Research Article

Cancer Epidemiology, Biomarkers & Prevention

Adolescent and Early Adulthood Dietary Carbohydrate Quantity and Quality in Relation to Breast Cancer Risk

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Abstract

Background: We investigated quantity and quality of dietary carbohydrate as well as insulin load and insulin index during adolescence and also early adulthood in relation to risk of breast cancer in the Nurses' Health Study II.

Methods: During 20 years of follow-up of 90,534 premenopausal women who completed a diet questionnaire in 1991, 2,833 invasive breast cancer cases were documented. In 1998, 44,263 of these women also completed a questionnaire about their diet during high school; among these women, we documented 1,118 cases of breast cancer. Multivariable-adjusted Cox proportional hazards regression was used to model relative risks (RR) and 95% confidence intervals (95% CI) for breast cancer across categories of dietary carbohydrate, glycemic index (GI), glycemic load (GL), as well as insulin load and insulin index scores.

Results: Adolescent or early adult intakes of GI or GL were not associated with risk of breast cancer. Comparing women in the highest versus lowest quintile, the multivariable-adjusted RRs were 1.14 (0.95–1.38) for adolescent GI scores and 1.03 (0.91–1.16) for early adulthood GI scores. We also did not observe associations with insulin index and insulin load scores in adolescence or early adulthood and breast cancer risk.

Conclusions: We found that diets high in GI, GL, insulin index, and insulin load during adolescence or early adulthood were not associated with an increased risk of breast cancer in this cohort study.

Impact: Diets with a high glucose or insulin response in adolescence or early adulthood were not significant predictors of breast cancer incidence. *Cancer Epidemiol Biomarkers Prev; 24(7); 1111–20. ©2015 AACR.*

Introduction

A higher incidence of breast cancer has been reported in individuals with type II diabetes (1). Among several possible underlying mechanisms, high circulating levels of insulin and insulin-like growth factor I (IGF-I) may play important roles in tumor growth and progression and may increase risk of breast cancer (2–5). IGF-I and estrogen may synergistically stimulate estrogen receptors and cellular proliferation (6).

Several dietary factors contribute to variations in levels of circulating insulin and IGF-I (7, 8). The quality and quantity of ingested carbohydrate, expressed as glycemic index (GI) and glycemic load (GL), respectively, are the major determinants of postprandial blood glucose levels and hence circulating insulin levels (9, 10). The GI is a ranking system for the carbohydrate content of foods based on their postprandial glycemic effects and is a measure of carbohydrate quality. The GL combines the total amounts of carbohydrate usually consumed and its GI values and is a combined measure of carbohydrate quality and quantity that most strongly relates to postprandial insulin (10). Given that protein and fat may also stimulate insulin secretion (11), dietary insulin index, and insulin load scores may more directly address the insulin hypothesis by combining postprandial insulin responses for individual food items, including those with low or no carbohydrate content (11). Although the association between quality and quantity of carbohydrate and breast cancers were not significant in most prospective cohort studies (12–19), a recent meta-analysis of 10 cohort studies found that a diet high in GI, but not GL, was positively associated with breast cancer risk (20). Studies regarding the impact of dietary insulin index and insulin load on breast cancer risk, however, are lacking. Although exposures in childhood and early adulthood may be critical in subsequent risk of cancer (21–23), limited attention has been paid to assess adolescent or early adulthood dietary intake in relation to breast cancer and most of the existing literature is based on diet during midlife and later. However, high intake of refined carbohydrate and added sugar with high GI are reported in adolescence and young adults (24–26); their role in incidence of breast cancer is unclear.

In previous analyses of the Nurses' Health Study II (NHSII; refs. 12, 13), dietary carbohydrate, GI and GL were not associated with risk of premenopausal breast cancer. The current analyses

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included twelve additional years of follow-up and almost four times the number of cases compared with our initial report. Therefore, we were able to examine quantity and quality of carbohydrate intakes as well as insulin load and dietary insulin index scores in adolescence and early adulthood in relation to breast cancers diagnosed before or after menopause. Furthermore, we investigated the associations between these scores and breast cancer by hormone receptor status.

Materials and Methods

Study population

The NHSII is an ongoing cohort study following 116,430 female registered nurses ages 25 to 42 years at enrollment in 1989 from 14 U.S. states. Information on dietary intake was first obtained on 1991 food-frequency questionnaire (FFQ), this served as baseline for starting follow-up. From the 97,813 women who returned the 1991 FFQ, we excluded women who had an implausible total energy intake (<600 or >3,500 kcal/day) or left more than 70 items blank, who were postmenopausal in 1991, had reported a prior diagnosis of cancer (except nonmelanoma skin cancer) before returning the 1991 questionnaire, or had missing information on age. After exclusions, data from 90,534 women were available for the analysis. The follow-up rate was 95% of total potential person-years of follow-up through 2011.

In 1997, participants were asked about their willingness to complete a supplemental food frequency questionnaire about diet during high school (HS-FFQ). From 64,380 women (55% of the entire cohort) who indicated willingness to complete, 47,355 of them returned the HS-FFQ in 1998. There were minimal differences in baseline demographic characteristics and breast cancer rate between participants who completed the HS-FFQ compared with women who did not provide information on high school diet (13). We excluded women who had any cancer except nonmelanoma skin cancer before 1998, or reported implausible daily caloric intake (<600 or $\geq$5,000 Kcal) or had missing information on age. After exclusion, data from 44,263 women were available for the present analysis.

This study was approved by the Human Subjects Committee at Brigham and Women's Hospital and Harvard T.H Chan School of Public Health (Boston, MA).

Dietary assessment

Dietary information during adulthood was evaluated via validated semiquantitative FFQ with approximately 130 items about usual dietary intake and alcohol consumption during the past year (27), which was sent to participants in 1991 and every 4 years thereafter. Dietary intakes in adolescence were obtained from a semiquantitative 124-item HS-FFQ that included food items typically consumed between 1960 and 1980 when they were in high school. To examine the reproducibility of the HS-FFQ, we readministered it to a random sample of 333 NHSII participants in January, 2003; the mean intraclass correlation coefficient was 0.65 (range, 0.50–0.77) for nutrient intakes and 0.58 for carbohydrate intake (28). The reproducibility of the HS-FFQ was also examined by comparing responses to HS-FFQ with 3 24-hour recalls with 10-year interval among 80 young women ages 23 to 29 years at the time of collecting second questionnaire; the mean of corrected correlation coefficients for energy-adjusted nutrient intakes was 0.45 (range, 0.16–0.68; ref. 29). For validity, adolescent dietary intakes reported by 272 NHSII participants using the HS-FFQ were compared with intakes of these participants reported by their mothers; the mean of correlations was 0.40 (range, 0.13–0.59) for nutrients, 0.33 for carbohydrate, 0.43 for GI, and 0.38 for GL (28).

Nutrient intakes were computed by multiplying the frequency of consumption of each unit of food or beverage by the nutrient content of the specified portions and then summing the contributions from all items. The U.S. Department of Agriculture, food manufacturers, and independent academic sources were used to calculate the nutrient intakes (30–32). The food composition database was updated every 4 years to account for changes in the food supply. To calculate the percentage of energy contributed by carbohydrates and other macronutrients, we divided energy intake from that nutrient by total energy intake. GI, GL, insulin load, and dietary insulin index scores were energy-adjusted using the residual method from the regression of these intakes as dependent variable on total energy intake as independent variable (33, 34).

Insulin index values for each food were obtained from either published estimates (31 foods; refs. 11, 35) or direct testing of U.S. food items (73 foods) at the University of Sydney (New South Wales, Australia). The method was described in detail elsewhere (11). Briefly, each person consumed a 1,000 kJ of test foods and the reference food (glucose) on separate days and serum insulin was measured every 15 minutes for 2 hours after consumption, then the area under the 120-minute insulin response curve for 1,000-kJ test food was divided by the area under the 120-minute insulin response curve for 1,000-kJ glucose. Dietary insulin load was calculated by multiplying the insulin index value of each food by the energy content of food, then, summing values for all food items reported [Σ(food insulin index $\times$ energy content of food (kcal/serving) $\times$ frequency of intake (serving/day)]. Each unit of dietary insulin load indicates the equivalent amount of insulin produced by 1 kcal of glucose. The dietary insulin index was calculated by dividing the dietary insulin load by the total energy intake (36).

GI was calculated from a published database (10) or values derived from direct testing of food items by Prof. David J. Jenkins at Nutrition Center of University of Toronto (Toronto, Ontario, Canada). The method was described in detail elsewhere (10). Briefly, dietary GI was measured by dividing the area under the 120-minute incremental blood glucose curve by ingestion of 50 g carbohydrate from test food by the area under the 120-minute incremental blood glucose curve by ingesting the same amount of glucose as a reference food. The average dietary GL was obtained by summing the products of carbohydrate intake for each food by its frequency of intake and dietary GI (37): $\mathrm{GL_{ave}} = \sum_{\alpha=1}^{n} GI\alpha \times CHO\alpha \times \mathrm{frequency}\alpha$, where n is the number of foods consumed, $GI\alpha$ is the glycemic index for food α, $CHO\alpha$ is the carbohydrate content per serving of food α, and frequencyα is the consumption frequency of one serving of food α during the past 12 months. The average dietary GI was calculated by dividing the average GL by the total amount of carbohydrate intake (38).

Documentation of breast cancer

Newly diagnosed invasive breast cancers were identified via biennial NHSII questionnaires. We asked the participant (or next of kin for those who had died) who reported breast cancer

Table 1. Age and age-standardized characteristics according to energy-adjusted glycemic index during early adulthood among women enrolled in the NHSII

	Glycemic index, quintile				
	1	2	3	4	5
Number	18,145	18,163	18,097	18,013	18,116
Mean ± SD					
Age, year	37.0 ± 4.5	36.7 ± 4.6	36.5 ± 4.6	36.2 ± 4.6	35.9 ± 4.7
Carbohydrate intake, percent of energy	47.3 ± 7.6	48.8 ± 6.9	49.5 ± 6.9	50.5 ± 7.1	52.7 ± 7.9
Glycemic index	49.1 ± 2.1	52.3 ± 0.6	54.0 ± 0.5	55.7 ± 0.5	58.3 ± 1.5
Glycemic load	105 ± 18	115 ± 16	121 ± 17	127 ± 18	139 ± 22
Dietary insulin index	41.3 ± 4.9	42.3 ± 3.9	43.1 ± 3.7	43.9 ± 3.7	45.5 ± 4.3
Insulin load	744 ± 91	764 ± 75	778 ± 73	794 ± 73	823 ± 87
Total energy intake, kcal/day	1756 ± 547	1829 ± 547	1830 ± 548	1817 ± 549	1722 ± 541
Alcohol consumption, g/day	4.8 ± 8.6	3.6 ± 6.3	3.0 ± 5.3	2.4 ± 4.7	1.7 ± 3.9
Total fiber intake, g/day	19.4 ± 6.5	19.1 ± 5.5	18.5 ± 5.0	17.9 ± 4.9	16.6 ± 4.9
Total red meat, serving/day	0.7 ± 0.5	0.8 ± 0.5	0.8 ± 0.6	0.9 ± 0.6	0.8 ± 0.6
Body mass index, kg/m^2	24.7 ± 5.0	24.6 ± 5.2	24.6 ± 5.3	24.5 ± 5.4	24.5 ± 5.6
Body mass index at age 18, kg/m^2	21.8 ± 3.5	21.4 ± 3.3	21.2 ± 3.3	21.0 ± 3.2	20.9 ± 3.3
Age at first birth, year	26.0 ± 4.3	26.0 ± 4.2	25.9 ± 4.1	25.8 ± 4.1	25.7 ± 4.1
Percentage					
Current smokers, %	14	12	11	11	12
Current oral contraceptive use, %	11	10	11	11	11
History of benign breast disease, %	9	9	9	9	10
Family history of breast cancer in mother or sisters, %	16	16	15	15	15
Nulliparous, %	33	27	25	24	25
Age at menarche <12 years, %	27	25	24	23	23

for confirmation of the diagnosis and for permission to obtain relevant hospital records and pathology reports. Because of 99% of the self-reported diagnosis of breast cancer were confirmed by pathology report, diagnoses confirmed by participants with missing medical record information ($n = 344$) were included in the analysis. Information on estrogen and progesterone receptor (ER, PR) status of the breast cancer was obtained from pathology reports. Deaths in this cohort were reported through family members and the postal service in response to the follow-up questionnaires or identified through annual review of the National Death Index.

Assessment of other variables

We collected data on potential risk factors for breast cancer from the biennial NHSII questionnaires including age, height, weight, family history of breast cancer, history of benign breast disease, smoking, race, menopausal status, age at menarche, postmenopausal hormone use, and oral contraceptive use. All variables except race, height, and age at menarche were updated to the most recent information, whenever available. Women were considered premenopausal if they still had periods or had hysterectomy with at least one ovary remaining and were younger than 46 years for smokers or younger than 48 years for nonsmokers. Women were considered postmenopausal if they reported natural menopause or had undergone bilateral oophorectomy. We defined women of unknown menopausal status or who had hysterectomy without bilateral oophorectomy as postmenopausal if they were 54 years or older for smokers or 56 years or older for nonsmokers (39).

Body mass index (BMI) at age 18 was obtained from the 1989 questionnaire and was used as a proxy for BMI during high school. Weight change from age 18 was calculated by taking the difference between current weight and recalled weight at age 18. Data on alcohol consumption during adolescence were obtained from the 1989 NHSII questionnaire.

Statistical analysis

We conducted the analyses in three groups: among all women, premenopausal women, and postmenopausal women. Follow-up time began with return of the baseline questionnaire in 1991 for early adulthood dietary intake and with return of HS-FFQ in 1998 for adolescent dietary intake, until either June 2011, the date of breast cancer or any other cancers diagnosis except nonmelanoma skin cancer, or death, whichever came first. In premenopausal group, only premenopausal women were included in analysis; therefore, we stopped follow-up after reporting postmenopausal or uncertain menopausal status in this group. For the postmenopausal group, women started contributing person-time from the first 2-year cycle in which they reported postmenopausal status. Cox proportional hazards models, stratified by age in months and 2-year follow-up cycle, were used to estimate relative risks (RR) and 95% confidence intervals (95% CI). Multivariable models also simultaneously adjusted for race, family history of breast cancer in mother or sisters, history of benign breast disease, smoking, height, age at menarche, parity and age at first birth, oral contraceptive use, menopausal status, postmenopausal hormone use, BMI at age 18 years, weight change since age 18 years, age at menopause, and early adulthood intakes of alcohol, and energy. For adolescent dietary intake and breast cancer risk, multivariable models were additionally adjusted for adolescent alcohol intake, and adolescent energy intake (instead of early adulthood energy intake). Tests for linear trend were conducted by modeling the median value for each quintile and treating this as a continuous variable in the regression model. We replaced missing covariate data, which comprised 5.5% of total person-years for oral contraceptive use and less than 5% of total person-years for BMI at age 18 years, smoking, height, age at menarche, age at menopause, parity, and age at first birth, with the carry forward method for continuous variables and missing indicator method for categorical variables (40). To evaluate the effect of dietary intake on

Table 2. RR and 95% CIs for breast cancer according to quintile of early adulthood energy-adjusted carbohydrate quality and quantity, dietary insulin index, and insulin load among women in the NHSII

	Quintile of intake					
	1	2	3	4	5	P_{trend}[a]
Carbohydrate						
All cases						
Median intake, percent of energy	40.6	45.9	49.6	53.3	59.2	
No. of cases/person-years	611/345,204	568/345,017	554/345,045	566/345,052	534/344,978	
Age-adjusted RR (95% CI)	1	0.95 (0.84–1.06)	0.94 (0.84–1.06)	0.96 (0.85–1.08)	0.91 (0.81–1.03)	0.19
Multivariable RR (95% CI)	1	0.93 (0.83–1.04)	0.91 (0.81–1.02)	0.92 (0.82–1.04)	0.88 (0.78–0.99)	0.05
Premenopausal cases						
Median intake, percent of energy	40.8	46.1	49.7	53.4	59.3	
No. of cases/person-years	351/232,377	345/232,254	311/231,914	344/231,789	308/231,688	
Age-adjusted RR (95% CI)	1	0.98 (0.85–1.14)	0.90 (0.77–1.05)	1.00 (0.86–1.16)	0.91 (0.78–1.06)	0.29
Multivariable RR (95% CI)	1	0.97 (0.83–1.13)	0.88 (0.75–1.03)	0.98 (0.84–1.14)	0.88 (0.75–1.03)	0.16
Postmenopausal cases						
Median intake, percent of energy	40.0	45.5	49.2	53.0	59.0	
No. of cases/person-years	190/81,123	152/81,193	183/81,280	173/81,377	177/81,321	
Age-adjusted RR (95% CI)	1	0.79 (0.63–0.97)	0.97 (0.79–1.19)	0.91 (0.74–1.12)	0.92 (0.74–1.12)	0.75
Multivariable RR (95% CI)	1	0.78 (0.62–0.96)	0.94 (0.76–1.16)	0.88 (0.71–1.09)	0.87 (0.70–1.08)	0.46
Glycemic index						
All cases						
Median	49.7	52.3	54.0	55.6	57.9	
No. of cases/person-years	582/344,454	584/346,150	590/345,280	544/343,634	533/345,777	
Age-adjusted RR (95% CI)	1	1.02 (0.91–1.15)	1.06 (0.94–1.18)	0.99 (0.88–1.12)	1.00 (0.88–1.12)	0.84
Multivariable RR (95% CI)	1	1.02 (0.91–1.14)	1.06 (0.95–1.19)	1.01 (0.90–1.14)	1.03 (0.91–1.16)	0.66
Premenopausal cases						
Median	49.7	52.4	54.0	55.7	58.0	
No. of cases/person-years	352/231,930	327/232,545	333/231,097	331/232,646	316/231,804	
Age-adjusted RR (95% CI)	1	0.95 (0.82–1.11)	0.99 (0.85–1.15)	1.00 (0.86–1.17)	0.99 (0.85–1.16)	0.89
Multivariable RR (95% CI)	1	0.97 (0.83–1.12)	1.02 (0.87–1.18)	1.04 (0.90–1.22)	1.05 (0.90–1.23)	0.37
Postmenopausal cases						
Median	49.4	52.1	53.9	55.5	57.8	
No. of cases/person-years	166/81,033	189/81,390	189/81,241	160/81,588	171/81,042	
Age-adjusted RR (95% CI)	1	1.15 (0.93–1.42)	1.17 (0.95–1.44)	1.00 (0.80–1.24)	1.08 (0.87–1.34)	0.86
Multivariable RR (95% CI)	1	1.15 (0.93–1.42)	1.17 (0.94–1.44)	1.00 (0.80–1.24)	1.08 (0.87–1.35)	0.84
Glycemic load						
All cases						
Median	96	110	120	131	149	
No. of cases/person-years	612/345,188	567/345,116	551/344,791	545/345,274	558/344,927	
Age-adjusted RR (95% CI)	1	0.95 (0.84–1.06)	0.94 (0.84–1.05)	0.94 (0.83–1.05)	0.97 (0.86–1.08)	0.55
Multivariable RR (95% CI)	1	0.93 (0.83–1.05)	0.91 (0.81–1.03)	0.91 (0.80–1.02)	0.94 (0.83–1.06)	0.31
Premenopausal cases						
Median	96	111	121	131	149	
No. of cases/person-years	370/232,488	330/232,165	312/231,723	321/231,831	326/231,814	
Age-adjusted RR (95% CI)	1	0.90 (0.78–1.05)	0.87 (0.75–1.01)	0.90 (0.78–1.05)	0.94 (0.80–1.09)	0.43
Multivariable RR (95% CI)	1	0.90 (0.78–1.05)	0.86 (0.74–1.01)	0.89 (0.76–1.04)	0.93 (0.79–1.09)	0.37
Postmenopausal cases						
Median	94	109	119	130	148	
No. of cases/person-years	185/81,139	167/81,194	162/81,335	178/81,329	183/81,296	
Age-adjusted RR (95% CI)	1	0.90 (0.73–1.11)	0.89 (0.72–1.09)	0.98 (0.79–1.20)	0.99 (0.80–1.21)	0.84
Multivariable RR (95% CI)	1	0.89 (0.72–1.10)	0.87 (0.70–1.08)	0.95 (0.76–1.17)	0.95 (0.76–1.18)	0.86
Dietary insulin index						
All cases						
Median	38.0	41.1	43.1	45.2	48.5	
No. of cases/person-years	637/345,358	526/343,696	592/346,455	548/344,014	530/345,773	
Age-adjusted RR (95% CI)	1	0.86 (0.76–0.96)	0.98 (0.87–1.09)	0.93 (0.83–1.04)	0.90 (0.80–1.01)	0.19
Multivariable RR (95% CI)	1	0.87 (0.77–0.98)	0.99 (0.88–1.11)	0.94 (0.83–1.06)	0.90 (0.80–1.02)	0.25
Premenopausal cases						
Median	38.2	41.3	43.3	45.3	48.6	
No. of cases/person-years	379/232,164	300/232,718	350/231,517	314/231,920	316/231,701	
Age-adjusted RR (95% CI)	1	0.81 (0.69–0.94)	0.96 (0.83–1.11)	0.88 (0.76–1.02)	0.89 (0.76–1.03)	0.25
Multivariable RR (95% CI)	1	0.83 (0.71–0.97)	0.99 (0.85–1.15)	0.92 (0.79–1.08)	0.92 (0.79–1.08)	0.64
Postmenopausal cases						
Median	37.6	40.8	42.9	44.9	48.2	
No. of cases/person-years	185/81,026	169/81,232	180/81,349	184/81,414	157/81,272	
Age-adjusted RR (95% CI)	1	0.93 (0.75–1.15)	0.98 (0.80–1.21)	1.01 (0.83–1.24)	0.86 (0.69–1.06)	0.31
Multivariable RR (95% CI)	1	0.94 (0.76–1.16)	0.98 (0.79–1.22)	0.99 (0.80–1.23)	0.84 (0.67–1.05)	0.21

(Continued on the following page)

Table 2. RR and 95% CIs for breast cancer according to quintile of early adulthood energy-adjusted carbohydrate quality and quantity, dietary insulin index, and insulin load among women in the NHSII (Cont'd)

	Quintile of intake					
	1	2	3	4	5	P_{trend}[a]
Insulin load						
All cases						
Median	682	739	777	817	882	
No. of cases/person-years	619/346,322	553/345,799	568/341,039	556/346,333	537/345,803	
Age-adjusted RR (95% CI)	1	0.92 (0.82–1.03)	0.98 (0.87–1.09)	0.96 (0.86–1.08)	0.93 (0.83–1.05)	0.41
Multivariable RR (95% CI)	1	0.93 (0.82–1.04)	0.98 (0.87–1.10)	0.97 (0.86–1.09)	0.93 (0.82–1.05)	0.41
Premenopausal cases						
Median	685	741	779	819	884	
No. of cases/person-years	368/232,639	303/229,250	358/236,869	312/228,645	318/232,618	
Age-adjusted RR (95% CI)	1	0.85 (0.72–0.98)	0.98 (0.85–1.14)	0.90 (0.78–1.05)	0.91 (0.78–1.06)	0.38
Multivariable RR (95% CI)	1	0.86 (0.74–1.01)	1.01 (0.87–1.18)	0.94 (0.80–1.10)	0.94 (0.80–1.10)	0.73
Postmenopausal cases						
Median	674	732	771	812	878	
No. of cases/person-years	182/80,176	163/81,582	184/81,493	183/82,108	163/80,934	
Age-adjusted RR (95% CI)	1	0.90 (0.72–1.11)	1.00 (0.81–1.23)	1.00 (0.81–1.23)	0.90 (0.72–1.11)	0.56
Multivariable RR (95% CI)	1	0.90 (0.72–1.12)	1.00 (0.81–1.24)	0.98 (0.79–1.22)	0.87 (0.70–1.09)	0.40

NOTE: Multivariable model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for race (white, non-white), family history of breast cancer in mother or sisters (yes, no), history of benign breast disease (yes, no), smoking (never, past, current 1 to 14/day, current 15 to 24/day, current ≥25/day), height (<62, 62 to <65, 65 to <68, ≥68 inches), BMI at age 18 years (<18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, ≥30.0 kg/m^2), weight change since age 18 years (≤−5, >−5–5, >5–10, >10–20, >20 kg), age at menarche (<12, 12, 13, ≥14 years), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity≤2 and age at first birth 25 to <30 years, parity ≤2 and age at first birth ≥30 years, parity 3 to 4 and age at first birth <25 years, parity 3 to 4 and age at first birth 25 to <30 years, parity 3 to 4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), oral contraceptive use (never, past, current), alcohol intake (nondrinker, <5, 5 to <15, ≥15 g/day), and energy (quintile). In postmenopausal women, we additionally adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users) and age at menopause (<45 years, 45 to 46 years, 47 to 48 years, 49 to 50 years, 51 to 52 years, ≥53 years). Among all women, we additionally adjusted for hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users, unknown menopausal status), and age at menopause (premenopausal, unknown menopause, <45 years, 45 to 46 years, 47 to 48 years, 49 to 50 years, 51 to 52 years, ≥53 years).

[a]P_{trend} calculated with median intake of each variable in each quintile as a continuous variable.

breast carcinogenesis over an extended period of time, for sensitivity analyses, we also calculated premenopausal cumulative averaged of GL, GI, insulin index, and insulin load using the 1991, 1995, 1999, 2003, and 2007 dietary data, and stopped updating when a woman reached menopause. Furthermore, we calculated mean of adolescent and early adulthood GI, GL, insulin index, and insulin load. To examine differential associations of dietary intake with breast cancer risk by hormone receptor status, we used Cox proportional cause-specific hazards regression model with a duplication method for competing risk data. This method permits estimation of separate associations of GI for tumors that are both estrogen and progesterone receptor positive (ER^+/PR^+) and negative (ER^-/PR^-), and has been used to assess whether a risk factor has statistically different regression coefficients for different tumor subtypes (41). We examined effect modification of the association between GL, GI, insulin index, and insulin load scores and breast cancer risk by BMI at age 18 years. A cross-product interaction term between BMI at age 18 and scores of GL, GI, insulin index, and insulin load was included in the multivariable model. *P* values for tests for interactions were derived using a likelihood ratio test. All *P* and 95% CI values were two-sided and all analyses were performed using SAS version 9.3 (SAS Institute Inc).

Results

During 1,725,295 person-years of follow-up of 90,534 women, 2,833 women were diagnosed with invasive breast carcinoma, (1,659 premenopausal breast cancers, 875 postmenopausal breast cancers, and 299 cases with uncertain menopausal status). Among 44,263 women with data on adolescent carbohydrate intake, 1,118 women were diagnosed with invasive breast cancer (544 premenopausal, 465 postmenopausal, and 109 uncertain menopausal status) from 1998 to 2011. The age range of the participants at baseline in 1991 was 27 to 44 years (mean 36.4 ± 4.6 years). Compared with women who had a lower GI diet, women with a diet higher in GI were more likely to be younger, to have a lower dietary fiber intake as well as less likely to drink alcohol, to be nulliparous, and to have earlier age at menarche (Table 1).

Among all women, higher early adulthood intake of carbohydrate was associated with lower risk of breast cancer (comparing the highest vs. lowest quintile, RR = 0.88; 95% CI, = 0.78–0.99; P_{trend} = 0.05). This association was not significant after additional adjustment for dietary fiber (RR for highest vs. lowest quintile = 0.92; 95% CI, = 0.81–1.04; P_{trend} = 0.26) or red meat (RR for highest vs. lowest quintile = 0.92; 95% CI, = 0.80–1.05; P_{trend} = 0.30). Among all women, higher GI in early adulthood was not significantly associated with risk of breast cancer (comparing the highest vs. lowest quintile, RR = 1.03; 95% CI, = 0.91–1.16; P_{trend} = 0.66; Table 2). Similar association was observed among either premenopausal or postmenopausal women. Furthermore, GL, dietary insulin index, and insulin load were not significant predictors of either overall breast cancer or breast cancers among premenopausal or postmenopausal women (Table 2). Results did not differ between age-adjusted and multivariable adjusted models. Additional adjustment for red meat, fruit and vegetables, or fiber intake did not materially change the results (data not shown).

To assess the effects of breast carcinogenesis over an extended period of time, we also calculated premenopausal cumulative average. Similar associations were observed. In multivariable-

Table 3. RRs and 95% CIs for breast cancer according to quintile of adolescent energy-adjusted carbohydrate quality and quantity, dietary insulin index, and insulin load among women in the NHSII

	Quintile of intake					
	1	2	3	4	5	P_{trend}[a]
Carbohydrate						
All cases						
Median intake, E%	38.2	42.4	45.1	47.9	52.2	
No. of cases/person-years	234/118,543	254/118,534	217/118,612	203/118,621	210/118,525	
Age-adjusted RR (95% CI)	1	1.14 (0.95–1.36)	0.99 (0.82–1.19)	0.94 (0.78–1.13)	1.02 (0.84–1.23)	0.57
Multivariable RR (95% CI)	1	1.12 (0.94–1.35)	0.98 (0.82–1.19)	0.93 (0.77–1.13)	1.00 (0.83–1.21)	0.47
Premenopausal cases						
Median intake, E%	38.6	42.8	45.5	48.3	52.5	
No. of cases/person-years	116/67,246	132/67,194	110/67,240	94/67,199	92/67,123	
Age-adjusted RR (95% CI)	1	1.18 (0.91–1.52)	1.01 (0.78–1.32)	0.87 (0.66–1.14)	0.90 (0.68–1.19)	0.14
Multivariable RR (95% CI)	1	1.18 (0.92–1.53)	1.01 (0.77–1.32)	0.87 (0.66–1.15)	0.89 (0.67–1.18)	0.12
Postmenopausal cases						
Median intake, E%	37.7	41.8	44.6	47.3	51.6	
No. of cases/person-years	102/41,408	85/41,339	92/41,289	90/41,171	96/41,101	
Age-adjusted RR (95% CI)	1	0.87 (0.65–1.16)	0.94 (0.71–1.26)	0.94 (0.71–1.26)	1.01 (0.76–1.35)	0.79
Multivariable RR (95% CI)	1	0.85 (0.63–1.14)	0.92 (0.69–1.23)	0.94 (0.70–1.25)	1.01 (0.76–1.35)	0.79
Glycemic index						
All cases						
Median intake/day	51.6	53.6	55.0	56.3	58.4	
No. of cases/person-years	227/118,292	262/118,727	191/118,920	209/118,614	229/118,283	
Age-adjusted RR (95% CI)	1	1.17 (0.98–1.40)	0.85 (0.70–1.03)	0.97 (0.80–1.17)	1.10 (0.91–1.32)	0.90
Multivariable RR (95% CI)	1	1.18 (0.99–1.41)	0.87 (0.72–1.06)	0.99 (0.82–1.20)	1.14 (0.95–1.38)	0.58
Premenopausal cases						
Median intake/day	51.6	53.7	55.0	56.4	58.4	
No. of cases/person-years	108/67,377	131/66,988	92/66,980	113/67,517	100/67,141	
Age-adjusted RR (95% CI)	1	1.25 (0.96–1.61)	0.89 (0.67–1.18)	1.13 (0.86–1.47)	1.07 (0.81–1.40)	0.91
Multivariable RR (95% CI)	1	1.27 (0.98–1.65)	0.92 (0.70–1.22)	1.15 (0.88–1.51)	1.09 (0.82–1.44)	0.78
Postmenopausal cases						
Median intake/day	51.5	53.6	54.9	56.2	58.3	
No. of cases/person-years	99/41,259	104/41,295	84/41,397	80/41,079	98/41,278	
Age-adjusted RR (95% CI)	1	1.05 (0.79–1.39)	0.86 (0.64–1.15)	0.84 (0.62–1.12)	1.06 (0.80–1.41)	0.86
Multivariable RR (95% CI)	1	1.05 (0.79–1.39)	0.88 (0.65–1.18)	0.85 (0.63–1.15)	1.10 (0.82–1.47)	0.95
Glycemic load						
All cases						
Median intake/day	141	158	170	182	203	
No. of cases/person-years	234/120,609	254/117,600	203/113,458	223/124,042	204/117,126	
Age-adjusted RR (95% CI)	1	1.16 (0.97–1.39)	0.98 (0.81–1.18)	1.01 (0.84–1.22)	1.02 (0.84–1.24)	0.73
Multivariable RR (95% CI)	1	1.16 (0.97–1.39)	0.98 (0.81–1.19)	1.00 (0.83–1.21)	1.02 (0.84–1.24)	0.73
Premenopausal cases						
Median intake/day	143	160	172	184	204	
No. of cases/person-years	112/65,879	133/70,911	112/64,737	94/65,995	93/68,480	
Age-adjusted RR (95% CI)	1	1.17 (0.91–1.51)	1.08 (0.83–1.41)	0.93 (0.70–1.23)	0.94 (0.71–1.24)	0.29
Multivariable RR (95% CI)	1	1.17 (0.91–1.52)	1.08 (0.83–1.41)	0.93 (0.70–1.23)	0.92 (0.69–1.22)	0.25
Postmenopausal cases						
Median intake/day	139	156	168	180	199	
No. of cases/person-years	101/42,622	100/41,393	76/40,285	84/40,297	104/41,710	
Age-adjusted RR (95% CI)	1	1.05 (0.79–1.39)	0.84 (0.62–1.13)	0.93 (0.69–1.24)	1.14 (0.86–1.51)	0.56
Multivariable RR (95% CI)	1	1.05 (0.79–1.39)	0.84 (0.62–1.14)	0.92 (0.68–1.23)	1.17 (0.88–1.54)	0.51
Dietary insulin index						
All cases						
Median intake/day	39.9	42.0	43.6	45.1	47.4	
No. of cases/person-years	261/118,350	233/118,532	215/118,660	221/118,491	188/118,803	
Age-adjusted RR (95% CI)	1	0.93 (0.78–1.11)	0.91 (0.75–1.09)	0.94 (0.79–1.13)	0.86 (0.71–1.04)	0.16
Multivariable RR (95% CI)	1	0.95 (0.79–1.13)	0.92 (0.76–1.10)	0.96 (0.80–1.15)	0.88 (0.73–1.07)	0.25
Premenopausal cases						
Median intake/day	40.1	42.4	43.9	45.4	47.6	
No. of cases/person-years	132/67,395	111/67,370	114/67,011	92/67,087	95/67,140	
Age-adjusted RR (95% CI)	1	0.89 (0.69–1.15)	0.97 (0.75–1.25)	0.77 (0.59–1.01)	0.87 (0.66–1.14)	0.17
Multivariable RR (95% CI)	1	0.91 (0.70–1.17)	0.99 (0.76–1.27)	0.78 (0.59–1.02)	0.88 (0.67–1.16)	0.20
Postmenopausal cases						
Median intake/day	39.5	41.6	43.1	44.6	46.9	
No. of cases/person-years	100/41,299	105/41,475	86/41,144	92/41,267	82/41,124	
Age-adjusted RR (95% CI)	1	1.06 (0.80–1.39)	0.92 (0.69–1.23)	1.00 (0.75–1.33)	0.92 (0.68–1.23)	0.49
Multivariable RR (95% CI)	1	1.10 (0.83–1.45)	0.95 (0.71–1.27)	1.04 (0.77–1.38)	0.95 (0.71–1.29)	0.67

(Continued on the following page)

Table 3. RRs and 95% CIs for breast cancer according to quintile of adolescent energy-adjusted carbohydrate quality and quantity, dietary insulin index, and insulin load among women in the NHSII (Cont'd)

	Quintile of intake					
	1	2	3	4	5	P_{trend}[a]
Insulin load						
All cases						
Median intake/day	1,100	1,160	1,202	1,244	1,308	
No. of cases/person-years	262/119,226	229/116,705	215/119,980	222/118,937	190/117,988	
Age-adjusted RR (95% CI)	1	0.93 (0.78–1.11)	0.89 (0.74–1.07)	0.94 (0.79–1.13)	0.87 (0.72–1.05)	0.19
Multivariable RR (95% CI)	1	0.94 (0.79–1.13)	0.90 (0.75–1.08)	0.96 (0.80–1.15)	0.89 (0.73–1.07)	0.27
Premenopausal cases						
Median intake/day	1,107	1,169	1,210	1,252	1,314	
No. of cases/person-years	132/67,226	112/67,124	103/67,776	102/66,434	95/67,442	
Age-adjusted RR (95% CI)	1	0.90 (0.70–1.16)	0.86 (0.66–1.11)	0.86 (0.66–1.11)	0.85 (0.65–1.12)	0.21
Multivariable RR (95% CI)	1	0.92 (0.71–1.19)	0.87 (0.67–1.14)	0.87 (0.67–1.13)	0.87 (0.66–1.14)	0.25
Postmenopausal cases						
Median intake/day	1,089	1,149	1,190	1,232	1,295	
No. of cases/person-years	98/40,977	102/41,795	91/41,377	91/41,190	83/40,970	
Age-adjusted RR (95% CI)	1	1.03 (0.78–1.36)	0.97 (0.73–1.30)	1.00 (0.75–1.33)	0.94 (0.70–1.27)	0.65
Multivariable RR (95% CI)	1	1.07 (0.80–1.41)	1.00 (0.75–1.34)	1.04 (0.78–1.39)	0.98 (0.72–1.32)	0.85

NOTE: Multivariable model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for smoking (never, past, current 1–14/day, current 15–24/day, current ≥25/day), race (white/non-white), 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 3–4 and age at first birth <25 years, parity 3–4 and age at first birth 25–<30 years, parity 3–4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), height (<62, 62–<65, 65–<68, ≥68 inches), BMI at age 18 years (<18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, ≥30.0 kg/m^2), weight change since age 18 (≤−5, >−5–5, >5–10, >10–20, >20 kg), age at menarche (<12, 12, 13, ≥14 years), family history of breast cancer (yes, no), history of benign breast disease (yes, no), oral contraceptive use (never, past, current), adolescent alcohol intake (nondrinker, <1.5, 1.5–<5, 5–<10, ≥10 g/day), adult alcohol intake (nondrinker, <5, 5–<15, ≥15 g/day), and adolescent energy intake (quintile). In postmenopausal women, we additionally adjusted for hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users), age at menopause (<45 years, 45 to 46 years, 47 to 48 years, 49 to 50 years, 51 to 52 years, ≥53 years). Among all women, we additionally adjusted for hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users, unknown menopausal status), and age at menopause (premenopausal, unknown menopause, <45 years, 45 to 46 years, 47 to 48 years, 49 to 50 years, 51 to 52 years, ≥53 years).

[a]P_{trend} calculated with median intake of each variable in each quintile as a continuous variable.

adjusted model, women in the highest quintile of premenopausal cumulative average GI had an RR of 1.08 (95% CI, 0.96–1.22; P_{trend} = 0.50) compared with women in the lowest quintile. RRs were 0.96 (95% CI, 0.85–1.08; P_{trend} = 0.46) for premenopausal cumulative average of GL in the highest quintile compared with lowest quintile. Furthermore, premenopausal cumulative average of either dietary insulin index or insulin load was not associated with breast cancer risk (comparing the highest vs. lowest quintile, RR for dietary insulin index = 1.00; 95% CI, = 0.89–1.14; P_{trend} = 0.82; and RR for insulin load = 1.01; 95% CI, = 0.90–1.15; P_{trend} = 0.82).

Adolescent carbohydrate, GI, GL, insulin index, and insulin load was only weakly correlated with early adult intake (1991). The intraclass correlation was 0.11 (0.10–0.12) for carbohydrate, 0.19 (0.18–0.20) for GI, and 0.16 (0.15–0.17) for insulin index. The estimated coefficient of within-subject variance was 0.14 for carbohydrate, 0.05 for GI, and 0.08 for insulin index. Associations between adolescent carbohydrates, GL, GI, insulin index, and insulin load and breast cancer risk are shown in Table 3. Adolescent intake of carbohydrate was not associated with lower risk of breast cancer. A diet high in GI in adolescence also was not associated with a higher risk of

Table 4. Risk of breast cancer by ER/PR status and glycemic index score in adolescence and early adulthood diet among all women in the NHSII

		Quintile of intake				
	No. of cases	1	2	3	4	5
Adolescence						
Estrogen and progesterone receptor positive	695	1	1.27 (1.01–1.59)	0.88 (0.69–1.13)	1.00 (0.79–1.28)	1.21 (0.95–1.53)
Estrogen and progesterone receptor negative	162	1	1.40 (0.89–2.20)	1.01 (0.62–1.66)	0.93 (0.56–1.55)	0.94 (0.56–1.57)
$P_{interaction}$			0.71	0.63	0.80	0.38
Early adulthood						
Estrogen and progesterone receptor positive	1,571	1	1.05 (0.90–1.23)	1.04 (0.89–1.22)	1.06 (0.90–1.24)	1.09 (0.93–1.28)
Estrogen and progesterone receptor negative	429	1	1.11 (0.83–1.49)	1.04 (0.77–1.41)	1.12 (0.84–1.51)	0.95 (0.69–1.30)
$P_{interaction}$			0.75	0.99	0.73	0.43

NOTE: Multivariable model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for race (white, non-white), family history of breast cancer in mother or sisters (yes, no), history of benign breast disease (yes, no), smoking (never, past, current 1 to 14/day, current 15 to 24/day, current ≥25/day), height (<62, 62 to <65, 65 to <68, ≥68 inches), BMI at age 18 years (<18.5, 18.5 to <20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, ≥30.0 kg/m^2), weight change since age 18 (≤−5, >−5–5, >5–10, >10–20, >20 kg), age at menarche (<12, 12, 13, ≥14 years), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity ≤2 and age at first birth 25 to <30 years, parity ≤2 and age at first birth ≥30 years, parity 3 to 4 and age at first birth <25 years, parity 3 to 4 and age at first birth 25 to <30 years, parity 3 to 4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), oral contraceptive use (never, past, current), alcohol intake (nondrinker, <5, 5 to <15, ≥15 g/day), energy (quintile), hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users, unknown menopausal status), and age at menopause (premenopausal, unknown menopause, <45 years, 45–46 years, 47–48 years, 49–50 years, 51–52 years, ≥53 years). For adolescent GI, we additionally adjusted for adolescent alcohol intake (nondrinker, <1.5, 1.5–<5, 5–<10, ≥10 g/day) and adolescent energy intake (instead of adult energy intake).

Table 5. Multivariable-adjusted HR of breast cancer by adolescent and early adulthood energy-adjusted glycemic index, glycemic load, dietary insulin index, and insulin load stratified by BMI at age 18 among women in the NHSII

		Quintile of intake						
	Cases/person-year	1	2	3	4	5	P_{trend}	$P_{interaction}$
Adolescence								
Glycemic index								
<25 kg/m^2	1,047/532,078	1	1.19 (0.99–1.43)	0.85 (0.70–1.04)	0.97 (0.79–1.17)	1.12 (0.92–1.36)	0.84	0.70
≥25 kg/m^2	63/56,401	1	1.66 (0.64–4.33)	1.92 (0.73–5.02)	1.86 (0.73–4.70)	2.52 (1.02–6.25)	0.05	
Glycemic load								
<25 kg/m^2	1,047/532,078	1	1.18 (0.98–1.42)	1.01 (0.83–1.23)	1.03 (0.85–1.25)	1.06 (0.87–1.29)	0.99	0.79
≥25 kg/m^2	63/56,401	1	1.26 (0.60–2.67)	1.03 (0.42–2.53)	0.76 (0.32–1.82)	1.04 (0.43–2.50)	0.72	
Dietary insulin index								
<25 kg/m^2	1,047/532,078	1	0.91 (0.76–1.10)	0.94 (0.78–1.14)	0.95 (0.79–1.15)	0.89 (0.73–1.09)	0.37	0.22
≥25 kg/m^2	63/56,401	1	1.79 (0.83–3.84)	0.72 (0.28–1.83)	1.24 (0.52–2.91)	1.05 (0.41–2.70)	0.79	
Insulin load								
<25 kg/m^2	1,047/532,078	1	0.90 (0.75–1.09)	0.91 (0.75–1.09)	0.96 (0.80–1.16)	0.89 (0.73–1.09)	0.39	0.27
≥25 kg/m^2	63/56,401	1	2.16 (0.96–4.83)	1.09 (0.45–2.60)	1.01 (0.40–2.52)	1.33 (0.53–3.36)	0.91	
Early adulthood								
Glycemic index								
<25 kg/m^2	2,619/1,534,255	1	1.01 (0.90–1.14)	1.05 (0.93–1.19)	1.03 (0.91–1.17)	1.04 (0.92–1.18)	0.49	0.59
≥25 kg/m^2	187/175,214	1	1.11 (0.71–1.74)	1.52 (0.98–2.36)	1.05 (0.64–1.71)	1.12 (0.68–1.85)	0.59	
Glycemic load								
<25 kg/m^2	2,619/1,534,255	1	0.91 (0.80–1.02)	0.88 (0.78–0.99)	0.89 (0.79–1.01)	0.94 (0.83–1.06)	0.34	0.20
≥25 kg/m^2	187/175,214	1	1.27 (0.82–1.97)	1.45 (0.93–2.25)	1.44 (0.90–2.30)	1.19 (0.70–2.03)	0.28	
Dietary insulin index								
<25 kg/m^2	2,619/1,534,255	1	0.89 (0.78–1.00)	1.01 (0.89–1.14)	0.93 (0.82–1.06)	0.90 (0.79–1.02)	0.22	0.21
≥25 kg/m^2	187/175,214	1	0.69 (0.43–1.09)	0.64 (0.39–1.05)	1.12 (0.72–1.76)	1.11 (0.70–1.78)	0.34	
Insulin load								
<25 kg/m^2	2,619/1,534,255	1	0.93 (0.82–1.05)	0.98 (0.87–1.11)	0.97 (0.86–1.10)	0.92 (0.81–1.05)	0.37	0.83
≥25 kg/m^2	187/175,214	1	0.91 (0.58–1.42)	0.83 (0.52–1.35)	1.02 (0.63–1.64)	1.30 (0.80–2.09)	0.29	

NOTE: Multivariable model was stratified by age in months at start of follow-up and calendar year of the current questionnaire cycle and was simultaneously adjusted for race (white, non-white), family history of breast cancer in mother or sisters (yes, no), history of benign breast disease (yes, no), smoking (never, past, current 1 to 14/day, current 15 to 24/day, current ≥25/day), height (<62, 62 to <65, 65 to <68, ≥68 inches), weight change since age 18 years (≤−5, >−5–5, >5–10, >10–20, >20 kg), age at menarche (<12, 12, 13, ≥14 years), parity and age at first birth (nulliparous, parity ≤2 and age at first birth <25 years, parity ≤2 and age at first birth 25 to <30 years, parity ≤2 and age at first birth ≥30 years, parity 3 to 4 and age at first birth <25 years, parity 3 to 4 and age at first birth 25 to <30 years, parity 3 to 4 and age at first birth ≥30 years, parity ≥5 and age at first birth <25 years, parity ≥5 and age at first birth ≥25 years), oral contraceptive use (never, past, current), alcohol intake (nondrinker, <5, 5 to <15, ≥15 g/day), energy (quintile), hormone use and menopausal status (premenopausal, postmenopausal never users, postmenopausal past users, postmenopausal current users, unknown menopausal status), and age at menopause (premenopausal, unknown menopause, <45 years, 45–46 years, 47–48 years, 49–50 years, 51 to 52 years, ≥53 years). For adolescent dietary scores, we additionally adjusted for adolescent alcohol intake (nondrinker, <1.5, 1.5–<5, 5–<10, ≥10 g/day) and adolescent energy intake (instead of adult energy intake).

breast cancer (for highest vs. lowest quintiles, multivariable RR, 1.14; 95% CI, 0.95–1.38, $P_{trend} = 0.58$). This association was not significant in either premenopausal or postmenopausal breast cancer (Table 3). Similarly, nonsignificant associations were observed for adolescent GL, insulin index, and insulin load and breast cancer risk. Additional adjustment for adult GI, GL, insulin index, or insulin load did not change the results (data not shown). Further adjustment for red meat, fruit and vegetables, or fiber intake did not materially change the results (data not shown). Among women with both early adulthood and adolescent dietary data ($n = 41{,}092$), we calculated the average of indices at both times. No significant association was observed (data not shown).

Table 4 presents the associations between adolescent and early adulthood GI scores and breast cancer according to hormone receptor status; data are presented for tumors with both ER$^+$/PR$^+$ and ER$^-$/PR$^-$. We did not observe associations for adolescent and early adulthood GI scores and breast cancer risk by hormone receptor status, and there was no significant heterogeneity. Furthermore, no significant association or significant heterogeneity was observed for GL and breast cancer risk (data not shown).

In our previous evaluation of quality and quantity of carbohydrate intake, the associations differed by body weight (12). Therefore, we also examined whether these dietary associations with breast cancer risk differed by BMI at age 18 (<25/≥25 kg/m^2) (Table 5). Although higher GI score during adolescence was associated with higher risk of breast cancer among women with BMI 25 or higher during adolescence, the interaction was not significant. Furthermore, no significant interaction was observed between BMI at age 18 years and GL, insulin index, or insulin load in adolescence or early adulthood (Table 5).

Discussion

In this large prospective analysis, we observed no overall association between quality and quantity of carbohydrate intake during adolescence or early adulthood and breast cancer risk. Furthermore, we found no evidence that a diet high in insulin load or insulin index is related to breast cancer risk.

Our results are largely consistent with those published earlier for the NHSII (12, 13) and do not support a positive association between dietary GI or GL and breast cancer risk. Previous cohort studies have produced mixed results. In a recent meta-analysis of 10 prospective cohort studies (20), there was no significant association between dietary GL and risk of breast cancer (RR, 1.04; 95% CI, 0.95–1.15). However, higher dietary GI was associated with 8% higher risk of breast cancer (RR, 1.08; 95% CI, 1.02–1.14). The foods with low GI have other properties that may

increase or decrease risk of breast cancer. In our study, women with high GI diet were more likely to have higher intake of red meat and lower intake of fiber. Diets high in red meat were associated positively with breast cancer risk in the current study population (42). However, additional adjustment for red meat, fruit and vegetable, or fiber intake did not change the associations. Similarly, diets low in carbohydrate can be high in red meat and low in fiber, which have been shown to increase risk of breast cancer (42, 43) and no association between carbohydrate and breast cancer was observed after additional adjustment for red meat or fiber intake.

Although there was a positive association between hyperinsulinemia and breast cancer in case–control studies nested within the Nurses' Health Study and NHSII cohorts (44), we observed no association between dietary insulin index and insulin load and risk of breast cancer. Similarly, dietary insulin index and insulin load were not associated with risk of other cancers (45–47). On the other hand, in a recent meta-analysis of 6 prospective studies (48), compared with women with lowest insulin levels, those with higher insulin levels were not at higher risk of breast cancer (pooled RR of breast cancer, 1.08; 95% CI, 0.66–1.78).

Potential limitations need to be considered. Because the participants were predominantly white, educated U.S. adults, generalizability to other race or ethnic groups is questionable; however, it is unlikely that the biology underlying this association differs by race or ethnicity. Assessment of dietary intake using FFQ is prone to random measurement error caused by within-person variation. However, we found similar associations using cumulative averages of repeated dietary assessments before menopause. In addition, high dietary GI measured in the same population with the same dietary assessment has been associated with an increased risk of type II diabetes (49). Women recalled their diet during adolescence when they were 33 to 52 years old. Some degree of measurement error is inevitably present. However, the associations were largely independent of adult diet, and evidence of validity came from the comparison of their dietary reports with the information provided 4 years later or from dietary intake reported by their mother (28, 29). Residual confounding is always of concern in any observational studies. Comprehensive adjustment for many potential confounders minimized residual confounding, although we could not rule out the influence of unmeasured or unknown confounders. We could not exclude the possibility of limited power to detect differences in risk in subgroups, particularly for adolescent diet.

Our study has several strengths. To evaluate the importance of timing, we assessed the association between quality and quantity of carbohydrate as well as insulin index and insulin load during specific life periods (adolescence, early adulthood, and cumulative average of premenopausal period). The large sample size and length of follow-up made it possible to evaluate the associations by menopausal and tumor hormone receptor status. Assessing adolescent and early adulthood dietary intake before breast cancer diagnosis minimized recall bias.

In summary, our results suggest that diets high in GI, GL, insulin index, and insulin load during adolescence or early adulthood were not associated with an increased risk of breast cancer in this cohort study. As the data on diet during childhood and later breast cancer risk remain limited, further studies are needed to better clarify the influence of timing of dietary exposures in relation to risk of breast cancer.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The study sponsors were not involved in the study design and collection, analysis and interpretation of data, or the writing of the article or the decision to submit it for publication. The authors were independent from study sponsors.

Authors' Contributions

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Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): A.H. Eliassen, W.C. Willett
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): M.S. Farvid, A.H. Eliassen, E. Cho, W.C. Willett
Writing, review, and/or revision of the manuscript: M.S. Farvid, A.H. Eliassen, E. Cho, W. Chen, W.C. Willett
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