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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 90,488 premenopausal women who completed a diet questionnaire in 1991, 2890 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 1135 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 vs lowest quintile, the multivariable-adjusted RRs were 1.15 (0.95–1.38) for adolescent GI scores and 1.01 (0.90–1.14) 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.

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Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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.

INTRODUCTION

A higher incidence of breast cancer has been reported in individuals with type 2 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); the role of them in incidence of breast cancer is unclear.

In previous analyses of the Nurses' Health Study II (NHSII) (12, 13), dietary carbohydrate, GI and GL were not associated with risk of premenopausal breast cancer. The current analyses included twelve additional years of follow-up and almost four times the number of cases compared to 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 aged 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 >3500 kcal/day) or left more than 70 items blank (n=2357), who were postmenopausal in 1991 (n=3747), or had reported a prior diagnosis of cancer (except non-melanoma skin cancer) before returning the 1991 questionnaire (n=1221). After exclusions, data from 90,488 women were available for the analysis. The follow-up rate was 95 percent 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 to women who did not provide information on high school diet (13). We excluded women who had any cancer except non-melanoma skin cancer before 1998 (n=1685), or reported implausible daily caloric intake (<600 or ≥5000 Kcal) (n=1407). 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, United States).

Dietary Assessment

Dietary information during adulthood was evaluated via validated semi-quantitative 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 semi-quantitative 124-item HS-FFQ that included foods items typically consumed between 1960 and 1980 when they were in high school. To examine the reproducibility of the HS-FFQ, we re-administered it to a random sample of 333 NHSII participants in January, 2003; the mean intra-class correlation coefficient was 0.65 (range, 0.50–0.77) for nutrients 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 aged 23–29 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) (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 US Department of Agriculture, food manufacturers and independent academic sources were used to calculate the nutrients intakes (30–32). The food composition database was updated every four 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 caloric intake as independent variable (33, 34).

Insulin index values for each food were obtained from either published estimates (31 foods) (11, 35) or direct testing of U.S. food items (73 foods) at the University of Sydney. The method was described in detail elsewhere (11). Briefly, each person consumed a 1000-KJ of test foods and the reference food (glucose) on separate days and serum insulin measured every 15 minutes for 2 hours after consumption, then the area under the 120-min insulin response curve for 1000 KJ test food was divided by the area under the 120-min insulin response curve for 1000 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 (∑[food insulin index × energy content of food (kcal/serving) × 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 at Nutrition Center of University of Toronto (Prof. David J. Jenkins). The method was described in detail elsewhere (10). Briefly, dietary GI was measured by dividing the area under the 120-min incremental blood glucose curve by ingestion of 50 gram carbohydrate from test food by the area under the 120-min incremental blood glucose curve by ingestion 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): $\mathrm{GL_{ave}}=\sum_{\alpha=1}^{n} GI\alpha \times CHO\alpha \times frequency\alpha$; where n is the number of foods consumed, *GI*α is the glycemic index for food α, *CHO*α is the carbohydrate content per serving of food α and *frequency*α 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, 39).

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) whom reported breast cancer 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=348) 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 non-smokers (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 smoking, alcohol consumption, physical activity and oral contraceptive use 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 diagnosis, 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, weight gain since age 18, 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, smoking, height, age at menarche, age at menopause, parity, and age at first birth, with the carried

forward method for continuous variables and missing indicator method for categorical variables (40). To evaluate the effect of dietary intake on 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, stopping 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 receptors positive (ER+/PR+) and both receptors negative (ER−/PR−), has been used to assessed whether a risk factor has statistically different regression coefficients for different tumor subtype (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. A cross-product interaction term between each factor and scores of GL, GI, insulin index and insulin load expressed as a continuous variable was included in the multivariable model. *P* values for tests for interactions were derived by using a likelihood ratio test with one degree of freedom. All *P* values and 95%CI were 2-sided and all analyses were performed using SAS version 9.3 (SAS Institute Inc, Cary NC).

Results

During 1,757,244 person-years of follow-up of 90,488 women, 2890 women were diagnosed with invasive breast carcinoma, (1547 premenopausal breast cancers, 919 postmenopausal breast cancers, and 424 cases with uncertain menopausal status). Among 44,263 women with data on adolescent fiber intake, 1135 women were diagnosed with invasive breast cancer (547 premenopausal, 483 postmenopausal and 105 uncertain menopausal status) from 1998 to 2011. The age range of the participants at baseline in 1991 was 27–44 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, and 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 somewhat associated with lower risk of breast cancer (comparing the highest vs lowest quintile, RR= 0.89; 95%CI= 0.79–1.00; P_{trend}=0.07). This association was not significant after additional adjustment for fruits and vegetables (RR for highest *vs* lowest quintile= 0.90; 95%CI= 0.79–1.02; P_{trend}=0.11) or red meat (RR for highest *vs* lowest quintile= 0.94; 95%CI= 0.82–1.07; P_{trend}=0.40). Among all women, higher GI in early adulthood was not significantly associated with risk of breast cancer (comparing the highest vs lowest quintile, RR= 1.01; 95%CI= 0.90–1.14; P_{trend}=0.80) (Table 2). Similar association was observed among either premenopausal or postmenopausal women. Intakes of carbohydrate, 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-adjusted model, women in the highest quintile of premenopausal cumulative average GI had an RR of 1.06 (95%CI, 0.94–1.20; P_{trend}=0.61) compared with women in the lowest quintile. RRs were 0.96 (95%CI, 0.85–1.08, P_{trend}=0.45) 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= 0.88–1.13; P_{trend}=0.86; and RR for insulin load= 1.01; 95%CI= 0.89–1.14; P_{trend}=0.88).

Adolescent carbohydrate, GI, GL, insulin index, and insulin load was only weakly correlated with early adult intake (1991). The intra-class correlation was 0.11 (0.10–0.12) for carbohydrate, 0.19 (0.18–0.20) for GI, 0 for GL, 0.16 (0.15–0.17) for insulin index and 0 for insulin load. The estimated coefficient of within-subject variance was 0.14 for carbohydrate, 0.05 for GI, 0.23 for GL, 0.08 for insulin index and 0.23 for insulin load. 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 weakly but significantly associated with lower risk of premenopausal breast cancer (for highest *vs* lowest quintiles, multivariable RR, 0.80; 95%CI, 0.60–1.05, P_{trend}=0.03). But this association was not significant after additional adjustment for fruits and vegetables (RR for highest *vs* lowest quintile= 0.82; 95%CI= 0.62–1.10; P_{trend}=0.06) or red meat (RR for highest *vs* lowest quintile= 0.88; 95%CI= 0.64–1.21; P_{trend}=0.24). However, carbohydrate intake was not associated with postmenopausal breast cancer or breast cancer overall. A diet high in GI in adolescence was not associated with a higher risk of breast cancer (for highest *vs* lowest quintiles, multivariable RR, 1.15; 95%CI 0.95–1.38, P_{trend}=0.54). This association was not significant in either premenopausal or postmenopausal breast cancer (Table 3). Similarly, non-significant 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). Among women with both early adulthood and adolescent dietary data (n=40,642), 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 and PR positive receptors (ER+/PR+) and for both negative receptors (ER−/PR−). We did not observe associations for adolescent and early adulthood GI scores by hormone receptor status, and there was no significant heterogeneity. Further, no significant associations or significant heterogeneity was observed for GL, insulin index or insulin load 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/≥25kg/m^2). The association between early adulthood GL and breast cancer was modified by BMI at age 18 (P for interaction=0.04), non-significant increased risk of breast cancer was observed among

women with BMI 25 or higher at age 18 (Table 5). However, no significant interaction was observed between BMI at age 18 and GI, 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. Further, 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 which 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 present study population (42). However, additional adjustment for red meat, animal fat or fiber did not change the associations. Similarly, diets low in carbohydrate can be high in red meat and low in fruits and vegetables, 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 fruit and vegetables.

Although there was a positive association between hyperinsulinemia and breast cancer in case-control studies nested within the NHS 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 to 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 US 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 2 diabetes (49). Women recalled their diet during adolescence when they were 33–52 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, early adulthood dietary intake prior to 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.

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The authors' responsibility were as follows: MSF, EC, WYC, HE and WCW: designed the research; MSF: analysis and wrote the manuscript; and WCW: had primary responsibility for the final content of the manuscript; and all authors: provided critical input in the writing of the manuscript and read and approved the final manuscript. The authors assume full responsibility for analyses and interpretation of these data.

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Table 1

Age and age-standardized characteristics according to energy-adjusted glycemic index during early adulthood among women enrolled in the Nurses' Health Study II

	Glycemic index, quintile				
	Q1	**Q2**	**Q3**	**Q4**	**Q5**
Number	18,064	18,138	18,072	18,105	18,109
Mean±SD					
Age, year	37.0±4.5	36.7±4.6	36.4±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	49.0±2.1	52.3±0.6	54.0±0.5	55.6±0.5	58.3±1.5
Glycemic load	105±18	115±16	120±17	127±18	139±22
Dietary insulin index	41.3±4.9	42.3±3.9	43.0±3.7	43.9±3.7	45.5±4.3
Insulin load	744±91	764±75	778±72	794±73	823±87
Total energy intake, kcal	1756±547	1829±547	1830±547	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	19.0±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±3.2	21.0±3.2	20.8±3.2
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
%					
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

Table 2

Relative risk (RR) and 95% confidence intervals (95%CI) for breast cancer according to quintile of energy-adjusted carbohydrate quality and quantity, insulin index and insulin load in 1991 among women in the Nurses' Health Study II

	Quintile of intake					
	1	**2**	**3**	**4**	**5**	P_{trend}
Carbohydrate						
All cases						
Median intake, percent of energy	40.6	45.9	49.6	53.3	59.2	
No. of cases/person-years	620/351,424	576/351,534	573/351,468	572/351,442	549/351,375	
Age-adjusted RR (95%CI)	1	0.94 (0.84–1.06)	0.96 (0.86–1.08)	0.95 (0.85–1.07)	0.93 (0.83–1.04)	0.25
Multivariable RR (95%CI)	1	0.93 (0.83–1.04)	0.93 (0.83–1.04)	0.92 (0.82–1.03)	0.89 (0.79–1.00)	0.07
Premenopausal cases						
Median intake, percent of energy	40.6	45.9	49.6	53.3	59.2	
No. of cases/person-years	333/218,609	320/218,603	286/218,414	322/218,369	286/218,225	
Age-adjusted RR (95%CI)	1	0.97 (0.83–1.13)	0.88 (0.75–1.03)	1.00 (0.86–1.17)	0.90 (0.77–1.06)	0.30
Multivariable RR (95%CI)	1	0.96 (0.82–1.12)	0.86 (0.74–1.02)	0.98 (0.84–1.15)	0.87 (0.74–1.03)	0.15
Postmenopausal cases						
Median intake, percent of energy	40.0	45.5	49.2	53.0	59.0	
No. of cases/person-years	199/85,958	154/86,001	197/86,102	180/86,235	189/86,091	
Age-adjusted RR (95%CI)	1	0.76 (0.62–0.94)	1.00 (0.82–1.22)	0.90 (0.74–1.11)	0.93 (0.76–1.14)	0.94
Multivariable RR (95%CI)	1	0.74 (0.60–0.92)	0.96 (0.78–1.18)	0.86 (0.70–1.06)	0.88 (0.72–1.09)	0.56
Glycemic index						
All cases						
Median	49.7	52.3	54.0	55.6	57.9	
No. of cases/person-years	599/351,303	591/351,648	603/351,157	559/351,454	538/351,682	
Age-adjusted RR (95%CI)	1	1.01 (0.90–1.13)	1.05 (0.94–1.18)	0.99 (0.88–1.11)	0.98 (0.87–1.10)	0.69
Multivariable RR (95%CI)	1	1.00 (0.90–1.13)	1.06 (0.95–1.19)	1.01 (0.90–1.14)	1.01 (0.90–1.14)	0.80
Premenopausal cases						
Median	49.7	52.3	54.0	55.6	57.9	
No. of cases/person-years	329/218,428	307/218,399	308/218,432	308/218,474	295/218,486	

	Quintile of intake					
	1	**2**	**3**	**4**	**5**	P_{trend}
Age-adjusted RR (95%CI)	1	0.97 (0.83–1.13)	0.99 (0.85–1.16)	1.02 (0.87–1.19)	1.01 (0.86–1.18)	0.77
Multivariable RR (95%CI)	1	0.98 (0.84–1.15)	1.02 (0.88–1.20)	1.05 (0.90–1.24)	1.06 (0.90–1.25)	0.32
Postmenopausal cases						
Median	49.4	52.1	53.8	55.5	57.8	
No. of cases/person-years	174/86,049	196/86,096	204/86,113	166/86,048	179/86,082	
Age-adjusted RR (95%CI)	1	1.14 (0.93–1.40)	1.21 (0.98–1.48)	0.99 (0.80–1.23)	1.08 (0.87–1.33)	0.84
Multivariable RR (95%CI)	1	1.13 (0.92–1.39)	1.20 (0.97–1.47)	0.99 (0.79–1.23)	1.07 (0.86–1.33)	0.87
Glycemic load						
All cases						
Median	95.6	110.1	120.1	130.9	148.6	
No. of cases/person-years	622/351,436	580/351,501	563/351,440	556/351,550	569/351,317	
Age-adjusted RR (95%CI)	1	0.96 (0.85–1.07)	0.94 (0.84–1.06)	0.94 (0.84–1.06)	0.97 (0.86–1.09)	0.58
Multivariable RR (95%CI)	1	0.94 (0.84–1.05)	0.92 (0.82–1.03)	0.91 (0.81–1.02)	0.95 (0.84–1.07)	0.34
Premenopausal cases						
Median	95.6	110.0	120.0	130.9	148.6	
No. of cases/person-years	351/218,590	303/218,532	293/218,479	297/218,296	303/218,321	
Age-adjusted RR (95%CI)	1	0.88 (0.76–1.03)	0.88 (0.75–1.02)	0.90 (0.77–1.05)	0.93 (0.80–1.09)	0.48
Multivariable RR (95%CI)	1	0.89 (0.76–1.04)	0.87 (0.74–1.02)	0.89 (0.76–1.04)	0.92 (0.79–1.09)	0.41
Postmenopausal cases						
Median	94.1	108.8	119.0	129.9	147.8	
No. of cases/person-years	191/85,946	174/86,070	176/86,115	184/86,148	194/86,109	
Age-adjusted RR (95%CI)	1	0.91 (0.74–1.12)	0.94 (0.76–1.15)	0.98 (0.80–1.20)	1.02 (0.83–1.24)	0.67
Multivariable RR (95%CI)	1	0.90 (0.72–1.10)	0.91 (0.74–1.12)	0.94 (0.76–1.16)	0.97 (0.79–1.20)	1.00
Dietary insulin index						
All cases						
Median	38.0	41.1	43.1	45.2	48.4	
No. of cases/person-years	649/351,064	542/351,806	602/351,431	558/351,310	539/351,633	
Age-adjusted RR (95%CI)	1	0.86 (0.77–0.97)	0.98 (0.88–1.10)	0.93 (0.83–1.04)	0.89 (0.80–1.00)	0.17

	Quintile of intake					
	1	**2**	**3**	**4**	**5**	P_{trend}
Multivariable RR (95%CI)	1	0.87 (0.77–0.98)	0.99 (0.88–1.11)	0.93 (0.83–1.05)	0.90 (0.80–1.02)	0.24
Premenopausal cases						
Median	38.0	41.1	43.1	45.2	48.4	
No. of cases/person-years	356/218,269	283/218,764	333/218,300	285/218,467	290/218,420	
Age-adjusted RR (95%CI)	1	0.82 (0.71–0.97)	1.00 (0.86–1.16)	0.87 (0.74–1.02)	0.89 (0.76–1.04)	0.24
Multivariable RR (95%CI)	1	0.85 (0.72–1.00)	1.04 (0.88–1.21)	0.92 (0.78–1.08)	0.93 (0.79–1.10)	0.64
Postmenopausal cases						
Median	37.6	40.8	42.8	44.9	48.2	
No. of cases/person-years	193/85,826	175/86,013	194/86,255	190/86,103	167/86,190	
Age-adjusted RR (95%CI)	1	0.93 (0.75–1.14)	1.02 (0.83–1.24)	1.01 (0.83–1.24)	0.88 (0.71–1.08)	0.40
Multivariable RR (95%CI)	1	0.92 (0.75–1.14)	1.02 (0.82–1.25)	0.99 (0.80–1.22)	0.86 (0.69–1.07)	0.29
Insulin load						
All cases						
Median	682	739	777	817	882	
No. of cases/person-years	635/352,963	564/352,499	580/347,330	564/352,174	547/352,278	
Age-adjusted RR (95%CI)	1	0.92 (0.82–1.02)	0.97 (0.87–1.09)	0.96 (0.85–1.07)	0.93 (0.82–1.04)	0.33
Multivariable RR (95%CI)	1	0.92 (0.82–1.03)	0.98 (0.87–1.10)	0.96 (0.85–1.08)	0.92 (0.82–1.04)	0.35
Premenopausal cases						
Median	682	739	777	817	882	
No. of cases/person-years	344/218,377	298/218,488	327/217,827	283/219,793	295/217,735	
Age-adjusted RR (95%CI)	1	0.89 (0.76–1.04)	1.00 (0.86–1.17)	0.89 (0.76–1.04)	0.93 (0.79–1.09)	0.38
Multivariable RR (95%CI)	1	0.91 (0.78–1.07)	1.04 (0.89–1.22)	0.93 (0.79–1.09)	0.97 (0.82–1.14)	0.77
Postmenopausal cases						
Median	674	732	771	812	878	
No. of cases/person-years	190/85,674	176/86,147	192/86,364	187/86,144	174/86,059	
Age-adjusted RR (95%CI)	1	0.94 (0.77–1.16)	1.02 (0.83–1.24)	1.01 (0.82–1.23)	0.92 (0.75–1.13)	0.61
Multivariable RR (95%CI)	1	0.94 (0.76–1.16)	1.01 (0.82–1.24)	0.99 (0.80–1.22)	0.90 (0.72–1.12)	0.45

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

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/m2), weight gain 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), and energy (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, 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, 49 to 50 years, 51 to 52 years, ≥53 years).

Table 3

Relative risk (RR) and 95% confidence intervals (95%CI) for breast cancer according to quintile of adolescent energy-adjusted carbohydrate quality and quantity, insulin index and insulin load among women in the Nurses' Health Study II

	Quintile of intake					
	1	**2**	**3**	**4**	**5**	P_{trend}
Carbohydrate						
All cases						
Median intake, E%	38.2	42.4	45.1	47.9	52.2	
No. of cases/person-years	236/120,472	247/120,546	242/120,661	203/120,694	207/120,507	
Age-adjusted RR (95%CI)	1	1.10 (0.92–1.31)	1.09 (0.91–1.31)	0.94 (0.77–1.13)	0.99 (0.82–1.19)	0.50
Multivariable RR (95%CI)	1	1.07 (0.90–1.28)	1.08 (0.90–1.29)	0.91 (0.75–1.10)	0.97 (0.80–1.17)	0.36
Premenopausal cases						
Median intake, E%	38.4	42.5	45.3	48.1	52.3	
No. of cases/person-years	126/67,602	133/67,736	104/67,812	95/67,881	89/67,714	
Age-adjusted RR (95%CI)	1	1.10 (0.86–1.41)	0.89 (0.68–1.16)	0.83 (0.63–1.09)	0.82 (0.62–1.08)	0.04
Multivariable RR (95%CI)	1	1.09 (0.85–1.40)	0.89 (0.68–1.16)	0.83 (0.63–1.09)	0.79 (0.60–1.04)	0.02
Postmenopausal cases						
Median intake, E%	37.6	41.8	44.6	47.3	51.6	
No. of cases/person-years	102/43,314	89/43,226	98/43,276	94/43,059	100/43,130	
Age-adjusted RR (95%CI)	1	0.91 (0.68–1.21)	1.01 (0.77–1.34)	0.98 (0.74–1.31)	1.06 (0.80–1.40)	0.56
Multivariable RR (95%CI)	1	0.89 (0.66–1.18)	1.01 (0.76–1.34)	0.96 (0.72–1.28)	1.06 (0.80–1.41)	0.59
Glycemic index						
All cases						
Median intake/day	51.6	53.6	55.0	56.3	58.4	
No. of cases/person-years	230/120,392	265/120,775	194/120,868	212/120,298	234/120,548	
Age-adjusted RR (95%CI)	1	1.17 (0.98–1.40)	0.86 (0.70–1.04)	0.97 (0.80–1.17)	1.11 (0.92–1.33)	0.84
Multivariable RR (95%CI)	1	1.18 (0.98–1.40)	0.87 (0.72–1.06)	0.99 (0.82–1.20)	1.15 (0.95–1.38)	0.54
Premenopausal cases						
Median intake/day	51.6	53.6	54.9	56.3	58.4	
No. of cases/person-years	109/67,681	133/67,797	91/67,810	111/67,615	103/67,842	

	Quintile of intake					
	1	**2**	**3**	**4**	**5**	P_{trend}
Age-adjusted RR (95%CI)	1	1.26 (0.97–1.63)	0.87 (0.65–1.15)	1.12 (0.86–1.47)	1.10 (0.84–1.44)	0.77
Multivariable RR (95%CI)	1	1.28 (0.99–1.66)	0.90 (0.68–1.19)	1.15 (0.88–1.50)	1.12 (0.85–1.47)	0.68
Postmenopausal cases						
Median intake/day	51.5	53.6	54.9	56.2	58.3	
No. of cases/person-years	102/43,268	104/43,185	87/43,260	85/43,198	105/43,094	
Age-adjusted RR (95%CI)	1	1.02 (0.78–1.35)	0.87 (0.65–1.15)	0.86 (0.64–1.14)	1.10 (0.83–1.45)	0.85
Multivariable RR (95%CI)	1	1.02 (0.77–1.34)	0.88 (0.66–1.18)	0.86 (0.65–1.16)	1.13 (0.86–1.50)	0.69
Glycemic load						
All cases						
Median intake/day	141	158	170	182	203	
No. of cases/person-years	240/122,851	256/119,561	206/115,371	228/126,140	205/118,956	
Age-adjusted RR (95%CI)	1	1.14 (0.96–1.37)	0.97 (0.80–1.17)	1.01 (0.84–1.22)	1.01 (0.83–1.22)	0.67
Multivariable RR (95%CI)	1	1.14 (0.96–1.37)	0.97 (0.80–1.17)	1.00 (0.83–1.20)	1.01 (0.83–1.22)	0.65
Premenopausal cases						
Median intake/day	142	158	170	183	203	
No. of cases/person-years	117/68,024	130/67,438	116/67,702	95/67,731	89/67,851	
Age-adjusted RR (95%CI)	1	1.18 (0.92–1.52)	1.10 (0.85–1.42)	0.92 (0.70–1.21)	0.92 (0.69–1.22)	0.23
Multivariable RR (95%CI)	1	1.19 (0.92–1.53)	1.10 (0.85–1.43)	0.92 (0.70–1.22)	0.90 (0.68–1.20)	0.19
Postmenopausal cases						
Median intake/day	139	156	168	180	200	
No. of cases/person-years	102/43,266	103/42,830	81/43,553	92/43,554	105/42,802	
Age-adjusted RR (95%CI)	1	1.05 (0.80–1.38)	0.83 (0.61–1.11)	0.94 (0.71–1.25)	1.14 (0.86–1.50)	0.56
Multivariable RR (95%CI)	1	1.04 (0.79–1.37)	0.82 (0.61–1.11)	0.92 (0.69–1.23)	1.15 (0.87–1.52)	0.52
Dietary insulin index						
All cases						
Median intake/day	39.8	42.0	43.6	45.1	47.4	
No. of cases/person-years	265/120,307	239/120,559	219/120,628	222/120,646	190/120,740	
Age-adjusted RR (95%CI)	1	0.94 (0.79–1.12)	0.91 (0.76–1.09)	0.93 (0.78–1.12)	0.86 (0.71–1.04)	0.13

	Quintile of intake					
	1	**2**	**3**	**4**	**5**	P_{trend}
Multivariable RR (95%CI)	1	0.96 (0.80–1.14)	0.92 (0.77–1.10)	0.95 (0.79–1.14)	0.88 (0.73–1.06)	0.21
Premenopausal cases						
Median intake/day	39.9	42.2	43.7	45.2	47.5	
No. of cases/person-years	139/67,654	109/67,902	117/67,564	88/67,871	94/67,754	
Age-adjusted RR (95%CI)	1	0.85 (0.66–1.10)	0.96 (0.75–1.23)	0.72 (0.55–0.94)	0.85 (0.65–1.11)	0.11
Multivariable RR (95%CI)	1	0.86 (0.67–1.12)	0.98 (0.76–1.26)	0.73 (0.55–0.96)	0.86 (0.66–1.13)	0.14
Postmenopausal cases						
Median intake/day	39.5	41.6	43.1	44.6	46.9	
No. of cases/person-years	104/43,199	109/43,191	91/43,153	95/43,200	84/43,263	
Age-adjusted RR (95%CI)	1	1.07 (0.81–1.40)	0.93 (0.70–1.24)	1.00 (0.75–1.32)	0.90 (0.67–1.21)	0.42
Multivariable RR (95%CI)	1	1.11 (0.84–1.46)	0.95 (0.72–1.27)	1.03 (0.78–1.37)	0.95 (0.70–1.27)	0.62
Insulin load						
All cases						
Median intake/day	1099	1160	1202	1244	1307	
No. of cases/person-years	267/120,427	236/120,399	217/121,288	222/120,179	193/120,588	
Age-adjusted RR (95%CI)	1	0.92 (0.77–1.10)	0.88 (0.74–1.06)	0.92 (0.77–1.11)	0.86 (0.71–1.04)	0.14
Multivariable RR (95%CI)	1	0.93 (0.78–1.11)	0.89 (0.74–1.07)	0.94 (0.78–1.12)	0.88 (0.72–1.06)	0.21
Premenopausal cases						
Median intake/day	1102	1163	1205	1247	1310	
No. of cases/person-years	138/67,630	111/67,388	108/68,108	100/67,985	90/67,635	
Age-adjusted RR (95%CI)	1	0.86 (0.67–1.11)	0.88 (0.68–1.14)	0.81 (0.62–1.05)	0.81 (0.62–1.07)	0.10
Multivariable RR (95%CI)	1	0.88 (0.68–1.14)	0.90 (0.69–1.16)	0.82 (0.63–1.07)	0.82 (0.63–1.08)	0.12
Postmenopausal cases						
Median intake/day	1090	1149	1190	1231	1295	
No. of cases/person-years	102/43,111	107/43,378	94/43,048	92/43,300	88/43,167	
Age-adjusted RR (95%CI)	1	1.07 (0.81–1.41)	0.98 (0.74–1.30)	0.98 (0.74–1.31)	0.97 (0.73–1.30)	0.69
Multivariable RR (95%CI)	1	1.10 (0.84–1.45)	1.00 (0.75–1.33)	1.02 (0.76–1.36)	1.01 (0.76–1.36)	0.90

*Ptrend calculated with median intake of each variable in each quintile as a continuous variable.

*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/m2), weight gain 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), menopausal status (premenopausal, postmenopausal, dubious), hormone use (postmenopausal never users, postmenopausal past users, postmenopausal current users), age at menopause (continuous), adolescent alcohol intake (nondrinker, <1.5, 1.5–<5, 5–<10, ≥10 g/day), adult alcohol intake (nondrinker, <5, 5–<15,≥15 g/day), adolescent energy intake (quintile).

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 Nurses' Health Study II

		Quintile of intake				
	No. of cases	**1**	**2**	**3**	**4**	**5**
Adolescence						
Estrogen and progesterone receptor positive	695	1	1.24 (0.99–1.55)	0.88 (0.69–1.13)	0.98 (0.77–1.25)	1.21 (0.95–1.53)
Estrogen and progesterone receptor negative	162	1	1.39 (0.88–2.20)	1.01 (0.62–1.66)	0.93 (0.56–1.55)	0.93 (0.56–1.56)
P-value, test for interaction			0.65	0.63	0.86	0.36
Early adulthood						
Estrogen and progesterone receptor positive	1571	1	1.02 (0.87–1.19)	1.02 (0.88–1.20)	1.03 (0.88–1.21)	1.05 (0.90–1.24)
Estrogen and progesterone receptor negative	433	1	1.15 (0.86–1.54)	1.03 (0.76–1.40)	1.13 (0.84–1.52)	0.96 (0.70–1.31)
P-value, test for interaction			0.46	0.96	0.59	0.59

*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/m2), weight gain 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), and energy (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, 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, 49 to 50 years, 51 to 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 hazard ratio of breast cancer by early adulthood energy-adjusted glycemic index, glycemic load, insulin index, and insulin load stratified by BMI at age 18 among women in the Nurses' Health Study II

		Quintile of intake						P-value, test for interaction
	Cases/Person-year	**1**	**2**	**3**	**4**	**5**	**P-value, test for trend**	
Adolescence								
Glycemic index								
<25 kg/m^2	1064/540,912	1	1.18 (0.99–1.42)	0.86 (0.70–1.04)	0.97 (0.80–1.18)	1.13 (0.93–1.36)	0.78	0.99
≥25 kg/m^2	63/57,568	1	1.62 (0.63–4.19)	1.88 (0.72–4.87)	1.83 (0.72–4.61)	2.36 (0.97–5.78)	0.06	
Glycemic load								
<25 kg/m^2	1064/540,912	1	1.16 (0.96–1.39)	1.00 (0.82–1.22)	1.03 (0.85–1.25)	1.04 (0.85–1.27)	0.94	0.31
≥25 kg/m^2	63/57,568	1	1.27 (0.60–2.69)	1.05 (0.42–2.58)	0.76 (0.32–1.82)	1.06 (0.44–2.55)	0.75	
Insulin index								
<25 kg/m^2	1064/540,912	1	0.92 (0.77–1.11)	0.95 (0.78–1.14)	0.94 (0.78–1.14)	0.89 (0.73–1.09)	0.33	0.34
≥25 kg/m^2	63/57,568	1	1.85 (0.86–3.96)	0.72 (0.28–1.85)	1.26 (0.53–2.95)	1.09 (0.43–2.79)	0.84	
Insulin load								
<25 kg/m^2	1064/540,912	1	0.90 (0.74–1.08)	0.90 (0.74–1.08)	0.94 (0.78–1.14)	0.88 (0.72–1.07)	0.31	0.34
≥25 kg/m^2	63/57,568	1	2.18 (0.97–4.86)	1.13 (0.47–2.69)	1.03 (0.42–2.57)	1.37 (0.54–3.44)	0.99	
Early adulthood								
Glycemic index								
<25 kg/m^2	2672/1,562,327	1	1.00 (0.88–1.12)	1.05 (0.93–1.18)	1.03 (0.91–1.16)	1.02 (0.90–1.16)	0.61	0.55
≥25 kg/m^2	190/178,868	1	1.10 (0.70–1.71)	1.56 (1.01–2.41)	1.00 (0.61–1.62)	1.09 (0.67–1.79)	0.66	
Glycemic load								
<25 kg/m^2	2672/1,562,327	1	0.92 (0.81–1.03)	0.89 (0.79–1.00)	0.90 (0.79–1.02)	0.94 (0.83–1.07)	0.37	0.04
≥25 kg/m^2	190/178,868	1	1.24 (0.81–1.92)	1.43 (0.92–2.22)	1.39 (0.87–2.22)	1.19 (0.70–2.02)	0.30	
Insulin index								
<25 kg/m^2	2672/1,562,327	1	0.89 (0.79–1.01)	1.01 (0.90–1.14)	0.94 (0.83–1.06)	0.90 (0.80–1.03)	0.23	0.55
≥25 kg/m^2	190/178,868	1	0.68 (0.43–1.07)	0.63 (0.39–1.03)	1.08 (0.69–1.68)	1.06 (0.67–1.69)	0.47	

		Quintile of intake						P-value, test for interaction
	Cases/Person-year	**1**	**2**	**3**	**4**	**5**	**P-value, test for trend**	
Insulin load								
<25 kg/m^2	2672/1,562,327	1	0.93 (0.82–1.05)	0.98 (0.87–1.11)	0.97 (0.85–1.09)	0.92 (0.81–1.04)	0.34	0.71
≥25 kg/m^2	190/178,868	1	0.91 (0.58–1.41)	0.82 (0.51–1.31)	0.98 (0.61–1.57)	1.24 (0.77–1.99)	0.40	

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 gain 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), and energy (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, 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, 49 to 50 years, 51 to 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).