

Citation:

Linos E, Willett WC, Cho E, Colditz G, Frazier LA. Red meat consumption during adolescence among premenopausal women and risk of breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2008 Aug;17(8):2146-51. Epub 2008 Jul 31

PubMed ID: [18669582](#)

Study Design:

prospective cohort study

Class:

B - [Click here](#) for explanation of classification scheme.

Research Design and Implementation Rating:

POSITIVE: See Research Design and Implementation Criteria Checklist below.

Research Purpose:

To assess the relationship between red meat intake during adolescence and premenopausal breast cancer

Inclusion Criteria:

- women in the Nurses' Health Study II cohort
- premenopausal at baseline

Exclusion Criteria:

- implausible daily caloric intake (< 500 and ≥ 5000 kcal; $n=21$ cases)
- diagnosis of any cancer, except non-melanoma skin cancer before 1999 ($n = 13$)
- carcinoma *in situ*

Description of Study Protocol:

Recruitment: Participants asked if they would be willing to complete a supplemental questionnaire about diet during high school

Design: prospective cohort study with retrospective dietary assessment

Blinding used (if applicable): N/A

Intervention (if applicable): N/A

Statistical Analysis

- breast cancer risk factors, breast cancer rates, total caloric intake, and adult red meat intake were compared for women who completed the HS-FFQ and those who did not reply
- follow-up time in person-month: from 1997 to either June, 2005, date of breast cancer diagnosis, or death, whichever came first
- Cox proportional hazards regression: to estimate relative risks (RR) and 95% confidence intervals (95% CI) for each category (quintiles) of red meat intake
 - reference = lowest quintile
- linear trends: examined by modeling red meat intake in grams continuously
- tests for trend across quintiles of intake: modeling the median value for each category of food or food group continuously
- missing value indicators created for covariates with missing data
- multivariate models adjusted for
 - age
 - total energy intake
 - age in 1989
 - age at onset of menarche
 - BMI at 18 years
 - menopausal status
 - family history of breast cancer
 - parity
 - history of benign breast disease
 - adult alcohol intake
 - weight gain since 18 years of age
- To assess hypothesized mechanisms, models were further adjusted for:
 - adolescent heme iron
 - animal fat intake
 - adult red meat consumption
- All P values and 95% CI are two-sided

Data Collection Summary:

- **Timing of Measurements**
- Baseline and biennially: questionnaires

Dependent Variables

- breast cancer incidence: ascertained on biennial follow-up questionnaire and by a search of the National Death Index; permission to access medical records and pathology reports requested

Independent Variables

- adult red meat intake: mean intake of food frequency questionnaires from 1991 and 1995 used to estimate current intake
- adolescent red meat intake: High School Food Frequency Questionnaire (HS-FFQ) (specifically designed to include foods commonly consumed between 1960 and 1980)
 - correlation between adult and adolescent red meat intake: $r = 0.32$
 - HS-FFQ has been shown to be reproducible in a random sample of 333 NHS II participants - correlation for adolescent nutrient intakes reported 4 years apart: $r =$

0.65, range = 0.50 - 0.77; mean correlation for red meat intake: $r = 0.52$.

- correlation between HS-FFQ and data provided 10 years earlier by the sample (N=80) when in high school: $r = 0.58$, range = 0.40 - 0.88
- mean nutrient correlation of from mothers' report versus nurses' own report: $r = 0.40$, range = 0.13 - 0.59

Control Variables

- 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 years, BMI at age 18 years, current oral contraceptive use, and adult alcohol use

Description of Actual Data Sample:

Initial N:

- N = 116,671 at enrollment in 1989
- N = 56,928 women (49%) who indicated willingness to complete supplemental questionnaire

Attrition (final N):

- N = 47,355 returned questionnaire (83%) in 1998

Age: 44 years, range = 34 to 53 years (in 1998)

Ethnicity: not specified

Other relevant demographics: none specified

Anthropometrics

Anthropometric data by quintile of red meat intake in high school

	Q 1	Q2	Q3	Q4	Q 5
	(N = 8,423)	(N = 7,963)	(N = 8,111)	(N = 7,794)	(N = 6,977)
Mean adult BMI (kg/m^2)	24.8	25.2	25.7	26.2	26.9
Mean adult height (m)	1.64	1.65	1.65	1.65	1.65
Mean BMI at age 18 (kg/m^2)	20.9	21.0	21.1	21.3	21.6
Mean weight gain (kg from age 18 y to 1997)	11	11	12	13	15

Location: United States

Summary of Results:

Key Findings

- Women in the highest quintile of red meat consumption during high school (mean = 2.62 servings/day) had a higher adjusted relative risk (RR = 1.34, 95% CI: 0.94 - 1.89) compared with those in the lowest quintile (mean = 0.68 servings/day) (P trend = 0.05)
- For every additional 100 grams 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).
 - The linear association was more pronounced in hormone receptor-positive tumors RR = 1.36, 95% CI; 1.08 - 1.70, P = 0.008) and
 - the linear association was not significant in receptor-negative tumors (RR = 0.99, 95% CI: 0.61 - 1.61, P = 0.97).

Subjects

- no differences between participants who completed the HS-FFQ and participants who did not for 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
- number of cases of invasive premenopausal breast cancer diagnosed between 1998 and 2005 in those who completed the HS-FFQ = 455
 - HR positive: N = 268 of 340 (79%)
 - HR negative: N = 72 (21% of 340 (21%)
- 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 = 7 years
- Meat intake
 - adult red meat consumption by quintile (mean servings/day)
 - Q 1: 0.51
 - Q2: 0.66
 - Q3: 0.75
 - Q4: 0.85
 - Q5: 1.00
 - red meat consumption in adolescence by quintile (mean servings/day)
 - Q1: 0.68
 - Q2: 1.12
 - Q3: 1.45
 - Q4: 1.83
 - Q5: 2.62

Associations between red meat consumption and premenopausal breast cancer

- women who consumed the highest amounts of red meat during high school had an elevated risk of breast cancer (RR = 1.34, 95% CI: 0.94 to 1.89, P trend = 0.05) compared with the lowest quintile in the multivariate-adjusted model
 - association persisted after adjustment for animal fat consumption and intake of heme iron
 - adjustment for adult red meat intake did not change the estimate for adolescent intake substantially (RR = .140, 95%CI: 0.98 - 2.00, P trend = 0.03) comparing highest with lowest quintile of adolescent red meat intake
- **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 considered as a continuous variable, risk of breast cancer increased by 20% for every additional 100 grams of red meat consumed (N = 455, RR = 1.20, 95% CI: 1.00 - 1.43, P =

0.053)

- this association was slightly stronger for ER and PR positive cancers (N = 268, RR = 1.36, 95% CI: 1.08 - 1.70)
- the association was null for ER and PR negative cancers (N = 72, RR = 0.99, 95% CI: 0.61 - 1.61, P = 0.97)
- **types of red meat** (number of servings per day of beef, pork, lamb, processed meats, bacon, hot dog, and meatloaf examined individually)
 - greater intakes were associated with increased breast cancer risk, but the trend was not statistically significant for most individual types of red meat
 - there was a significant association for frequent hot dog consumption and a borderline association for processed meat intake

Other Findings

Author Conclusion:

Higher consumption of red meat in adolescence may increase the risk of premenopausal breast cancer. This relationship deserves further evaluation, including examination of potential mechanisms.

Reviewer Comments:

Research Design and Implementation Criteria Checklist: Primary Research

Relevance Questions

- | | | |
|----|---|-----|
| 1. | Would implementing the studied intervention or procedure (if found successful) result in improved outcomes for the patients/clients/population group? (Not Applicable for some epidemiological studies) | Yes |
| 2. | Did the authors study an outcome (dependent variable) or topic that the patients/clients/population group would care about? | Yes |
| 3. | Is the focus of the intervention or procedure (independent variable) or topic of study a common issue of concern to nutrition or dietetics practice? | Yes |
| 4. | Is the intervention or procedure feasible? (NA for some epidemiological studies) | Yes |

Validity Questions

- | | | |
|------|---|-----|
| 1. | Was the research question clearly stated? | Yes |
| 1.1. | Was (were) the specific intervention(s) or procedure(s) [independent variable(s)] identified? | Yes |
| 1.2. | Was (were) the outcome(s) [dependent variable(s)] clearly indicated? | Yes |

1.3.	Were the target population and setting specified?	Yes
2.	Was the selection of study subjects/patients free from bias?	Yes
2.1.	Were inclusion/exclusion criteria specified (e.g., risk, point in disease progression, diagnostic or prognosis criteria), and with sufficient detail and without omitting criteria critical to the study?	Yes
2.2.	Were criteria applied equally to all study groups?	Yes
2.3.	Were health, demographics, and other characteristics of subjects described?	Yes
2.4.	Were the subjects/patients a representative sample of the relevant population?	Yes
3.	Were study groups comparable?	Yes
3.1.	Was the method of assigning subjects/patients to groups described and unbiased? (Method of randomization identified if RCT)	N/A
3.2.	Were distribution of disease status, prognostic factors, and other factors (e.g., demographics) similar across study groups at baseline?	Yes
3.3.	Were concurrent controls used? (Concurrent preferred over historical controls.)	Yes
3.4.	If cohort study or cross-sectional study, were groups comparable on important confounding factors and/or were preexisting differences accounted for by using appropriate adjustments in statistical analysis?	Yes
3.5.	If case control or cross-sectional study, were potential confounding factors comparable for cases and controls? (If case series or trial with subjects serving as own control, this criterion is not applicable. Criterion may not be applicable in some cross-sectional studies.)	Yes
3.6.	If diagnostic test, was there an independent blind comparison with an appropriate reference standard (e.g., "gold standard")?	N/A
4.	Was method of handling withdrawals described?	Yes
4.1.	Were follow-up methods described and the same for all groups?	Yes
4.2.	Was the number, characteristics of withdrawals (i.e., dropouts, lost to follow up, attrition rate) and/or response rate (cross-sectional studies) described for each group? (Follow up goal for a strong study is 80%.)	Yes
4.3.	Were all enrolled subjects/patients (in the original sample) accounted for?	Yes
4.4.	Were reasons for withdrawals similar across groups?	N/A
4.5.	If diagnostic test, was decision to perform reference test not dependent on results of test under study?	N/A

5.	Was blinding used to prevent introduction of bias?	N/A
5.1.	In intervention study, were subjects, clinicians/practitioners, and investigators blinded to treatment group, as appropriate?	N/A
5.2.	Were data collectors blinded for outcomes assessment? (If outcome is measured using an objective test, such as a lab value, this criterion is assumed to be met.)	N/A
5.3.	In cohort study or cross-sectional study, were measurements of outcomes and risk factors blinded?	N/A
5.4.	In case control study, was case definition explicit and case ascertainment not influenced by exposure status?	N/A
5.5.	In diagnostic study, were test results blinded to patient history and other test results?	N/A
6.	Were intervention/therapeutic regimens/exposure factor or procedure and any comparison(s) described in detail? Were intervening factors described?	Yes
6.1.	In RCT or other intervention trial, were protocols described for all regimens studied?	N/A
6.2.	In observational study, were interventions, study settings, and clinicians/provider described?	Yes
6.3.	Was the intensity and duration of the intervention or exposure factor sufficient to produce a meaningful effect?	Yes
6.4.	Was the amount of exposure and, if relevant, subject/patient compliance measured?	Yes
6.5.	Were co-interventions (e.g., ancillary treatments, other therapies) described?	N/A
6.6.	Were extra or unplanned treatments described?	N/A
6.7.	Was the information for 6.4, 6.5, and 6.6 assessed the same way for all groups?	Yes
6.8.	In diagnostic study, were details of test administration and replication sufficient?	N/A
7.	Were outcomes clearly defined and the measurements valid and reliable?	Yes
7.1.	Were primary and secondary endpoints described and relevant to the question?	Yes
7.2.	Were nutrition measures appropriate to question and outcomes of concern?	Yes
7.3.	Was the period of follow-up long enough for important outcome(s) to occur?	Yes
7.4.	Were the observations and measurements based on standard, valid, and reliable data collection instruments/tests/procedures?	Yes
7.5.	Was the measurement of effect at an appropriate level of precision?	Yes

7.6.	Were other factors accounted for (measured) that could affect outcomes?	Yes
7.7.	Were the measurements conducted consistently across groups?	Yes
8.	Was the statistical analysis appropriate for the study design and type of outcome indicators?	Yes
8.1.	Were statistical analyses adequately described and the results reported appropriately?	Yes
8.2.	Were correct statistical tests used and assumptions of test not violated?	Yes
8.3.	Were statistics reported with levels of significance and/or confidence intervals?	Yes
8.4.	Was "intent to treat" analysis of outcomes done (and as appropriate, was there an analysis of outcomes for those maximally exposed or a dose-response analysis)?	N/A
8.5.	Were adequate adjustments made for effects of confounding factors that might have affected the outcomes (e.g., multivariate analyses)?	Yes
8.6.	Was clinical significance as well as statistical significance reported?	Yes
8.7.	If negative findings, was a power calculation reported to address type 2 error?	N/A
9.	Are conclusions supported by results with biases and limitations taken into consideration?	Yes
9.1.	Is there a discussion of findings?	Yes
9.2.	Are biases and study limitations identified and discussed?	Yes
10.	Is bias due to study's funding or sponsorship unlikely?	Yes
10.1.	Were sources of funding and investigators' affiliations described?	Yes
10.2.	Was the study free from apparent conflict of interest?	Yes

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