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Dietary carbohydrates and breast cancer risk: A prospective study of the roles of overall glycemic index and glycemic load

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We examined breast cancer risk in association with overall glycemic index (GI), glycemic load (GL), and dietary carbohydrate and sugar intake in a prospective cohort of 49,613 Canadian women enrolled in the National Breast Screening Study who completed a self-administered food frequency questionnaire between 1980 and 1985. Linkages to national mortality and cancer databases yielded data on deaths and cancer incidence, with follow-up ending between 1998 and 2000. During a mean follow-up of 16.6 years, we observed 1,461 incident breast cancer cases. GI, GL, total carbohydrate and total sugar intake were not associated with breast cancer risk in the total cohort. However, there was evidence of effect modification of the association between GI and breast cancer risk by menopausal status ($p = 0.01$), the hazard ratio for the highest versus the lowest quintile level of GI being 0.78 (95% CI = 0.52–1.16; $p_{\text{trend}} = 0.12$) in premenopausal women and 1.87 (95% CI = 1.18–2.97; $p_{\text{trend}} = 0.01$) in postmenopausal women. The associations between GI and GL were not modified by body mass index (BMI) or by vigorous physical activity among pre- or postmenopausal women. Similarly, the associations between GI/GL and risk in postmenopausal women were not modified by BMI, vigorous physical activity, or ever use of hormone replacement therapy (HRT), although the associations were slightly stronger among those who reported no vigorous physical activity ($p_{\text{trend}} = 0.02$), among those who reported ever using HRT ($p_{\text{trend}} = 0.02$) and among normal-weight women (BMI < 25 kg/m²; $p_{\text{trend}} = 0.03$). Our data suggest that consumption of diets with high GI values may be associated with increased risk of breast cancer among postmenopausal women, possibly more so among subgroups defined by participation in vigorous physical activity, ever use of HRT and those who are not overweight.

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Key words: breast neoplasms; glycemic index; glycemic load; prospective cohort; National Breast Screening Study (NBSS)

Glycemic index (GI) is a means of classifying the carbohydrate content of individual foods according to their postprandial glycemic effects and hence their effects on blood insulin levels.^{1–3} Using glycemic index values and the carbohydrate content of foods, the total glycemic effect of the diet (glycemic load) can be estimated.⁴ Consumption of high GI diets has been associated with hyperinsulinemia,^{1,4,5} while low GI diets have been shown to be associated with a lower postprandial rise in insulin,⁶ thus maintaining insulin sensitivity.⁷

Hyperinsulinemia has been shown to be associated with increased breast cancer risk,^{8,9} and it is conceivable that this reflects an underlying association with high glycemic index diets. To date, there have been several studies of the association between dietary glycemic load and glycemic index and breast cancer risk.^{10–15} The results of 3 of these investigations were null,^{11,12,14} whereas the other 3 studies observed associations either overall¹⁵ or within subgroups defined by physical activity¹³ or obesity.¹⁰ Given the mixed results of previous studies, we examined the relationship between overall glycemic index and glycemic load, as well as total carbohydrate and total sugar consumption (included because of their strong association with postprandial insulin response¹⁶), and breast cancer risk in a prospective cohort study of Canadian women. We examined risk overall and across strata defined by menopausal status, body mass index (BMI), physical activity and hormone replacement therapy (HRT) use.

Material and methods

Study population

The study, which has been described in detail elsewhere,¹⁷ was conducted among participants in the Canadian National Breast Screening Study (NBSS), a randomized controlled trial of screening for breast cancer.¹⁸ A total of 89,835 women aged 40–59 years were recruited into the trial between 1980 and 1985.

Questionnaires

At recruitment into the study, participants completed a self-administered questionnaire that sought information on demographic characteristics, lifestyle factors, menstrual and reproductive history, as well as use of oral contraceptives and replacement estrogens. Starting in 1982 (that is, after some participants had completed their scheduled visits to the screening centers), a self-administered food frequency questionnaire (FFQ) was distributed to all new attendees at all screening centers and to women returning to the screening centers for rescreening.¹⁹ The FFQ sought information on usual portion size and frequency of consumption of 86 food items and included photographs of various portion sizes to assist respondents with quantifying intake. A comparison between the self-administered questionnaire and a full interviewer-administered questionnaire, which has been subjected to both validity and reliability testing¹⁹ and used in a number of epidemiologic studies,²⁰ revealed that the 2 methods gave estimates of intake of the major macronutrients and dietary fiber that were moderately to strongly correlated with each other (reported correlation coefficients ranged from 0.47 to 0.72).¹⁹ A total of 49,613 dietary questionnaires were returned and available for analysis.

Calculation of nutrient intake, overall glycemic index and glycemic load

Data from the completed self-administered food frequency questionnaires were used to estimate daily intake of nutrients using a database for Canadian foods that has been described elsewhere.²⁰ Data from the food frequency questionnaire were also used to estimate overall glycemic index and glycemic load. Glycemic index values of foods were obtained from published reports based on studies in North America.⁴ Overall glycemic index was calculated by multiplying the carbohydrate content (in grams) of a given food item by the number of servings per day of that food item and its glycemic index value, summing all food items reported and dividing by the total carbohydrate in the diet. Total dietary glycemic load was calculated by multiplying the carbohydrate content of a given food item by the number of servings consumed per day and its glycemic index value and summing the values for all food items reported. Each unit increase in glycemic load represents the insulin response to the equivalent of 1 g glucose or carbohydrate

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from white bread (depending on the standard used).²¹ When the reported glycemic index values for foods were observed to vary across studies,⁴ we used the mean of the reported values of glycemic index for that food. The main foods contributing to glycemic load in the cohort are listed in a footnote to Table I.

Ascertainment of incident breast cancer cases and deaths

Cases were women who were diagnosed during follow-up with incident breast cancer, ascertained by means of computerized record linkage to the Canadian Cancer Database. Deaths were ascertained by means of record linkage to the National Mortality Database. Both of these databases are maintained by Statistics Canada. The linkages to the databases yielded data on cancer incidence and mortality to 31 December 2000 for women in Ontario, 31 December 1998 for women in Quebec and 31 December 1999 for women in other provinces in Canada. Among the women for whom dietary data were available, we identified 1,461 incident breast cancers.

Statistical analysis

Of the 49,613 women with dietary data, we excluded women with extreme energy intake values (at least 3 standard deviations above or below the mean value for \log_e caloric intake; $n = 502$). These exclusions left 49,111 women available for analysis, among whom there were 1,450 incident cases of breast cancer.

Cox proportional hazards models (using age as the time scale) were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) for the association between energy-adjusted quintile levels of glycemic load, overall glycemic index, total carbohydrates and total sugar, as well as breast cancer risk; energy adjustment was performed using the residual method.²² For these analyses, cases contributed person-time to the study from their date of enrollment until the date of diagnosis of their breast cancer, and noncases contributed person-time from their date of enrollment until the termination of follow-up (the date to which cancer incidence data were available for women in the corresponding province) or death, whichever occurred earlier. Multivariate models included the variables listed in the footnote of Table II. To test for trend, we fitted the median value of each quintile as an ordinal variable in the risk models and evaluated the statistical significance

of the coefficient using the Wald test.²³ We examined the associations overall and within strata defined by menopausal status. Women who reported having regular menstrual periods within the past 12 months or who had had a hysterectomy without bilateral oophorectomy and were less than 45 years of age were classified as premenopausal. Women whose menstrual periods ceased prior to 12 months before baseline, those who had had a bilateral oophorectomy and those who had had a hysterectomy and were over 55 years of age were considered postmenopausal.²⁴ In addition, the associations overall and within menopausal strata were examined further within subgroups defined by body mass index [defined as weight (kg)/height (m²); weight and height were measured at baseline²⁵], self-reported vigorous physical activity (defined as jogging, running, brisk walking, vigorous sport, bicycling, heavy housework, *etc.*) and use of hormone replacement therapy (ever vs. never). Given the relatively small number of cases within each stratum of pre- and postmenopausal women, we categorized overall glycemic index and glycemic load by quartiles for the latter analyses. Stratum-specific multivariate models included the variables listed in a footnote in Table III. Interaction effects were tested independently of each other such that in the analysis of interaction with BMI, physical activity and HRT use were controlled for; in the analysis of interaction with physical activity, BMI and HRT use were controlled for; and in the analysis of interaction with HRT use, BMI and physical activity were controlled for. Tests for interaction were based on likelihood ratio tests comparing models with and without product terms representing the variables of interest. Use of the life test procedure in SAS showed that the proportional hazards assumption was met in this data set. All analyses were performed using SAS version 9 (SAS Institute, Cary, NC).

Results

The average duration of follow-up for cohort members was 16.6 years, corresponding to a total of 811,649 person-years of follow-up for the cohort. The mean age at diagnosis for the cases was 54.8 ± 6.5 years. For the cohort as a whole, the mean \pm SD of the energy-adjusted overall glycemic index and glycemic load were 74.6 ± 12.2 and 144.5 ± 42.5 g/day, respectively. There was a

TABLE I—AGE-ADJUSTED BASELINE DISTRIBUTIONS OF BREAST CANCER RISK FACTORS BY QUINTILES OF ENERGY-ADJUSTED GLYCEMIC LOAD

	Quintiles of energy-adjusted glycemic load (g/day)				
	<119	120–139	140–155	156–175	> 175
Mean overall glycemic index	72.5 (53.7)* ¹	78.4 (53.6)	79.7 (53.6)	81.7 (53.7)	84.3 (53.7)
Mean glycemic load (g/day)	98.6 (28.7)	129.5 (28.7)	147.2 (28.7)	164.5 (28.7)	196.0 (28.7)
Mean total carbohydrates (g/day)	149.8 (137.9)	179.0 (137.8)	198.6 (137.8)	216.6 (137.8)	253.9 (137.9)
Mean total sugar (g/day)	58.7 (73.3)	71.6 (73.2)	79.6 (73.2)	86.3 (73.2)	103.0 (73.3)
Mean total fiber (g/day)	17.4 (14.3)	20.0 (14.3)	21.2 (14.3)	22.1 (14.3)	23.2 (14.3)
Mean energy intake (kcal/day)	2106 (1442)	2027 (1441)	2046 (1441)	2059 (1441)	2121 (1441)
Mean age (years)	48.1 (5.5)	48.4 (5.5)	48.5 (5.7)	48.8 (5.7)	48.9 (5.7)
Postmenopausal at baseline (%)	18.0	19.4	19.8	21.1	21.9
Mean BMI (kg/m ²)	25.2 (10.2)	25.1 (10.2)	24.7 (10.2)	24.6 (10.2)	24.3 (10.2)
Ever smoker (%)	24.9	21.7	19.3	17.8	16.4
Mean alcohol intake (g/day)	16.1 (28.0)	10.0 (27.9)	7.6 (27.9)	5.5 (27.9)	3.6 (27.8)
Some vigorous physical activity (%)	18.8	20.5	20.8	21.0	19.1
Age at menarche \leq 12 years (%)	20.8	20.7	20.4	19.4	18.8
Mean duration of oral contraceptive use (months)	37.6 (108.6)	35.7 (108.6)	33.8 (108.6)	32.0 (108.6)	28.3 (108.6)
Mean duration of hormone replacement therapy use (months) ²	14.4 (85.3)	13.5 (85.2)	13.1 (85.2)	12.6 (85.2)	13.7 (85.2)
Mean number of live births	2.6 (6.1)	2.6 (6.1)	2.6 (6.1)	2.6 (6.1)	2.6 (6.1)
First-degree relative with breast cancer (% yes)	20.0	19.8	20.5	20.5	19.3
Age at first birth	23.8 (10.5)	24.2 (10.4)	24.4 (10.4)	24.5 (10.4)	24.6 (10.5)

*The main foods contributing to glycemic load in the cohort include white bread (sliced), rolls, muffins, potatoes (baked, boiled, mashed), French fries, cakes, cookies, rice, pasta, pizza, cold breakfast cereals, pies and tarts, cola, other soft drinks, citrus fruits and juices and other fruits, crisp snacks (such as potato chips or popcorn), candy, chocolate, peas, beans and lentils, hot breakfast cereals, dark and whole grain breads, corn, root vegetables other than potatoes, jam, jelly and honey, sugar in tea or coffee, icecream, peanut butter.⁻¹Numbers in parentheses represent the standard deviation.⁻²Among postmenopausal women only.

TABLE II – ADJUSTED HAZARD RATIOS AND 95% CONFIDENCE INTERVALS FOR THE ASSOCIATION BETWEEN OVERALL GLYCEMIC INDEX AND GLYCEMIC LOAD AND RISK OF BREAST CANCER

	Cases/person-years	Hazard ratio (95% CI)	
		Age and energy adjusted	Multivariate adjusted
Glycemic load (g/day)			
< 119	297/163,012	1.0 (referent)	1.0 (referent)
120–139	285/162,580	0.95 (0.80–1.13)	0.95 (0.80–1.14)
140–155	300/162,186	1.03 (0.87–1.22)	1.02 (0.86–1.22)
156–175	286/162,307	1.00 (0.84–1.19)	0.97 (0.81–1.16)
> 175	282/161,563	1.00 (0.84–1.18)	0.95 (0.79–1.14)
<i>p</i> for trend		0.84	0.70
Overall glycemic index			
< 60	293/161,898	1.0 (referent)	1.0 (referent)
61–71	307/162,474	0.99 (0.81–1.21)	1.01 (0.82–1.24)
72–81	281/162,182	0.91 (0.72–1.15)	0.94 (0.74–1.19)
82–96	287/162,623	0.93 (0.71–1.22)	0.96 (0.73–1.26)
>96	282/162,471	0.88 (0.64–1.21)	0.88 (0.63–1.22)
<i>p</i> for trend		0.41	0.38
Total carbohydrate (g/day)			
<143	284/162,780	1.0 (referent)	1.0 (referent)
144–175	302/162,771	1.11 (0.93–1.17)	1.09 (0.91–1.31)
176–206	265/162,475	0.92 (0.76–0.96)	0.90 (0.74–1.11)
207–249	323/162,366	1.18 (0.97–1.13)	1.12 (0.90–1.38)
>249	276/161,257	1.01 (0.79–0.93)	0.93 (0.70–1.22)
<i>p</i> for trend		0.67	0.86
Total sugar (g/day)			
< 52	284/162,201	1.0 (referent)	1.0 (referent)
53–68	284/162,631	1.02 (0.86–1.22)	1.00 (0.84–1.20)
69–83	315/162,812	1.14 (0.96–1.36)	1.08 (0.90–1.30)
84–103	291/162,443	1.08 (0.89–1.30)	0.98 (0.80–1.20)
> 103	276/161,562	1.00 (0.81–1.24)	0.88 (0.70–1.12)
<i>R</i> for Trend		0.74	0.38

Multivariable models included age (age at baseline), BMI in kg/m² (< 25, 25–29, ≥ 30), menopausal status, alcohol (zero plus 4 levels of intake), use of hormone replacement therapy (never plus four levels of duration), use of oral contraceptives (never plus four levels of duration), parity (zero plus 3 levels), age at menarche (≤ 12 vs. > 12 years of age), age at first live birth (< 25, 25–29, ≥ 30), first-degree relative with breast cancer (yes/no), history of benign breast disease (yes/no), intake of energy (as a continuous variable), energy-adjusted total fiber intake (as a continuous variable), study center and randomization group.

TABLE III – ADJUSTED HAZARD RATIOS AND 95% CONFIDENCE INTERVALS FOR THE ASSOCIATION BETWEEN OVERALL GLYCEMIC INDEX AND GLYCEMIC LOAD AND RISK OF BREAST CANCER STRATIFIED BY MENOPAUSAL STATUS

No. of cases/person years	Hazard ratio (95% CI)		<i>p</i> for interaction
	Premenopausal 670–400,673	Postmenopausal 575/300,048	
Glycemic load (g/day)			
<125	1.0 (referent)	1.0 (referent)	
125–147	0.95 (0.76–1.18)	1.18 (0.92–1.54)	
148–169	0.81 (0.64–1.02)	1.20 (0.93–1.56)	
> 169	0.96 (0.76–1.22)	1.08 (0.82–1.41)	
	<i>p</i> = 0.44	<i>p</i> = 0.68	0.08
Overall glycemic index			
<63	1.0 (referent)	1.0 (referent)	
64–76	0.95 (0.73–1.23)	1.43 (1.04–1.97)	
77–92	0.77 (0.55–1.06)	1.80 (1.24–2.62)	
>92	0.78 (0.52–1.16)	1.87 (1.18–2.97)	
	<i>p</i> = 0.12	<i>p</i> = 0.01	0.01

Multivariable models included age (age at baseline), BMI in kg/m² (< 25, 25–29, ≥ 30), alcohol (zero plus 4 levels of intake), use of hormone replacement therapy (never plus 4 levels of duration), use of oral contraceptives (never plus 4 levels of duration), parity (zero plus 3 levels), age at menarche (≤ 12 vs. > 12 years of age), age at first live birth (< 25, 25–29, ≥ 30), first-degree relative with breast cancer (yes/no), history of benign breast disease (yes/no), intake of energy (as a continuous variable), energy-adjusted total fiber intake (as a continuous variable), study center and randomization group.

2-fold variation in mean glycemic load values between the lowest and highest quintile levels (Table I).

Compared to those with relatively low glycemic load values, women with high glycemic load values reported lower alcohol consumption, were less likely to have ever smoked, had a shorter

mean duration of oral contraceptive use, had a longer mean duration of hormone replacement therapy, had slightly lower mean body mass index, were more likely to be postmenopausal at baseline, were less likely to have a relatively early age at menarche and consumed more total carbohydrates, sugar and fiber (Table I). No appreciable variation was observed in mean energy intake, participation in vigorous physical activity, parity, or age at first birth by quintile levels of glycemic load. The patterns for overall glycemic index were similar to those for the glycemic load (data not shown).

Table II shows that in age- and energy-adjusted models, there was no association between glycemic load, overall glycemic index, total carbohydrate, or total sugar intake and risk of breast cancer. After multivariate adjustment, the hazard ratios remained essentially unchanged.

Risk of breast cancer associated with glycemic load differed little between premenopausal and postmenopausal women. However, there was some suggestion of effect modification of the association between overall glycemic index and breast cancer risk by menopausal status (Table III). Among premenopausal women, the highest *versus* the lowest quartile level of overall glycemic index was associated with a 22% reduction in risk (95% CI = 0.52–1.16; *p*_{trend} = 0.12), while among postmenopausal women, the highest *versus* lowest quartile level of overall glycemic index was associated with an 87% increased risk of breast cancer (95% CI = 1.18–2.97; *p*_{trend} = 0.01). On formal testing, the interaction between overall glycemic index and menopausal status was statistically significant [chi-square (3) = 12.05; *p* = 0.01]. There was no association between total sugar intake and breast cancer risk among pre- or postmenopausal women (*p*_{trend} = 0.74 and 0.19, respectively; data not shown). Likewise, total carbohydrate consumption was not associated with risk among either pre- or postmenopausal women (*p*_{trend} = 0.73 and 0.58, respectively; data not

shown). On formal testing, menopausal status did not modify the association between either total sugar intake [chi-square (3) = 2.34; $p = 0.50$] or total carbohydrate consumption [chi-square (3) = 2.94; $p = 0.40$] and breast cancer risk.

Within the total study population, there was no evidence of effect modification of the association between glycemic load and overall glycemic index and breast cancer risk by BMI or vigorous physical activity (data not shown). Likewise, Table IV shows that the associations between glycemic load and overall glycemic index and breast cancer risk among premenopausal women were not modified by BMI or vigorous physical activity. In addition, BMI and participation in vigorous physical activity did not modify the association between either total sugar intake or total carbohydrate intake and breast cancer risk (data not shown).

Table V shows the associations between glycemic load and overall glycemic index and breast cancer risk among postmenopausal women, stratified by BMI, participation in vigorous physical activity and HRT use. As with premenopausal women, the association between glycemic load and breast cancer risk among postmenopausal women did not appear to be modified by any of these variables. With respect to overall glycemic index, the highest *versus* lowest quartile level was associated with increased risk among both overweight/obese (HR = 1.57; 95% CI = 0.78–3.13; $p_{\text{trend}} = 0.25$) and normal weight postmenopausal women (HR = 1.99; 95% CI = 1.06–3.72; $p_{\text{trend}} = 0.03$). As well, among women who participated in vigorous physical activity, the highest *versus* lowest quartile level of overall glycemic index was associated with a 78% increase in risk (95% CI = 0.76–4.18; $p_{\text{trend}} = 0.26$), while a hazard ratio of 1.86 (95% CI = 1.07–3.21; $p_{\text{trend}} = 0.02$) was observed for the highest *versus* the lowest quartile level among postmenopausal women who did not participate in any vigorous physical activity. Furthermore, among ever users of HRT, the highest *versus* lowest quartile level of overall glycemic index was associated with a 2.2-fold increased risk of breast cancer (95% CI = 1.16–4.00; $p_{\text{trend}} = 0.02$), whereas among never users, there was a 58% (95% CI = 0.79–3.18; $p_{\text{trend}} = 0.27$) increased risk of breast cancer at the uppermost quartile level. There was no statistical evidence for interactions between overall glycemic index and BMI [chi-square (3) = 2.01; $p = 0.57$], participation in vigorous physical activity [chi-square (3) = 2.10; $p = 0.55$], or HRT use [chi-square (3) = 2.09; $p = 0.55$] in relation to breast cancer risk among postmenopausal women. Similarly, the associations between total sugar intake and total carbohydrate intake and risk of breast cancer did not appear to be modified by BMI, participation in vigorous physical activity, or HRT use among postmenopausal women (data not shown).

Discussion

High glycemic index diets are associated with increased insulin secretion,^{1,4,5,26} which may affect breast cancer risk by several mechanisms, including alteration of cell cycle kinetics (insulin facilitates the transit of cells through the G1 phase of the cell cycle),²⁷ inhibition of apoptosis²⁸ and elevation of plasma estrogen levels via lower production of sex hormone-binding globulin.²⁹

In the prospective study reported here, there was no association between either overall glycemic index or glycemic load and breast cancer risk over a 16-year follow-up period in the total study population. Likewise, no association was found between either total sugar or total carbohydrate intake and risk of breast cancer. There was some suggestion of increased risk in association with overall glycemic index among women who were postmenopausal at baseline, while statistically nonsignificant reductions in risk were observed at each level of overall glycemic index (above that for the reference category) among premenopausal women. The differences between pre- and postmenopausal women were characterized further upon stratification by body mass index (kg/m^2) and participation in vigorous physical activity, wherein small, statistically nonsignificant decreases in risk were observed in association with glycemic load and overall glycemic index within strata of BMI and participation in vigorous physical activity among premenopausal women, and positive associations were found within strata of BMI and vigorous physical activity in postmenopausal women. In postmenopausal women, there were also increases in risk within strata defined by HRT use. There was some suggestion that the associations were slightly stronger among women who had ever used HRT and those who never participated in vigorous physical activity, but there was no statistical evidence of effect modification by these variables.

In our study population, glycemic load was not associated with risk, whereas overall glycemic index was associated with breast cancer risk within specific subgroups. In trying to understand these differences, it is important to note that these indexes reflect slightly different characteristics of dietary carbohydrate intake. Overall glycemic index provides information on overall carbohydrate quality in the diet by comparing the effect of isoenergetic intakes of carbohydrate, while total dietary glycemic load, by taking into account the amount of carbohydrate consumed, provides information on both the quality and quantity of total dietary carbohydrate intake.⁴ Thus, while the study participants who developed breast cancer may have consumed a wider variety of high glycemic index foods (and thus had a poorer-quality diet with respect to carbohydrate) in comparison to women who did not develop breast cancer during follow-up, they may not have consumed these foods in

TABLE IV – ADJUSTED HAZARD RATIOS (95% CONFIDENCE INTERVALS) FOR THE ASSOCIATION BETWEEN GLYCEMIC LOAD (QUARTILES) AND OVERALL GLYCEMIC INDEX AND RISK OF BREAST CANCER AMONG PREMENOPAUSAL WOMEN BY LEVELS OF BODY MASS INDEX AND VIGOROUS PHYSICAL ACTIVITY

	BMI (kg/m^2)		p for interaction	Vigorous physical Act		p for interaction
	< 25	≥ 25		None	Some	
No. of cases/person years	448/266,991	216/129,246		155/132,850	230/186,185	
Glycemic load (g/day)						
< 125	1.0 (referent)	1.0 (referent)		1.0 (referent)	1.0 (referent)	
125–147	0.96 (0.73–1.27)	0.94 (0.65–1.36)		0.92 (0.70–1.22)	0.97 (0.67–1.40)	
148–169	0.76 (0.57–1.02)	0.92 (0.62–1.361)		0.87 (0.66–1.17)	0.69 (0.46–1.04)	
> 169	1.01 (0.76–1.35)	0.85 (0.55–1.31)		0.93 (0.70–1.25)	0.92 (0.61–1.38)	
	$p = 0.70$	$p = 0.46$	0.57	$p = 0.55$	$p = 0.36$	0.70
Overall glycemic index						
< 63	1.0 (referent)	1.0 (referent)		1.0 (referent)	1.0 (referent)	
64–76	1.01 (0.73–1.40)	0.84 (0.53–1.31)		0.85 (0.61–1.18)	1.11 (0.71–1.73)	
77–92	0.84 (0.56–1.26)	0.65 (0.37–1.13)		0.71 (0.48–1.06)	0.80 (0.46–1.40)	
> 92	0.89 (0.54–1.45)	0.62 (0.32–1.23)		0.71 (0.44–1.16)	0.81 (0.41–1.62)	
	$p = 0.44$	$p = 0.13$	0.99	$p = 0.15$	$p = 0.28$	0.74

Multivariable models included age (age at baseline), BMI in kg/m^2 (< 25, 25–29, ≥ 30), alcohol (zero plus 4 levels of intake), use of oral contraceptives (never plus 4 levels of duration), parity (zero plus 3 levels), age at menarche (≤ 12 vs. > 12 years of age), age at first live birth (< 25, 25–29, ≥ 30), first-degree relative with breast cancer (yes/no), history of benign breast disease (yes/no), intake of energy (as a continuous variable), energy-adjusted total fiber intake (as a continuous variable), study center and randomization group.

TABLE V – ADJUSTED HAZARD RATIOS (95% CONFIDENCE INTERVALS) FOR THE ASSOCIATION BETWEEN GLYCEMIC LOAD (QUARTILES) AND OVERALL GLYCEMIC INDEX AND RISK OF BREAST CANCER AMONG POSTMENOPAUSAL WOMEN BY LEVELS OF BODY MASS INDEX, VIGOROUS PHYSICAL ACTIVITY AND HORMONE REPLACEMENT THERAPY USE

	BMI (kg/m ²)		<i>p</i> for interaction	Vigorous physical activity			Hormone replacement therapy use		
	< 25	≥ 25		None	Some	<i>p</i> for interaction	Never	Ever	<i>p</i> for interaction
Number of cases/person years	321/503,391	251/299,799		153/110,562	155/123,251		293/156,538	282/143,510	
Glycemic load (g/day)									
< 125	1.0 (referent)	1.0 (referent)		1.0 (referent)	1.0 (referent)		1.0 (referent)	1.0 (referent)	
125–147	1.29 (0.92–1.81)	1.08 (0.72–1.62)		1.15 (0.84–1.56)	1.31 (0.81–2.12)		1.08 (0.75–1.57)	1.27 (0.88–1.83)	
148–169	1.06 (0.75–1.51)	1.36 (0.92–2.00)		1.24 (0.91–1.68)	1.07 (0.64–1.76)		1.06 (0.73–1.54)	1.34 (0.93–1.93)	
> 169	0.97 (0.68–1.39)	1.22 (0.82–1.82)		1.04 (0.76–1.42)	1.16 (0.69–1.93)		0.94 (0.65–1.38)	1.20 (0.82–1.76)	
	<i>p</i> = 0.48	<i>p</i> = 0.21	0.24	<i>p</i> = 0.80	<i>p</i> = 0.85	0.65	<i>p</i> = 0.69	<i>p</i> = 0.37	0.93
Overall glycemic index									
< 63	1.0 (referent)	1.0 (referent)		1.0 (referent)	1.0 (referent)		1.0 (referent)	1.0 (referent)	
64–76	1.44 (0.94–2.23)	1.39 (0.85–2.25)		1.38 (0.94–2.03)	1.42 (0.80–2.52)		1.46 (0.91–2.35)	1.43 (0.92–2.21)	
77–92	1.89 (1.14–3.13)	1.63 (0.93–2.88)		1.85 (1.19–2.89)	1.47 (0.73–2.94)		1.85 (1.06–3.22)	1.75 (2.05–2.93)	
> 92	1.99 (1.06–9.72)	1.57 (0.78–3.13)		1.86 (1.07–3.21)	1.78 (0.76–4.18)		1.58 (0.79–3.18)	2.15 (1.16–4.00)	
	<i>p</i> = 0.03	<i>p</i> = 0.25	0.57	<i>p</i> = 0.02	<i>p</i> = 0.26	0.55	<i>p</i> = 0.27	<i>p</i> = 0.02	0.50

Multivariable models included age (age at baseline), BMI in kg/m² (<25, 25–29, ≥ 30), alcohol (zero plus for levels of intake), use of hormone replacement therapy (never plus four levels of duration), use of oral contraceptives (never plus four levels of duration), parity (zero plus 3 levels), age at menarche (≤ 12 vs. > 12 years of age), age at first live birth (< 25, 25–29, ≥ 30), first degree relative with breast cancer (yes/no), history of benign breast disease (yes/no), intake of energy (as a continuous variable), energy-adjusted total fiber intake (as a continuous variable), study center and randomization group.

large enough quantities for glycemic load to have an effect on breast cancer risk.

Given that high body mass index and lack of physical activity are generally associated with increased fasting insulin²⁶ and decreased insulin sensitivity,^{30–32} women who are obese or who do not participate in physical activity may have a more pronounced insulin response to foods with higher glycemic values. Further, high glycemic value diets are associated with higher free estrogen levels due to the effect of insulin in lowering sex hormone-binding globulin (SHBG) production^{31,33} and enhancing aromatization of androgens.^{30,34} Hence, it is possible that postmenopausal women who use hormone replacement therapy and whose diets are characterized by consumption of high glycemic index foods may be at increased risk of hormone-mediated neoplasms, such as breast cancer, due to greater exposure to free estrogen through a combination of pathways.

Previous studies of overall GI and GL have yielded mixed results. For example, Augustin *et al.*,¹⁵ in a hospital-based case-control study of Italian women, reported statistically significant increased risks associated with the highest versus lowest quintile level of both overall GI (OR = 1.36; 95% CI = 1.14–1.64; *p*_{trend} < 0.01) and GL (OR = 1.34; 95% CI = 1.10–1.61; *p*_{trend} < 0.01). In addition, the relationship between glycemic load/index and breast cancer has been examined in 5 prospective studies.^{10–14} In keeping with our findings, Holmes *et al.*,¹⁴ in an analysis of data from the Nurses' Health Study (NHS), which included 4,092 incident cases of breast cancer, observed no association between glycemic load or overall glycemic index and risk of breast cancer overall, but reported a borderline positive association between overall glycemic index and breast cancer risk among postmenopausal women. In contrast, Jonas *et al.*¹² and Folsom *et al.*,¹¹ in analyses of data from the CPS II Nutrition Cohort (1,442 incident cases) and Iowa Women's Health Study (2,031 incident cases), respectively, reported no association between glycemic load/index and breast cancer risk among postmenopausal women.

In the present study, there was some suggestion of an inverse association between overall glycemic index and risk among premenopausal women. In contrast, Cho *et al.*,¹⁰ in an analysis of 714 incident breast cancer cases from the Nurses' Health Study II, did not find any association between glycemic load/index among premenopausal women, and Higgenbotham *et al.*¹³ (946 incident cases) reported a positive association between glycemic load and risk among premenopausal women, but observed no association in the total study population of pre- and postmenopausal women.

Three of the previous studies also examined dietary carbohydrate and/or dietary sugar intake in relation to breast cancer risk. Holmes *et al.*¹⁴ found no association between either dietary carbohydrates or dietary fiber and breast cancer risk, whereas Cho *et al.*¹⁰ reported an inverse association with carbohydrate intake among premenopausal women with a BMI < 25 kg/m² (*p*_{trend} = 0.02). Augustin *et al.*¹⁵ reported a positive trend with white bread consumption among postmenopausal women (*p*_{trend} = 0.02), but not among premenopausal women (*p*_{trend} = 0.17), as well as evidence of a positive association with sugar intake among both pre- and postmenopausal women (*p*_{trend} = 0.09 and 0.03, respectively). In a recent case-control study, Romieu *et al.*³⁵ also reported a statistically significant increased risk of breast cancer for the highest versus the lowest quartile level of carbohydrate consumption (OR = 2.22; 95% CI = 1.63–3.04). Each of these studies differed with respect to age at baseline, mean age at diagnosis and/or the range of glycemic load/index values, both from each other and from our study, making it difficult to draw firm conclusions regarding the role of glycemic load in breast cancer etiology.

Our data are limited by the possibility of error with respect to the measurement of diet and the calculation of glycemic load. Error in the measurement of daily intake of carbohydrates and sugars may have resulted from inaccurate recall.³⁶ Furthermore, measurement error might have occurred due to the fact that the glycemic index values of some foods are currently based on only 1 or 2 often small studies.⁴ However, this applies to the previous studies of glycemic index/load and breast cancer as well. Additional limitations include the fact that information on menopausal status was collected only at baseline. Given that the minimum age at baseline was 40 and an average of 16 years of follow-up, it is likely that most of those who were premenopausal at enrollment would have become postmenopausal during the course of follow-up. Thus, it is likely that our results for premenopausal women are largely accounted for by a mix of breast cancers diagnosed pre- and postmenopausally. In addition, the results stratified by physical activity should be interpreted with caution given that approximately 22% of the study subjects were missing information on physical activity. Also, although we adjusted our estimates for a wide range of potentially confounding variables, uncontrolled confounding by dietary and other factors cannot be excluded.

In conclusion, the results of our study suggest that dietary glycemic load is not associated with risk of breast cancer. In contrast, while overall glycemic index was not associated with risk of breast cancer in the total study population, a relatively high

overall glycemic index might be associated with increased risk among women who are postmenopausal, perhaps more so among those who do not participate in vigorous physical activity or who have ever used HRT. However, these observations require confirmation in other studies.

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