intakes of up to 450 g/d, but in amounts greater than 450 g/d, up to 1300 g/d, the risk increased by approximately 30% (**Figure 4B**).

### Yogurt

There were 6 studies, with 28 291 breast cancer cases, included in the linear dose-response meta-analysis of yogurt intake and breast cancer risk (8, 21, 39, 42, 64, 92). No

significant association was observed for each additional 200-g/d increase of yogurt intake (RR, 0.91; 95% CI, 0.79–1.05;  $I^2$ , 71.5%;  $P$ -heterogeneity, 0.004; **Supplemental Figure 13**).

There was no evidence of a nonlinear dose-response association ( $P$ -nonlinearity, 0.06;  $n$  = 4 studies). The risk of breast cancer decreased by approximately 7.5% with an increasing intake of yogurt, up to 100 g/d (**Figure 4C**).

### Cheese

There were 10 studies, with 39 703 breast cancer cases, included in the linear dose-response meta-analysis of cheese intake and breast cancer risk (8, 18, 21, 23, 39, 40, 42, 45, 63, 64). A small, inverse association was observed for each additional 30-g/d increase of cheese intake (RR, 0.95; 95% CI, 0.91–0.996;  $I^2$ , 75.1%;  $P$ -heterogeneity < 0.001; **Supplemental Figure 14**). Subgroup analyses for menopause status, follow-up duration, and geographical location were not statistically significant (**Table 2**). A subgroup analysis for the number of cases revealed a stronger inverse association for studies with case numbers of <1000 (**Table 2**).

There was no evidence of a nonlinear dose-response association ( $P$ -nonlinearity, 0.07;  $n$  = 9 studies; **Figure 4D**).

### Total cereals

There were 14 studies, with 16 857 breast cancer cases, included in the linear dose-response meta-analysis of total cereal intake and breast cancer risk (9, 15, 24, 31, 35, 44, 51, 60, 69, 70, 74, 78, 86, 90). No significant association was observed for each additional 20-g/d increase of total cereal intake (RR, 1.0; 95% CI, 0.99–1.01;  $I^2$ , 17.4%;  $P$ -heterogeneity = 0.26; **Supplemental Figure 15**). In subgroup analyses by menopause status, follow-up duration, geographic location, number of cases, and refined- vs. whole-grain cereal intake, no significant difference was found in the effect sizes between the subgroups (**Table 2**). Although evidence of a nonlinear dose-response association was detected ( $P$ -nonlinearity 0.04;  $n$  = 7 studies), the shape of the curve did not yield any valuable information (**Figure 4E**).

### Soy and soy products

There were 7 studies, with 4055 breast cancer cases, included in the linear dose-response meta-analysis of soy and soy product intake and breast cancer risk (15, 24, 44, 49, 69, 71, 84). A significant association was observed for each additional 30-g/d increase of soy and/or soy product intake (RR, 0.965; 95% CI, 0.94–0.99;  $I^2$ , 0.0%;  $P$ -heterogeneity = 0.64; **Supplemental Figure 16**). There was no evidence of a nonlinear dose-response association ( $P$ -nonlinearity, 0.87;  $n$  = 5 studies; **Figure 4F**).

### Nuts

There were 6 studies, with 9219 breast cancer cases, included in the linear dose-response meta-analysis of nut intake and breast cancer risk (15, 36, 58, 67, 78, 82). No significant association was observed for each additional 28-g/d increase

of nut intake (RR, 0.92; 95% CI, 0.83–1.01;  $I^2$ , 9.7%;  $P$ -heterogeneity, 0.35; **Supplemental Figure 17**).

### Legumes

There were 4 studies that investigated the association of legumes, besides soy, with breast cancer risk (15, 24, 47, 58). No significant association was observed for each additional 50-g/d increase of legume intake (RR, 0.95; 95% CI, 0.87–1.05;  $I^2$ , 32.1%;  $P$ -heterogeneity, 0.22).

### Publication bias

Based on Egger's test, publication bias was evident only for total meat ( $P$  = 0.007), red meat ( $P$  = 0.002), and fish ( $P$  = 0.03) intakes, and their funnel plots (**Supplemental Figure 18A, B, and E**) were asymmetric. There was no publication bias and the associated funnel plots were symmetrical for processed meat (**Supplemental Figure 18C**), poultry (**Supplemental Figure 18D**), fruit (**Supplemental Figure 19A**), vegetable (**Supplemental Figure 19B**), dairy (**Supplemental Figure 19C**), milk (**Supplemental Figure 19D**), cheese (**Supplemental Figure 19E**), and cereal (**Supplemental Figure 19F**) intakes.

### Data quality

The quality of most of the studies was classified as good, while 13 studies were classified as being of fair quality (23–26, 34, 37, 62, 64, 70, 71, 75, 77, 83) and 2 studies were classified as being of poor quality (44, 74) (**Supplemental Table 2**). To discern whether study quality had an effect on the results, we excluded the studies rated as being of fair or poor quality from the analysis; no statistically significant changes were seen, except for in the analysis of total meat. After excluding studies with fair quality, the association of total meat intake with the risk of breast cancer was not significant.

Additionally, the NutriGrade meta-evidence rating indicated moderate confidence in the effect estimates for all of the food categories, except poultry, fish, cereals, and legumes, which had low confidence ratings (**Table 3**).

### Discussion

In the present systematic review and meta-analyses, the associations of preselected foods and food groups—total meat, red meat, poultry, fish, processed meat, egg, fruits, vegetables, dairy, milk, yogurt, cheese, grains, soybeans, nuts, and legumes—and the risk of breast cancer were evaluated using data reported within and across prospective studies. We identified decreased risks of breast cancer with increased intakes of fruits, vegetables, soybeans, and cheese, and there was a positive association between red meat and processed meat consumption and the risk of breast cancer. No linear dose-response associations were observed for egg, dairy, milk, yogurt, grain, nut, and legume intakes and breast cancer risks, whilst a nonlinear dose-response association was observed for milk intake. We observed moderate confidence in the effect estimates for all food items, except poultry, fish, cereal, and legumes, which had low confidence ratings.

**TABLE 3** NutriGrade assessment of confidence in estimate effect of studies evaluated the association between various food groups and risk of breast cancer

Outcomes	Risk of bias <sup>1</sup>	Precision <sup>2</sup>	Indirectness	Heterogeneity <sup>3</sup>	Publication bias <sup>4</sup>	Effect size <sup>5</sup>	Dose response	Funding bias	Total score	Confidence of evidence <sup>6</sup>
Total meat	2	1	1	0.5	0	0	1	1	6.5	Moderate
Red meat	2	1	1	0.5	0	0	1	1	6.5	Moderate
Processed meat	1	1	1	0.5	1	0	1	1	6.5	Moderate
Poultry	1	1	1	0.5	1	0	0	1	5.5	Low
Fish	2	1	1	0.5	0	0	0	1	5.5	Low
Egg	2	1	1	0.5	1	0	0	1	6.5	Moderate
Dairy	2	1	1	0.5	1	0	0	1	6.5	Moderate
Milk	2	1	1	0.5	1	0	1	1	7.5	Moderate
Yogurt	2	0	1	0.5	0.5	0	0	1	7	Moderate
Cheese	2	1	1	0.5	1	0	1	1	6.5	Moderate
Fruit	2	1	1	0.5	1	0	1	1	6.5	Moderate
Vegetable	2	1	1	0.5	1	0	1	1	7.5	Moderate
Fruit + vegetable	2	1	1	0.5	0.5	0	1	1	7	Moderate
Juice	2	1	1	0.5	0.5	0	0	1	6	Moderate
Cereals	1	1	1	0.5	1	0	0	1	5.5	Low
Soy	1	1	1	0.5	0.5	0	1	1	6	Moderate
Nut	2	1	1	0.5	0.5	0	0	1	6	Moderate
Legume	1	1	1	0.5	0	0	0	1	4.5	Low

NutriGrade, Nutrition Grading of Recommendations Assessment, Development and Evaluation; RR, risk ratio.

<sup>1</sup>Risk of bias was based on the Newcastle-Ottawa Scale, where  $\geq 7 = 2$  points;  $4-6.9 = 1$  point; and  $0-3.9 = 0$  points.

<sup>2</sup>Precision is 1 point if the number of events  $\geq 500$  and the 95% CI excludes the null value; precision is 0 points if the number of events  $< 500$  or number of events  $\geq 500$ , but 95% CI includes the null value (i.e., CI includes RR of 1.0) and 95% CI fails to exclude an important benefit (RR of 0.8) or harm (RR of 1.2).

<sup>3</sup>When  $I^2$  was  $< 40\%$  or  $I^2$  was  $\geq 40\%$  but the source of heterogeneity was found by subgroup analysis 1 point was assigned; otherwise, 0 points were assigned.

<sup>4</sup>Based on the funnel plots, Egger or Begg's test. For the outcomes with small number of studies ( $n < 10$ ), the risk of publication bias was not formally assessed.

<sup>5</sup>If the RR or HR  $< 0.80-0.50$  and  $> 1.20-2.00$ , respectively, 1 point is assigned and the corresponding test is statistically significant; if the RR or HR  $< 0.50$  and  $> 2.00$ , respectively, 0 points are assigned and the corresponding test is statistically significant.

<sup>6</sup>Moderate quality indicates that we are moderately confident in the effect estimate: the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different. Low quality indicates that our confidence in the effect estimate is limited: the true effect may be substantially different from the estimate of the effect.



Lifestyle and environmental factors, including diet, are considered as important factors in the prevention of breast cancer (93). The International Agency for Research on Cancer reported that red meat and processed meat may be potential carcinogens for humans (94); indeed, in the present meta-analysis, the risk of breast cancer increased by 10% for red meat, 7% for total meat, and 18% for processed meat. Similarly, a previous meta-analysis reported a significant, positive association between processed meat consumption and the risk of breast cancer (95), but the authors only compared the highest category with the lowest category of red and processed meat consumption.

The carcinogenicity of red meat and processed meat may be attributed to mutagenic compounds, such as polycyclic aromatic hydrocarbons and heterocyclic amines, which are by-products of cooking red meat at high temperatures (96, 97). Also, heme iron, fat, and animal sugar molecule N-glycolylneuraminic acid, found in red meat, are posited to potentially increase inflammation, oxidative stress, and tumor formation (96), and in some countries, hormone residue of the exogenous hormones used to stimulate the growth of beef cattle has also been suggested as an independent risk factor of breast cancer (96).

To ameliorate the cancer risk, fish and poultry represent good substitutes for red meat in the dietary composition. As in the present meta-analysis, poultry and fish had no significant association with the breast cancer risk. Indeed, red meat and poultry differ in their relative percentages of heme iron and saturated fat content. Also, consumption of poultry has been associated with less mutagenic activity, oxidative stress, and DNA damage (93).

Breast cancer has a heterogeneous etiology, so, in the present study, subgroup analyses were conducted based on several factors. In a subgroup analysis, the association of red meat, total meat, and processed meat consumption and breast cancer risk was stronger in the studies from Europe. Indeed, this stronger association might be attributed to the fact that breast cancer is the most common cancer type in Europe (98), and such differences might be manifest from the prevalence and distribution of known risk factors of breast cancer in European countries (98).

Considering the association between red meat and total meat intake and the breast cancer risk, larger and significant effects were seen in follow-up durations of more than 10 y, which might be attributed to the higher number of cancer cases that occurred in longer follow-ups. Also, cumulative effects of risk factors concomitant to increasing age and an increasing number of post-menopause cancer cases in long follow-ups could be considered, notwithstanding the fact that the effect of red meat consumption on the breast cancer risk was not significant in a subgroup analysis of menopausal status. While some studies revealed that the risks of breast cancer following red meat consumption are different in pre- and postmenopausal women (29), in the present study such differences were seen for processed meat intake, which had a stronger association with breast cancer risk in postmenopausal women. Regarding case numbers,

larger and significant effects were identified for total and processed meat consumption and breast cancer risk in the subgroup of studies with case numbers <1000; however, it is conceivable that such differences might be attributed to the higher level of bias in lower case numbers.

A contentious issue in the relationship between diet and breast cancer risk is dairy consumption. In the present study, a null association was seen between dairy product, milk, and yogurt consumption and breast cancer risks in linear dose-response analyses. A positive nonlinear dose-dependent association was seen for milk intake, although no association was observed for consumption of less than 450 g/d of milk, but in amounts greater than 450 g/d, the risk of breast cancer increased by approximately 30%, with increasing milk intake up to 1300 g/d. In a subgroup analysis, the association of dairy consumption with breast cancer risk was larger and was significant in follow-ups of <10 y. The results of a previous meta-analysis investigating the association between milk consumption and breast cancer risk did not provide consistent evidence for such an association (99). Indeed, in the aforementioned study, the authors only assessed the relationship between the highest versus lowest intakes of milk; moreover, their literature search was limited to PubMed and Chinese biomedicine databases up to 2009 (99), so a number of studies were missing. The association between milk consumption and breast cancer risk might be related to the presence of fat-soluble hormones in the milk, which come from pregnant cows, leading to an increased risk of hormone-dependent cancers, such as breast, ovarian, and corpus uteri cancers (100). Milk consumption is among the most important routes of human exposure to estrogens; in fact, milk is considered as the predominant source of animal-derived estrogens in the human diet, accounting for 60–80% of the estrogens consumed (100). Moreover, milk contains insulin-like growth factor I (IGF-I), which stimulates cell proliferation and neoplasm formation (101). The association between milk consumption and IGF-I tumorigenesis was only suggested for milk and not for other dairy products (101). Indeed, considering these mechanisms, it is noteworthy to mention that previous meta-analyses showed significant, positive associations between milk consumption and reproductive cancers, such as ovarian cancer (102) and prostate cancer (101).

In the present study, a small, inverse association was seen between cheese consumption and breast cancer risk, such that the breast cancer risk decreased by 5%. In a subgroup analysis, this association was stronger in studies from Europe. To the best of our knowledge, no meta-analysis has been conducted regarding the association of cheese consumption with breast cancer risk. Cheese is a good dietary source of proteins; several vitamins, such as A, B6, B12, D, and K; and minerals, including calcium, iodine, magnesium, potassium, phosphorus, and zinc. The ameliorative effects of cheese on the breast cancer risk might be because cheese consumption is representative of a relatively healthy diet (103). Also, desaturase inhibitors in cheese, which inhibit triglyceride synthesis, reduce the pathogenic effects of fat (102), whilst



cancer-protective properties of fermented products, such as cheese, might be attributed to live microorganisms acting as probiotics (102, 104).

In our study, an inverse association was detected between fruit and vegetable consumption and breast cancer risk, such that the risk of breast cancer decreased by 3% for increased fruit intake, by 4% for increased vegetable intake, and by 2% for increased combined fruit and vegetable consumption. The most recent meta-analysis on the associations of fruit and vegetable intakes with breast cancer risk, which was published in 2012, reported that high intakes of fruits alone and of fruits and vegetables combined, but not of vegetables alone, were associated with weak reductions in the breast cancer risk (105). There were 9 studies included in this previous study (in a linear dose-response analysis), while our results are based on 15 studies. Anti-cancer properties of fruits and vegetables are possibly due to their high content of antioxidant nutrients, including fiber, vitamins C and E, carotenoids, and other bioactive substances (56). In the present study, a subgroup analysis revealed a larger and significant association between vegetable intake and estrogen receptor-negative breast cancer. This might be due to the dominant role of hormonal exposure and hormone-related factors in the etiology of estrogen receptor-positive tumors (56, 106). Moreover, vegetables contain phytochemical compounds that can reduce the levels of epidermal growth factor receptor, nuclear factor kappa B, and cyclin E, which may, in turn, reduce the risk of developing estrogen receptor-negative breast cancer (106).

Besides the antioxidant content of fruits and vegetables, high fiber intake has been shown to interfere with bile acids and decrease estrogen deconjugation, leading to increased fecal excretion of estrogen and reduced plasma concentration of this hormone (107). This explanation might also pertain to the significant differences that were seen in a subgroup analysis between refined- and whole-grain consumption in the present study, while a null association was observed between overall grain consumption and breast cancer risk. Also, high glycemic-index foods were shown to be associated with higher insulin levels, and the insulin-IGF-I axis has been shown to be directly associated with cancer promotion (108). Similar findings were reported by a previous meta-analysis on whole-grain intake and breast cancer risk, suggesting that intermediate and high intake levels of whole grains were associated with modest reductions of breast cancer risks, but this inverse association was only observed in case-control and not cohort studies (109), and the mentioned meta-analysis only assessed studies published specifically on whole grains.

In the present study, soybean consumption was associated with a 3.5% reduction in breast cancer risk. In previous meta-analyses of the association of soy intake and breast cancer, most of the included studies assessed the soy isoflavones. We did not include these studies, since the aim of our study was to investigate the association of food groups, rather than the food component, with breast cancer. There were 2 recent meta-analyses on soy isoflavones that indicated a reduction

of breast cancer risk with soy intake, especially in larger amounts. Accordingly, 1 of these studies indicated that high versus low consumption of soy was associated with a lower risk of breast cancer ( $n = 6$  studies), while moderate versus low intake of soy did not significantly affect the breast cancer risk ( $n = 4$  studies) (110). Another study, which evaluated the risk in Chinese women, revealed that every 10 mg/day of soy isoflavone intake was associated with a 3% reduction in breast cancer risk (111). Indeed, the results of previous studies indicate that menopause status may influence the association of soy consumption and breast cancer (112); however, because of the small number of studies included in our meta-analysis, we could not conduct a subgroup analysis based on menopause status.

The novelties of our study compared to previously published meta-analyses on single food groups (95, 99, 105, 109, 113) have been explicated above. The only meta-analysis considering several food groups was conducted by Wu et al. in 2016 (96), on dietary protein sources and breast cancer risk, where the literature search was conducted up to 2015. Thus, given that a substantive period of time (5 y) has elapsed and a number of large-scale prospective studies have been published, especially on red meat, processed meat, and fish, an up-to-date synthesis was urgently required. Moreover, former meta-analyses have rarely assessed the quality of evidence that is important for generating guidelines and recommendations, while we comprehensively assessed the quality of meta-evidence using the NutriGrade scoring system.

As a limitation to the present study it is worth noting that, for some of the food groups, residual components may influence the association with breast cancer: for example, in low-fat versus high-fat dairy, lean meat versus high-fat meat, or low-sugar versus sweetened fruit juices. Since the primary studies did not report results according to fat or sugar contents of food, we could not perform subgroup analyses or conduct the analysis separately according to these factors; therefore, a limitation of this study is that the results may be confounded by a component of the food. For legumes, nuts, and soy, the results were derived from a small number of studies. Most of the studies on these food groups assessed their components, such as fiber, protein, and isoflavones, and so were excluded based on our inclusion criteria. Moreover, meta-evidence for poultry, fish, cereals, and legumes was low; therefore, results for these food groups should be interpreted with caution. Moreover, it should be noted that numerous analyses were performed, and it is conceivable that some associations could be statistically significant as a result of multiple comparisons. Finally, it should be acknowledged that due to the observational design of the primary studies, causality cannot be inferred from these statistical correlations.

This meta-analysis has several strengths; for instance, we are moderately confident in the veracity of the results for most of the food groups, as the primary studies were mostly assessed as being of good quality. The adequate number of included studies also allowed us to conduct multiple

subgroup analyses for important factors, such as menopausal status and presence of estrogen receptor. Additionally, we conducted both linear and nonlinear dose-response analyses, which provide detailed insight into the associations.

In conclusion, the findings of the present meta-analysis show that high intakes of fruits, vegetables, soybeans, and cheese and low intakes of red meat and processed meat are associated with reduced risks of breast cancer. A null association was noted between poultry, fish, egg, fruit juice, dairy, milk (<450 g/day), yogurt, grain, nut, and legume consumption and breast cancer risk, whilst consumption of milk in amounts more than 450 g/day was associated with an increased risk. Finally, it should be acknowledged that causality cannot be inferred from these statistical correlations, indicating the need for further well-conducted RCTs.

## Acknowledgment

We thank Dr Dominik Alexander for the internal peer review of the manuscript.

The authors' responsibilities were as follows—AK: designed the study; AK, RB-B, MA, and SS: literature search and screening; AK, RB-B, ZE, and NM: data extraction; AK and SS: quality assessment; AK, MA, and SB: wrote the initial draft, which was modified after feedback from all coauthors; CCTC: critical revising of the manuscript; AK: had primary responsibility for content; and all authors: read and approved the final manuscript.

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