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Adolescent diet and risk of breast cancer

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Abstract

Objectives: To investigate the components of adolescent diet that may influence risk of breast cancer as an adult.
Methods: Retrospective cohort study among 47,355 participants in the Nurses Health Study II who answered a 131-item food frequency questionnaire about diet during high school. Cox proportional hazards regression was used to estimate relative risks and 95% confidence intervals among incident cases of breast cancer between 1989 (inception of the study) and 1998 (when high school diet was assessed).
Results: Intakes of fat and fiber were not significantly related to risk of breast cancer in multivariate analysis, but increased intake of vegetable fat (Q_5 *versus* Q_1 multivariate RR = 0.58, 95% CI (0.38–0.86); test for trend $p = 0.005$) and vitamin E (Q_5 *versus* Q_1 multivariate RR = 0.61, 95% CI (0.42–0.89); test for trend $p = 0.003$) were associated with a lower risk. A higher dietary glycemic index (Q_5 *versus* Q_1 multivariate RR = 1.47, 95% CI (1.04–2.08); test for trend $p = 0.01$) was associated with increased risk of breast cancer.
Conclusions: The apparent protective effects of vegetable fat and vitamin E and adverse effect of high glycemic foods on risk of breast cancer need confirmation in prospective analyses.

Abbreviations: BBD – benign breast disease; FFQ – food frequency questionnaire; NHS – nurses' health study; Q – quintile

Introduction

The etiologic role of adolescent diet in breast cancer has been suggested by studies that have shown that exposures during early life are associated with increased risk of breast cancer as an adult [1]. The mammary gland develops postnatally, during the adolescent growth spurt, in contrast to other organs that develop primarily in utero [2, 3]. The hormonal and micronutrient status of the adolescent, therefore, may have significant impact on the likelihood of malignant transformation of the developing adolescent breast. In animal models, energy restriction in the peripubertal period inhibits mammary tissue proliferation and reduces subsequent risk of mammary tumors [4, 5]. Likewise, Norwegian women who were adolescents during the 'Hunger Winter' of World War II, when average caloric intake dropped 22%, have a reduced incidence of breast cancer, supporting the hypothesis that energy restriction during this period may reduce risk [6]. Also, increased adult height, an indicator of ample nutrition in early life, has been associated with increased risk of breast cancer [7]. Breast cancer rates among Asian immigrants to the United States do not rise to the level of US white women until the second or third generation, again supporting the hypothesis that exposures during early life, including diet, may be fundamental in establishing later risk of

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breast cancer [8, 9]. Carcinogenic exposures during adolescence appear to be more potent than exposures that occur later in life. For instance, exposure of rats to chemical carcinogens prior to *versus* after first pregnancy increases incidence of mammary tumors [10, 11]. Among humans, exposure to ionizing radiation increases risk of breast cancer, but the rate elevation is much greater if exposed as a child or young adult [12].

One possible biologic explanation for these observations comes from the study of mammary gland development in rats [10, 11]. During adolescence, the solid terminal end buds either branch into a system of ducts or become alveolar buds, which in turn differentiate into milk-producing lobuloalveoli during pregnancy [10, 11]. This tissue remodeling is accomplished by changing rates of cell proliferation and apoptosis. Deficiencies or excesses in the micronutrient and/or hormonal environment during adolescence may directly affect cellular growth, differentiation and programmed cell death. Another possible direct mechanism for adolescent diet and risk of breast cancer is the influence that diet may have on the secretion of growth factors, such as IGF-1, known to be associated with risk of premenopausal breast cancer [13]. In addition, the effect of adolescent diet may be more indirect, for instance, by causing later age at menarche. Later age at menarche is associated with a delay in the onset of regular ovulatory cycles, as well as significantly lower levels of both estradiol and sex hormone binding globulin (SHBG) than women with earlier menarche [14]. Lower hormone levels persist not just throughout puberty but into young adulthood as well [14].

To evaluate the role of adolescent diet in breast cancer etiology, we conducted a retrospective study among participants in the Nurses' Health Study II (NHS II). We specifically examined several factors that have been hypothesized to increase risk (total and animal fat and high glycemic index) or to reduce risk (dietary fiber, antioxidants, and vitamin A), [15] and we also explored associations with a wide variety of dietary components because existing data on adolescent diet and breast cancer are limited.

Materials and methods

NHS II

The NHS II is a prospective cohort of 116,671 women who have completed biennial questionnaires on medical events and lifestyle factors since the initiation of the study in 1989 when they were 25–42 years of age. The study has been approved by the institutional review board at the Harvard School of Public Health.

High school food-frequency questionnaire (FFQ)

In 1997, on the biannual NHS II questionnaire, participants were asked whether they would be willing to fill out a supplemental questionnaire on diet during high school, and 56,928 participants so indicated (48.7% of the total cohort). In 1998, when participants were 34–51 years of age, they were sent a 131-item FFQ about diet during high school. (The years that the participants would have been in high school range from 1962 to 1982.) Categories included main dishes, bread and cereals, fruits, vegetables, condiments, snack foods, dairy products and beverages and was similar in design to the questionnaire we have used for adult dietary assessment [16]. The FFQ was designed to include foods that were common during high school (*e.g.* milkshakes and other snack foods) and did not include foods that were not prevalent when this cohort of women would have been in high school (*e.g.* low-fat snack products). Foods that account for major sources of fat, antioxidant vitamins, and carotenoids were included. For each food item on the FFQ, a unit or portion size was specified. Subjects were asked how often, on average, they had consumed the specified amount of each item. Nine possible responses were provided ranging from 'never' to 'six or more per day. Recall of adolescent diet has been shown to be reproducible and not highly correlated with current diet in a cohort of older women [17].

Nutrient intakes were computed for each subject by assigning a weight proportional to the frequency of use of each food, multiplying this weight by the nutrient value for the specified portion size, and summing the contributions of all foods. The nutrient database used in this study was derived from the US Department of Agriculture Handbook [18] with additional information from McCance and Widdowson's *The Composition of Foods* [19], data obtained from food manufacturers and other independent academic sources, *e.g.* [20]. To control for total energy intake, all nutrients were adjusted for total energy using the residual method [21].

Each individual food on the questionnaire was analyzed for its relation to risk of breast cancer. In addition, we grouped foods to evaluate a more general effect of a certain category of food. Groupings included high fat dairy, low fat dairy, total dairy, red meat, vegetables, fruit, chicken, fish and bread. (Foods included in each grouping are detailed in the footnote to Table 2.) We derived for each participant an average dietary glycemic index value. The glycemic index ranks foods on the basis of the postprandial rise in serum glucose compared to the rise in serum glucose for a specified amount of reference carbohydrate (white bread) [22]. The total glycemic index value for an individual is calculated by

summing the carbohydrate content per serving of each food [23] times the reported average number of servings per day of that food times the published glycemic index for that food [24], all divided by the total amount of daily carbohydrate intake [25]. Glycemic load is calculated in a similar fashion, except that the total glycemic index value is not divided by the total daily intake of carbohydrate.

Study population

Participants who completed the high school FFQ were eligible for the study (n = 47,355 participants; 83% of those who had indicated willingness). Incident cases of invasive breast cancer (n = 838), confirmed by medical record review, who were diagnosed after the initiation of the study in 1989 and before the high school FFQ was mailed in June 1998 were identified for inclusion in the study. 469 cases indicated on the 1997 questionnaire that they would be willing to fill out the high school FFQ (56% of total cases); this rate is slightly higher than the rate of willingness among the entire cohort (48%). Among those who indicated that they were willing to fill out a high school FFQ, 80% of cases (n = 373) actually completed and returned the high school FFQ (similar to 83% response rate in the overall cohort). Forty-eight of the cases had died prior to 1998. Women were excluded from the analysis if the total calories reported on high school diet were implausible, *i.e*. less than 500 or greater than 5000 (n = 9 cases), or if they had previously been diagnosed with cancer other than breast cancer (n = 2 cases), or had been diagnosed with breast cancer prior to initiation of the study in 1989 (n = 1 case). The final case number (n = 361) included 43% of the cases diagnosed between 1989 and June 1998. Included cases had later age at menarche, were more likely to be postmenopausal, and were more likely to report a family history of breast cancer than cases not included in the analysis. We compared current adult diet (1995) between included *versus* excluded cases. Intake of vegetable fat, vitamin E, total bread intake were not significantly different (data not shown); excluded cases has slightly higher glycemic index than included cases (76.5 *versus* 75.5).

Statistical analysis

The risk factor status of both cases and non-cases was updated from the questionnaire most recently completed before date of diagnosis. Risk factors that were updated included: menopausal status, family history of breast cancer, diagnosis of benign breast disease (BBD), parity and age at first birth, oral contraceptive use and weight gain since age 18. All tests of significance were two-sided. Differences in risk factor status between cases and non-cases were tested using χ^2 or *t*-tests.

Person-months of follow-up were counted from the date of return of the 1989 questionnaire to the date of diagnosis of invasive breast cancer, to death or to June 1998, whichever came first. Nutrients were analyzed using quintiles of intake. Cox proportional hazards regression was used to estimate relative risks (and 95% confidence intervals) while controlling simultaneously for potentially confounding variables [26]. Monotonic trends across quintiles of nutrient intake were tested by modeling median intake per quintile as a continuous variable in a logistic model. Multivariate models included age, family history of breast cancer in mother or sister, diagnosis of BBD, age at menarche, body mass index at age 18, weight gain since age 18, adult height, adult alcohol consumption, total caloric intake in high school, menopausal status, current oral contraceptive use, and reproductive history. Analyses were also adjusted for current animal fat intake from the 1995 NHS II dietary questionnaire because this nutrient has been shown to be related to adult risk of breast cancer [27], but this addition to the multivariate model did not substantially change any of the results report (data not shown).

Results

Table 1 presents the distribution of risk factors for breast cancer among cases *versus* non-cases. Cases were older than non-cases (40.9 *versus* 38.3 years), taller (65.3 *versus* 64.9 cm) and reported a later age at first birth (26.5 *versus* 26.1 years). Cases were more likely to report an early age at menarche (less than age 12) (29 *versus* 25%), family history of breast cancer (18.8 *versus* 9.5%), history of BBD (51.2 *versus* 38.5%). Differences in parity, menopausal status, current oral contraceptive use, current smoking, BMI at age 18, current BMI and weight gain since age 18 were not significant.

Food groups were examined for possible association with risk of breast cancer (Table 2). Intake of total dairy products, high and low fat dairy products, fruits, vegetables, and meat were each unrelated to risk.

Total bread intake was positively associated with risk of breast cancer (Q_5 *versus* Q_1 multivariate RR = 1.40, 95% CI (0.96–2.04); test for trend $p = 0.01$). Among the 131 individual food items, only white bread showed a significant positive relation (data not shown).

We next evaluated total energy intake and types of fat in relation to risk of breast cancer (Table 3). Higher total caloric intake was associated with increased risk of breast cancer (Q_5 *versus* Q_1 multivariate RR = 1.39,

Table 1. Distribution of breast cancer cases and non-cases according to selected risk factors

Variable	Cases (n = 361)	Non-cases (n = 47,517)	Test of significance *p*-Value
Mean			
Age in 1989 (years)	40.9	38.3	<0.0001
Age at first birth (years)	26.5	26.1	0.04
BMI at age 18 (kg/m^2)	20.8	21.2	0.17
BMI in 1989 (kg/m^2)	23.2	23.8	0.34
Weight gain since age 18 (kg)	8.3	9.2	0.10
Height (cm)	65.3	64.9	0.02
Percent of group			
Postmenopausal	5.2%	5.8%	0.52
Age at menarche < 12 years	29%	25%	0.002
Parity ≥3	19.5%	22.3%	0.55
Current oral contraceptive use	9.8%	9.9%	0.51
Current smoker	13.7%	10.2%	0.64
Family history of breast cancer	18.8%	9.5%	<0.0001
History of BBD	51.2%	38.5%	<0.0001

Table 2. Relative risk of breast cancer according to quintile of food group intake during adolescence among women in the NHS II

Food groups[a]	Quintile of intake					Test for trend
	1	2	3	4	5	
Total dairy (w/out butter)						
Cases per quintile	65	64	79	85	68	
Median servings per day	1.0	1.9	2.8	3.6	4.9	
Age/calorie-adjusted RR (95% CI)	1.00	0.96 (0.67–1.36)	1.11 (0.79–1.56)	1.14 (0.81–1.61)	0.93 (0.63–1.38)	0.86
Multivariate[b] RR	1.00	0.92 (0.65–1.31)	1.05 (0.75–1.48)	1.06 (0.75–1.50)	0.83 (0.56–1.24)	0.81
High fat dairy						
Cases per quintile	53	58	72	91	87	
Median servings per day	0.6	1.2	2.0	3.3	5.2	
Age/calorie-adjusted RR (95% CI)	1.00	1.00 (0.68–1.50)	1.11 (0.77–1.59)	1.29 (0.90–1.82)	1.17 (0.80–1.71)	0.13
Multivariate[b] RR (95% CI)	1.00	0.99 (0.68–1.44)	1.08 (0.75–1.56)	1.26 (0.88–1.79)	1.11 (0.76–1.62)	0.20
Low fat dairy						
Cases per quintile	52	130	64	56	59	
Median servings per day	0	0.1	0.3	0.8	2.6	
Age/calorie-adjusted RR (95% CI)	1.00	1.10 (0.80–1.51)	0.94 (0.65–1.36)	0.79 (0.54–1.15)	0.94 (0.65–1.36)	0.36
Multivariate[b] RR (95% CI)	1.00	1.08 (0.78–1.49)	0.90 (0.62–1.30)	0.75 (0.51–1.11)	0.88 (0.60–1.29)	0.24
Total red meat						
Cases per quintile	55	63	71	96	76	
Median servings per day	0.7	1.1	1.4	1.9	2.5	
Age/calorie-adjusted RR (95% CI)	1.00	1.08 (0.75–1.56)	1.14 (0.80–1.64)	1.44 (1.01–2.06)	1.13 (0.76–1.69)	0.26
Multivariate[b] RR	1.00	1.09 (0.75–1.57)	1.16 (0.81–1.67)	1.48 (1.03–2.11)	1.22 (0.82–1.82)	0.17
Total vegetables						
Cases per quintile	61	75	66	85	74	
Median servings per day	1.3	2.0	2.7	3.6	5.3	
Age/calorie-adjusted RR (95% CI)	1.00	1.20(0.85–1.68)	0.99 (0.69–1.41)	1.22 (0.87–1.72)	1.03 (0.71–1.48)	0.82
Multivariate[b] RR	1.00	1.18 (0.84–1.66)	0.97(0.68–1.38)	1.18 (0.84–1.66)	1.00 (0.69–1.44)	0.97
Total fruit						
Cases per quintile	77	51	72	87	73	
Median servings per day	0.7	1.4	2.1	2.8	4.1	
Age/calorie-adjusted RR (95% CI)	1.00	0.63 (0.44–0.89)	0.84 (0.60–1.16)	1.01 (0.74–1.39)	0.83 (0.58–1.18)	0.84
Multivariate[b] RR	1.00	0.59 (0.41–0.85)	0.80 (0.57–1.11)	0.93 (0.68–1.29)	0.75 (0.53–1.07)	0.84
Total chicken						
Cases per quintile	64	77	78	86	55	
Median servings per day	0.1	0.2	0.3	0.6	0.9	

Table 2. (Continued)

Food groups[a]	Quintile of intake					Test for trend
	1	2	3	4	5	
Age/calorie-adjusted RR (95% CI)	1.00	1.56 (1.12–2.17)	1.03 (0.74–1.44)	1.02 (0.74–1.43)	1.31 (0.90–1.91)	0.94
Multivariate[b] RR	1.00	1.52 (1.09–2.13)	1.01 (0.72–1.41)	0.99 (0.71–1.38)	1.29 (0.88–1.88)	0.94
Total fish						
Cases per quintile	72	79	59	73	78	
Median servings per day	0.1	0.1	0.2	0.3	0.6	
Age/calorie-adjusted RR (95% CI)	1.00	0.95 (0.69–1.31)	0.75 (0.53–1.06)	0.83 (0.60–1.15)	0.95 (0.68–1.32)	0.97
Multivariate[b] RR	1.00	0.93 (0.67–1.28)	0.73 (0.52–1.04)	0.80 (0.57–1.11)	0.94 (0.67–1.31)	0.97
Total Bread						
Cases per quintile	57	60	63	99	82	
Median servings per day	0.6	1.1	1.9	2.8	3.9	
Age-adjusted RR (95% CI)	1.00	1.09 (0.76–1.57)	1.13 (0.78–1.63)	1.49 (1.06–2.09)	1.40 (0.97–2.04)	0.02
Multivariate[b] RR	1.00	1.08 (0.75–1.55)	1.11 (0.77–1.60)	1.49 (1.06–2.10)	1.40 (0.96–2.04)	0.01

[a] Composition of food groups.
High fat dairy: whole milk, whole chocolate milk, ice cream, milkshake or frappe, cream cheese, cheese, butter.
Low fat dairy: skim milk, skim chocolate milk, sherbet, yogurt, cottage or ricotta cheese, instant breakfast drink.
Red meat: hot dog, bacon, processed meat, hamburger, beef, pork or lamb as a sandwich, pork as main dish, beef or lamb as main dish, meatloaf.
Vegetable: tomatoes, tomato sauce, string beans, broccoli or brussel sprouts, cauliflower, corn, peas or lima beans, mixed vegetables, raw or cooked spinach, mustard kale chard greens, green peppers, eggplant, zucchini, yams, raw or cooked carrots, celery, radish, lettuce or tossed salad, cabbage or cole slaw, onions as garnish in salad, onion.
Fruits: raisins, grapes, bananas, apples, applesauce, cantaloupe or melons, pears, oranges or grapefruit, strawberries, peaches plums apricots, pineapples, orange juice, apple juice, other fruit juice.
Total fish: breaded fish, tuna, dark fish, other fish.
Total chicken: chicken or turkey main dish, chicken or turkey sandwich.
Total bread: white bread, dark bread, muffin or bagel, cornbread or corn toasties, biscuit or roll.

[b] Multivariate model was adjusted for age, time period (2 year interval), total caloric intake, height (<62, 62–<65, 65–<68, 68+ in.), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity ≤2 and age at first birth 25–<30 years, parity ≤2 and age at first birth 30+ years, parity 3+ and age at first birth <25 years, parity 3+ and age at first birth 25+ years), body mass index at age 18 (<18.5, 18.5–22.4, 22.5–29.9, 30.0+ kg/m^2), age at menarche (<12, 12, 13, ≥14 years), family history of breast cancer (yes, no), history of BBD (yes, no), menopausal status (premenopausal, postmenopausal, dubious, unsure), alcohol intake (non-drinkers, <5, 5–<10, 10–<20, 20+ g/d), oral contraceptive use (never, past ≥4 years, past <4 years, current <8 years, current ≥8 years), weight gain since age 18 (weight loss greater than 5 kg, weight gain or loss 5 kg, weight gain 5–10 kg, weight gain 10–20 kg, weight gain >20 kg).

95% CI (0.99–1.96); test for trend $p = 0.01$). Higher intake of vegetable fat was associated with decreased risk of breast cancer (Q_5 *versus* Q_1 multivariate RR = 0.58, 95% CI (0.38–0.86); test for trend $p = 0.005$). None of the other fats evaluated were related to risk. When results were adjusted for current adult intake of animal fat, none of the results changed appreciably except that the association with saturated fat became somewhat more inverse (p for trend = 0.06).

We next analyzed the relation of micronutrients to risk of breast cancer (Table 4). Vitamin E was the only antioxidant vitamin that was inversely associated with risk of breast cancer (Q_5 *versus* Q_1 multivariate RR = 0.61, 95% CI (0.42–0.89); test for trend $p = 0.003$). Because intakes of vegetable fat and vitamin E were highly correlated ($r = 0.6$, $p < 0.001$), vegetable fat and vitamin E were entered into the model simultaneously; only vitamin E retained its significance.

In the analysis of carbohydrates, (Table 5), a higher dietary glycemic index was positively associated with higher risk of breast cancer (Q_5 *versus* Q_1 multivariate RR = 1.47, 95% CI (1.04–2.08); test for trend $p = 0.01$). Intakes of total fiber, carbohydrates, sucrose and fructose were not associated with risk of breast cancer.

Stratified analyses were undertaken to evaluate effect modification by current smoking, smoking at age 18, family history of breast cancer, history of BBD, body mass index at age 18, current body mass index. No effect modification was evident in any of the subanalyses (data not shown).

Discussion

In this retrospective cohort study, the relation of adolescent diet to risk of breast cancer was evaluated among participants in the NHS II who had completed a 131-item FFQ about diet during high school. Higher intakes of vitamin E and vegetable fat were associated with lower risk of breast cancer. The major dietary

Table 3. Relative risk of breast cancer according to quintile of adolescent caloric and fat intake in women in the NHS II

Nutrient	Quintile of intake					Test for trend
	1	2	3	4	5	
Total calories						
Cases per quintile	58	58	76	87	82	
Median intake per quintile	1782	2282	2676	3118	3833	
Age-adjusted RR (95% CI)	1.00	1.00 (0.70–1.45)	1.34(0.95–1.88)	1.56 (1.12–2.17)	1.46 (1.04–2.05)	0.003
Multivariate RR[a] (95% CI)	1.00	0.99 (0.68–1.42)	1.29 (0.91–1.81)	1.48 (1.06–2.07)	1.39 (0.99–1.96)	0.01
Total fat						
Cases per quintile	79	63	57	71	91	
Median intake per quintile (g/day)	107	117.7	124.5	131.2	140.7	
Age adjusted RR (95% CI)	1.00	0.72 (0.52–1.01)	0.61 (0.44–0.87)	0.73 (0.53–1.01)	0.90 (0.66–1.22)	0.61
Multivariate RR[a] (95% CI)	1.00	0.72 (0.52–1.00)	0.61 (0.43–0.85)	0.74 (0.53–1.02)	0.91 (0.67–1.24)	0.68
Animal fat						
Cases per quintile	51	63	69	87	91	
Median intake per quintile (g/day)	57.5	69.7	78.6	87.7	101.1	
Age adjusted RR (95% CI)	1.00	1.03 (0.71–1.50)	1.00 (0.69–1.45)	1.16 (0.81–1.66)	1.13 (0.79–1.63)	0.37
Multivariate RR[a] (95% CI)	1.00	1.02 (0.70–1.48)	0.99 (0.69–1.44)	1.15 (0.81–1.66)	1.12 (0.78–1.61)	0.38
Vegetable fat						
Cases per quintile	87	95	84	60	35	
Median intake per quintile (g/day)	30.1	38.4	44.4	50.9	60.9	
Age adjusted RR (95% CI)	1.00	1.17 (0.87–1.56)	1.09 (0.81–1.48)	0.85 (0.61–1.19)	0.57 (0.38–0.86)	0.004
Multivariate RR[a] (95% CI)	1.00	1.15 (0.86–1.54)	1.08 (0.80–1.46)	0.86 (0.61–1.19)	0.58 (0.38–0.86)	0.005
Saturated fat						
Cases per quintile	66	61	72	71	91	
Median intake per quintile (g/day)	39.7	45.1	48.9	52.9	58.9	
Age adjusted RR (95% CI)	1.00	0.82 (0.57–1.16)	0.86 (0.61–1.20)	0.78 (0.55–1.10)	0.94 (0.68–1.31)	0.82
Multivariate RR[a] (95% CI)	1.00	0.81 (0.57–1.14)	0.85 (0.61–1.20)	0.78 (0.55–1.09)	0.93 (0.67–1.29)	0.79
Monounsaturated fat						
Cases per quintile	83	63	54	81	80	
Median intake per quintile (g/day)	37.7	41.8	44.5	47.2	51.2	
Age adjusted RR (95% CI)	1.00	0.70 (0.50–0.97)	0.59 (0.42–0.83)	0.86 (0.63–1.17)	0.83 (0.61–1.13)	0.52
Multivariate RR[a] (95% CI)	1.00	0.70 (0.50–0.97)	0.59 (0.42–0.83)	0.87 (0.64–1.18)	0.86 (0.63–1.18)	0.69
Polyunsaturated fat						
Cases per quintile	79	93	67	63	59	
Median intake per quintile (g/day)	15.4	18.0	19.9	22.0	25.5	
Age adjusted RR (95% CI)	1.00	1.20 (0.89–1.62)	0.89 (0.64–1.23)	0.86 (0.62–1.20)	0.86 (0.61–1.20)	0.11
Multivariate RR[a] (95% CI)	1.00	1.19 (0.88–1.60)	0.88 (0.63–1.21)	0.85 (0.61–1.19)	0.86 (0.61–1.20)	0.11

[a] Multivariate model was adjusted for age, time period (two year interval), height (<62, 62–<65, 65–<68, 68+ in.), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity ≤2 and age at first birth 25–<30 years, parity ≤2 and age at first birth 30+ years, parity 3+ and age at first birth <25 years, parity 3+ and age at first birth 25+ years), body mass index at age 18 (<18.5, 18.5–22.4, 22.5–29.9, 30.0+ kg/m^2), age at menarche (<12, 12, 13, ≥14 years), family history of breast cancer (yes, no), history of BBD (yes, no), menopausal status (premenopausal, postmenopausal, dubious, unsure), alcohol intake (non-drinkers, <5, 5–<10, 10–<20, 20+ g/d), oral- contraceptive use (never, past ≥4 years, past <4 years, current <8 years, current ≥8 years), weight gain since age 18 (weight loss greater than 5 kg, weight gain or loss 5 kg, weight gain 5–10 kg, weight gain 10–20 kg, weight gain >20 kg).

sources of vegetable fat and vitamin E were similar and included salad dressing, peanut butter, margarine, mayonnaise, and potato chips. When both items were entered simultaneously in the same model, only vitamin E retained its significance, suggesting that vegetable fat may be the vehicle for delivery of the vitamin E. A higher dietary glycemic index and a higher number of servings per day of bread were associated with a higher risk of invasive breast cancer in this cohort. Higher total caloric intake in adolescence was also associated with increased risk of breast cancer, but this finding may be due to recall bias because total caloric intake has consistently not been associated with risk of breast cancer in prospective studies.

Two other studies have noted an inverse relation between adolescent vegetable fat and risk of breast

Table 4. Relative risk of breast cancer according to quintile of adolescent fiber and vitamin intake in women in the NHS II

Nutrient	Quintile of intake					Test for trend
	1	2	3	4	5	
Folate						
Cases per quintile	80	70	75	75	61	
Median intake (mcg/day)	225.6	271.5	308.3	350.7	437.9	
Age adjusted RR (95% CI)	1.00	0.86 (0.62–1.18)	0.93 (0.68–1.27)	0.96 (0.70–1.32)	0.95 (0.68–1.34)	0.98
Multivariate[a] RR (95% CI)	1.00	0.83 (0.60–1.14)	0.88 (0.64–1.20)	0.90 (0.66–1.24)	0.88 (0.63–1.24)	0.66
Vitamin A						
Cases per quintile	63	85	69	65	80	
Median intake (IU/day)	5905.0	8538.0	10876.0	14215.0	21059.0	
Age adjusted RR (95% CI)	1.00	1.15 (0.83–1.60)	1.15 (0.83–1.60)	0.76 (0.53–1.09)	1.25 (0.90–1.72)	0.52
Multivariate[a] RR (95% CI)	1.00	1.10 (0.79–1.52)	1.10 (0.79–1.53)	0.72 (0.50–1.04)	1.17 (0.85–1.62)	0.72
Retinol						
Cases per quintile	78	67	69	73	74	
Median intake (IU/day)	1417.0	1868.0	2310.0	3012.0	5721.0	
Age adjusted RR (95% CI)	1.00	0.83 (0.60–1.14)	0.85 (0.61–1.17)	0.92 (0.67–1.27)	0.92 (0.67–1.27)	0.97
Multivariate[a] RR (95% CI)	1.00	0.81 (0.58–1.12)	0.82 (0.59–1.13)	0.88 (0.64–1.21)	0.86 (0.63–1.19)	0.76
Vitamin C						
Cases per quintile	65	77	70	81	68	
Median intake (mg/day)	76.1	108.3	138.2	172.1	244.1	
Age adjusted RR (95% CI)	1.00	1.15 (0.83–1.60)	1.03 (0.74–1.45)	1.19 (0.86–1.65)	1.08 (0.77–1.52)	0.70
Multivariate[a] RR (95% CI)	1.00	1.12 (0.80–1.55)	0.99 (0.71–1.39)	1.13 (0.81–1.56)	1.00 (0.71–1.41)	0.91
Vitamin D						
Cases per quintile	72	60	82	74	73	
Median intake (IU/day)	159.6	236.9	324.2	410.6	591.0	
Age adjusted RR (95% CI)	1.00	0.81 (0.57–1.13)	1.03 (0.75–1.41)	0.96 (0.69–1.32)	0.97 (0.70–1.34)	0.78
Multivariate[a] RR (95% CI)	1.00	0.80 (0.57–1.13)	0.99 (0.72–1.37)	0.91 (0.66–1.27)	0.92 (0.66–1.27)	0.91
Vitamin E						
Cases per quintile	80	95	77	68	41	
Median intake (mg/day)	9.8	11.3	12.4	13.5	15.6	
Age adjusted RR (95% CI)	1.00	1.25 (0.93–1.68)	1.05 (0.77–1.43)	0.94 (0.68–1.30)	0.62 (0.42–0.90)	0.004
Multivariate[a] RR (95% CI)	1.00	1.23 (0.92–1.66)	1.04 (0.76–1.42)	0.93 (0.67–1.28)	0.61 (0.42–0.89)	0.003

[a] Multivariate model was adjusted for age, time period (2 year interval), height (<62, 62–<65, 65–<68, 68+ in.), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity ≤2 and age at first birth 25–<30 years, parity ≤2 and age at first birth 30+ years, parity 3+ and age at first birth <25 years, parity 3+ and age at first birth 25+ years), body mass index at age 18 (<18.5, 18.5–22.4, 22.5–29.9, 30.0+ kg/m^2), age at menarche (<12, 12, 13, ≥14 years), family history of breast cancer (yes, no), history of BBD (yes, no), menopausal status (premenopausal, postmenopausal, dubious, unsure), alcohol intake (non-drinkers, <5, 5–<10, 10–<20, 20+ g/d), energy (continuous), oral contraceptive use (never, past ≥4 years, past <4 years, current <8 years, current ≥8 years), weight gain since age 18 (weight loss greater than 5 kg, weight gain or loss 5 kg, weight gain 5–10 kg, weight gain 10–20 kg, weight gain >20 kg).

cancer [28, 29]. In a case–control study conducted in British Columbia with 846 incident cases of breast cancer, women were asked to recall dietary intake of 31 foods during early childhood (up to age 13) [28]. Consumption of vegetable oils was associated with reduced risk among premenopausal women (Q_5 *versus* Q_1 multivariate RR = 0.48, 95% CI (0.25–0.89)). In a nested case–control study among participants in the NHS (a cohort of older women than those who participate in NHS II), women who had higher consumption during adolescence of vegetable fat (Q_5 *versus* Q_1 multivariate RR = 0.85, 95% CI (0.66–1.10); test for trend $p = 0.05$) had a lower risk of breast cancer [29]. This study also noted a non-significant inverse relation between vitamin E and risk of breast cancer (Q_5 *versus* Q_1 multivariate RR = 0.87, 95% CI (0.67–1.14) test for trend $p = 0.18$) [29]. An inverse association between vitamin E and breast cancer has been noted in two case–control studies of adult diet and risk of breast cancer [30, 31], although one prospective study found a modest increase in risk among premenopausal women while other studies have reported null results [15]. Vitamin E succinate induces apoptosis in breast cancer cells *in vitro* [32, 33]; this activity may be important during the remodeling of the terminal end buds during adolescence [10, 11]. In addition, vitamin E succinate inhibits breast

Table 5. Relative risk of breast cancer according to quintile of adolescent glycemic load index and sugar intake in women in the NHS II

Nutrient	Quintile of intake					Test for trend
	1	2	3	4	5	
Total carbohydrate						
Cases per quintile	84	77	61	55	84	
Median intake (gm/day)	263.3	291.4	310.1	329.3	359.1	
Age adjusted RR (95% CI)	1.00	0.94 (0.69–1.29)	0.77 (0.55–1.07)	0.73 (0.52–1.03)	1.21 (0.89–1.64)	0.57
Multivariate[a] RR (95% CI)	1.00	0.93 (0.69–1.27)	0.75 (0.54–1.05)	0.71 (0.50–1.00)	1.21 (0.89–1.64)	0.59
Glycemic load						
Cases per quintile	87	61	65	63	85	
Median glycemic load	202	226	243	260	289	
Age adjusted RR (95% CI)	1.00	0.72 (0.52–1.00)	0.79 (0.58–1.10)	0.81 (0.59–1.12)	1.20 (0.89–1.62)	0.18
Multivariate[a] RR (95% CI)	1.00	0.72 (0.52–1.00)	0.79 (0.57–1.09)	0.82 (0.59–1.13)	1.23 (0.91–1.67)	0.14
Glycemic index						
Cases per quintile	60	72	73	82	74	
Median glycemic index	73.6	76.6	78.5	80.5	83.5	
Age adjusted RR (95% CI)	1.00	1.18 (0.84–1.67)	1.22 (0.87–1.72)	1.43 (1.02–1.99)	1.38 (0.98–1.95)	0.03
Multivariate[a] RR (95% CI)	1.00	1.18 (0.84–1.66)	1.26 (0.89–1.77)	1.49 (1.06–2.08)	1.47 (1.04–2.08)	0.01
Total fiber						
Cases per quintile	82	83	68	66	62	
Median intake (gm/day)	15.1	18.0	20.3	22.8	27.5	
Age adjusted RR (95% CI)	1.00	1.02 (0.75–1.39)	0.85 (0.62–1.18)	0.83 (0.60–1.15)	0.83 (0.59–1.15)	0.13
Multivariate[a] RR (95% CI)	1.00	1.01 (0.74–1.37)	0.84 (0.61–1.16)	0.82 (0.59–1.13)	0.81 (0.58–1.13)	0.11
Sucrose						
Cases per quintile	69	72	80	79	61	
Median intake (gm/day)	50.10	62.50	72.10	83.00	102.4	
Age adjusted RR (95% CI)	1.00	1.05 (0.76–1.47)	1.18 (0.85–1.62)	1.20 (0.87–1.66)	0.96 (0.68–1.35)	0.96
Multivariate[a] RR (95% CI)	1.00	1.05 (0.75–1.46)	1.18 (0.86–1.64)	1.22 (0.88–1.69)	0.98 (0.70–1.39)	0.87
Fructose						
Cases per quintile	66	73	81	59	82	
Median intake (gm/day)	16.98	24.10	29.62	35.86	48.17	
Age adjusted RR (95% CI)	1.00	1.07 (0.77–1.50)	1.21 (0.87–1.67)	0.89 (0.63–1.27)	1.29 (0.93–1.78)	0.24
Multivariate[a] RR (95% CI)	1.00	1.05 (0.75–1.47)	1.18 (0.85–1.63)	0.86 (0.60–1.22)	1.25 (0.91–1.74)	0.32

[a] Multivariate model was adjusted for age, time period (2 year interval), height (<62, 62–<65, 65–<68, 68+ in.), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity ≤2 and age at first birth 25–<30 years, parity ≤2 and age at first birth 30+ years, parity 3+ and age at first birth <25 years, parity 3+ and age at first birth 25+ years), body mass index at age 18 (<18.5, 18.5–22.4, 22.5–29.9, 30.0+ kg/m), age at menarche (<12, 12, 13, ≥14 years), family history of breast cancer (yes, no), history of BBD (yes, no), menopausal status (premenopausal, postmenopausal, dubious, unsure), alcohol intake (non-drinkers, <5, 5–<10, 10–<20, 20+ g/d), energy (continuous), oral contraceptive use (never, past ≥4 years, past <4 years, current <8 years, current ≥8 years), weight gain since age 18 (weight loss greater than 5 kg, weight gain or loss 5 kg, weight gain 5–10 kg, weight gain 10–20 kg, weight gain >20 kg.

tumor growth *in vivo* in the nude mouse model and also inhibits the expression of vascular endothelial growth factor, a potent angiogenic factor [32].

No prior study of adolescent diet and risk of breast cancer has reported on relation of dietary glycemic index to risk of breast cancer, but a case–control study in Italy reported a positive association between the dietary glycemic index of adult diets and risk of breast cancer (Q_5 *versus* Q_1 multivariate OR = 1.4; test for trend $p < 0.01$); consumption of specific high-glycemic index foods was also associated with risk [34]. In an earlier case–control study from Italy, diets higher in carbohydrate and starch were associated with increased risk of breast cancer [35]. High glycemic diets have also been associated with increased risk of colorectal cancer [36] and pancreatic cancer [37]. The Western diet is replete with refined carbohydrate foods that have a high glycemic index, such as bread, potatoes, breakfast cereals, cakes, and cookies. Diets high in these foods result in higher blood levels of glucose and insulin that in turn stimulate the late postprandial secretion of growth factors such as IGF-1 [38]. IGF-1 has a direct mitogenic and anti-apoptotic effect on breast cancer cells *in vitro* [38] and higher levels of IGF-1 have been shown to be associated with higher risk of breast cancer, particularly among premenopausal women [38].

Several other studies of adolescent diet and breast cancer have been conducted besides those previously cited. A case–control study in Utah assessed the impact of adolescent fat and fiber intake on breast cancer risk using a modification of the Block questionnaire [39]. Higher intake of fat from dairy sources was associated with decreased risk of breast cancer for both pre- and postmenopausal women. Higher intake of fiber from grains was related to a lower risk among both pre- and postmenopausal women, whereas overall intake of total fiber was associated with increased risk of breast cancer among postmenopausal women. A case–control study among 1647 cases diagnosed before 45 years of age assessed intake of 29 foods at ages 12–13 [40]. Increased consumption of chicken or high-fat meats was associated with increased risk of breast cancer, whereas increased consumption of fruits and vegetables was associated with a non-significant but lower risk of breast cancer. The effect of adolescent soy intake was assessed in a case–control study of 1459 breast cancer cases living in Shanghai, China [41]. Higher intake of soy as an adolescent was associated with a reduced risk of breast cancer, even after adjustment for other major sources of energy and for adult soy food intake (Q_5 *versus* Q_1 multivariate OR = 0.51, 95% CI (0.40–0.65); test for trend $p < 0.001$). This finding was replicated in a case–control study among of 501 Asian-Americans breast cancer patients living in Los Angeles County [42].

Our study has important limitations. The validity of diet data recalled from the distant past is unknown. Although we have shown that this recall of high school diet is reproducible and that reported high school diet is not highly correlated with current diet among an older cohort of women participating in the NHS [17], we can only infer validity. When Potischman *et al.* interviewed mothers and their adult daughters separately about their daughter's diet during adolescence, she found that there was strong concordance between the report of mother and the report of daughter about foods consumed during the daughter's adolescence, [40], implying that the reports have reasonable inherent accuracy. Others have shown, however, that recall of diet from the distant past is imprecise [43]. Because the breast cancer cases in our study were relatively young, the random error in recall may be less than in some other studied. In the absence of dietary data actually collected during adolescence, recall of high school diet provides the best estimate of possible relationships between diet during adolescence and the risk of breast cancer. A second limitation of the current study is the possibility of recall bias because the high school diet history was obtained after diagnosis of breast cancer. One of the most prevalent dietary hypotheses among the general population in 1998 was the notion that increased fat consumption significantly increased risk. However, in this study, the lack of association with total fat intake suggests that recall bias with respect to dietary consumption was probably not a major factor. A third limitation to the study is response bias. Although the percentage of cases that completed the high school FFQ did not differ significantly from the response rate in the overall cohort, the reasons for non-response may have differed. If women who ate a certain type of diet, for instance a high fat diet, were systematically more likely or less likely to fill out a high school FFQ, then our results would be biased. An advantage of our study is that both cases and non-cases derived from a defined cohort, reducing the likelihood of selection bias. Another limitation is survivor bias. However, because only 48 cases of the 838 total cases died prior to 1998, this is not likely to be a serious source of error. Finally, this analysis was largely exploratory in nature so that some of the finding could be due to chance.

Conclusions

In this retrospective cohort study of adolescent diet and risk of breast cancer, lower intake of vegetable fat and vitamin E and higher intake of high glycemic foods during adolescence was associated with a greater risk of breast cancer as an adult. These findings warrant confirmation in a prospective study.

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