RESEARCH

Dietary protein sources in early adulthood and breast cancer incidence: prospective cohort study

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Abstract

Objective To investigate the association between dietary protein sources in early adulthood and risk of breast cancer.

Design Prospective cohort study.

Setting Health professionals in the United States.

Participants 88 803 premenopausal women from the Nurses' Health Study II who completed a questionnaire on diet in 1991.

Main outcome measure Incident cases of invasive breast carcinoma, identified through self report and confirmed by pathology report.

Results We documented 2830 cases of breast cancer during 20 years of follow-up. Higher intake of total red meat was associated with an increased risk of breast cancer overall (relative risk 1.22, 95% confidence interval 1.06 to 1.40; P_{trend}=0.01, for highest fifth *v* lowest fifth of intake). However, higher intakes of poultry, fish, eggs, legumes, and nuts were not related to breast cancer overall. When the association was evaluated by menopausal status, higher intake of poultry was associated with a lower risk of breast cancer in postmenopausal women (0.73, 0.58 to 0.91; P_{trend}=0.02, for highest fifth *v* lowest fifth of intake) but not in premenopausal women (0.93, 0.78 to 1.11; P_{trend}=0.60, for highest fifth *v* lowest fifth of intake). In estimating the effects of exchanging different protein sources, substituting one serving/day of legumes for one serving/day of red meat was associated with a 15% lower risk of breast cancer among all women (0.85, 0.73 to 0.98) and a 19% lower risk among premenopausal women (0.81, 0.66 to 0.99). Also, substituting one serving/day of poultry for one serving/day of red meat was associated with a 17% lower risk of breast cancer overall (0.83, 0.72 to 0.96) and a 24% lower risk of postmenopausal breast cancer (0.76, 0.59 to 0.99). Furthermore, substituting one serving/day of combined legumes, nuts, poultry, and fish for one serving/day of red meat was associated with a 14% lower risk of breast cancer overall (0.86, 0.78 to 0.94) and premenopausal breast cancer (0.86, 0.76 to 0.98).

Conclusion Higher red meat intake in early adulthood may be a risk factor for breast cancer, and replacing red meat with a combination of legumes, poultry, nuts and fish may reduce the risk of breast cancer.

Introduction

The potential influence of dietary protein on risk of breast cancer has created considerable scientific attention.[1] High protein intake may affect the risk of breast cancer by increasing the insulin-like growth factor 1 that plays important roles in tissue growth and tumor progression.[1][2] However, foods that are major sources of protein differ widely in their nutrient profiles and may have different effects on breast cancer risk. The overall evidence from prospective cohort studies has suggested no significant association between red meat intake and breast cancer. A pooled analysis of eight cohort studies found a null association between intake of red meat and risk of breast cancer.[3] Also, a recent review and meta-analysis of prospective cohort studies[4] and a recent prospective study[5] did not show effects of red meat intake on breast cancer risk. However, most of the evidence has come from studies that evaluated diet during midlife and later. In the Nurses' Health Study II cohort, red meat intake during early adulthood was associated with an increased risk of breast cancer in premenopausal women.[6] Moreover, in most prospective studies, little relation has been seen between intakes of other protein rich foods such as fish, poultry, eggs, legumes, or nuts

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and risk of breast cancer, but data from early adult life are also limited.[7-11]

The exposures between menarche and first pregnancy may be more important in the development of breast cancer. Epidemiologic studies of women who survived the atomic bombing in Hiroshima and Nagasaki and radiation treatment for Hodgkin's lymphoma have shown that exposure to radiation in childhood and early adulthood was associated with subsequent risk of cancer, but radiation was less strongly related to risk of breast cancer among women older than 30 years at the time of exposure.[12-14]

Although breast tumors vary by estrogen and progesterone receptor status, most previous studies have evaluated the relation between dietary sources of protein and breast cancer, with limited information on how the cancers differed by hormone receptor status.[5 6] In an early analysis from the Nurses' Health Study II with 12 years of follow-up,[6] we reported a positive association between red meat intake and breast cancer in premenopausal women, especially tumors with positive hormone receptors. However, it was not clear whether the positive findings were due to early age at dietary assessment or the relatively young age of women at diagnosis of breast cancer. In this updated analysis with longer follow-up and approximately three times the number of cases of breast cancer, we investigated the association of total intakes of unprocessed and processed red meat before menopause with risk of breast cancer overall and separately among premenopausal and postmenopausal women. In addition we examined the associations between breast cancer and other protein rich foods, including poultry, fish, eggs, legumes, and nuts. Furthermore, we evaluated whether the association between red meat and breast cancer differs by hormone receptor status.

Methods

Study population

The Nurses' Health Study II began in 1989 and is a prospective cohort study of 116 430 female registered nurses who were 24 to 43 years of age. In 1991, participants were asked to complete a food frequency questionnaire about usual dietary intake in the past year. A total of 97 813 women answered the questionnaire. We excluded those who had an implausible daily energy intake (<2508 or ≥14630 kJ) or left more than 70 food items blank on the food frequency questionnaire. Of the remaining 95 452, we excluded women who were postmenopausal in 1991. Participants were also excluded if they had a diagnosis of any cancer except non-melanoma skin cancer, diabetes, coronary heart disease, or stroke before returning the 1991 questionnaire, or had missing data on age or red meat intake. We included 88 803 women in the analysis. The cumulative response rate among living participants was 95%.

Dietary assessment

Participants completed a semi-quantitative food frequency questionnaire with approximately 130 items in 1991, 1995, 1999, 2003, and 2007 about usual dietary intake and alcohol consumption during the past year (available at www.channing. harvard.edu/nhs/?page_id=246). Total red meat items listed on the food frequency questionnaire included unprocessed red meat (beef, pork, or lamb as a sandwich, pork as a main dish, beef or lamb as a main dish, and hamburger) and processed red meat (hot dogs, bacon, and other processed meat such as sausage, salami, bologna); poultry included chicken and turkey; fish included tuna, dark meat fish (for example, mackerel, salmon, sardines, bluefish, swordfish), and other fish; legumes included

tofu or soybeans, string beans, beans, or lentils, and peas or lima beans; and nuts included peanut, peanut butter, and other nuts. Responses were given for commonly used portion sizes and nine categories of intake frequency ranging from "never or less than once per month" to "six or more per day."

Food intake during adolescence was measured in 1998 using a 124 item food frequency questionnaire, which was specifically designed to contain foods that were usually consumed during the periods from 1960 to 1980 when these women would have been in high school. Food items included in the food frequency questionnaire for adolescents and response categories were similar to those in the food frequency questionnaire for adults.

We calculated nutrient intakes by multiplying the frequency of consumption of each item by the nutrient content of the specified portions and then summing across all items. Nutrient values in foods were obtained from the US Department of Agriculture, food manufacturers, independent academic sources, and our own fatty acid analyses of commonly used margarines, cooking oils, and baked foods.[15-17] Every four years, the food composition database was updated to account for changes in the food supply. We calculated the percentage of energy from total fat by dividing energy intake from total fat by total energy intake. Using the residuals from the regression of nutrient intake on total energy intake, we adjusted total iron and heme iron for energy.[18 19] We did not adjust food intakes for total energy intake, as the correlation between individual foods and total energy intake was low.

The reproducibility and validity of food frequency questionnaires for measuring individual red meat items have been evaluated in 173 women from the Nurses' Health Study. The correlation coefficients for intake of individual red meat items comparing diet records with the food frequency questionnaire were mostly higher than 0.5 after correction for attenuation because of within person variation in diet records.[20]

Documentation of breast cancer

We identified new cases of breast cancers from biennial questionnaires. Then we got permission from women with breast cancer or next of kin for those who had died to review hospital records and pathology reports. Deaths in this cohort were reported through family members and the postal service in response to the follow-up questionnaires or identified through annual review of the national death index. Medical records were obtained for 88% of cases in the Nurses' Health Study II included in this analysis. More than 98% of self reported breast cancers were confirmed through review of pathology reports. Therefore we included self reported cases with missing pathology reports in the analysis. We excluded cases of carcinoma in situ from the analyses. To determine the estrogen and progesterone receptor status of the breast cancer we abstracted information from pathology reports.

Assessment of other variables

From the biennial Nurses' Health Study II questionnaires we collected information on risk factors for breast cancer, including age, height, weight, family history of breast cancer, history of benign breast disease, smoking, race, age at menarche, parity, age at first birth, menopausal status, postmenopausal hormone use, age at menopause, and oral contraceptive use. All variables except race, height, and age at menarche were updated to the most recent information before date of diagnosis, whenever available. We considered women to be premenopausal if they still had menstrual periods or had hysterectomy with at least one ovary remaining and were younger than 46 years for

smokers or younger than 48 years for non-smokers. Women were considered as postmenopausal if they reported permanent cessation of menstrual periods or had undergone bilateral oophorectomy. We defined women of unknown menopausal status or who had hysterectomy without bilateral oophorectomy as postmenopausal if they were 54 years or older for smokers or 56 years or older for non-smokers.[21]

Statistical analysis

We calculated person years from the return date of the 1991 questionnaire until the date of breast cancer diagnosis, death, or end of follow-up (1 June 2011), whichever came first. We used the dietary intake in 1991 in the primary analysis as this represents the dietary intake in early adulthood. Women were divided into five categories according to food group or nutrient intake. We used Cox proportional hazards models, stratified by age in months and questionnaire year, to estimate relative risk and 95% confidence intervals. Multivariable models adjusted for race, family history of breast cancer in mother or sisters, history of benign breast disease, smoking, height, body mass index, age at menarche, parity, age at first birth, oral contraceptive use, and alcohol and energy intakes, and, for postmenopausal women, age at menopause and hormone use. For all women, we additionally adjusted for menopausal status. We replaced missing covariate data, which comprised 5.5% of total person years for oral contraceptive use and less than 5% of total person years for body mass index, smoking, height, age at menarche, age at menopause, parity, and age at first birth, with the carried forward method for continuous variables and missing indicator method for categorical variables.

To best represent long term effects of food intake on breast carcinogenesis and to minimize measurement error caused by within person variation, we calculated premenopausal cumulative averaged intakes of food groups using the 1991, 1995, 1999, 2003, and 2007 dietary data for a sensitivity analysis. To evaluate the effects of diet during the premenopausal period on risk of breast cancer, we stopped updating the dietary data when the participants reported change in menopausal status. We used the median value of each variable in each fifth as a continuous variable for tests for trend. We estimated the effect of substituting one serving/day of poultry, fish, legumes, eggs, or nuts for one serving/day of total red meat by including simultaneously these food items as well as low fat dairy products and high fat dairy products as continuous variables in the multivariable model. The relative risk and the 95% confidence intervals for the substitution effect were derived from the difference between the regression coefficients, variances, and covariance.[22] We examined effect modification for the association between red meat and breast cancer risk by other measures of breast cancer risk factors. A cross product interaction term between each factor and intake of red meat expressed as a continuous variable was included in the multivariable model. We used a likelihood ratio test with one degree of freedom to derive P values for tests for interactions. We also tested the differential association between total red meat intake and breast cancer risk by estrogen and progesterone receptor status using Cox proportional cause specific hazards regression model with a duplication method for competing risk data. This method permits the estimation of separate associations of red meat with each of positive estrogen and progesterone receptors and negative estrogen and progesterone receptors, and has been used to assess whether red meat intake has statistically different regression coefficients for different tumor subtype. We used SAS version 9.3 (SAS Institute, Cary, NC) for all analyses. All P values are two sided.

Results

During 1 725 419 person years of follow-up of 88 803 premenopausal women, 2830 cases of invasive breast carcinoma were documented (1511 premenopausal breast cancer, 918 postmenopausal breast cancer, and 401 uncertain menopausal status) between 1991 and 2011. The average age of the participants in 1991 was 36.4 (SD 4.6) years (range 26-45 years) and the average age of breast cancer diagnosis was 45 years in premenopausal women (range 27-60 years) and 55 years in postmenopausal women (range 39-64 years). Table 1⇓ shows the age adjusted distribution of breast cancer risk factors according to fifths of total red meat intake. Compared with women who consumed a lower amount of red meat, women with a higher intake were more likely to have a larger body mass index, to have higher energy intake, to smoke, and to have three or more children as well as less likely to use oral contraceptives and to have a history of benign breast disease.

Among all women, higher total red meat intake in 1991 was associated with an increased risk of breast cancer in multivariable analysis (relative risk 1.22, 95% confidence interval 1.06 to 1.40; P_{trend}=0.01, for highest fifth *v* lowest fifth) (table 2⇓). Similar point estimates were observed among premenopausal and postmenopausal women, separately, though they did not reach statistical significance. Among all women, the positive association between total red meat was still significant after additional adjustment for total fat intake (for highest *v* lowest fifth: relative risk 1.20, 1.03 to 1.40; P_{trend}=0.04), fruits and vegetables intake (for highest *v* lowest fifth: 1.19, 1.04 to 1.37, P_{trend}=0.03), or heme iron (for highest *v* lowest fifth: 1.21, 1.04 to 1.41; P_{trend}=0.03). We also controlled for the frequency of having fried foods at home and away from home, but the results were not appreciably altered (data not shown). When total red meat intake was modeled as a continuous variable, each additional serving/day increase in total red meat was associated with a 13% increase in risk of breast cancer among all women (relative risk 1.13, 1.04 to 1.22), 12% increase among premenopausal women (1.12, 1.01 to 1.25), and 8% increase among postmenopausal women (1.08, 0.94 to 1.23). Additional adjustment for red meat intake during adolescence did not appreciably attenuate the relative risk. Among women with dietary data for both adulthood and adolescence (n=40 644), the relative risk for one serving/day of total red meat intake during adulthood was 1.20 (1.07 to 1.34) for breast cancer overall and 1.24 (1.07 to 1.44) for premenopausal breast cancer. After additional adjustment for red meat intake during adolescence, the relative risk was 1.18 (1.06 to 1.33) for breast cancer overall and 1.20 (1.03 to 1.40) for premenopausal breast cancer. In a sensitivity analysis using the cumulative average of premenopausal intake, similar results have been found (for each additional serving/day: relative risk among all women 1.12, 1.03 to 1.22 and among premenopausal women 1.15, 1.02 to 1.29).

Poultry intake in 1991 was associated with a lower risk of postmenopausal breast cancer (highest *v* lowest fifth: relative risk 0.73, 0.58 to 0.91; P_{trend}=0.02) (table 2⇓), and the estimate was unchanged with adjustment for fat or fruits and vegetables intakes (data not shown). Also, cumulative average of premenopausal intake of poultry was associated with a lower risk of postmenopausal breast cancer: each additional serving/day of poultry was associated with a 25% lower risk of postmenopausal breast cancer (relative risk 0.75, 0.58 to 0.98). Neither baseline intakes of poultry, nor the cumulative average of premenopausal poultry intakes, were associated with premenopausal risk of breast cancer. Intakes of legumes, fish, eggs, and nuts were not associated with either premenopausal

or postmenopausal breast cancer (tables 2 and 3⇓). In age adjusted and multivariable adjusted models, none of the tests for trend were significant across fifths of total iron and heme iron intakes in early adulthood and breast cancer incidence in either premenopausal or postmenopausal women (see supplementary table S1).

Based on diet in 1991, substituting one serving/day of legumes for one serving/day of total red meat was associated with a lower risk of breast cancer among all women (relative risk 0.85, 0.73 to 0.98) and among premenopausal women (0.81, 0.66 to 0.99; figure⇓). Replacement of one serving/day of total red meat with one serving/day of poultry was associated with a lower risk of breast cancer in all women (0.83, 0.72 to 0.96) and postmenopausal women (0.76, 0.59 to 0.99). Furthermore, substituting one serving/day of combined legumes, nuts, poultry, and fish for one serving/day of red meat was associated with a 14% lower risk of breast cancer overall (0.86, 0.78 to 0.94) and a 14% lower risk of premenopausal breast cancer (0.86, 0.76 to 0.98, figure).

We had information on estrogen receptor status for 81% (n=2306) of breast cancers and progesterone receptor status for 80% (n=2275) of breast cancers. Supplementary table S2 presents the associations between total red meat intake and breast cancer risk according to hormone receptor status; data are presented for both tumors with positive estrogen and progesterone receptors and tumors with negative estrogen and progesterone receptors. We did not observe significant heterogeneity between total red meat intake and tumor status in either premenopausal or postmenopausal breast cancer (see supplementary table S2).

We also examined whether the association between intake of red meat and breast cancer risk differed by levels of risk factors for breast cancer, including family history of breast cancer, body mass index, oral contraceptive use, smoking, history of benign breast disease, alcohol intake, postmenopausal hormone use, age at first birth, and parity. The association between red meat intake and breast cancer risk was modified by oral contraceptives. For each serving/day of total red meat, the risk of breast cancer was 54% higher among women who currently used oral contraceptives (relative risk 1.54, 1.13 to 2.08) and 11% higher in women who were former users (1.11, 1.02 to 1.22), with no association in non-users (1.04, 0.84 to 1.28) (P for interaction=0.007); the interaction was also significant among premenopausal women (P for interaction=0.009).

Discussion

We found that higher consumption of red meat in women during early adulthood was associated with a higher risk of breast cancer. Adjusting for animal fat, fruits and vegetables, and heme iron did not appreciably change the association between red meat intake and breast cancer risk. Moreover, poultry intake was associated with a lower risk of breast cancer in postmenopausal women. Although intakes of legumes, fish, eggs, and nuts were not significantly associated with breast cancer in either premenopausal or postmenopausal women, substituting legumes or poultry or the combination of poultry, fish, legumes, and nuts for red meat was associated with a lower risk of breast cancer. In addition, higher intakes of total iron or heme iron were not associated with risk of breast cancer.

Results in relation to other studies

The evidence from prospective studies concerning a role of red meat intake during adulthood in risk of breast cancer is not consistent.[3 5 7 8] A recent review and meta-analysis of prospective

studies on consumption of unprocessed and processed red meat and breast cancer incidence found that the intake of the red meat was not independently associated with increasing breast cancer risk.[4] However, most of the results have been derived from diet during midlife and later, and red meat intake during early adulthood may be more related to an increased risk of breast cancer. Carcinogenic byproducts such as heterocyclic amines and polycyclic aromatic hydrocarbons, created during high temperature cooking of meat; animal fat and heme iron from red meat; and hormone residues of the exogenous hormones for growth stimulation in beef cattle are some of the mechanisms that may explain the positive association between high intake of red meat and risk of breast cancer.[23-28] We had only limited information on cooking methods of red meat. Controlling for the frequency of fried foods at home and away from home in this analysis did not alter the results. Furthermore, our findings persisted after adjustment for heme iron or total fat, thus reducing the possibility that they were due to higher intake of heme iron and fat.

We found that the risk of breast cancer was lower in women who replaced red meat with legumes in early adulthood. Legumes contain several components such as fiber and phytoestrogen, which have been negatively associated with breast cancer incidence.[29 30] The anticarcinogenic effects of beans have been shown in animal models.[31] An intervention study reported that substituting a diet high in vegetable fat and protein for a diet high in animal fat and protein could reduce the circulating estrogen levels by more than 40%.[32] Reduction in insulin, insulin-like growth factor, and inflammatory biomarkers, or alterations in lipid metabolism are mechanisms that could explain the inverse association between legumes and risk of breast cancer.[33]

We did not detect any association between breast cancer in premenopausal women and poultry intake. However, this association was significant for breast cancer in postmenopausal women. Intake of poultry was not associated with a lower risk of breast cancer in some other prospective studies.[3 5 11] Poultry contains higher amounts of polyunsaturated fat than does red meat, and processing and cooking methods for poultry likely differ from that of red meat. Similar to the findings from recent meta-analysis of 11 prospective cohort studies with over 13 000 breast cancer events and over 687 000 participants,[34] we did not observe a clear association with fish intake. The results of the Singapore Chinese Health Study indicated that high consumption of fish (mean intake ≥58.3 g/day) has been inversely associated with breast cancer in postmenopausal women; this intake was higher than in our study.[10]

A non-linear association between egg intake and breast cancer risk has been found in the European Prospective Investigation into Cancer and Nutrition cohort.[8] Although egg consumption has been associated with a borderline linear trend toward increased risk of breast cancer in premenopausal women in the Nurses' Health Study,[7] we found no evidence that intake of eggs in early adulthood was associated with breast cancers in premenopausal or postmenopausal women in the current analysis. The inconsistencies among the cohort study results may be due to chance or differences in the consumption level. The median intake of eggs in the highest fourth in our study population was 0.43 eggs per day, smaller than the two eggs per day that have been significantly associated with a higher risk of breast cancer in a pooled analysis of eight cohort studies.[3]

Limitations and strengths of this study

Potential limitations need to be considered. Because the participants were predominantly white, educated US adults, we cannot determine whether our findings are generalizable to other race or ethnic groups; however, race/ethnic specific risk factors for breast cancer have not been documented. Because dietary intake was assessed by food frequency questionnaires, some degree of measurement error is inevitably present, and thus to reduce measurement error we used the cumulative average of multiple measurements in a sensitivity analysis.

Residual confounders are always of concern in any observational studies. Although we adjusted for a wide range of potential confounders for breast cancer, we still could not rule out the possibility that other unmeasured or inadequately measured factors have confounded the true association. We indirectly estimated the effects of substitution of legumes, poultry, and other protein sources for red meat on risk of breast cancer. Although trials on dietary modification would be ideal to support these substitutions, trials with sufficiently large sample sizes, long follow-up, and adequate compliance are not feasible. In addition, we made multiple comparisons (different food groups and nutrients, premenopausal and postmenopausal subgroups, and subtype of tumors) in this analysis, and we cannot exclude the possibility of type I errors. However, the central finding of an association with red meat was a prior hypothesis.

The strengths of this study include the large number of cases, length of follow-up, and ability to examine subtypes of breast cancers. The detailed prospective and updated assessments of diet and lifestyle factors allowed adjustment for many potential confounders. Recall bias would not be present because the study was strictly prospective and dietary assessment was conducted on all participants before the diagnosis of breast cancer.

Conclusions

This analysis supports an association between higher consumption of total red meat during early adulthood and increased risk of breast cancer that was not clearly restricted to breast cancers in premenopausal women. Although the association was not significant in postmenopausal women alone, this may be due to lower statistical power in that group so we are not able to say with confidence that there is no association. In the current study, each serving per day increase in red meat was associated with a 13% increase in risk of breast cancer. When this relatively small relative risk is applied to breast cancer, which has a high lifetime incidence, the absolute number of excess cases attributable to red meat intake would be substantial, and hence a public health concern. Moreover, higher consumption of poultry was related to a lower incidence of breast cancer in postmenopausal women. Consistent with the American Cancer Society guidelines,[35] replacement of unprocessed and processed red meat with legumes and poultry during early adulthood may help to decrease the risk of breast cancer. Further study of the relation between diet in early adulthood and risk of breast cancer is needed.

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What is already known on this topic

Foods that are major sources of animal or vegetable proteins are not consistently associated with risk of breast cancer

Most of the evidence has been based on diet during midlife and later, and many lines of evidence suggest that some exposures, potentially including dietary factors, may have greater effects on breast carcinogenesis during early adulthood

What this study adds

Higher consumption of total red meat during early adulthood was associated with an increased risk of breast cancer

Higher consumption of poultry during early adulthood was related to a lower incidence of breast cancer in postmenopausal women

Substituting a combination of poultry, fish, legumes, and nuts as protein sources for red meat during early life seems beneficial for the prevention of breast cancer

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Tables

Table 1| Age standardized distribution of potential risk factors for breast cancer according to fifths of total red meat intake in 1991 among women enrolled in the Nurses' Health Study II

Potential risk factors	Total red meat intake fifth				
	Lowest fifth (n=15 763)	2nd fifth (n=21 366)	3rd fifth (n=15 929)	4th fifth (n=18 196)	Highest fifth (n=17 549)
Mean (SD) age (years)	36.6 (4.7)	36.5 (4.6)	36.5 (4.6)	36.4 (4.6)	36.2 (4.6)
Mean (SD) total red meat intake (serving/day)	0.2 (0.1)	0.5 (0.1)	0.7 (0.1)	1.0 (0.1)	1.6 (0.5)
Mean (SD) body mass index (weight (kg)/(height (m)^2)	23.3 (4.4)	24.2 (4.8)	24.5 (5.1)	24.9 (5.4)	25.7 (6.0)
Mean (SD) total energy intake (kJ)	6266 (2057)	6688 (1960)	7265 (1977)	7963 (1998)	9271 (2186)
Mean (SD) alcohol consumption (g/day)	3.2 (5.7)	3.2 (6.0)	3.1 (6.1)	3.1 (6.1)	3.0 (6.4)
Mean (SD) age at first birth (years)	26.4 (4.6)	26.1 (4.2)	25.9 (4.1)	25.7 (4.0)	25.4 (4.0)
Current smokers (%)	9	11	12	13	15
Current oral contraceptive use (%)	12	12	11	10	10
History of benign breast disease (%)	35	33	34	32	31
Family history of breast cancer in mother or sisters (%)	16	15	15	15	15
Parity ≥3 (%)	12	19	22	24	26
Age at menarche <12 (%)	25	24	24	24	25

Table 2| Relative risk for breast cancer according to fifths of dietary sources of animal protein in 1991 among women in the Nurses' Health Study II. Values are relative risks (95% confidence intervals) unless stated otherwise

Variables	Fifths of intake					P_{trend}*	Per 1 serving/day
	Lowest fifth	2nd fifth	3rd fifth	4th fifth	Highest fifth		
Total red meat (unprocessed and processed)							
All women:							
Median intake (serving/day)	0.14	0.49	0.70	0.99	1.50		—
No of cases/person years	493/306 298	698/414 838	522/309 562	564/353 554	553/341 169		—
Age adjusted model	1	1.07 (0.95 to 1.20)	1.07 (0.94 to 1.21)	1.02 (0.90 to 1.15)	1.05 (0.93 to 1.19)	0.70	1.02 (0.95 to 1.09)
Multivariable model	1	1.10 (0.98 to 1.24)	1.12 (0.99 to 1.28)	1.10 (0.97 to 1.25)	1.22 (1.06 to 1.40)	0.01	1.13 (1.04 to 1.22)
Premenopausal women:							
Median intake (serving/day)	0.14	0.49	0.70	0.99	1.50		—
No of cases/person years	275/188 826	361/259 112	285/193 578	297/220 096	293/213 370		—
Age adjusted model	1	0.97 (0.83 to 1.13)	1.03 (0.87 to 1.22)	0.95 (0.81 to 1.12)	0.99 (0.84 to 1.16)	0.85	1.03 (0.94 to 1.13)
Multivariable model	1	1.02 (0.87 to 1.19)	1.11 (0.94 to 1.32)	1.05 (0.88 to 1.25)	1.12 (0.93 to 1.35)	0.22	1.12 (1.01 to 1.25)
Postmenopausal women:							
Median intake (serving/day)	0.14	0.43	0.70	0.99	1.50		—
No of cases/person years	151/76 506	226/103 319	180/77 658	184/86 274	177/86 591		—
Age adjusted model	1	1.16 (0.94 to 1.43)	1.23 (0.99 to 1.53)	1.14 (0.92 to 1.42)	1.12 (0.90 to 1.39)	0.55	1.01 (0.90 to 1.14)
Multivariable model	1	1.18 (0.96 to 1.46)	1.26 (1.00 to 1.57)	1.19 (0.95 to 1.50)	1.23 (0.96 to 1.57)	0.18	1.08 (0.94 to 1.23)
Poultry (chicken and turkey)							
All women:							
Median intake (serving/day)	0.14	0.21	0.43	0.57	0.86		—
No of cases/person years	461/276 836	694/418 805	661/409 599	466/269 434	544/348 154		—
Age adjusted model	1	1.00 (0.89 to 1.13)	0.97 (0.86 to 1.10)	1.05 (0.92 to 1.19)	0.94 (0.82 to 1.06)	0.33	0.91 (0.81 to 1.02)
Multivariable model	1	0.98 (0.87 to 1.11)	0.94 (0.83 to 1.06)	1.02 (0.89 to 1.16)	0.91 (0.80 to 1.03)	0.19	0.89 (0.79 to 1.01)
Premenopausal women:							
Median intake (serving/day)	0.14	0.21	0.43	0.57	0.86		—
No of cases/person years	241/170 019	365/262 730	355/257 204	247/169 033	301/214 330		—
Age adjusted model	1	0.97 (0.83 to 1.15)	0.96 (0.82 to 1.13)	1.02 (0.85 to 1.22)	0.96 (0.81 to 1.14)	0.83	0.94 (0.80 to 1.11)
Multivariable model	1	0.96 (0.81 to 1.13)	0.94 (0.79 to 1.11)	1.00 (0.83 to 1.20)	0.93 (0.78 to 1.11)	0.60	0.92 (0.77 to 1.09)
Postmenopausal women:							
Median intake (serving/day)	0.14	0.21	0.43	0.57	0.86		—
No of cases/person years	167/71 035	225/104 588	210/101 267	156/65 822	159/87 041		—
Age adjusted model	1	0.94 (0.77 to 1.15)	0.90 (0.73 to 1.10)	1.04 (0.83 to 1.29)	0.78 (0.63 to 0.98)	0.07	0.85 (0.69 to 1.04)
Multivariable model	1	0.90 (0.73 to 1.11)	0.85 (0.69 to 1.05)	0.96 (0.76 to 1.20)	0.73 (0.58 to 0.91)	0.02	0.79 (0.63 to 0.99)
Fish							
All women:							
Median intake (serving/day)	0.07	0.14	0.21	0.28	0.50		—
No of cases/person years	718/457 537	658/408 919	549/307 666	302/185 186	602/365 424		—
Age adjusted model	1	1.02 (0.91 to 1.13)	1.12 (1.00 to 1.25)	1.00 (0.87 to 1.14)	1.01 (0.90 to 1.12)	0.91	0.91 (0.77 to 1.07)
Multivariable model	1	1.00 (0.90 to 1.11)	1.08 (0.97 to 1.21)	0.96 (0.83 to 1.10)	0.98 (0.88 to 1.10)	0.60	0.88 (0.74 to 1.05)
Premenopausal women:							
Median intake (serving/day)	0.07	0.14	0.21	0.28	0.50		—
No of cases/person years	378/285 514	347/256 333	271/181 730	192/127 014	323/223 997		—
Age adjusted model	1	1.01 (0.87 to 1.17)	1.15 (0.98 to 1.35)	1.01 (0.84 to 1.20)	1.04 (0.90 to 1.21)	0.64	0.98 (0.78 to 1.24)
Multivariable model	1	0.99 (0.85 to 1.15)	1.11 (0.95 to 1.30)	0.96 (0.81 to 1.15)	0.99 (0.85 to 1.16)	0.86	0.92 (0.72 to 1.17)
Postmenopausal women:							
Median intake (serving/day)	0.07	0.14	0.21	0.28	0.57		—
No of cases/person years	232/111 313	211/99 858	173/75 817	120/60 674	181/82 487		—
Age adjusted model	1	1.01 (0.84 to 1.22)	1.09 (0.89 to 1.32)	0.91 (0.73 to 1.14)	1.03 (0.85 to 1.25)	0.88	0.89 (0.67 to 1.19)

Table 2 (continued)

Variables	Fifths of intake					P_{trend}*	Per 1 serving/day
	Lowest fifth	2nd fifth	3rd fifth	4th fifth	Highest fifth		
Multivariable model	1	1.01 (0.83 to 1.22)	1.07 (0.87 to 1.30)	0.89 (0.71 to 1.12)	1.02 (0.84 to 1.25)	0.93	0.88 (0.65 to 1.19)
Eggs†							
All women:							
Median intake (serving/day)	0	0.07	0.14	0.43	—		—
No of cases/person years	411/250 596	934/565 114	793/480 134	688/426 985	—		—
Age adjusted model	1	1.02 (0.91 to 1.15)	1.02 (0.91 to 1.15)	0.98 (0.86 to 1.10)	—	0.40	0.93 (0.78 to 1.12)
Multivariable model	1	1.04 (0.92 to 1.17)	1.04 (0.92 to 1.17)	1.01 (0.89 to 1.15)	—	0.76	0.99 (0.82 to 1.20)
Premenopausal women:							
Median intake (serving/day)	0	0.07	0.14	0.43	—		—
No of cases/person years	203/154 272	488/351 848	442/303 565	376/263 631	—		—
Age adjusted model	1	1.07 (0.91 to 1.27)	1.12 (0.94 to 1.32)	1.07 (0.90 to 1.27)	—	0.80	1.02 (0.79 to 1.31)
Multivariable model	1	1.09 (0.92 to 1.28)	1.15 (0.97 to 1.36)	1.11 (0.93 to 1.33)	—	0.53	1.07 (0.82 to 1.39)
Postmenopausal women:							
Median intake (serving/day)	0	0.07	0.14	0.43	—		—
No of cases/person years	141/63 327	297/138 500	247/117 197	232/110 728	—		—
Age adjusted model	1	1.00 (0.81 to 1.22)	0.98 (0.80 to 1.21)	0.95 (0.77 to 1.18)	—	0.60	0.95 (0.70 to 1.30)
Multivariable model	1	1.00 (0.82 to 1.23)	0.99 (0.80 to 1.22)	0.97 (0.78 to 1.21)	—	0.71	1.00 (0.72 to 1.38)

Multivariable model was stratified by age in months at start of follow-up and calendar year of current questionnaire cycle and was simultaneously adjusted for race (white, non-white), family history of breast cancer in mother or sisters (yes, no), history of benign breast disease (yes, no), smoking (never, former, current 1-14/day, current 15-24/day, current ≥25/day), height (<157.5, 157.5 to <165, 165 to <173, ≥173 cm), body mass index (<18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, 30 to <35.0, ≥35.0 kg/m²), age at menarche (<12, 12, 13, ≥14 years), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity ≤2 and age at first birth 25 to <30 years, parity ≤2 and age at first birth ≥30 years, parity 3-4 and age at first birth <25 years, parity 3-4 and age at first birth 25 to <30 years, parity 3-4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), oral contraceptive use (never, former, current), alcohol intake (non-drinker, <5, 5 to <15, ≥15 g/day), and energy (fifth). In postmenopausal women, we additionally adjusted for postmenopausal hormone use (never users, former users, current users), and age at menopause (<45 years, 45-46 years, 47-48, 49-50 years, 51-52 years, ≥53 years). Among all women, we additionally adjusted for hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal former users, postmenopausal current users, unknown menopausal status), and age at menopause (premenopausal, unknown menopause, <45 years, 45-46 years, 47-48, 49-50 years, 51-52 years, ≥53 years).

*Calculated with median intake of each variable in each fifth as a continuous variable.

†Fourth of intake.

Table 3| Relative risk for breast cancer according to fifths of legumes and nuts intakes in 1991 among women in the Nurses' Health Study II. Values are relative risks (95% confidence intervals) unless stated otherwise

Variables	Fifth of intake					P_{trend}*	Per 1 serving/day
	Lowest fifth	2nd fifth	3rd fifth	4th fifth	Highest fifth		
Legumes							
All women:							
Median intake (serving/day)	0.07	0.21	0.28	0.42	0.86		—
No of cases/person years	377/229 805	823/500 473	393/236 579	728/441 572	509/316 117		—
Age adjusted model	1	0.95 (0.84 to 1.07)	0.95 (0.82 to 1.09)	0.93 (0.82 to 1.06)	0.91 (0.79 to 1.04)	0.20	0.92 (0.81 to 1.03)
Multivariable model	1	0.93 (0.82 to 1.05)	0.93 (0.80 to 1.07)	0.92 (0.81 to 1.05)	0.90 (0.78 to 1.03)	0.23	0.92 (0.81 to 1.04)
Premenopausal women:							
Median intake (serving/day)	0.07	0.21	0.28	0.42	0.86		—
No of cases/person years	211/145 459	431/311 721	206/147 834	401/274 519	262/194 856		—
Age adjusted model	1	0.89 (0.76 to 1.05)	0.88 (0.72 to 1.07)	0.93 (0.79 to 1.10)	0.85 (0.71 to 1.02)	0.24	0.89 (0.76 to 1.05)
Multivariable model	1	0.88 (0.75 to 1.04)	0.86 (0.71 to 1.05)	0.92 (0.78 to 1.10)	0.84 (0.69 to 1.01)	0.21	0.88 (0.74 to 1.05)
Postmenopausal women:							
Median intake (serving/day)	0.14	0.21	0.28	0.50	0.86		—
No of cases/person years	227/111 566	150/65 134	219/97 890	151/74 726	171/80 881		—
Age adjusted model	1	1.12 (0.91 to 1.38)	1.08 (0.90 to 1.31)	0.99 (0.81 to 1.22)	1.04 (0.85 to 1.26)	0.83	0.99 (0.81 to 1.20)
Multivariable model	1	1.10 (0.89 to 1.36)	1.08 (0.90 to 1.31)	0.99 (0.80 to 1.22)	1.03 (0.83 to 1.27)	0.79	0.99 (0.80 to 1.21)
Nuts							
All women:							
Median intake (serving/day)	0	0.07	0.14	0.21	0.57		—
No of cases/person years	595/351 150	615/356 802	528/333 529	463/279 569	629/404 370		—
Age adjusted model	1	1.04 (0.93 to 1.16)	0.96 (0.86 to 1.08)	0.99 (0.87 to 1.11)	0.96 (0.86 to 1.07)	0.28	0.99 (0.89 to 1.10)
Multivariable model	1	1.03 (0.92 to 1.15)	0.94 (0.83 to 1.06)	0.96 (0.85 to 1.09)	0.94 (0.83 to 1.05)	0.18	0.98 (0.88 to 1.10)
Premenopausal women:							
Median intake (serving/day)	0	0.07	0.14	0.21	0.57		—
No of cases/person years	298/210 559	337/222 317	286/209 546	275/200 752	315/231 808		—
Age adjusted model	1	1.09 (0.93 to 1.27)	0.98 (0.83 to 1.15)	0.92 (0.78 to 1.09)	1.03 (0.88 to 1.21)	1.00	1.00 (0.86 to 1.15)
Multivariable model	1	1.09 (0.93 to 1.28)	0.97 (0.82 to 1.14)	0.90 (0.76 to 1.07)	1.01 (0.85 to 1.20)	0.85	0.98 (0.84 to 1.14)
Postmenopausal women:							
Median intake (serving/day)	0	0.07	0.14	0.21	0.57		—
No of cases/person years	192/92 373	198/89 088	167/81 865	155/70 959	206/96 063		—
Age adjusted model	1	1.09 (0.89 to 1.33)	1.00 (0.81 to 1.23)	1.06 (0.86 to 1.32)	1.06 (0.87 to 1.30)	0.67	1.12 (0.94 to 1.32)
Multivariable model	1	1.08 (0.88 to 1.32)	0.98 (0.79 to 1.21)	1.05 (0.84 to 1.30)	1.05 (0.85 to 1.29)	0.76	1.12 (0.94 to 1.33)

Multivariable model was stratified by age in months at start of follow-up and calendar year of current questionnaire cycle and was simultaneously adjusted for race (white, non-white), family history of breast cancer in mother or sisters (yes, no), history of benign breast disease (yes, no), smoking (never, former, current 1-14/day, current 15-24/day, current ≥25/day), height (<157.5, 157.5 to <165, 165 to <173, ≥173 cm), body mass index (<18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, 30 to <35.0, ≥35.0 kg/m²), age at menarche (<12, 12, 13, ≥14 years), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity ≤2 and age at first birth 25 to <30 years, parity ≤2 and age at first birth ≥30 years, parity 3-4 and age at first birth <25 years, parity 3-4 and age at first birth 25 to <30 years, parity 3-4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), oral contraceptive use (never, former, current), alcohol intake (non-drinker, <5, 5 to <15, ≥15 g/day), and energy (fifth). In postmenopausal women, we additionally adjusted for postmenopausal hormone use (never users, former users, current users) and age at menopause (<45 years, 45-46 years, 47-48, 49-50 years, 51-52 years, ≥53 years). Among all women, we additionally adjusted for hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal former users, postmenopausal current users, unknown menopausal status), and age at menopause (premenopausal, unknown menopause, <45 years, 45-46 years, 47-48, 49-50 years, 51-52 years, ≥53 years).

*Calculated with median intake of each variable in each fifth as continuous variable.

Figure
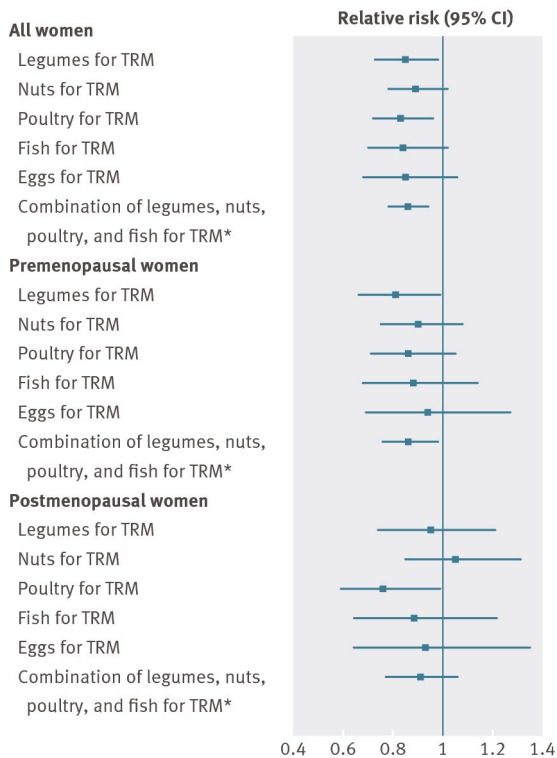
Multivariable relative risk and 95% confidence intervals for breast cancer associated with substitution of dietary sources of protein for total red meat (TRM) among women in Nurses' Health Study II. Multivariable model was adjusted for variables in footnote of table 2 as well as total red meat (continuous), legumes (continuous), nuts (continuous), poultry (continuous), fish (continuous), eggs (continuous), low fat dairy (continuous), and high fat dairy (continuous). *This model was adjusted for variables in footnote of table 2 as well as total red meat (continuous), sum of legumes, nuts, poultry, and fish intake (continuous), eggs (continuous), low fat dairy (continuous), and high fat dairy (continuous)