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Meat, eggs, dairy products, and risk of breast cancer in the European Prospective Investigation into Cancer and Nutrition (EPIC) cohort[1–3]

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ABSTRACT

Background: A Western diet is associated with breast cancer risk.

Objective: We investigated the relation of meat, egg, and dairy product consumption with breast cancer risk by using data from the European Prospective Investigation into Cancer and Nutrition (EPIC).

Design: Between 1992 and 2003, information on diet was collected from 319,826 women. Disease hazard ratios were estimated with multivariate Cox proportional hazard models.

Results: Breast cancer cases (n = 7119) were observed during 8.8 y (median) of follow-up. No consistent association was found between breast cancer risk and the consumption of any of the food groups under study, when analyzed by both categorical and continuous exposure variable models. High processed meat consumption was associated with a modest increase in breast cancer risk in the categorical model (hazard ratio: 1.10; 95% CI: 1.00, 1.20; highest compared with lowest quintile: P for trend = 0.07). Subgroup analyses suggested an association with butter consumption, limited to premenopausal women (hazard ratio: 1.28; 95% CI: 1.06, 1.53; highest compared with lowest quintile: P for trend = 0.21). Between-country heterogeneity was found for red meat (Q statistic = 18.03; P = 0.05) and was significantly explained (P = 0.023) by the proportion of meat cooked at high temperature.

Conclusions: We have not consistently identified intakes of meat, eggs, or dairy products as risk factors for breast cancer. Future studies should investigate the possible role of high-temperature cooking in the relation of red meat intake with breast cancer risk.

INTRODUCTION

There is considerable evidence that breast cancer risk is related to modifiable lifestyle factors (1–5), which makes it possible for women to reduce their risk by changing lifestyle, for example by remaining physically active, avoiding weight gain, limiting alcohol intake, and eating a "healthy" diet. Epidemiologic studies implicate a Western diet and the Westernization of diet as probable causes of the increasing incidence of this disease (6–9). However, there is much uncertainty as to which components of the Western diet should be reduced and which alternatives may best contribute to reducing breast cancer risk while at the same time promoting women's overall health (10–12).

Meat, eggs, and dairy products—prominent features of the Western diet (6, 13)—have been consistently associated with increased breast cancer incidence (14, 15) and mortality (16) in ecological studies; moreover, there has been an ecological trend of increasing breast cancer mortality coincident with the increase in consumption of animal products that occurred after World War II (17).

Recent observational studies indicate that breast cancer risk increases (18–22), is unrelated to (19–23), or even decreases (24, 25) with increasing intake of one or more animal foods. The 2007 World Cancer Research Fund report (26) concluded that observational epidemiologic studies do not consistently implicate consumption of any animal food in breast cancer risk.

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The lack of consistent findings regarding the risks of such pervasive dietary components makes it difficult to produce consensus dietary recommendations that aim to reduce the overall breast cancer burden. Null findings may reflect true absence of association but could also be due to high measurement error. All but one (22) of the prospective studies of diet and breast cancer risk have been conducted on population groups characterized by fairly uniform dietary habits, so that the measurement error—which can be considerable when food consumption is assessed—would have obscured all but very large associations of breast cancer with dietary components. The effect of exposure measurement error can be reduced by studying populations in which between-person variation in consumption of various food groups is marked. This was the approach adopted by the European Prospective Investigation into Cancer and Nutrition (EPIC), which recruited cohorts from 10 European countries. In the present article, we report the results of an analysis conducted on data from 367,993 women participants of EPIC to investigate whether the consumption of meat, eggs, and dairy products is associated with breast cancer risk.

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SUBJECTS AND METHODS

Subjects

EPIC is a large prospective cohort study conducted in 23 centers in the countries of Denmark (Aarhus and Copenhagen), France, Germany (Heidelberg and Potsdam), Greece, Italy (Florence, Varese, Ragusa, Turin, and Naples), Norway, Spain (Asturias, Granada, Murcia, Navarra, and San Sebastian), Sweden (Malmö and Umeå), the Netherlands (Bilthoven and Utrecht), and the United Kingdom (Cambridge and Oxford). Eligible men and women were invited to participate; those who accepted gave informed consent and compiled questionnaires on diet, lifestyle, and medical history. EPIC recruited 367,993 women, most in the age range 25–70 y. In most centers, participants came from the general population. However, the French cohort was recruited from female members of a health insurance scheme for school and university employees, the Turin and Ragusa (Italy) and the Spanish centers included blood donors, participants in Utrecht were recruited from a mammographic screening program, the Florence cohort included screening program participants, and half the Oxford cohort consisted of "health conscious" persons from England, Wales, Scotland, and Northern Ireland (27).

Women with prevalent cancers at any site at recruitment (n = 19,707) or with missing diagnosis or censoring date (n = 2291) were excluded, which left 345,995 women and 9162 breast cancer cases. We further excluded those with in situ breast cancer (n = 1272), those who did not complete at least one of the questionnaires on diet and lifestyle (n = 3320) and those in whom the ratio of total energy intake (determined from the questionnaire) to basal metabolic rate was at either extreme of the distribution (cutoffs: first and last percentiles) (n = 6764). We also excluded women outside of the 20–70 y age range (n = 6401), as well as those with missing values of the exposure and confounding variables considered in the adjusted models (n = 8412). Thus, the analysis was performed in 319,826 EPIC women aged 20–70 y with complete exposure information. Within this group, 7119 women with invasive breast cancer were identified after a median follow-up of 8.8 y. The study was approved by the International Agency for Research on Cancer ethical committee and the local ethical committees of the participating centers.

Dietary assessment

Dietary and lifestyle questionnaires were completed by participants at enrollment when anthropometric measurements were also taken. Diet was assessed by using country-specific (in Italy and Sweden center-specific) food questionnaires (FQs) designed to capture habitual consumption of food over the preceding year. Eight countries used self-administered FQs, whereas the questionnaires were administered by interviewers in Greece and southern Italy (Naples and Ragusa).

In most countries, the questionnaires were extensive quantitative instruments ≤260 food items. In Denmark, Norway, Umeå (Sweden), and Naples (Italy), semiquantitative food-frequency questionnaires (FFQs) were administered (27). In Malmö (Sweden), a method combining a short nonquantitative FQ with a 7-d dietary diary was used (27). In the United Kingdom, an FFQ and a 7-d dietary diary were used, but the present results are from the FFQ. All dietary questionnaires had been previously validated (28–35). The methods of analyzing the questionnaires and measurements are reported elsewhere (27, 36).

In addition, highly standardized 24-h dietary recall (24-HDR) interviews were conducted, using EPIC-soft software (37) on a random sample (5–12%) of each EPIC cohort. Foods from the FQ items were mapped to the food groups defined in EPIC-soft, which allowed direct comparison between FQ items and 24-HDRs. 24-HDR data were used for the calibration procedure (*see* below) to correct for systematic differences between the dietary questionnaires.

The exposure variables considered in the present analysis were total daily intake (g/d) of red meat, poultry, processed meat, eggs, milk, cheese, and butter. Red meat consisted of fresh, minced, and frozen beef, veal, pork, and lamb. Poultry included all fresh, frozen, and minced chicken, and, in some centers, turkey. Processed meats were mostly pork and beef preserved by methods other than freezing, such as salting, smoking, marinating, air-drying, or heating and included ham, bacon, sausages, blood sausages, liver pâté, salami, mortadella, tinned meat, and others. Egg intake was the sum of eggs consumed as such, and as components of recipes, and was not available for Umeå (Sweden).

Total milk was assessed as the sum of all types of milk consumed (whole-fat, skim, semiskim, and not specified) and, in Norway, included fermented milk. When information was available, we also considered exposure to various types of milk. Information on skim milk, defined as milk with $<$0.5% fat, was not available for Greece, Germany, and Norway and 3 Italian centers (Varese, Florence, and Turin). Information on semiskim milk, defined as milk with a fat content in the range 0.5–2.5%, was not available for Greece, Germany, or Norway. Information on whole-fat milk, defined as milk with $>$3.5% fat, was not available for Norway. Cheese included all kinds of fresh, fermented, and matured cheese. Butter included normal and low-fat varieties. The proportion of red meat cooked by high temperature was estimated for each country based on the data of Rohrmann et al (38), which was estimated for a representative sample of women from each EPIC center. Meat cooked at high temperature was defined as that cooked by frying, deep-frying, roasting, barbecuing, and grilling. The EPIC countries were divided into 2 groups based on the percentage of red meat cooked at high temperature: $\leq$45% (Italy, Germany, Norway, Greece, and United Kingdom) and $>$45% (Spain, Sweden, France, Denmark, and Netherlands). The health-conscious UK cohort was excluded from the analysis on high-temperature cooking because this group was characterized by a high proportion with zero meat consumption.

Calibration of dietary data

A linear calibration approach (39) was applied to correct the diet-breast cancer association for random and systematic measurement errors in estimates of intake from the FQs. The calibration model also aimed to correct for differences in FQs between countries arising from the fact that these instruments differed for each country and sometimes (Italy and Sweden) differed within a country. The calibration models produced predicted values of consumption of each food group for each individual. The method used 24-HDR data as a reference measure for each food group (37, 40); these reference measurements were regressed on measurements obtained from the FQ by using country-specific linear calibration models. Women with zero intake on the FQ for a given food were excluded from the calibration model; as a consequence, for those women, not only the observed but also the calibrated (predicted) estimation of intake for that food was left (unchanged) as zero.

Negative values arising from the models were imputed to zero. Age at recruitment and other adjustment factors used in the Cox models (energy, weight, height, alcohol consumption, smoking, educational attainment, and menopausal status) were included as covariates in these calibration models. In all calibration models, data were weighted to account for the uneven distribution of 24-HDR interviews among weekdays and seasons. The weighting procedure was applied to correct this uneven distribution and give equal representation of each day and season. The predicted values for food item consumption obtained by this approach were modeled as continuous variables in the risk models.

Anthropometric measurements

Weight and height were measured at baseline, while the subjects were not wearing shoes, to the nearest 0.1 kg, or–depending on the center–to the nearest 0.1, 0.5, or 1.0 cm (41, 42). However, in France, Norway, and Oxford, height and weight were self-reported on a questionnaire. The procedures used to account for protocol differences between centers are described elsewhere (41, 42).

Outcome assessment

Cancer diagnoses were those reported by population-based cancer registries in Denmark, the Netherlands, Norway, Spain, Sweden, the United Kingdom and the Italian centers of Varese, Turin, Florence, and Ragusa. Active follow-up of study participants and next-of-kin, as well as of social security records and cancer and pathology registries was used in France, Germany, Greece and Naples (Italy).

Each participant was followed for breast cancer occurrence from study entry to cancer diagnosis, loss to follow-up, death, or end of follow-up (27). For centers covered by cancer registries, follow-up was completed as follows: December 2002 (Granada), December 2003 (Florence, Varese, Murcia, Bilthoven, Aarhus, and Copenhagen), December 2004 (Ragusa, Turin, Asturias, Navarra, Cambridge, Oxford, Utrecht, and Malmö), June 2005 (Umeå), and December 2005 (San Sebastian and Norway). For centers using ad hoc follow-up (France, Germany, Naples, and Greece), end of follow-up was the latest known contact, date of diagnosis, or date of death. Invasive breast cancer was that coded as C50.0–50 in the International Classification of Diseases for Oncology, second revision (ICD-O-2).

Statistical methods

Descriptive statistics

Country-specific medians of age at enrollment and years of follow-up were calculated. Means intakes (g/d) were calculated for each food group investigated.

Models and confounders

Cox proportional hazards regression models were used to quantify the association of intake of red meat, poultry, processed meat, eggs, all types of milk, whole milk, semiskim milk, skim milk, cheese, and butter with breast cancer. Age was the primary time variable, and the Breslow method was adopted for handling ties. Time at entry was age at recruitment; exit time was age at cancer diagnosis, death, loss to follow-up, or end of follow-up, whichever came first. Models were stratified by center to control for differences in questionnaire design, follow-up procedures, and other center effects. Further stratification was by age at recruitment (1-y categories) to account for possible departures from proportionality of hazards with time. Systematic adjustments were undertaken for menopausal status (dichotomized as postmenopausal versus other), energy intake, weight and height (all continuous), smoking (never, former, and current), educational attainment (continuous as years of schooling), and alcohol intake (abstainer, ≤12 g/d, and >12 g/d).

Models that included the hormone-related risk factors: at least one pregnancy to term versus nulliparous, age at menarche (<12, 12–15, and >15 y), age at birth of first child (<21, 21–30, and >30 y), and hormone treatment (categorized as never, <1 y, and >1 y) were also run. These excluded 28,620 women (671 cases), for whom one or more of these variables was missing. The results of the analyses on this subset were closely similar to those without adjustments for hormone-related factors, so only models unadjusted for hormone-related factors are presented.

We ran models that considered food consumption as categorical and as continuous variables. For the former, quintiles of consumption of each food group were determined for the entire cohort. Hazard ratios (HRs) were estimated for quintiles of dietary intake with first quintile as reference. In view of the high proportion of nonconsumers for milk subtypes (whole-fat, skim, and semiskim), the zero consumers were pooled as the reference group. *P* values for trends across quintiles were obtained by comparing the log likelihood of a model with median intakes within quintiles as score variable and the model without it with a chi-square distribution with one df.

The models considering food intake as a continuous variable produced risk estimates (HRs) for increments of food intake; the increments used were 150 g/d for red meat and poultry, 40 g/d for processed meat, 7 g/d for eggs, 150 g/d for milk (all kinds), 50 g/d for cheese, and 5 g/d for butter. These increments generally correspond to a standard food portion, except for eggs, for which an increment of 7 g/d (one egg per week) was chosen because of the very low mean and median. Models were run with the exclusion of women who developed breast cancer during the first 2 y of follow-up, but the results did not differ from those including the entire cohort and are not presented.

We investigated the interaction of high-temperature cooking with the association of red meat consumption to breast cancer risk by including in the risk model red meat intake (g/d) multiplied by an indicator (0 = low; 1 = high) of the proportion of high-temperature cooking, together with the main effect terms. The significance of interaction was tested by the Wald test on the β of the product term of meat intake and high-temperature indicator.

Proportional hazards assumption

We tested the proportional hazard assumption for each food variable in relation to breast cancer risk by using the method of Grambsch and Therneau (43). In all cases, the proportional hazards assumption was satisfied (data not shown).

Statistical heterogeneity

Statistical heterogeneity was estimated by using the *Q* test statistic to test the hypothesis that the true effects were the same in all of the countries, with the Oxford health conscious cohort considered as a country (44). We next investigated, using meta-regression, the extent to which a particular covariate can explain between-country heterogeneity (eg, proportion of meat cooked at high temperature investigated as an explanatory covariate for the heterogeneity of HRs in relation to red meat consumption). The restricted maximum likelihood estimate of the tau squared statistic (45) was the variance parameter used to account for residual HR heterogeneity between countries. Statistical tests were 2 sided, and *P* values <0.05 were considered significant. The analyses were performed by using Stata version 7 (Stata Corp, College Station, TX).

TABLE 1
Women and breast cancer cases of European Prospective Investigation into Cancer and Nutrition (EPIC) cohort by country

Country	Participants per cohort	Age at enrollment[1]	Age at end of follow-up[1]	Breast cancer cases per cohort	Follow-up	
					Duration[1]	Duration per cohort
	n	*y*	*y*	*n*	*y*	*person-years*
Denmark	28,571	56.2	63.8	822	7.7	214,842
France	63,088	51.5	62.5	2272	11.9	691,567
Germany	27,804	48.4	56.7	457	8.3	226,510
Greece	12,899	51.8	59.3	103	7.9	93,832
Italy	30,239	50.8	59.1	670	8.7	255,538
Norway	33,250	47.9	53.9	441	6.1	198,456
Spain	24,789	47.7	57.5	319	9.8	240,836
Sweden	24,744	50.3	61.8	648	10.8	257,185
Netherlands	26,333	52.5	61.4	567	8.9	227,662
United Kingdom, general	14,455	54.1	63.2	423	9.2	130,141
United Kingdom, health conscious	33,654	40.5	48.7	397	8.4	276,038
Total	319,826	50.8	59.6	7119	8.8	2,812,610

[1] All values are medians.

TABLE 2

Mean intakes of meat, eggs, and dairy products in women participating in the European Prospective Investigation into Cancer and Nutrition (EPIC) overall and by EPIC center[1]

Country and participants per cohort	Red meat	Poultry	Processed meat	Eggs	All types of milk	Whole milk	Semiskim milk	Skim milk	Cheese	Butter
	g/d	*g/d*	*g/d*	*g/d*	*g/d*	*g/d*	*g/d*	*g/d*	*g/d*	*g/d*
Denmark (28,571)	46.41 ± 0.07	17.09 ± 0.04	25.42 ± 0.05	16.62 ± 0.05	177.92 ± 0.94	19.03 ± 0.24	76.03 ± 0.61	58.51 ± 0.82	29.78 ± 0.07	2.33 ± 0.03
France (63,088)	43.91 ± 0.08	19.16 ± 0.04	29.18 ± 0.03	14.09 ± 0.02	90.70 ± 0.39	5.95 ± 0.13	58.66 ± 0.33	12.59 ± 0.17	45.30 ± 0.06	8.75 ± 0.02
Germany (27,804)	35.88 ± 0.10	14.41 ± 0.03	39.09 ± 0.07	11.77 ± 0.03	99.67 ± 0.48	31.84 ± 0.36	NA	NA	29.45 ± 0.06	12.90 ± 0.06
Greece (12,899)	29.24 ± 0.09	13.62 ± 0.07	6.19 ± 0.04	9.70 ± 0.03	104.19 ± 0.50	59.31 ± 0.36	NA	NA	40.16 ± 0.13	0.52 ± 0.02
Italy (30,239)	47.66 ± 0.11	23.27 ± 0.05	20.70 ± 0.05	9.47 ± 0.02	121.39 ± 0.49	33.49 ± 0.36	59.18 ± 0.41	5.60 ± 0.22[2]	39.02 ± 0.07	1.68 ± 0.01
Norway (33,250)	44.94 ± 0.07	12.86 ± 0.05	34.93 ± 0.07	15.31 ± 0.04	177.10 ± 0.73	NA	NA	NA	39.20 ± 0.06	2.48 ± 0.03
Spain (24,789)	44.57 ±. 13	27.50 ± 0.06	28.08 ± 0.07	21.80 ± 0.06	298.56 ± 0.73	126.12 ± 0.73	11.79 ± 0.31	79.20 ± 0.74	13.88 ± 0.06	0.34 ± 0.01
Sweden (24,744)	40.20 ± 0.06	7.58 ± 0.03	39.65 ± 0.07	15.70 ± 0.07[3]	189.28 ± 0.63	40.26 ± 0.41	68.81 ± 0.53	57.26 ± 0.54	30.92 ± 0.06	1.09 ± 0.02
Netherlands (26,333)	42.46 ± 0.09	13.30 ± 0.05	35.80 ± 0.09	13.63 ± 0.03	203.68 ± 0.84	19.67 ± 0.26	111.72 ± 0.71	13.02 ± 0.24	33.08 ± 0.08	4.46 ± 0.04
United Kingdom, general (14,455)	28.11 ± 0.10	22.65 ± 0.10	21.45 ± 0.09	10.32 ± 0.06	232.54 ± 0.77	29.68 ± 0.61	122.27 ± 1.09	40.54 ± 0.70	11.37 ± 0.05	4.39 ± 0.05
United Kingdom, health conscious (33,654)	7.28 ± 0.04	9.85 ± 0.07	5.77 ± 0.04	9.20 ± 0.04	194.93 ± 0.56	26.83 ± 0.30	93.68 ± 0.64	41.71 ± 0.45	13.87 ± 0.03	5.65 ± 0.03
Total (319,826)	38.38 ± 0.04	16.52 ± 0.02	27.03 ± 0.03	13.55 ± 0.01	162.12 ± 0.23	33.34 ± 0.13	71.25 ± 0.20	36.76 ± 0.18	31.71 ± 0.03	4.77 ± 0.01

[1] All values are means ± SEMs. Food intakes are predicted by "calibration" procedure, which is described in Subjects and Methods. NA, not available.
[2] Italian cohorts of Varese, Florence, and Turin excluded.
[3] Swedish cohort of Umeå excluded.

RESULTS

The numbers of breast cancer cases according to country, with number of cohort members, median age at study entry, median age at end of follow-up, median follow-up, and person-years of follow-up are shown in **Table 1**. Median follow-up was 8.8 y, with 2,812,610 person-years of follow-up since 1992.

Mean predicted (from calibration procedure) intakes of meat, eggs, and dairy products at recruitment are shown in **Table 2**. Consumption of all food items varied considerably across centers. Women from the UK health-conscious group generally consumed the fewest animal products, except for milk and butter. For the other countries, the greatest variations were for butter (from <0.6 g/d for Spain and Greece to >8 g/d in France and Germany) and processed meat (from 6.2 g/d for Greece to >39 g/d for Germany and Sweden).

The results of the categorical and continuous multivariate analyses in the entire cohort are shown in **Table 3** and **Table 4**. All models were adjusted for energy intake, weight, height, alcohol consumption, smoking, education, and menopausal status. No consistent association of any food group with breast cancer was found in both the categorical and the continuous models.

Processed meat was significantly associated with breast cancer risk in the categorical model (HR: 1.10; 95% CI: 1.00, 1.20 for the last compared with the first quintile of intake), but the trend of quintile medians was not significant (P = 0.065); the continuous models showed no significant association of processed meat with breast cancer. For eggs, breast cancer risk was significantly greater for the second and fourth quintiles compared with the first quintile, with no linear trend.

No clear associations of breast cancer with milk emerged. For whole milk consumption, HRs for breast cancer risk increased nonlinearly across quintiles, and the difference was significant for the fourth but not the fifth versus the first plus the second quintiles. A modest association of breast cancer risk with predicted semiskim milk consumption (HR: 1.04; 95% CI: 1.00, 1.09 for each 150 g/d) was also found with the continuous model. Data on milk subtypes were available only for some centers: for whole-fat milk, data were available for 286,576 women (6678 breast cancer cases); for semiskim milk, data were available for 245,873 women (6118 breast cancer cases).

For red meat, significant between-country heterogeneity of HRs was found (Q statistic =18.03, P = 0.05). To explore the between-country heterogeneity for red meat consumption, we ran meta-regression models in which the country-specific (38) proportion of high-temperature cooking methods was used to predict heterogeneity. We found that this covariate was able to significantly (P = 0.023) explain most of the between-country heterogeneity.

We next looked at the association of breast cancer risk with red meat consumption, stratifying countries into those with high and low proportions of red meat cooked at high temperature. A significant association of red meat consumption with breast cancer was found in countries with a high proportion of high-temperature cooking (HR: 1.16; 95% CI: 1.03, 1.32 for each 150-g/d increase) but no association was evident for countries with a low proportion of high-temperature cooking (HR: 0.82; 95% CI: 0.63, 1.07 for each 150-g/d increase). A significant interaction of high-temperature cooking strata with red meat consumption and breast cancer risk was also found (P for trend = 0.017) (data not shown in Table 4).

TABLE 3
Multivariate hazard ratios (HRs) with 95% CIs for breast cancer by quintile of intake of meat, eggs, and dairy products: categorical model[1]

Food group and quintile	Median intake	Population per quintile	Breast cancer cases per quintile	HR (95% CI) by quintiles of food intake	*P* for trend
	g/d	*n*	*n*		
Red meat					0.19
1	1.4	63,966	1266	1	
2	21.3	63,965	1244	1.04 (0.96, 1.14)	
3	36.0	63,965	1322	1.03 (0.95, 1.12)	
4	54.4	63,965	1537	1.06 (0.98, 1.15)	
5	84.6	63,965	1750	1.06 (0.98, 1.14)	
Poultry					0.50
1	0.0	63,967	1356	1	
2	6.3	63,971	1320	1.01 (0.93, 1.10)	
3	14.8	66,770	1426	1.02 (0.94, 1.10)	
4	22.5	62,481	1544	1.07 (0.99, 1.16)	
5	46.1	62,637	1473	1.02 (0.95, 1.11)	
Processed meat					0.07
1	1.7	63,966	1016	1	
2	11.0	63,965	1489	1.04 (0.96, 1.14)	
3	20.1	63,965	1553	1.08 (0.99, 1.17)	
4	32.3	63,980	1555	1.09 (1.00, 1.19)	
5	56.5	63,950	1506	1.10 (1.00, 1.20)	
Eggs[2]					0.36
1	3.3	61,558	1156	1	
2	8.5	61,709	1276	1.09 (1.00, 1.18)	
3	14.4	61,405	1356	1.07 (0.98, 1.16)	
4	21.6	61,557	1452	1.08 (1.00, 1.17)	
5	36.7	61,557	1655	1.07 (0.98, 1.16)	
All types of milk					0.55
1	0.0	63,967	1601	1	
2	35.6	63,964	1409	1.04 (0.97, 1.12)	
3	146.5	63,965	1328	1.05 (0.97, 1.14)	
4	273.4	63,965	1355	0.98 (0.91, 1.06)	
5	439.0	63,965	1426	1.05 (0.97, 1.14)	
Whole milk[3]					0.64
1	0.0	121,077	3316	1[4]	
2	—	—	—	—	
3	1.5	52,642	934	1.02 (0.91, 1.14)	
4	9.2	55,618	1315	1.12 (1.02, 1.24)	
5	150.0	57,239	1113	1.06 (0.97, 1.15)	
Semiskim milk[5]					0.39
1	0.0	116,977	2823	1[4]	
2	—	—	—	—	
3	8.8	30,952	834	1.07 (0.97, 1.18)	
4	100.0	48,770	1249	1.05 (0.98, 1.13)	
5	292.5	49,174	1212	1.05 (0.97, 1.12)	
Skim milk[6]					0.05
1	0.0	152,319	3971	1[7]	
2	—	—	—	—	
3	—	—	—	—	
4	13.0	26,686	626	1.04 (0.93, 1.16)	
5	210.0	44,680	965	0.93 (0.87, 1.01)	
Cheese					0.21
1	5.7	63,966	1251	1	
2	18.4	63,983	1373	1.07 (0.99, 1.16)	
3	30.5	63,978	1411	1.02 (0.94, 1.10)	
4	47.8	63,934	1537	1.03 (0.95, 1.12)	
5	82.1	63,965	1547	0.97 (0.89, 1.06)	

(Continued)

TABLE 3 (*Continued*)

Food group and quintile	Median intake	Population per quintile	Breast cancer cases per quintile	HR (95% CI) by quintiles of food intake	*P* for trend
Butter					0.60
1	0.0	93,142	2026	1	
2	0.1	36,893	599	1.02 (0.92, 1.14)	
3	0.4	61,862	1228	1.05 (0.96, 1.15)	
4	2.9	63,965	1562	1.07 (0.98, 1.16)	
5	12.6	63,964	1704	1.05 (0.97, 1.14)	

[1] Models adjusted for energy, height, weight, years of schooling, smoking, and menopause; stratified by center and age (1-y strata). Observed consumption only.

[2] Data on eggs not available for Swedish cohort of Umeå.

[3] Data on whole milk not available for Norway.

[4] First + second quintiles combined because of the high number of zero consumers.

[5] Data on semiskim milk not available for Greece, Germany, and Norway.

[6] Data on skim milk not available for Greece, Germany, Norway, and the Italian cohorts of Varese, Florence, and Turin.

[7] First + second + third quintiles combined because of the high number of zero consumers.

The results of the analyses stratified by menopausal status (premenopausal versus postmenopausal) are presented in **Table 5**. The adverse effect of processed meat, first identified in all women, was confined to postmenopausal women in this analysis (HR: 1.13; 95% CI: 1, 1.28 for the fifth versus the first quintile); the trend of quintile medians was not significant ($P = 0.06$). High butter consumption was significantly associated with increased breast cancer risk (HR: 1.28; 95% CI: 1.06, 1.53 for the fifth versus the first quintile) in premenopausal women only: for this group, breast cancer risk increased significantly with butter consumption from the third to the fifth quintiles in comparison with zero consumption (first category), but the trend of quintile medians was not significant ($P = 0.21$).

DISCUSSION

In this prospective study of 319,826 European women and 7119 breast cancer cases, we found no consistent association of breast cancer risk with consumption of the meat, egg, or dairy foods investigated. These findings agree with the 2007 expert panel report of the World Cancer Research Fund (26) and the result of a pooled analysis of prospective cohorts (22). The tendency for high processed meat intake to be associated with increased breast cancer risk in all women was found to be significant in postmenopausal women (at recruitment) when pre- and postmenopausal women were analyzed separately. Similarly, butter consumption (compared with zero consumption) was significantly associated with increased breast cancer risk in premenopausal women only.

We found some suggestion of increased breast cancer risk with higher intakes of whole and semiskim (but not skim) milk, but neither a dose-response relation nor consistency across models emerged. Whereas red meat consumption was not associated with breast cancer risk, we found significant between-country heterogeneity (Table 4), and high red meat consumption was associated with increased breast cancer risk in some countries.

TABLE 4
Multivariate hazard ratios (HRs) with 95% CIs for breast cancer by increase in intake of meat, eggs, and dairy products: continuous model[1]

Food group	Increase in intake	HR (95% CI)		Heterogeneity test	
		Observed consumption	Predicted consumption[2]	Q (10 df)	P
	g				
Red meat	150	1.08 (0.97, 1.21)	1.23 (0.97, 1.57)	18.03	0.05
Poultry	150	1.04 (0.85, 1.26)	1.44 (0.96, 2.14)	3.53	0.96
Processed meat	40	1.01 (0.96, 1.05)	1.04 (0.93, 1.15)	11.18	0.34
Eggs[3]	7	1.00 (0.99, 1.01)	1.01 (0.98, 1.04)	15.83	0.10
All types of milk	150	1.01 (0.99, 1.03)	1.02 (0.99, 1.06)	8.16	0.61
Whole milk[4]	150	1.02 (0.98, 1.06)	1.03 (0.97, 1.10)	13.84	0.13
Semiskim milk[5]	150	1.02 (1.00, 1.05)	1.04 (1.00, 1.09)	10.71	0.15
Skim milk[6]	150	0.97 (0.94, 1.01)	0.97 (0.92, 1.02)	5.25	0.63
Cheese	50	0.97 (0.94, 1.01)	0.96 (0.85, 1.07)	13.89	0.18
Butter	5	1.01 (0.99, 1.02)	1.01 (0.99, 1.04)	10.12	0.43

[1] Models adjusted for energy, height, weight, years of schooling, smoking, and menopause; stratified by center and age (1-y strata). Observed consumption only.
[2] Predicted by using the calibration procedure described in Subjects and Methods.
[3] Data on eggs not available for Swedish cohort of Umeå.
[4] Data on whole milk not available for Norway.
[5] Data on semiskim milk not available for Greece, Germany, and Norway.
[6] Data on skim milk not available for Greece, Germany, Norway, and the Italian cohorts of Varese, Florence, and Turin.

Further analysis suggested cooking method as a possible cause of this between-country heterogeneity, and red meat emerged as being significantly associated with breast cancer risk in countries where red meat was cooked, in a high percentage of cases, at high temperature. High-temperature cooking (particularly on an open flame) increases the formation of potentially carcinogenic products such as heterocyclic amines and polycyclic aromatic hydrocarbons (46), but epidemiologic studies that have examined the association of meat preparation methods with breast cancer risk have yielded conflicting results. A positive dose-response relation between the intensity of meat cooking and breast cancer risk was found in a US cohort study (47), whereas a Danish population-based nested case-control study found a positive association of breast cancer with red meat intake, which was confined to fried meat, and was especially evident when the meat was "well done" (48). A more recent prospective cohort study provided no support for the hypothesis that intake of meat cooked at high temperatures is associated with an increased risk of postmenopausal breast cancer (49).

Our classification of countries in 2 groups as frequent (>45%) and less frequent (≤45%) users of high-temperature cooking may share with ecological studies the "ecological fallacy": we found that in the first group, but not in the second, red meat was significantly associated with breast cancer risk. We cannot exclude that the divergent effect of red meat on breast cancer risk was driven by other particular features of population, of exposure, or of outcome measures in these countries and that these features were the true cause of heterogeneity of the results.

Although poultry was not significantly associated with breast cancer risk in any model, the observed (HR: 1.04) and the calibrated (HR: 1.44) risk estimates differed considerably (Table 4). A possible reason for this was that poultry had a large FQ measurement error because of the large variation in poultry portion sizes that the questionnaire may not be able to capture, whereas portion sizes were well captured by the 24-HDR.

Our data suggesting a nonlinear association of egg consumption with breast cancer are not completely new, although case-control studies have produced conflicting results: 6 showed no association (50–55), 2 suggested higher risk (56, 57), and 1 carried out in China (58) found that eggs conferred significant protection. Nevertheless, a relation of eggs to increased breast cancer risk is supported by a pooled analysis of European and North American cohort studies, which reported a significantly increased relative risk (1.22; 95% CI: 1.03, 1.45) for consumption of 100 g/d, whereas categorical analyses suggested a reduced risk in women consuming <2 eggs/wk and an increased risk in women consuming ≥7 eggs/wk (both compared with nonconsumers) (22). The Nurses' Health Study also found a linear trend (P for trend = 0.08) toward increased breast cancer risk with high egg consumption, but only in premenopausal women (19). We found no relation of breast cancer with total milk intake, which agrees with the results of a pooled analysis of cohort studies (22) and the Nurses' Health Study (19). Analysis of milk subtypes did not provide any further insights.

Our finding that butter was only associated with increased breast cancer risk in premenopausal women is difficult to explain given the absence of a dose-response relation and lack of literature data on an effect of butter confined to young women. The possibility of a link with behavior suggests itself. However, we investigated this possibility by adjusting, in the models for education, smoking, and drinking. We also adjusted for physical activity (data not shown), which had no effect. High consumption of saturated fats is a recognized risk factor for several diseases, and, given the persistent campaigns against saturated fat consumption (59–61), it appears possible that young women who consume butter may pay less attention to their health than other women and this may have some connection with breast cancer.

A bias due to an influence of preclinical disease on diet is unlikely, because the results were essentially unchanged after the

TABLE 5
Multivariate hazard ratios (HRs) with 95% CIs for breast cancer in relation to intake of meat and dairy food groups by menopausal status[1]

		Postmenopausal (n = 135,529; cases = 3673)				Premenopausal (n = 114,812; cases = 1699)			
Food group and quintile[2]	Median intake (all women)	Population per quintile	Cases per quintile	HR (95% CI)	P for trend	Population per quintile	Cases per quintile	HR (95% CI)	P for trend
	g								
Red meat					0.22				0.42
1	1.4	22,766	622	1		29,313	343	1	
2	21.3	26,621	634	1.03 (0.92, 1.16)		23,851	306	0.99 (0.84, 1.17)	
3	36.0	27,970	693	1.03 (0.92, 1.15)		21,502	299	0.96 (0.81, 1.13)	
4	54.4	29,586	860	1.13 (1.01, 1.26)		19,869	341	0.98 (0.83, 1.15)	
5	84.6	28,586	864	1.05 (0.94, 1.18)		20,277	410	0.94 (0.80, 1.10)	
Poultry					0.29				0.83
1	0.0	25,390	742	1		26,236	292	1	
2	6.3	27,913	689	0.99 (0.88, 1.10)		22,103	299	1.01 (0.85, 1.19)	
3	14.8	28,388	760	1.05 (0.95, 1.17)		23,058	327	0.98 (0.83, 1.16)	
4	22.5	27,601	758	1.05 (0.94, 1.17)		20,351	383	1.07 (0.90, 1.26)	
5	46.1	26,237	724	1.05 (0.94, 1.17)		23,064	398	0.98 (0.83, 1.16)	
Processed meat					0.06				0.72
1	1.7	25,359	542	1		28,534	274	1	
2	11.0	29,971	846	1.08 (0.96, 1.20)		19,537	307	0.97 (0.81, 1.16)	
3	20.1	28,806	771	1.01 (0.90, 1.14)		20,116	368	1.07 (0.90, 1.28)	
4	32.3	26,625	776	1.09 (0.97, 1.23)		22,153	363	0.99 (0.82, 1.18)	
5	56.5	24,768	738	1.13 (1.00, 1.28)		24,472	387	0.99 (0.82, 1.19)	
Eggs[3]					0.39				0.83
1	2.0	26,490	620	1		26,142	300	1	
2	7.8	27,825	738	1.14 (1.02, 1.27)		23,536	293	0.99 (0.84, 1.17)	
3	14.3	27,322	706	1.05 (0.94, 1.17)		20,750	307	0.94 (0.79, 1.11)	
4	21.5	26,288	768	1.14 (1.02, 1.27)		23,820	380	0.98 (0.84, 1.16)	
5	36.1	27,604	841	1.08 (0.97, 1.21)		20,564	419	1.02 (0.87, 1.21)	
All types of milk					0.13				0.62
1	0.0	25,973	759	1		22,849	415	1	
2	35.6	27,922	717	1.02 (0.92, 1.14)		21,290	325	1.08 (0.93, 1.25)	
3	146.5	24,991	642	1.04 (0.94, 1.17)		25,118	347	1.04 (0.90, 1.21)	
4	273.4	28,231	747	1.01 (0.91, 1.13)		23,432	320	0.98 (0.84, 1.14)	
5	439.0	28,412	808	1.09 (0.98, 1.22)		22,123	292	1.00 (0.85, 1.18)	
Whole milk[4]					0.68				0.45
1	0.0	54,624	1673	1[5]		38,574	826	1[5]	
2	—	—	—	—		—	—	—	
3	1.5	19,511	496	0.99 (0.85, 1.14)		24,496	226	0.92 (0.75, 1.15)	
4	9.2	27,694	774	1.05 (0.92, 1.19)		16,820	217	1.01 (0.84, 1.22)	
5	150.0	24,005	581	1.03 (0.92, 1.16)		23,148	317	1.04 (0.89, 1.22)	
Semiskim milk[6]					0.62				0.60
1	0.0	48,032	1420	1[5]		44,335	734	1[5]	
2	—	—	—	—		—	—	—	
3	8.8	17,638	517	1.01 (0.90, 1.17)		6465	111	1.01 (0.81, 1.26)	
4	100.0	21,793	644	1.11 (0.89, 1.09)		16,422	294	1.11 (0.96, 1.28)	
5	292.5	21,700	653	1.03 (0.94, 1.14)		17,886	275	1.03 (0.89, 1.19)	
Skim milk[7]					0.42				0.21
1	0.0	66,455	2070	1[8]		152,319	3971	1[8]	
2	—	—	—	—		—	—	—	
3	—	—	—	—		—	—	—	
4	13.0	12,524	350	0.94 (0.81, 1.08)		26,686	623	1.05 (0.82, 1.35)	
5	210.0	20,384	564	0.96 (0.87, 1.05)		44,680	965	0.91 (0.77, 1.07)	
Cheese					0.17				0.82
1	5.71	27,016	672	1.00		24,617	298	1.00	
2	18.4	26,843	753	1.09 (0.99, 1.22)		24,320	301	1.01 (0.86, 1.19)	
3	30.5	27,513	738	1.01 (0.91, 1.13)		22,453	314	0.98 0.83, 1.16)	
4	47.8	27,980	791	1.03 (0.92, 1.15)		21,151	377	1.09 (0.92, 1.28)	
5	82.1	26,177	719	0.96 (0.86, 1.08)		22,271	409	0.97 (0.82, 1.15)	

(Continued)

TABLE 5 (*Continued*)

Food group and quintile[2]	Median intake (all women)	Postmenopausal (n = 135,529; cases = 3673) Population per quintile	Cases per quintile	HR (95% CI)	P for trend	Premenopausal (n = 114,812; cases = 1699) Population per quintile	Cases per quintile	HR (95% CI)	P for trend
	g								
Butter					0.68				0.21
1	0.0	47,145	1198	1		25,039	324	1	
2	0.1	12,638	265	1.00 (0.86, 1.17)		16,396	172	1.17 (0.95, 1.46)	
3	0.4	22,171	588	1.07 (0.95, 1.21)		27,157	364	1.25 (1.04, 1.50)	
4	2.9	26,537	796	1.06 (0.95, 1.19)		23,539	396	1.27 (1.06, 1.52)	
5	12.6	27,038	826	1.02 (0.91, 1.13)		22,681	443	1.28 (1.06, 1.53)	

[1] Models adjusted for energy, height, weight, years of schooling, alcohol intake, and smoking; stratified by center and age (1-y strata).
[2] Quintiles calculated for whole group.
[3] Data on eggs not available for Swedish cohort of Umeå.
[4] Data on whole milk not available for Norway.
[5] First + second quintiles combined because of the high number of zero consumers.
[6] Data on semiskim milk not available for Greece, Germany, and Norway.
[7] Data on skim milk not available for Greece, Germany, Norway, and the Italian cohorts of Varese, Florence, and Turin.
[8] First + second + third quintiles combined because of the high number of zero consumers.

exclusion of cases diagnosed early in follow-up (data not shown). Note that the molecular classifications of the diagnosed breast cancers were not available for our cases. Breast cancer is a heterogeneous disease, and dietary factors may differentially affect different breast cancer subtypes: recent studies suggest that environmental risk factors can influence the development of some types of breast cancer (defined, eg, by HER2, estrogen receptor, progesterone receptor, or p53 status) (62–66). There is some evidence that, in premenopausal women, high red meat intake may favor the development of estrogen and progesterone receptor-positive breast cancers, but not receptor-negative cancers (67). Future studies should therefore attempt to characterize associations according to tumor characteristics.

Although the EPIC FQs used in the various centers were similar, they necessarily differed in detail because each was designed to capture the eating habits of the local population. To compensate for errors generated by differences in the dietary assessment, we "corrected" the dietary intake data using more detailed dietary data assessed by the interviewer-led 24-HDR (40). We are also aware that the dietary information collected by FQs at baseline may not accurately reflect eating habits over time: early-life dietary exposure to animal foods (and animal food–related substances such as growth-promoting hormones used in animal farming) may be of particular importance in mammary carcinogenesis. A recent study found a significant association of meat intake between menarche and first pregnancy and premenopausal breast cancer risk (68). We have no information on the early-life eating habits of our EPIC cohort volunteers and speculate that the adult dietary behavior we have quantified has only a weak correlation with early life eating.

We conclude by emphasizing that this EPIC study was unable to consistently identify intake of meat, eggs, or dairy products as significant risk factors for breast cancer; nevertheless, the difficulties discussed above all militate toward a null result, so the lack of consistent association of consumption of animal products with breast cancer risk should be interpreted cautiously. The possible adverse effects on breast cancer risk suggested for processed meat and butter consumption were inconsistent among pre- and postmenopausal groups of women and showed no linear trend. Future studies should attempt to characterize associations between diet and the development of specific types of breast cancer and further investigate the importance of high-temperature cooking as a factor in the association between red meat intake and breast cancer risk.

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