

Red Meat Consumption during Adolescence among Premenopausal Women and Risk of Breast Cancer

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Abstract

Background: Adolescence may be a period of increased susceptibility to breast cancer due to regular division of undifferentiated cells that occurs between puberty and first birth. Red meat consumption during early adult life has been associated with breast cancer, but intake during adolescence has not been examined prospectively. We aimed to assess the relationship between red meat intake during adolescence and premenopausal breast cancer.

Methods: We examined the incidence of invasive premenopausal breast cancer prospectively within the Nurses' Health Study II. A total of 39,268 premenopausal women who completed a validated 124-item food frequency questionnaire on their diet during high school, were followed for 7 years, from 1998 to 2005. Cox proportional hazards regression was used to estimate relative risks (RR) and 95% confidence intervals (95% CI).

Results: 455 cases of invasive premenopausal breast cancer were diagnosed between 1998 and 2005. Compared with women in the lowest quintile of red meat intake during high school, the multivariate-adjusted RR for the highest quintile of intake was 1.34 (95% CI, 0.94-1.89; $P_{\text{trend}} = 0.05$). A significant linear association was observed with every additional 100 g of red meat consumed per day (RR, 1.20; 95% CI, 1.00-1.43; $P = 0.05$). This association was more pronounced in hormone receptor-positive tumors (RR, 1.36; 95% CI, 1.08-1.70; $P = 0.008$) and was not significant in hormone receptor-negative tumors (RR, 0.99; 95% CI, 0.61-1.61, $P = 0.97$).

Conclusion: Higher red meat intake in adolescence may increase the risk of premenopausal breast cancer. (Cancer Epidemiol Biomarkers Prev 2008; 17(8):2146-51)

Introduction

Exposures that occur between menarche and first pregnancy may be especially important in determining subsequent risk of breast cancer (1). Mammary tissue develops during puberty but does not undergo terminal differentiation and lobule formation until onset of first pregnancy in preparation for lactation (2). Results from animal studies support the theory that there is a window of increased susceptibility to mammary carcinogens in early life (3, 4). Several lines of epidemiologic evidence in humans also suggest a similar period of vulnerability of the breast to carcinogenesis early in a woman's life. For example, a marked increase in breast cancer risk was noted in women ages <20 years who survived the atomic bomb in Hiroshima and Nagasaki, whereas no increase in risk was observed among women ages >35 years at the time of the bombing (5, 6). Moreover, a 13% reduction in risk of breast cancer was observed among women who were pubertal during the World War II-induced famine in Norway, characterized by a shortage of food, fat, dairy, and meat, compared with women who were older during this famine (7).

Taken together, these findings suggest that environmental exposures during adolescence, compared with those that occur at older ages, may significantly affect breast cancer risk. Therefore, dietary exposures including red meat may be of particular importance in mammary carcinogenesis when consumed in early life compared with adulthood.

Consumption of red meat in adult women has been associated with increased breast cancer risk among premenopausal women (8), but no association was noted in a pooled analysis of prospective studies (9) that includes mostly older, postmenopausal women. Several hypotheses exist to explain how intake of red meat could induce carcinogenesis: its highly bioavailable iron content (10), growth-promoting hormones used in animal production (11), carcinogenic heterocyclic amines formed in cooking (12), and its specific fatty acid content may all contribute. To our knowledge, this is the first prospective study to examine the relationship between red meat consumption in adolescence and subsequent breast cancer risk.

Materials and Methods

Study Population. The Nurses' Health Study II (NHS II) is a prospective cohort of 116,671 female registered nurses ages 25 to 43 years at enrollment in 1989 who have completed biennial questionnaires on lifestyle and medical events. The study has maintained a response

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rate of $\geq 90\%$ (13). Incident cases of breast cancer are ascertained on biennial follow-up questionnaire and by a search of the National Death Index. We contact the participant or next of kin to confirm all reported cases, and permission to access medical records and pathology reports is requested. Pathology reports confirm 98% of the self-reported cancers and provide information on estrogen receptor (ER) and progesterone receptor (PR) status of the tumor. Cases of carcinoma *in situ* were excluded from this analysis. Age, height, body mass index (BMI) at age 18 years, age at menopause and menarche, family history of breast cancer, and history of benign breast disease were obtained from the biennial questionnaires. BMI was calculated as weight divided by height squared (kg/m^2) to estimate total adiposity.

In 1997, participants were asked if they would be willing to complete a supplemental questionnaire about diet [food frequency questionnaire (FFQ)] during high school (HS-FFQ); 56,928 women (49% of the entire cohort) indicated willingness and 47,355 women returned the HS-FFQ in 1998 (83% of those sent the questionnaire). Participants with implausible daily caloric intake (<500 or $\geq 5,000$ kcal; $n = 21$ cases) and participants diagnosed with any cancer, except non-melanoma skin cancer before 1999, were excluded ($n = 13$ cases). The majority of diagnoses during this period were of premenopausal breast cancer (88%). We therefore restricted our analysis to women who were premenopausal at baseline to have a more homogeneous study population. The overall number of women who met the inclusion criteria was 39,268, and 455 incident cases of invasive premenopausal breast cancer were diagnosed between return of the HS-FFQ in 1998 and June 2005 among the 39,268 women included.

Adult and High School Dietary Assessment. In 1991 and 1995, participants of the NHS II study completed a semiquantitative FFQ of usual dietary intake during the past year. The mean of the 1991 and 1995 FFQ is used to estimate current adult red meat intake. Individual red meat items included beef or lamb as a main dish; pork as a main dish; beef, pork, or lamb as a sandwich or mixed dish; hamburger; bacon; hotdogs; and other processed meats.

Adolescent diet was measured using the 124-item HS-FFQ, which includes questions on main dishes, bread and cereals, fruits, vegetables, condiments, snack foods, dairy products, and beverages. This questionnaire was specifically designed to include foods that were commonly consumed during the period from 1960 to 1980 when these women would have been in high school (e.g., milkshakes, peanut butter, and French fries). The individual red meat items on the HS-FFQ were identical to those included on the adult FFQ. The correlation between adult and adolescent red meat intake was moderate ($r = 0.32$).

Participants reported their dietary intake 16 to 35 years after high school; however, recall of adolescent diet among NHS II participants has been shown to be reproducible (14). The HS-FFQ was administered twice at a 4-year interval to a random sample of 333 NHS II participants; the correlation for adolescent nutrient intakes reported 4 years apart was 0.65 (range, 0.50-0.77), whereas current adult diet was only weakly correlated with recalled adolescent diet (mean nutrient

correlation, 0.20). The mean correlation for red meat intake reported in the reproducibility study was 0.52 (14). Underreporting and overreporting of high school diet assessed by estimating the nurses' basal metabolic requirements did not affect the correlations as described previously by Maruti et al. (14). The validity of this measure was further assessed by administering the HS-FFQ to 80 young adults who had provided information 10 years earlier about their current diet while in high school (15). The mean of correlations for nutrients between the two FFQs administered 10 years apart was 0.58 (range, 0.40-0.88). Furthermore, data on the diet of the participants during high school were collected from their mothers. The mean nutrient correlation of the mothers' versus nurses' own report was 0.40 (range, 0.13-0.59).

Nutrient intakes on the HS-FFQ were computed by multiplying the frequency of consumption of each unit of food by the nutrient content of the specified portions and then summing the contributions from all foods. Nutrient values for foods were obtained from the U.S. Department of Agriculture (16), food manufacturers, and independent academic sources (17, 18). All nutrients were energy adjusted by using the residuals from the regression of nutrient intake on total caloric intake (19, 20). Energy-adjusted nutrient values were then divided into quintiles according to the distribution of all women who completed the HS-FFQ. Red meat quintiles were not energy adjusted in Table 1.

Statistical Analysis. We compared breast cancer risk factors, breast cancer rates, total caloric intake, and adult red meat intake in women who completed the HS-FFQ and those who did not reply.

Follow-up time in person-months extended from 1997 until either June 2005, date of breast cancer diagnosis, or death, whichever came first. Cox proportional hazards regression was used to estimate relative risks (RR) and 95% confidence intervals (95% CI) for each category of red meat intake, using the lowest quintile of intake as the reference category, while controlling for potential confounding variables (21). Linear trends were examined by modeling red meat intake in grams as a continuous variable. Tests for trend across quintiles of intake were conducted modeling the median value for each category of food or food group as a continuous variable. Missing value indicators were created for covariates with missing data (22).

Multivariate models were adjusted for age, total energy intake, age in 1989, age at onset of menarche, BMI at age 18 years, menopausal status, family history of breast cancer, current oral contraceptive use, age at first birth, parity, history of benign breast disease, adult alcohol intake, and weight gain since age 18 years. To assess hypothesized mechanisms, we further adjusted multivariate models for adolescent heme iron, animal fat intake, and adult red meat consumption. These risk factors were updated from the biennial questionnaires to the most recent information before date of diagnosis. All P values and 95% CI are two-sided.

Results

The mean age of all participants in 1998 was 44 years (range, 34-53). There were no major differences between

Table 1. Age-standardized distribution of potential risk factors for breast cancer according to high school red meat intake as reported in 1998 among 39,268 women ages 33 to 53 y

Variable	Red meat intake in high school				
	Q1 (n = 8,423)	Q2 (n = 7,963)	Q3 (n = 8,111)	Q4 (n = 7,794)	Q5 (n = 6,977)
Adolescence					
Mean red meat (servings per day)	0.68	1.12	1.45	1.83	2.62
Total calories per day	2178	2505	2734	2986	3441
Mean BMI at age 18 y (kg/m ²)	20.9	21.0	21.1	21.3	21.6
Adulthood (1997)					
Mean BMI (kg/m ²)	24.8	25.2	25.7	26.2	26.9
Mean height (m)	1.64	1.65	1.65	1.65	1.65
Mean alcohol (g/d)	3.5	3.8	3.8	3.9	3.9
Mean age at first birth in parous women	27	27	27	26	26
Mean weight gain (kg from age 18 y to 1997)	11	11	12	13	15
Mean red meat (servings per day)	0.51	0.66	0.75	0.85	1.00
% Current smokers	7	8	8	9	9
% Current oral contraceptive users	9	9	9	9	9
% History of biopsy confirmed benign breast disease	18	18	19	18	19
% Family history of breast cancer in mother or sister	11	12	12	12	11
% Parity ≥3 children	27	29	29	29	27
% Age at menarche <12 y	23	24	24	25	26

participants who completed the HS-FFQ and participants who did not provide information on high school diet across breast cancer risk factors including BMI, age at menarche, parity, age at first birth, height, weight gain, oral contraceptive use, red meat intake in adulthood, or rates of breast cancer (data not shown). Among premenopausal participants who had completed the adolescent HS-FFQ, 455 new cases of invasive premenopausal breast cancer were diagnosed between 1998 and 2005. ER and PR status was available on 340 cases; 268 (79%) were ER positive and 72 (21%) were ER negative. The distributions of breast cancer risk factors according to quintiles of red meat intake during adolescence are shown in Table 1. Women with higher consumption of red meat during high school were more likely to be current smokers, have a higher adult BMI and caloric intake, and have gained more weight during adulthood. Mean follow-up time was 7 years.

The energy-adjusted and multivariate-adjusted associations between red meat consumption during adolescence and premenopausal breast cancer are presented in Table 2. Women who consumed the highest amounts of red meat intake during high school (Q5) had an elevated risk of breast cancer (RR, 1.34; 95% CI, 0.94-1.89;

$P_{\text{trend}} = 0.05$) compared with the lowest quintile in the multivariate-adjusted model. The association between adolescent red meat intake and breast cancer persisted after adjustment for animal fat consumption and intake of heme iron (Table 2). Adult red meat intake was not significantly associated with breast cancer in this group from 1997 to 2005 (RR, 0.99; 95% CI, 0.82-1.21; $P = 0.95$) when modeled as a continuous variable, and adjustment for adult intake of red meat did not change the estimate for adolescent intake substantially (RR, 1.40; 95% CI, 0.98-2.00; $P_{\text{trend}} = 0.03$) comparing highest with lowest quintile of adolescent red meat intake. Restricting the analysis to subgroups of women without a history of biopsy-confirmed benign breast disease or women without a family history of breast cancer did not significantly change the results (data not shown).

Types of red meat including number of servings per day of beef, pork, lamb, processed meats, bacon, hotdog, and meatloaf were also examined individually in relation to breast cancer. Although greater intakes of these foods were associated with increased breast cancer risk, the trend was not statistically significant for most individual types of meat (Table 3). There was a significant association for frequent hotdog consumption and a

Table 2. RR (95% CI) of breast cancer according to high school intake of red meat

Variable	Red meat intake during high school					P_{trend}
	Q1 (68 g)	Q2 (112 g)	Q3 (145 g)	Q4 (1.83 g)	Q5 (2.62 g)	
No. cases	88	85	92	100	90	
Median servings per day	0.71	1.13	1.42	1.85	2.49	
Age and calorie adjusted RR	1.00	1.02 (0.75-1.38)	1.09 (0.80-1.47)	1.22 (0.89-1.78)	1.26 (0.89-1.77)	0.11
Multivariate* RR	1.00	1.03 (0.76-1.40)	1.13 (0.83-1.53)	1.27 (0.93-1.74)	1.34 (0.94-1.89)	0.045
Multivariate* RR also adjusted for adult meat [†]	1.00	1.09 (0.80-1.48)	1.16 (0.85-1.58)	1.33 (0.96-1.83)	1.40 (0.98-2.00)	0.033
Multivariate* RR also adjusted for heme iron	1.00	1.03 (0.76-1.41)	1.13 (0.82-1.57)	1.28 (0.91-1.81)	1.35 (0.89-2.04)	0.089
Multivariate* RR also adjusted for animal fat	1.00	1.05 (0.76-1.43)	1.15 (0.83-1.59)	1.31 (0.93-1.84)	1.39 (0.93-2.08)	0.059

*Multivariate models were adjusted for age, total energy intake, family history of breast cancer, history of benign breast disease, menopausal status, age at menarche, parity, age at first birth, weight gain since age 18 y, BMI at age 18 y, current oral contraceptive, and adult alcohol use.

[†] Twelve cases were excluded from this analysis because of missing data on adult diet. Adult red meat consumption was nonsignificantly inversely associated with breast cancer in this analysis.

Table 3. Multivariate adjusted RR (95% CI) of breast cancer according to high school intake of specific types of red meat

Variable	Frequency of consumption					<i>P</i> _{trend}
	Never	1-3/mo	1/wk	2-4/wk	>5/wk	
Multivariate-adjusted RR						
Bacon	1.00	0.98 (0.72-1.32)	1.02 (0.75-1.38)	0.97 (0.68-1.39)	1.00 (0.52-1.93)	0.93
Processed meat	1.00	0.84 (0.60-1.18)	0.76 (0.55-1.06)	1.03 (0.76-1.39)	1.09 (0.74-1.59)	0.07
Beef, pork or lamb sandwich, stew	1.00	0.85 (0.63-1.16)	1.00 (0.75-1.34)	0.96 (0.68-1.34)		0.87
Hotdog	1.00	1.00 (0.74-1.35)	1.02 (0.74-1.37)	1.36 (0.95-1.95)		0.03
Meatloaf	1.00	1.08 (0.8-1.47)	1.13 (0.83-1.54)	0.95 (0.50-2.80)		0.92
Beef or lamb as main dish		1.00	1.07 (0.81-1.41)	1.13 (0.85-1.49)	1.27 (0.82-1.98)	0.26
Hamburger		1.00	0.93 (0.72-1.20)	0.92 (0.69-1.22)	1.26 (0.72-2.19)	0.75
Pork as a main dish		1.00	1.01 (0.83-1.24)	1.26 (0.94-1.70)		0.11

borderline significant association for processed meat intake.

For every additional 100 g of red meat consumed each day, the risk of breast cancer increased by 20% (RR, 1.20; 95% CI, 1.00-1.43; *P* = 0.05; Table 4). This association was slightly stronger when the analysis was restricted to ER- and PR-positive cancers (*n* = 268; RR, 1.36; 95% CI, 1.08-1.70) for each 100 g/d increment (*P* = 0.008; Table 4). Among ER- and PR-negative cancers (*n* = 72), the association between high school red meat consumption and breast cancer was null (RR, 0.99; 95% CI, 0.61-1.61; *P* = 0.97 for each additional 100 g increment).

Discussion

In this study of 39,268 premenopausal women, participants who consumed the greatest quantity of red meat during high school had a 30% to 40% higher risk of breast cancer compared with women with the lowest intake of red meat. The association persisted after adjusting for heme iron and animal fat and was present in women without benign breast disease or a positive family history. Furthermore, the association was stronger for ER- and PR-positive tumors. Adult red meat intake was not a strong independent predictor of overall breast cancer risk in this subgroup of the NHS II cohort, and adjusting for adult red meat intake did not appreciably change the association between adolescent red meat intake and breast cancer intake.

This is one of the largest and most thorough studies of adolescent diet and breast cancer to date that significantly adds to the growing body of literature on early-life risk factors for breast cancer. In the absence of data collected during adolescence with many decades of follow-up, the use of the NHS II HS-FFQ, a validated and reproducible retrospective questionnaire (14, 15), is a good alternative for assessment of dietary exposures

during adolescence. The prospective design of the study, in which only cases diagnosed after the participant had completed the HS-FFQ were included, limits the potential for recall bias caused by knowledge of disease status. The large sample size and high rates of follow-up provide adequate power, and repeated measures allow for updated estimation of relevant covariates. Thorough case ascertainment, including examination of both medical record and pathology report, limits the potential for outcome misclassification. Nonetheless, several limitations may have affected our results. Although the study is prospective with respect to case ascertainment, it is retrospective in terms of dietary assessment. The HS-FFQ has been shown to be reasonably valid and reproducible when administered several decades later; however, recall of diet during high school inevitably includes some nondifferential measurement error that would likely bias results toward the null. This study did not have sufficient power to examine effect modification formally according to hormone receptor status or enough information on cooking of meat to address plausible mechanistic hypotheses.

The relationship between adult diet and breast cancer has been extensively investigated, yet studies on adult red meat intake and breast cancer remain inconsistent. No association was observed in the pooling project analysis of prospective studies that included mostly older postmenopausal women (*n* = 7,379 cases; ref. 9). A meta-analysis of case-control and cohort studies showed a modest association of red meat intake with breast cancer incidence (RR, 1.17; 95% CI, 1.06-1.29; ref. 23). More recent reports from two large prospective cohorts found an elevated risk with higher red meat consumption. The NHS II (*n* = 1,021 cases) reported a stronger association especially for ER- and PR-positive breast cancers among premenopausal women (ref. 8; RR, 1.97; 95% CI, 1.35-2.88) comparing more than 1.5 servings per day to ≤ 3 servings per week. The UK Women's Cohort

Table 4. Red meat intake as a continuous variable and risk of breast cancer according to hormone receptor status

	100 g/d increment of red meat,* multivariate-adjusted RR (95% CI)	<i>P</i>
All breast cancer (<i>n</i> = 455)	1.20 (1.00-1.43)	0.053
ER- and PR-positive breast cancer (<i>n</i> = 268)	1.36 (1.08-1.70)	0.008
ER- and PR-negative breast cancer (<i>n</i> = 72)	0.99 (0.61-1.61)	0.97

*Multivariate models were adjusted for age, total energy intake, family history of breast cancer, history of benign breast disease, menopausal status, age at menarche, parity, age at first birth, weight gain since age 18 y, BMI at age 18 y, current oral contraceptive, and adult alcohol use.

study ($n = 678$ cases) observed an increased risk of premenopausal breast cancer among women with high red meat intake compared with none (RR, 1.20; 95% CI, 0.86-1.68; ref. 24).

Fewer studies on diet during early life and breast cancer are available probably due to the methodologic challenges involved in accurate exposure assessment. Adolescent red meat intake was examined in one case-control study of women diagnosed with premenopausal breast cancer before age 45 years. Investigators noted a positive association with higher consumption of high-fat meat during adolescence (ages 12-13 years), which persisted after augmenting dietary history with information from the participants' mothers (25). In an analysis of the NHS II cohort using 361 cases diagnosed before filling out the HS-FFQ in 1998, Frazier et al. noted a nonsignificant positive association with red meat intake (RR, 1.22; 95% CI, 0.82-1.82) comparing the highest with the lowest quintile of intake (26). Our findings are consistent with these retrospective analyses and to our knowledge provide the first prospective evidence of the association between adolescent red meat consumption and breast cancer. Although these findings are consistent with the hypothesis of a susceptibility period during early life, there is still insufficient evidence to specify the precise time during which dietary exposures may be most influential in relation to puberty and first pregnancy.

Several biological mechanisms could explain the association between high intake of red meat and breast cancer. Heterocyclic amines, created during high-temperature cooking of meat, are estrogenic *in vitro* (12, 27), and mechanisms for breast tissue-specific carcinogenic activity of these chemicals have been proposed (12, 28). In a nested case-control study among the Iowa Women's Health Study cohort (29), regular consumption of well-done and fried meats was associated with >4-fold increase in breast cancer risk compared with consumption of meat that is cooked medium or rare (odds ratio, 4.62; 95% CI, 1.36-15.70). A positive relationship between well-done, deep-fried animal foods and breast cancer was also shown in a large case-control study from Shanghai (highest to lowest quintile odds ratio, 1.92; 95% CI, 1.30-2.83; ref. 30). Furthermore, in a study from Finland, the risk of breast cancer was 80% higher in those consuming fried meat (highest versus lowest tertile RR, 1.80; 95% CI, 1.03-3.16), whereas other meat consumption was not associated with breast cancer (31).

A second mechanism that could explain this finding is the hormone content of meat. Exogenous hormones for growth stimulation in cattle have been used in the United States since 1954, and residual amounts of these hormones in beef are detectable and may have implications for human health (11). Diethylstilbestrol was the first hormone introduced and was heavily used until it was banned by the Food and Drug Administration in 1979 when detectable diethylstilbestrol residues in cows' livers raised concern about risk of carcinogenicity (32). The specific type of hormones used in agriculture has changed drastically since the 1950s and doses have been decreased in more recent decades (32). The meat consumed by the study participants in high school during the 1960s and 1970s may therefore have been treated with higher doses of hormones, including diethylstilbestrol, than the meat they consumed as adults.

Iron from meat has also been implicated in the etiology of several cancers including breast cancer (10). Dietary iron was shown to enhance estrogen carcinogenicity in rodents possibly by promoting free radical damage to DNA (33). Hereditary hemochromatosis, a disease of iron overload, is caused by a mutation in the HFE gene and higher rates of HFE mutations among breast cancer patients have been reported in some case-control studies (34-38). This finding indirectly implicates iron overload in breast cancer pathogenesis. Heme iron from red meat is a readily bioavailable form of iron and significantly contributes to stored body iron. Controlling for heme iron in this analysis did not significantly alter the results, suggesting that alternative mechanisms may be more relevant in this population. Although an association of animal fat consumption in adult life and breast cancer has been observed in a previous analysis of this cohort of young women (39), the effect of red meat appears to be independent of animal fat intake during adolescence. Finally, the foods with the most statistically significant associations included processed meat and hotdogs; this may suggest that commercial meat processing may play a role in the observed link with breast cancer.

Conclusion

In this study, higher consumption of red meat during high school was associated with elevated rates of premenopausal breast cancer. As diet is one of the few potentially modifiable risk factors for breast cancer, this relation deserves further evaluation, including examination of potential mechanisms.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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E. Linos had access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Contributions: conception and design (W.C. Willett, G. Colditz, and L.A. Frazier), data acquisition and statistical analysis (E. Linos and E. Cho), and critical revision of the article (E. Linos, W.C. Willett, G. Colditz, E. Cho, and L.A. Frazier).

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BLOOD CANCER DISCOVERY

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