

An Adolescent and Early Adulthood Dietary Pattern Associated with Inflammation and the Incidence of Breast Cancer

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Abstract

Adolescence is a highly susceptible period for mammary carcinogenesis, but few prospective studies have examined the role of adolescent diet in breast cancer risk. Reduced rank regression has previously been used to identify a dietary pattern associated with markers of inflammation (C-reactive protein, IL6, and TNF α receptor 2). We investigated whether an adolescent and early adulthood inflammatory dietary pattern was associated with breast cancer among 45,204 women in the Nurses' Health Study II using reduced rank regression. Participants completed a food frequency questionnaire in 1998 about their high school diet (HS-FFQ) and a FFQ in 1991 when they were ages 27–44 years. Among women who completed the HS-FFQ, 1,477 cases of breast cancer were diagnosed during 22 years of follow-up. An adolescent and early adulthood dietary pattern characterized by inflammation was associated with an increased

incidence of premenopausal but not postmenopausal breast cancer. Women in the fifth quintile of the inflammatory pattern score had multivariable adjusted HRs for premenopausal breast cancer of 1.35 for adolescent diet [95% confidence interval (95% CI), 1.06–1.73; $P_{\text{trend}} = 0.002$] and 1.41 for early adulthood diet (95% CI, 1.11–1.78; $P_{\text{trend}} = 0.006$) compared with women in the first quintile. The corresponding RRs for postmenopausal breast cancer were 0.84 (95% CI, 0.60–1.17) for adolescent and 0.76 (95% CI, 0.54–1.06) for adult intake. Overall, our findings support the notion that an adolescent and early adulthood diet characterized by high intake of sugar-sweetened and diet soft drinks, refined grains, red and processed meat, and margarine, and low intake of green leafy vegetables, cruciferous vegetables, and coffee may increase the incidence of premenopausal breast cancer. *Cancer Res*; 77(5); 1179–87. ©2017 AACR.

Introduction

Adolescence and early adulthood are highly susceptible periods for breast cancer carcinogenesis during a woman's life course. Mathematical models of breast cancer etiology have demonstrated that the years before first birth are critical in establishing breast cancer risk (1) and animal models support this period of increased vulnerability (2–5). Thus, the focus on dietary exposures during later adulthood may not target periods of heightened vulnerability.

Adult dietary patterns and breast cancer risk have been examined in several studies and recent review articles of this literature have suggested a possible inverse association between "prudent" or healthy dietary patterns and breast cancer risk but the results are not conclusive (6–9) and only one study has examined adolescent dietary patterns and breast cancer risk (10). Most previous studies on dietary patterns and breast cancer risk have used principal components analysis (PCA), which results in patterns that reflect the correlation structure between foods and consequently the derivation of the dietary patterns is independent of the endpoint of interest. Reduced rank regression, another technique for deriving dietary patterns, allows the selection of intermediate biomarkers that are specifically associated with the endpoint of interest and may be more predictive of disease risk (11).

We sought to investigate the relation between an adolescent and early adulthood dietary pattern associated with markers of inflammation and breast cancer among women in the Nurses' Health Study II. We also examined whether the associations between the adolescent and early adulthood dietary patterns and breast cancer differed by the menopausal status of the cases and the hormone receptor status of the tumor.

Patients and Methods

Study population

The Nurses' Health Study II (NHS II) was established in 1989 when 116,430 registered nurses from 14 states completed a baseline questionnaire on lifestyle factors and medical history. Follow-up questionnaires are sent to participants every 2 years to

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collect updated information on lifestyle factors, diseases, and other health-related topics. Implied consent was assumed upon completion and return of the questionnaire. This study was approved by the institutional review board at Brigham and Women's Hospital.

In 1997, participants were asked if they would be willing to complete a supplemental food frequency questionnaire about diet during high school (HS-FFQ; ref. 12). The HS-FFQ was completed by 47,355 women (83% of those sent the questionnaire) in 1998 when they were 33–52 years old. Women were excluded from the current analyses if they had an implausible daily caloric intake (<500 or $\geq 5,000$ cal; $n = 1,407$), left more than 20 items on the HS-FFQ blank ($n = 219$), were missing height ($n = 126$), or were diagnosed with any cancer, except nonmelanoma skin cancer ($n = 399$) before 1989.

Dietary assessment and dietary pattern identification

Adolescent diet was measured using the 124-item HS-FFQ. This questionnaire was specifically designed to include foods that were commonly consumed during the period from 1960 to 1980 when the women would have been in high school. Adult diet was assessed first in 1991 (dietary baseline), when participants were ages 27–44 years, and every 4 years after using a FFQ listing over 130 food items. Participants were asked how often, on average, they had consumed each type of food or beverage between the ages of 13–18 years (HS-FFQ) or during the previous year (adult FFQ). Nine responses were possible, ranging from never to 6 or more times a day. The validity of the HS-FFQ has been assessed in a population of young adults who had provided information 10 years earlier about their current diet while in high school. The HS-FFQ was compared to three 24-hour diet recalls and two 131-item self-administered Youth/Adolescent Questionnaires (YAQ), which were administered when the participants were ages 13–18 years (13). For the daily intake of 25 nutrients, the mean corrected correlation between the HS-FFQ and the YAQs was 0.58 (range = 0.40–0.88). In addition, within a subset of NHS II participants, recall of adolescent diet was reasonably reproducible and valid (14). To assess reproducibility, the HS-FFQ was readministered to 333 NHS II participants 4 years after the initial HS-FFQ and to assess validity, the mothers of NHS II participants reported information on their daughters' adolescent diets using the HS-FFQ. The average Pearson correlations for nutrients were 0.65 (range = 0.50–0.77) for NHS II participants and 0.40 (range = 0.13–0.59) for mothers report. The average Spearman rank correlation for foods were 0.60 (range = 0.37–0.77) and 0.30 (range = 0.10–0.61), respectively (14).

The inflammatory dietary pattern has been previously identified in a subset of women in the NHS using reduced rank regression (RRR), the derivation of this pattern has been described in detail elsewhere (11, 15, 16). In brief, biomarkers of C-reactive protein (CRP), IL6, and TNF α receptor 2 (15, 16) were assayed in a subsample of adult women who were controls from previous nested case-control and validation studies. The mean adult dietary intake from two FFQs completed within 0–3 years of blood draw was calculated and foods were grouped into up to 39 food groups. RRR was used to produce a linear function of food groups that explained the variation in the response variables (the biomarkers of interest). Food groups were retained in the pattern if the P value of the coefficient of the stepwise regression

model was <0.05 . A simplified pattern was then generated using stepwise linear regression with the RRR factor score as outcome and the food groups as predictors. Using the inflammatory pattern previously derived as described above, we then calculated simplified pattern scores for adolescent diet and early adult diet (1991 FFQ) by summing the intakes of the identified food groups taking into account their positive or negative associations with the original pattern scores (17). The inflammatory dietary pattern was characterized by higher intake of sugar-sweetened and diet soft drinks, refined grains (white bread, English muffins, bagels or rolls, muffins or biscuits, white rice, pasta, tortillas, pancakes, or waffles), red (hamburger, beef, lamb, pork, and meatloaf) and processed meat (hot dog, bacon, sausage, salami, and bologna), margarine, corn, other vegetables (celery, mushrooms, green pepper, eggplant, summer squash, and mixed vegetables), and fish (tuna, mackerel, salmon, sardines, bluefish, swordfish, and other fish), and lower intake of green leafy vegetables (spinach, iceberg or head lettuce, romaine or leaf lettuce), yellow vegetables (carrots, yellow/winter squash, yams), cruciferous vegetables (broccoli, brussel sprouts, cauliflower, kale/mustard/chard greens, cabbage/coleslaw), and coffee.

Ascertainment of breast cancer

On each biennial questionnaire, participants were asked whether they had been diagnosed with breast cancer in the previous 2 years. All participants who reported breast cancer were asked for permission to review the relevant medical records and pathology reports, to confirm the diagnosis. Estrogen receptor (ER) and progesterone receptor (PR) status information was available for 86% of the cases in our analytic cohort. Cases of carcinoma *in situ* were censored at the time of diagnosis.

Covariate assessment

Information on known and potential risk factors for breast cancer was collected on the baseline and biennial questionnaires. Women were considered premenopausal if they still had periods or had at least one ovary remaining and were <46 (for smokers) or <48 (for nonsmokers) years old. Women were considered postmenopausal in the analysis if they reported being postmenopausal during follow-up due to natural menopause or surgery with bilateral oophorectomy. Women who reported hysterectomy without bilateral oophorectomy or whose type of menopause was unknown were not classified as postmenopausal until they reached the age at which 90% of the cohort had reached natural menopause (54 years for current smokers, 56 years for nonsmokers; refs. 18, 19).

Statistical analysis

We examined three exposure windows for early life dietary patterns; adolescent intake (ages 13–18), early adulthood intake (assessed in 1991 when participants were ages 27–44 years), and the average of adolescent and early adulthood intake (representing cumulative exposure from adolescence to early/middle reproductive years). In the primary analyses of these three exposures participants contributed person-time from study entry until diagnosis of breast cancer, diagnosis of any other cancer (except nonmelanoma skin cancer), death, loss to follow-up, menopause (only for the premenopausal analysis), or end of follow-up on June 1, 2011, whichever occurred first (described hereafter as the combined analysis).

This analysis includes all cases of breast cancer diagnosed before and after return of the HS-FFQ. In sensitivity analyses, participants contributed person-time from return of the HS-FFQ (1998; described hereafter as the prospective analysis). This analysis was restricted to only incident cases of breast cancer diagnosed after return of the HS-FFQ. Cox proportional hazards regression models with age and questionnaire period as the time scale were used to calculate HRs and 95% confidence intervals (95% CI) with the lowest quintile as the reference. Tests for linear trend were performed by assigning the median value of each category to all participants in that group.

We considered two main covariate-adjusted models; the first adjusted for adolescent characteristics and the second additionally adjusted for adult characteristics. We included the following *a priori* potential confounders in the adolescent characteristics model: age (continuous), total adolescence calories (continuous), height at age 18 (continuous), age at menarche (<11, 11, 12, 13, 14, 15+ years), body mass index (BMI) at age 18 (continuous), adolescent physical activity (<21, 21–35.9, 36–53.9, 54–80.9, 81+ metabolic equivalent tasks [METs]/week), and family history of breast cancer (yes, no). In addition, the following covariates were included in the adolescent and adult characteristics model which represents the final model: age at first birth (<25, 25–30, 31+ years), parity (nulliparous, 0, 1, 2, 3, 4+), oral contraceptive use (never use, past use <5 years, past use 5+ years, current use <5 years, current use 5–9 years, current use 10+ years), adult physical activity (<3, 3–8, 9–17, 18–26, 27–41, 42+ metabolic equivalent tasks/week), alcohol consumption (nondrinker, <7.5, 7.5–15, 15–29, 30+ g/day), weight change since age 18 years (continuous), and history of benign breast disease (yes, no). In the analyses including postmenopausal women, we additionally adjusted for menopausal status/age at menopause (premenopausal, unknown menopause, <45 years, 45–46 years, 47–48 years, 49–50 years, 51–52 years, 53+ years), and hormone use (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users). Categories were created for missing data. The derivation of menopausal status in this cohort has been described previously (18, 19).

Competing risks analyses were used to examine whether the associations between each dietary pattern and breast cancer differed by hormone receptor status (20). This method allows for the estimation of separate associations of each dietary pattern in tumors with both ER- and PR-positive receptors and ER- and PR-negative receptors, and tests whether each dietary pattern has statistically different regression coefficients for different subtypes. All tests of statistical significance were two sided. Statistical analyses were performed using SAS Version 9.3 (SAS Institute Inc.).

Results

Among the 45,204 women who completed the HS-FFQ, 1,477 total cases of invasive breast cancer were diagnosed during 22 years of follow-up including 870 cases of premenopausal breast cancer and 490 cases of postmenopausal breast cancer. Women in the highest quintile of adolescent inflammatory pattern score had a higher BMI at age 18, were less physically active in adulthood, had gained more weight since

age 18, and were more likely to have ever used oral contraceptives than those with in the lowest quintile (Table 1). Women in the highest quintile of adolescent inflammatory pattern score had an average intake of refined grains and red meat of 3.3 and 1.2 servings/day, respectively, whereas those in the lowest quintile had an average intake of 1.5 and 0.6 servings/day, respectively. In contrast, those in the lowest quintile of adolescent inflammatory pattern score had an average intake of leafy vegetables of 0.7 servings/day compared with 0.3 servings/day in the highest quintile (Table 1). Similar differences in intake levels were observed for foods in early adulthood (Table 1). The Spearman correlation between the adolescent inflammatory pattern score and early adulthood inflammatory pattern score was 0.31, the correlation between adolescent and later adulthood was 0.24, and between early adulthood and later adulthood was 0.34.

Among all women there was no significant association between a higher inflammatory dietary pattern score in adolescence and overall breast cancer incidence; however, a significant association was observed between a higher adolescent inflammatory dietary pattern score and incidence of premenopausal breast cancer. Women in the fifth quintile of adolescent inflammatory pattern score had a multivariable adjusted HR of 1.35 (95% CI, 1.06–1.73) for premenopausal breast cancer compared with those in the first quintile ($P_{\text{trend}} = 0.002$). The association observed in the prospective analysis ($n = 536$ cases) was slightly attenuated but the trend was still statistically significant (HR for fifth quintile, 1.32; 95% CI, 0.97–1.80; $P_{\text{trend}} = 0.01$). No association was observed with postmenopausal breast cancer (HR, 0.84; 95% CI, 0.60–1.17; $P_{\text{trend}} = 0.33$). A similar pattern was observed for the inflammatory dietary pattern in early adulthood, with no significant association overall or among postmenopausal women and a significant increased risk of premenopausal breast cancer among those consuming an early adulthood dietary pattern associated with inflammatory markers (HR comparing the fifth to first quintile, 1.41; 95% CI, 1.11–1.78; $P_{\text{trend}} = 0.006$; Table 2).

Among women who had completed both the adolescent and early adulthood FFQ ($n = 42,770$), we examined the average of the two intakes. Among all women a significant association was observed between a higher average inflammatory dietary pattern score and overall breast cancer incidence (HR, 1.25; 95% CI, 1.03–1.52; $P_{\text{trend}} = 0.04$). This appeared to be driven by the association with premenopausal breast cancer (HR, 1.49; 95% CI, 1.16–1.90; $P_{\text{trend}} = 0.002$) while there was no significant association with postmenopausal breast cancer incidence (HR, 1.01; 95% CI, 0.71–1.43; $P_{\text{trend}} = 0.62$; Table 2). The associations between the adolescent and early adulthood inflammatory dietary patterns and breast cancer remained the same when we adjusted for a more recent adult inflammatory pattern (data not shown).

We also evaluated the relation between the inflammatory dietary pattern and risk of breast cancer for ER-positive/PR-positive and ER-negative/PR-negative tumors (Table 3). No significant differences were observed in the effect estimates when ER-positive/PR-positive and ER-negative/PR-negative cases were compared (all $P_{\text{heterogeneity}} \geq 0.06$); however, the strongest association was observed for the average of adolescent and early adulthood intake and premenopausal ER-negative/PR-negative cases (HR for fifth quintile, 2.21; 95% CI, 1.17–4.16; $P_{\text{trend}} = 0.009$).

Table 1. Age-adjusted adolescent and adult characteristics in 1997 by adolescent inflammatory dietary pattern, NHS II

	Inflammatory pattern ^a				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
<i>N</i>	9,017	9,035	9,044	9,060	9,048
Age in years in 1997 ^b	42.4 (4.7)	42.2 (4.7)	42.2 (4.7)	42.2 (4.7)	42.0 (4.6)
BMI at age 18 (kg/m ²)	20.8 (2.6)	20.9 (2.7)	21.0 (2.8)	21.2 (2.9)	21.6 (3.2)
Height (inches)	64.9 (2.6)	64.9 (2.6)	64.9 (2.6)	64.9 (2.6)	64.9 (2.6)
Adolescent physical activity (MET-hour/week)	54.1 (37.0)	51.4 (36.1)	52.2 (36.4)	52.5 (36.6)	54.3 (37.9)
Age at menarche (years)	12.4 (1.5)	12.5 (1.4)	12.4 (1.4)	12.4 (1.4)	12.3 (1.4)
BMI in 1997 (kg/m ²)	24.9 (5.3)	25.2 (5.4)	25.5 (5.6)	26.2 (6.0)	27.3 (6.8)
Weight gain since age 18 (pounds)	23.7 (27.1)	25.4 (26.8)	26.7 (27.4)	29.2 (29.6)	33.0 (32.6)
Adult physical activity (MET-hour/week)	22.8 (26.6)	19.5 (23.1)	18.9 (23.3)	18.0 (22.3)	17.2 (21.1)
Nulliparous, %	22	20	19	19	21
Age at first birth (years)	27.0 (4.7)	26.7 (4.6)	26.5 (4.5)	26.2 (4.5)	25.9 (4.6)
Number of children among parous women	2.2 (0.9)	2.3 (0.9)	2.3 (0.9)	2.3 (0.9)	2.2 (0.9)
Ever use oral contraceptives, %	80	82	83	84	85
Family history of breast cancer, %	22	21	21	20	20
History of benign breast disease, %	16	15	16	16	16
Adolescent dietary intake					
Total calories in adolescence	2,293 (726)	2,436 (660)	2,668 (658)	2,937 (663)	3,408 (719)
Regular soda (servings/day)	0.2 (0.4)	0.3 (0.4)	0.4 (0.5)	0.5 (0.7)	0.9 (1.1)
Diet soda (servings/day)	0.2 (0.5)	0.2 (0.5)	0.3 (0.6)	0.4 (0.7)	0.6 (1.2)
Refined grains (servings/day)	1.5 (1.1)	1.9 (1.2)	2.2 (1.3)	2.7 (1.4)	3.3 (1.6)
Red meat (servings/day)	0.6 (0.5)	0.7 (0.4)	0.9 (0.4)	1.0 (0.5)	1.2 (0.6)
Processed meat (servings/day)	0.3 (0.4)	0.4 (0.4)	0.5 (0.4)	0.6 (0.4)	0.9 (0.7)
Margarine (servings/day)	0.5 (0.7)	0.6 (0.8)	0.8 (0.9)	1.1 (1.1)	1.6 (1.4)
Corn (servings/day)	0.2 (0.1)	0.2 (0.2)	0.3 (0.2)	0.3 (0.2)	0.4 (0.2)
Other vegetables (servings/day)	0.4 (0.4)	0.4 (0.3)	0.4 (0.3)	0.4 (0.4)	0.4 (0.4)
Fish (servings/day)	0.2 (0.3)	0.2 (0.3)	0.2 (0.3)	0.3 (0.3)	0.4 (0.6)
Leafy vegetables (servings/day)	0.7 (0.6)	0.4 (0.4)	0.4 (0.4)	0.3 (0.4)	0.3 (0.4)
Yellow vegetables (servings/day)	0.7 (0.7)	0.4 (0.5)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)
Cruciferous vegetables (servings/day)	0.5 (0.5)	0.3 (0.3)	0.3 (0.3)	0.2 (0.3)	0.2 (0.3)
Coffee (servings/day)	0.4 (0.9)	0.2 (0.3)	0.1 (0.4)	0.1 (0.3)	0.1 (0.3)
Early adult dietary intake					
Total calories in adulthood	1,547 (671)	1,589 (648)	1,647 (659)	1,705 (694)	1,794 (746)
Regular soda (servings/day)	0.3 (0.7)	0.4 (0.8)	0.4 (0.8)	0.5 (0.9)	0.6 (1.1)
Diet soda (servings/day)	0.8 (1.2)	0.8 (1.3)	1.0 (1.3)	1.1 (1.5)	1.4 (1.8)
Refined grains (servings/day)	1.3 (0.9)	1.3 (1.0)	1.4 (1.0)	1.5 (1.0)	1.7 (1.2)
Red meat (servings/day)	0.4 (0.3)	0.5 (0.3)	0.6 (0.4)	0.6 (0.4)	0.7 (0.5)
Processed meat (servings/day)	0.2 (0.2)	0.2 (0.2)	0.2 (0.3)	0.2 (0.3)	0.3 (0.3)
Margarine (servings/day)	2.6 (1.9)	2.8 (1.9)	3.0 (1.9)	3.2 (1.9)	3.4 (1.9)
Corn (servings/day)	0.1 (0.2)	0.1 (0.1)	0.2 (0.2)	0.2 (0.2)	0.2 (0.2)
Other vegetables (servings/day)	0.6 (0.7)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5 (0.6)
Fish (servings/day)	0.3 (0.3)	0.3 (0.2)	0.3 (0.2)	0.3 (0.2)	0.3 (0.4)
Leafy vegetables (servings/day)	0.8 (0.8)	0.7 (0.6)	0.6 (0.5)	0.6 (0.6)	0.7 (0.6)
Yellow vegetables (servings/day)	0.6 (0.7)	0.5 (0.5)	0.5 (0.5)	0.5 (0.5)	0.5 (0.6)
Cruciferous vegetables (servings/day)	0.5 (0.5)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)	0.4 (0.4)
Coffee (servings/day)	1.7 (1.8)	1.6 (1.7)	1.5 (1.7)	1.5 (1.8)	1.5 (1.8)

NOTE: Values are means (SD) or percentages and are standardized to the age distribution of the study population.

^aThe inflammatory pattern is characterized by higher intake of sugar-sweetened and diet soft drinks, refined grains, red and processed meat, margarine, corn, other vegetables, and fish and lower intake of green leafy vegetables, yellow vegetables, cruciferous vegetables, and coffee.

^bValue is not age-adjusted.

We also examined the individual components of the inflammatory pattern score to explore if any specific food or food groups were driving the observed association with premenopausal breast cancer. Higher adolescent intake of processed meat was the most strongly associated with premenopausal breast cancer risk (HR for fifth quintile, 1.34; 95% CI, 1.07–1.68). None of the other adolescent food groups were statistically significantly associated with increased premenopausal breast cancer risk, although a suggestion of an increased risk was also seen with adolescent refined grain intake (HR for fifth quintile, 1.23; 95% CI, 0.96–1.56). When the average of adolescent and early adulthood intake was examined, none of the individual food groups were statistically significantly associated with risk but the highest suggested risks were observed for processed meat (HR for fifth quintile, 1.20;

95% CI, 0.94–1.54), red meat (HR for fifth quintile, 1.19; 95% CI, 0.92–1.53), and refined grains (HR for fifth quintile, 1.16; 95% CI, 0.91–1.48).

Discussion

Our findings suggest an increased risk of premenopausal breast cancer among women consuming an adolescent and early adulthood diet that is associated with markers of inflammation. This increased risk did not extend to postmenopausal breast cancer and was not significantly different by hormone receptor subtype.

Few studies on adolescent diet and breast cancer have been undertaken because of the difficulty in assessing diet during

Table 2. Adolescent and early adulthood inflammatory dietary pattern^a and breast cancer, NHS II, 1989–2011

	Quintile of intake					P _{trend} ^b
	1	2	3	4	5	
Adolescent inflammatory pattern						
Premenopausal cases						
No. of cases	162	154	180	189	185	
Person-years	131,603	133,112	132,213	131,417	129,387	
Age-adjusted RR	1.00	0.94 (0.75–1.17)	1.11 (0.89–1.38)	1.21 (0.97–1.51)	1.23 (0.97–1.56)	0.02
Adjusted for adolescent characteristics ^c	1.00	0.95 (0.76–1.18)	1.11 (0.90–1.39)	1.25 (1.00–1.56)	1.30 (1.02–1.65)	0.007
Adjusted for adolescent and adult characteristics ^d	1.00	0.96 (0.77–1.20)	1.14 (0.92–1.42)	1.30 (1.04–1.62)	1.35 (1.06–1.73)	0.002
Postmenopausal cases						
No. of cases	104	108	92	104	82	
Person-years	42,409	41,848	42,314	43,041	44,510	
Age-adjusted RR	1.00	1.03 (0.79–1.35)	0.89 (0.67–1.18)	0.99 (0.74–1.32)	0.78 (0.56–1.08)	0.15
Adjusted for adolescent characteristics ^c	1.00	1.03 (0.78–1.35)	0.89 (0.67–1.19)	0.99 (0.74–1.33)	0.82 (0.59–1.14)	0.25
Adjusted for adolescent and adult characteristics ^d	1.00	1.03 (0.78–1.36)	0.90 (0.67–1.21)	1.01 (0.75–1.35)	0.84 (0.60–1.17)	0.33
All cases						
No. of cases	280	297	295	318	287	
Person-years	182,457	183,842	183,627	183,743	183,080	
Age-adjusted RR	1.00	1.04 (0.88–1.23)	1.05 (0.89–1.24)	1.13 (0.96–1.34)	1.02 (0.85–1.23)	0.62
Adjusted for adolescent characteristics ^c	1.00	1.05 (0.89–1.23)	1.06 (0.90–1.25)	1.16 (0.98–1.37)	1.08 (0.89–1.29)	0.28
Adjusted for adolescent and adult characteristics ^d	1.00	1.05 (0.89–1.24)	1.07 (0.90–1.27)	1.18 (1.00–1.40)	1.11 (0.92–1.34)	0.16
Early adulthood inflammatory pattern						
Premenopausal cases						
No. of cases	168	163	175	155	161	
Person-years	128,118	127,650	128,066	123,731	115,401	
Age-adjusted RR	1.00	1.02 (0.82–1.27)	1.14 (0.92–1.41)	1.06 (0.85–1.32)	1.24 (0.99–1.55)	0.06
Adjusted for adolescent characteristics ^c	1.00	1.02 (0.82–1.27)	1.13 (0.91–1.40)	1.04 (0.84–1.30)	1.26 (1.00–1.57)	0.06
Adjusted for adolescent and adult characteristics ^d	1.00	1.05 (0.85–1.31)	1.19 (0.96–1.48)	1.12 (0.89–1.40)	1.41 (1.11–1.78)	0.006
Postmenopausal cases						
No. of cases	124	109	92	87	56	
Person-years	49,735	43,102	39,881	37,052	33,510	
Age-adjusted RR	1.00	1.07 (0.82–1.38)	0.98 (0.75–1.29)	0.98 (0.74–1.30)	0.74 (0.54–1.03)	0.09
Adjusted for adolescent characteristics ^c	1.00	1.06 (0.82–1.38)	0.98 (0.74–1.28)	0.97 (0.73–1.28)	0.75 (0.54–1.04)	0.10
Adjusted for adolescent and adult characteristics ^d	1.00	1.05 (0.81–1.37)	0.98 (0.74–1.29)	0.99 (0.74–1.32)	0.76 (0.54–1.06)	0.14
All cases						
No. of cases	313	290	295	267	234	
Person-years	187,213	179,486	176,507	168,808	156,452	
Age-adjusted RR	1.00	1.03 (0.88–1.21)	1.09 (0.93–1.28)	1.05 (0.89–1.24)	1.04 (0.87–1.24)	0.62
Adjusted for adolescent characteristics ^c	1.00	1.02 (0.87–1.20)	1.08 (0.92–1.27)	1.04 (0.88–1.22)	1.04 (0.88–1.24)	0.60
Adjusted for adolescent and adult characteristics ^d	1.00	1.04 (0.88–1.22)	1.11 (0.94–1.30)	1.08 (0.91–1.28)	1.11 (0.93–1.33)	0.22
Average of adolescent and early adult inflammatory pattern						
Premenopausal cases						
No. of cases	151	162	167	166	176	
Person-years	121,899	124,191	124,665	126,767	125,443	
Age-adjusted RR	1.00	1.08 (0.86–1.35)	1.12 (0.90–1.41)	1.14 (0.90–1.43)	1.29 (1.02–1.64)	0.04
Adjusted for adolescent characteristics ^b	1.00	1.10 (0.88–1.37)	1.14 (0.91–1.43)	1.16 (0.92–1.45)	1.35 (1.06–1.71)	0.02
Adjusted for adolescent and adult characteristics ^c	1.00	1.12 (0.89–1.40)	1.19 (0.95–1.49)	1.23 (0.97–1.55)	1.49 (1.16–1.90)	0.002
Postmenopausal cases						
No. of cases	93	115	110	77	73	
Person-years	43,070	41,079	41,193	38,753	39,186	
Age-adjusted RR	1.00	1.28 (0.97–1.69)	1.26 (0.95–1.68)	0.95 (0.69–1.30)	0.94 (0.67–1.31)	0.37
Adjusted for adolescent characteristics ^c	1.00	1.29 (0.97–1.70)	1.27 (0.96–1.69)	0.95 (0.69–1.31)	0.98 (0.70–1.36)	0.49
Adjusted for adolescent and adult characteristics ^d	1.00	1.29 (0.97–1.71)	1.30 (0.97–1.73)	0.95 (0.69–1.31)	1.01 (0.71–1.43)	0.62
All cases						
No. of cases	263	295	301	270	270	
Person-years	172,972	173,937	174,412	173,870	173,275	
Age-adjusted RR	1.00	1.14 (0.96–1.35)	1.18 (0.99–1.39)	1.09 (0.91–1.29)	1.13 (0.94–1.36)	0.30
Adjusted for adolescent characteristics ^c	1.00	1.15 (0.97–1.36)	1.19 (1.01–1.41)	1.10 (0.92–1.31)	1.18 (0.98–1.42)	0.16
Adjusted for adolescent and adult characteristics ^d	1.00	1.15 (0.97–1.36)	1.22 (1.03–1.44)	1.13 (0.94–1.35)	1.25 (1.03–1.52)	0.04

^aThe inflammatory pattern is characterized by higher intake of sugar-sweetened and diet soft drinks, refined grains, red and processed meat, margarine, corn, other vegetables, and fish and lower intake of green leafy vegetables, yellow vegetables, cruciferous vegetables, and coffee.

^bTrend based on median values of each quintile.

^cAdjusted for age (continuous), total calories in adolescence (continuous), height at age 18 (continuous), age at menarche (<11, 11, 12, 13, 14, 15+), BMI at age 18 (continuous), physical activity in adolescence (<21, 21–35, 36–53, 54–80, 81+ metabolic equivalent tasks/week), and family history of breast cancer (yes, no).

^dAdjusted for the variables above plus age at first birth (<25, 25–30, 31+ years), parity (nulliparous, 0, 1, 2, 3, 4+), oral contraceptive use (never use, past use <5 years, past use 5+ years, current use <5 years, current use 5–9 years, current use 10+ years), physical activity in adulthood (<3, 3–8, 9–17, 18–26, 27–41, 42+ metabolic equivalent tasks/week), alcohol consumption (non-drinker, <7.5, 7.5–15, 15–29, 30+ grams/day), weight change since age 18 (continuous), and history of benign breast disease (yes, no). In the analyses including postmenopausal women, we additionally adjusted for hormone replacement therapy use (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users) and menopausal status/age at menopause (premenopausal, unknown menopause, <45, 45–46, 47–48, 49–50, 51–52, 53+ years).

Table 3. Adolescent and early adulthood inflammatory dietary pattern^a and breast cancer risk by hormone receptor status, NHS II, 1989–2011

	Quintile of intake					<i>P</i> _{trend} ^b	<i>P</i> _{heterogeneity} ^c
	1	2	3	4	5		
Adolescent inflammatory pattern							
Premenopausal cases							
ER+/PR+, No. of cases	100	94	117	102	105		0.47
Multivariable model ^d	1.00	0.95 (0.71–1.27)	1.22 (0.93–1.61)	1.19 (0.88–1.59)	1.34 (0.97–1.84)	0.04	
ER–/PR–, No. of cases	28	25	24	39	32		
Multivariable model ^d	1.00	0.89 (0.51–1.54)	0.85 (0.49–1.49)	1.41 (0.84–2.37)	1.22 (0.67–2.19)	0.24	
Postmenopausal cases							
ER+/PR+, No. of cases	62	66	55	49	53		0.77
Multivariable model ^d	1.00	1.06 (0.74–1.52)	0.94 (0.64–1.37)	0.86 (0.58–1.28)	1.01 (0.66–1.55)	0.75	
ER–/PR–, No. of cases	15	16	20	19	9		
Multivariable model ^d	1.00	0.99 (0.48–2.04)	1.16 (0.57–2.37)	0.97 (0.46–2.06)	0.49 (0.19–1.24)	0.18	
Early adulthood inflammatory pattern							
Premenopausal cases							
ER+/PR+, No. of cases	101	101	105	86	100		0.27
Multivariable model ^d	1.00	1.07 (0.81–1.42)	1.16 (0.87–1.53)	1.03 (0.76–1.38)	1.48 (1.09–1.99)	0.03	
ER–/PR–, No. of cases	24	21	36	25	32		
Multivariable model ^d	1.00	0.91 (0.50–1.64)	1.75 (1.03–2.97)	1.26 (0.70–2.25)	1.81 (1.02–3.22)	0.03	
Postmenopausal cases							
ER+/PR+, No. of cases	73	56	53	58	35		0.35
Multivariable model ^d	1.00	0.87 (0.61–1.24)	0.95 (0.66–1.37)	1.13 (0.78–1.62)	0.83 (0.54–1.27)	0.78	
ER–/PR–, No. of cases	22	14	20	12	8		
Multivariable model ^d	1.00	0.74 (0.36–1.49)	1.07 (0.56–2.04)	0.72 (0.34–1.51)	0.44 (0.18–1.08)	0.11	
Average of adolescent and early adult inflammatory pattern							
Premenopausal cases							
ER+/PR+, No. of cases	93	101	107	88	104		0.06
Multivariable model ^d	1.00	1.14 (0.85–1.52)	1.25 (0.93–1.66)	1.08 (0.79–1.48)	1.55 (1.12–2.13)	0.02	
ER–/PR–, No. of cases	19	27	22	34	36		
Multivariable model ^d	1.00	1.47 (0.81–2.67)	1.25 (0.66–2.35)	1.92 (1.06–3.48)	2.21 (1.17–4.16)	0.009	
Postmenopausal cases							
ER+/PR+, No. of cases	73	56	53	58	35		0.94
Multivariable model ^d	1.00	1.10 (0.76–1.60)	1.32 (0.91–1.91)	0.93 (0.61–1.40)	1.13 (0.72–1.76)	0.80	
ER–/PR–, No. of cases	22	14	20	12	8		
Multivariable model ^d	1.00	1.67 (0.82–3.40)	1.07 (0.50–2.29)	0.90 (0.40–2.06)	0.93 (0.39–2.24)	0.48	

^aThe inflammatory pattern is characterized by higher intake of sugar-sweetened and diet soft drinks, refined grains, red and processed meat, margarine, corn, other vegetables, and fish and lower intake of green leafy vegetables, yellow vegetables, cruciferous vegetables, and coffee.

^bTrend based on median values of each quintile.

^cUsing a likelihood ratio test, a model with separate HRs for each hormone receptor subtype was compared to a model with a common HR.

^dAdjusted for age (continuous), total calories in adolescence (continuous), height at age 18 (continuous), age at menarche (<11, 11, 12, 13, 14, 15+), BMI at age 18 (continuous), physical activity in adolescence (<21, 21–35, 36–53, 54–80, 81+ metabolic equivalent tasks/week), family history of breast cancer (yes, no), age at first birth (<25, 25–30, 31+ years), parity (nulliparous, 0, 1, 2, 3, 4+), oral contraceptive use (never use, past use <5 years, past use 5+ years, current use <5 years, current use 5–9 years, current use 10+ years), physical activity in adulthood (<3, 3–8, 9–17, 18–26, 27–41, 42+ metabolic equivalent tasks/week), alcohol consumption (non-drinker, <7.5, 7.5–15, 15–29, 30+ grams/day), weight change since age 18 (continuous), and history of benign breast disease (yes, no). In the analyses including postmenopausal women, we additionally adjusted for hormone replacement therapy use (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users) and menopausal status/age at menopause (premenopausal, unknown menopause, <45, 45–46, 47–48, 49–50, 51–52, 53+ years).

this time period. Among the limited number of previous studies, higher adolescent soy (21–24) and fiber (25–28) intake have been suggested to have an inverse association with breast cancer risk, whereas red meat has been suggested to increase risk only among premenopausal women (29). Dietary pattern analysis, in which different combinations of food intake are examined, is a complementary approach to the study of individual foods and nutrients that takes into account diet as whole by examining the cumulative effects of foods (30). However, adolescent and early adulthood dietary patterns have rarely been examined in the context of breast cancer risk.

Most previous studies examining dietary patterns and breast cancer risk have focused on adult dietary patterns derived using principal components analysis (PCA)/factor analysis (6–9). More recently, a dietary inflammatory index (DII) has been developed on the basis of an extensive literature review of diet and inflam-

matory markers (31). A meta-analysis of adult dietary patterns derived using PCA/factor analysis has suggested an 7% reduced risk of breast cancer for women in the highest category of adult prudent/healthy dietary pattern score (95% CI, 0.88–0.98; ref. 7). Among the three study populations that have examined adult dietary inflammation potential and breast cancer outcomes, two reported no significant association with overall breast cancer risk (32–34) and one reported a borderline positive association between DII and breast cancer (35). To our knowledge, the NHS II cohort is the only study to examine adolescent dietary patterns derived by PCA, whereas no studies have examined an adolescent diet DII and breast cancer risk. In an analysis including both pre- and postmenopausal breast cancer cases, we previously observed a significant inverse trend with greater intake of a "prudent" adolescent dietary pattern, characterized by high intake of vegetables, fruits, legumes, fish, and poultry but no association with a "Western" dietary pattern, characterized by high intake of refined

grains, red and processed meats, sweets, and potatoes (10). In PCA, the derived patterns reflect the correlation structure between foods thus are independent of the outcome of interest. The method for deriving dietary patterns that we utilized in the current analyses reduced rank regression, may result in dietary patterns more predictive of disease risk as this method utilizes intermediate biomarkers that are associated or potentially associated with the endpoint of interest (11).

The inflammatory pattern we examined has previously been associated with type II diabetes (16) and depression (15) in the Nurses' Health Study. However, to our knowledge, no previous studies have examined the association between this dietary pattern and incidence of breast cancer. The increased risk we observed for this dietary pattern was limited to premenopausal breast cancer. The risk factor profiles for pre- and postmenopausal breast cancer differ. Postmenopausal breast cancer has been found to be more strongly driven by hormonally related risk factors, whereas fewer modifiable risk factors have been identified for premenopausal breast cancer (36–39). Some studies have suggested that hyperinsulinemia and glucose are associated with increased premenopausal breast cancer risk (40–42). The association between the biomarkers used to define our inflammatory pattern (CRP, IL6, and TNF α receptor 2) and breast cancer risk is not entirely clear; however, this may be due to previous studies of these biomarkers examining primarily postmenopausal breast cancer. CRP has generated nonsignificant positive associations (43–45), significant associations among subgroups (46), or no association (47) with predominantly postmenopausal breast cancer risk in previous studies. IL6 has been nonsignificantly associated with postmenopausal breast cancer in a pooled analysis of two studies (43) and may have prognostic value in women with breast cancer (48), whereas TNF α has been shown to contribute to tumor progression in mammary cell lines (49). Our inflammatory dietary pattern was characterized by higher intake of sweetened soft drinks, diet soft drinks, refined grains, red meat, processed meat, margarine, corn, other vegetables, fish, and lower intake of green leafy vegetables, yellow vegetables, cruciferous vegetables, and coffee. The mechanism(s) through which this type of diet during adolescence and early adulthood may influence risk is not clear; however, these results are consistent with the established association between chronic inflammation and multiple types of cancer (50). This pattern may influence the risk of premenopausal breast cancer through pathways unrelated to the specific inflammatory biomarkers used in the pattern derivation.

There are several limitations to our study. First, we did not have biomarkers available from our participants during adolescence to identify the inflammatory pattern. Instead, we utilized a dietary pattern previously derived in primarily postmenopausal women in the NHS (15, 16) and then used a simplified score approach (17) to create these patterns in the women who had completed the HS-FFQ and early adulthood FFQ. If food intake during adolescence or early adulthood has different influences on inflammatory biomarker levels, this would not be reflected in our adolescent dietary pattern. In addition, the inflammatory biomarkers were not specifically chosen for their association with breast cancer. However, regardless of how the pattern was derived, we observed a clear association between the inflammatory pattern in adolescence

and early adulthood and premenopausal breast cancer that is unlikely to be entirely explained by bias or chance.

Another limitation is that diet during high school was self-reported by participants when they were 33–52 years old and some error in its measurement is expected. However, the recall of adolescent diet in the NHS II has been demonstrated to be reasonably valid and reproducible (13, 14). In addition, our combined and prospective analyses yielded consistent results, thus any misclassification was likely nondifferential resulting in an attenuation of the true effect. Because a purely prospective cohort study linking adolescent diet to breast cancer would span many decades of data collection, the use of recalled diet in a prospective analysis provides an important means for studying dietary exposures and later life outcomes.

In conclusion, we observed an association between an adolescent and early adulthood inflammatory dietary pattern, characterized by high intake of sugar-sweetened and diet soft drinks, refined grains, red and processed meat, margarine, corn, other vegetables, and fish, and lower intake of green leafy vegetables, cruciferous vegetables, and coffee and the risk of premenopausal breast cancer. This association was strongest when the cumulative effect of adolescent and early adulthood diet were considered together but did not influence risk of postmenopausal breast cancer. This is an important finding as much less is known about modifiable risk factors for premenopausal breast cancer. Whether this association is mediated through inflammatory processes or other mechanisms deserves further study.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: H.R. Harris, W.C. Willett, K.B. Michels

Development of methodology: H.R. Harris

Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): K.B. Michels

Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): H.R. Harris, W.C. Willett, R.L. Vaidya, K.B. Michels

Writing, review, and/or revision of the manuscript: H.R. Harris, W.C. Willett, R.L. Vaidya, K.B. Michels

Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): W.C. Willett

Study supervision: K.B. Michels

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