Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study[1–3]

Sabina Sieri, Valeria Pala, Furio Brighenti, Nicoletta Pellegrini, Paola Muti, Andrea Micheli, Alberto Evangelista, Sara Grioni, Paolo Contiero, Franco Berrino, and Vittorio Krogh

ABSTRACT

Background: Interest in the roles of glycemic index (GI) and glycemic load (GL) in breast cancer etiology has been stimulated by indications that disease risk is linked to insulinemia, sex hormone bioavailability, and insulin-like growth factor 1.

Objective: We aimed to determine whether GI and GL were associated with the risk of breast cancer in a cohort of Italian women volunteers from Northern Italy, who enrolled between 1987–1992 in the Hormones and Diet in the Etiology of Breast Tumors Study (ORDET Study).

Design: Volunteers completed a semiquantitative food-frequency questionnaire, and anthropometric and lifestyle data were collected. Dietary GI and GL in relation to breast cancer risk were examined in 8926 cohort women, including 289 with breast cancer identified after a mean follow-up of 11.5 y.

Results: The relative risk (RR) of breast cancer in the highest (versus lowest) quintiles of GI and GL was 1.57 (95% CI: 1.04, 2.36; *P* for trend = 0.040) and 2.53 (95% CI: 1.54, 4.16; *P* for trend = 0.001), respectively. Total carbohydrate intake was not associated with greater breast cancer risk, but high carbohydrate from high-GI foods was. When women were categorized by baseline menopausal status and body mass index (BMI; in kg/m^2), the increased risk of dietary GL was confined to those who were premenopausal (RR = 3.89; 95% CI: 1.81, 8.34) and who had normal BMI (ie, <25) (RR = 5.79; 95% CI: 2.60, 12.90) (*P* for trend = 0.001 for both).

Conclusions: A high-GL diet may increase the risk of breast cancer in Italian women. The effect is particularly evident in premenopausal women and those with BMI < 25. *Am J Clin Nutr* 2007;86: 1160–6.

KEY WORDS Glycemic index, glycemic load, breast cancer risk, women

INTRODUCTION

Worldwide, breast cancer is the most common cancer in women. The risk of developing breast cancer increases in women from low-risk countries who immigrate to high-risk countries, which suggests that this cancer is influenced by modifiable lifestyle or environmental factors (1). The growing recognition that breast cancer may be promoted by hyperinsulinemia and insulin resistance suggests that a diet rich in carbohydrates, which results in high glycemia and consequent high insulinemia, may favor a metabolic environment promoting tumor growth (2, 3). Carbohydrates vary markedly in physical form, chemical structure, particle size, and fiber content, and different carbohydrates induce widely differing plasma glucose concentrations and insulin responses. The glycemic index (GI), introduced by Jenkins et al in 1981 (4), ranks the carbohydrate content of individual foods according to their postprandial glycemic effects, which in turn are a major determinant of postprandial insulinemia. However, the quantity and the quality of the ingested carbohydrates influence the postprandial glycemic response; a suitable estimate of this is the glycemic load (GL), which is the product of the GI of a food item and the available carbohydrate content of the portion ingested.

High GI and high GL have been related to a greater risk of adult-onset diabetes (5), heart disease (6, 7), and several types of cancer, including those of the upper aerodigestive tract (8), colorectum (9), stomach (10), pancreas (11), prostate (12), ovary (13), endometrium (14), and breast (15–24). However, although 2 case-control studies found a greater breast cancer risk in women with high GL (15, 21), prospective studies reported no association between dietary GI or GL and breast cancer (16–20, 22, 24). We prospectively evaluated the association between breast cancer risk and high-GI or -GL diets in women of the cohort of Italian volunteers in the Hormones and Diet in the Etiology of Breast Tumors Study (ORDET Study).

SUBJECTS AND METHODS

Subjects

Between June 1987 and June 1992, 10 786 healthy women aged 34–70 y who were residents of the province of Varese in Northern Italy were recruited to the prospective ORDET Study.

[1] From the Nutritional Epidemiology Unit (SS, VP, AE, SG, and VK), the Descriptive Epidemiology and Health Planning Unit (AM), the Cancer Registry Division (PC), and the Etiological and Preventive Epidemiology Unit (FB), National Cancer Institute, Milan, Italy; the Department of Public Health, University of Parma, Parma, Italy (FB and NP); and the Epidemiology and Prevention Unit, Istituto Regina Elena, Rome, Italy (PM).

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[3] Reprints not available. Address correspondence to S Sieri, Nutritional Epidemiology Unit, Fondazione IRCS Istituto Nazionale dei Tumori, Via Venezian,1, 20133 Milan, Italy. E-mail: sabina.sieri@istitutotumori.mi.it.

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The women were volunteers from the general population who had learned of the study at public meetings, through advertising, or at breast cancer early-diagnosis units. Women who were taking hormone therapy in the 3 mo before recruitment, who had a history of cancer, who had current chronic or acute liver disease, or who had undergone bilateral ovariectomy were excluded.

Information on menstrual and reproductive history and lifestyle characteristics was collected by trained nurses at recruitment. Height, weight, waist and hip dimensions, and other anthropometric measures were also taken by the nurses according to a standardized protocol. The volunteers also completed a self-administered semiquantitative food-frequency questionnaire (FFQ) (25).

Cancer incidence information, available from the local cancer registry (Varese Cancer Registry) was linked to the ORDET Study file to identify incident breast cancer cases in the cohort up to December 2001. The Varese Cancer Registry is characterized by high quality and completeness of the data: <2% of breast cancer cases are known to the registry by death certificate only, and 96.3% of cases are confirmed histologically or cytologically (26). The ORDET Study file was also linked to the Varese residents' file to check vital status.

After the exclusion of 51 women who had a cancer diagnosis before enrollment or who were lost to early follow-up, 10 735 women were followed. An additional 1552 women were excluded because they enrolled at the beginning of the study when the FFQ was not available. Also excluded were women in whom the ratio of total energy intake (determined from the FFQ) to basal metabolic rate [determined by Harris-Benedict equation (27)] was at either extreme of the distribution (cutoffs were first and last half-percentiles), to reduce the effect of implausible extreme values on the analysis. This cohort was further reduced to 8959 women (mean follow-up: 11.5 y; total follow-up: 100 074.6 person-years) by exclusion of women for whom values for anthropometric and reproductive variables were missing. The final cohort consisted of 289 breast cancer cases (269 invasive and 20 in situ).

All participants provided written informed consent. The Ethics Review Board of the Italian National Cancer Institute of Milan approved the study.

Food questionnaire

After compilation at recruitment, the FFQ was reviewed by a nurse with the volunteer to complete any missing items. The questionnaire consisted of 107 items; it was designed to ascertain in detail the quantities and kinds of foods consumed over the previous year by using illustrations of 2 or 3 sample dishes of definite sizes or by reference to standard portion sizes. The frequency of consumption of items could be specified by day, week, or month. Questions on seasoning and food preparation were also included. From the FFQ data, an average daily diet, consisting of food items and portion sizes, was calculated for each volunteer. The food groups included in the FFQ were vegetables (divided into cooked, raw vegetables, tomatoes, pulses, etc), potatoes, fruit, cereals (categories of bread, pasta, rice, and pizza), meat and meat products, fish, dairy products (categories of cheese, milk, and yogurt), eggs, cakes, added fat, and alcoholic beverages. Nutrient values for each food item were obtained from the Italian food composition tables (28). GIs of food items containing available carbohydrates were obtained from measurements of common Italian foods (F Brighenti et al, Italian glycemic index table, manuscript in preparation, 2007). This database includes staple Italian food items and preparations and their GIs, as well as revised data from the literature reporting GIs for foods similar to those consumed in Italy. The table contains >150 food items and covers >90% of the carbohydrate intake of persons living in Northern Italy. If no item in the table was sufficiently similar to the actual food item, GIs published elsewhere and not specifically related to an Italian diet were used (29).

The GI for a food is defined as the area under the blood glucose curve produced after ingestion of a portion of the food containing 50 g available carbohydrate, relative to the area produced after consumption of a standard amount of glucose. The average dietary GI for each volunteer was calculated as the sum of the GIs of each food item consumed, which was multiplied by the average daily amount consumed and the percentage carbohydrate content and then divided by the total daily carbohydrate intake. The GL was calculated similarly but without the division by total carbohydrate intake. Each unit of GL represents a glycemic response equivalent to that of 1 g glucose.

The relation between carbohydrate intake and breast cancer risk was further investigated by dividing total carbohydrate intake into carbohydrates from high-GI foods, whose main representatives in the present study were bread (52.7%), cookies (12.4%), and pizza (9.7%), and carbohydrates from low-GI foods, whose main representatives were pasta (33%), fruit (32.4%), and cakes (15.3%). For this investigation, we chose a GI of 57 as the cutoff between low- and high-GI foods. Adoption of this cutoff allowed high- and low-GI foods each to contribute ≈50% to total carbohydrate intake.

Blood collection and laboratory assays

In a previous nested case-control study in ORDET Study women (30, 31), stored serum samples from 720 subjects (144 cases and 576 controls) had been assayed for total serum glucose and fructosamine. In 379 controls who had filled in the FFQ (and hence had an assessment of GL), we assessed the correlation of serum glucose and fructosamine concentrations with GL as determined from the FFQ.

Statistical analyses

GLs and GIs were adjusted for the energy intake of each person by using the regression-residual method (32); next, they were categorized into quintiles. Relative risks (RR) of breast cancer in relation to GI and GL were determined by multivariate Cox hazard modeling, which compared the highest quintile of GI or GL with the lowest quintile. Age at menarche, oral contraception use (yes or no), smoking status (smoker, never smoker, or former smoker), height, weight, years of education, parity, alcohol intake, and total energy intake were included as covariates. Additional models also included saturated fat and fiber intake as covariates. As a test for trend, we used a likelihood ratio test comparing models that included or omitted the variable whose value was the median of the quintile to which the subject belonged.

The effect on breast cancer of total carbohydrates, carbohydrates from high-GI foods, and carbohydrates from low-GI foods was analyzed by using the energy partition method (32). This method is a nonisocaloric method that tests the effect of adding energy from a specific macronutrient—in this case, carbohydrates—while keeping energy from other macronutrients constant. For total carbohydrates, high-GI carbohydrates, and

TABLE 1
Baseline distribution of values for nutrients and other variables by quintile (Q) of mean energy-adjusted dietary glycemic index (GI) and mean dietary glycemic load (GL) in Italian women in the ORDET Study[1]

	Quintile of energy-adjusted GI				Quintile of energy-adjusted GL			
	Q1	Q3	Q5	*P* for trend[2]	Q1	Q3	Q5	*P* for trend[2]
Dietary GI	51.9 ± 0.03[3]	55.5 ± 0.02	59.2 ± 0.02	0.000	54.2 ± 0.06	55.6 ± 0.06	56.7 ± 0.06	0.000
Dietary GL (g/d)	104.2 ± 0.83	121.5 ± 0.82	121.9 ± 0.82	0.000	96.6 ± 0.72	113.0 ± 0.72	150.5 ± 0.72	0.000
Protein (% of energy/d)	17.6 ± 0.07	17.0 ± 0.07	17.0 ± 0.07	0.000	18.5 ± 0.06	17.2 ± 0.06	15.7 ± 0.06	0.000
Fat (% of energy/d)	35.4 ± 0.14	33.6 ± 0.14	32.7 ± 0.14	0.000	39.7 ± 0.11	33.3 ± 0.11	28.6 ± 0.11	0.000
Carbohydrate (% of energy/d)	46.7 ± 0.18	48.4 ± 0.18	48.6 ± 0.18	0.000	37.9 ± 0.08	48.6 ± 0.08	57.5 ± 0.08	0.000
Fiber (g/d)	20.4 ± 0.14	19.8 ± 0.14	17.9 ± 0.14	0.000	17.5 ± 0.13	18.7 ± 0.13	23.4 ± 0.13	0.000
Fiber from fruit (g/d)	7.6 ± 0.08	5.3 ± 0.08	3.6 ± 0.08	0.000	4.7 ± 0.08	5.3 ± 0.08	6.6 ± 0.08	0.000
Fiber from vegetables (g/d)	4.3 ± 0.04	3.5 ± 0.04	3.0 ± 0.04	0.000	4.4 ± 0.05	3.4 ± 0.04	3.2 ± 0.04	0.188
Fiber from pulses (g/d)	1.2 ± 0.02	1.1 ± 0.02	0.9 ± 0.02	0.000	1.09 ± 0.02	1.06 ± 0.02	1.15 ± 0.02	0.000
Fiber from cereals (g/d)	6.3 ± 0.08	8.8 ± 0.08	9.4 ± 0.08	0.000	6.3 ± 0.07	8.0 ± 0.07	11.4 ± 0.07	0.000
Fiber from potatoes (g/d)	0.62 ± 0.01	0.70 ± 0.01	0.69 ± 0.01	0.000	0.76 ± 0.01	0.66 ± 0.01	0.67 ± 0.01	0.000
Alcohol (% of energy/d)	3.2 ± 0.12	3.9 ± 0.12	4.8 ± 0.12	0.000	6.4 ± 0.12	3.9 ± 0.12	1.7 ± 0.12	0.000
Energy (kcal/d)	1710 ± 11.26	1818 ± 11.18	1704 ± 11.17	0.524	1863 ± 11.21	1683 ± 11.12	1861 ± 11.10	0.966
BMI (kg/m^2)	25.4 ± 0.10	25.3 ± 0.10	25.3 ± 0.10	0.752	25.7 ± 0.10	25.4 ± 0.10	25.0 ± 0.10	0.000
Waist (cm)	79.3 ± 0.22	79.5 ± 0.22	79.6 ± 0.22	0.152	80.3 ± 0.22	79.4 ± 0.22	78.7 ± 0.22	0.000
Education (y)	7.7 ± 0.08	7.8 ± 0.08	7.7 ± 0.08	0.478	7.8 ± 0.08	7.6 ± 0.08	8.0 ± 0.08	0.246
Current smoker (%)	20.5	18.6	21.2	0.281	25.2	18.5	16.5	0.000

[1] ORDET Study, the Hormones and Diet in the Etiology of Breast Tumors Study.
[2] *P* for a test for interquintile trend.
[3] $\bar{x}$ ± SE (all such values).

low-GI carbohydrates, RRs of breast cancer were calculated for a 5% increase of energy from each of these sources in turn, including age at menarche, oral contraception use (yes or no), smoking status (smoker, never smoker, or former smoker), height, weight, years of education, and parity as covariates. We hypothesized that the effect of high dietary GI and GL would be modified by factors associated with hormone status and insulin resistance. To explore this possibility, we performed analyses stratified by baseline menopausal status (premenopausal or postmenopausal) and body mass index [(BMI; in kg/m^2) $<$ 25 or $\geq$25]. We examined whether associations for GI and GL differed according to BMI and menopausal status by employing product terms (0 and 1 for BMI $<$ 25 and $\geq$ 25, respectively, and also for premenopausal or postmenopausal status respectively) and multiplying them by the median of the GI and GL quintile to which the subject belonged. To assess the significance of interaction differences, we used a likelihood ratio test that compared the model that included the product term and the model that did not include it. In all Cox models, age at recruitment was the primary time variable. Spearman's rank correlation was used to assess relations between dietary GL and serum fructosamine and glucose concentrations. All analyses were performed with STATA software (version 7.0; Stata Corp, College Station, TX).

RESULTS

The distribution of nutrients and other pertinent variables by quintile of energy-adjusted dietary GI and dietary GL in the ORDET Study cohort is shown in **Table 1**. Dietary GI varied in a narrow range of 51.9 to 59.2 from the lowest to highest quintile, whereas there was a variation of ≈50% in dietary GL. Women in the highest quintile of dietary GI consumed more alcohol and less fiber overall than did women with low GI; in particular, women with a high GI consumed less fiber from fruit, vegetables, and pulses but more fiber from cereals than did women with a low GI.

Women in the higher GL quintiles consumed more carbohydrate and fiber, especially fiber from fruit, pulses, and cereals, but consumed less protein, fat, and alcohol than did women in the lower GL quintiles. Women in the highest GL quintile also were more educated, smoked less, and had a very slightly lower BMI than did women in the lowest GL quintile. Mean energy intake varied little and nonsystematically by quintiles of GI and GL.

Adjusted RRs for developing breast cancer by quintiles of dietary GI and dietary GL are shown in **Table 2**. Women in the highest GI quintile had a significantly greater risk of breast cancer than did those in the lowest GI quintile (RR = 1.68; 95% CI: 1.13, 2.49; *P* for trend = 0.010). After adjustment for saturated fat and fiber intakes, the RR was lower but still significant (RR = 1.57; 95% CI: 1.04, 2.36; *P* for trend = 0.040). Women in the highest GL quintile had a significantly greater risk of breast cancer than did those in lowest GL quintile (RR = 1.65; 95% CI: 1.11, 2.46; *P* for trend = 0.031). After adjustment for saturated fat and fiber intakes, the RR increased to 2.53 (95% CI: 1.54, 4.16; *P* for trend = 0.001).

The effects of increasing energy intake from total carbohydrates, high-GI carbohydrates, and low-GI carbohydrates by 5%, while keeping constant other energy sources (ie, fat, protein, and alcohol), are shown in **Table 3**. No significant association between total carbohydrate intake and breast cancer risk was found. However, increasing the intake of high-GI carbohydrates was significantly associated with a greater risk of breast cancer, whereas increasing the intake of low-GI carbohydrates was not.

The results of the stratified analysis to assess the effects of baseline menopausal status on associations of dietary GL and dietary GI with breast cancer risk are shown in **Table 4**. *P* for trend is reported when an interaction was significant. The risk of

TABLE 2
Relative risks (RR) (and 95% CIs) of breast cancer in relation to energy-adjusted glycemic index and glycemic load in Italian women in the ORDET Study[1]

	Range	Cases	RR by increasing quintile	
			RR[2]	RR[3]
		n		
Glycemic Index				
Q1	<53.5	40	1	1
Q2	53.5–54.9	54	1.48 (0.98, 2.23)[4]	1.44 (0.95, 2.17)
Q3	55.0–56.1	64	1.69 (1.13, 2.51)	1.62 (1.08, 2.42)
Q4	56.2–57.5	64	1.70 (1.14, 2.53)	1.62 (1.08, 2.44)
Q5	>57.5	67	1.68 (1.13, 2.49)	1.57 (1.04, 2.36)
P for trend[5]			0.010	0.040
Glycemic Load				
Q1	<103.2	44	1	1
Q2	103.3–114.1	62	1.38 (0.93, 2.04)	1.60 (1.07, 2.41)
Q3	114.2–122.9	59	1.38 (0.93, 2.05)	1.73 (1.13, 2.67)
Q4	123.0–133.7	54	1.28 (0.85, 1.93)	1.70 (1.07, 2.70)
Q5	>133.7	70	1.65 (1.11, 2.46)	2.53 (1.54, 4.16)
P for trend[5]			0.031	0.001

[1] *n* = 289 breast cancer cases. ORDET Study, the Hormones and Diet in the Etiology of Breast Tumors Study.
[2] Adjusted for height, weight, age at menarche, smoking status, education, oral contraceptive use, parity, energy intake, and alcohol intake.
[3] Also adjusted for fiber and saturated for intakes.
[4] 95% CIs in parentheses (all such values).
[5] Test for linear trend was performed by using the median intake in each quintile.

TABLE 4
Adjusted relative risks (RR) (and 95% CIs) of breast cancer by energy-adjusted quintile (Q) of glycemic index and glycemic load in Italian women in the ORDET Study, stratified by baseline menopausal status[1]

	Cases	Premenopausal women (*n* = 146)	Postmenopausal women (*n* = 128)	*P* for interaction[2]
	n			
Glycemic index				0.251
Q1	18	1	1	
Q2	30	1.38 (0.77, 2.49)[3]	1.18 (0.64, 2.16)	
Q3	35	1.89 (1.06, 3.39)	1.26 (0.70, 2.26)	
Q4	27	1.31 (0.71, 2.42)	1.61 (0.91, 2.84)	
Q5	36	1.82 (1.01, 3.27)	1.12 (0.62, 2.02)	
Glycemic load				0.027
Q1	22	1	1	
Q2	21	1.83 (0.98, 3.43)	1.35 (0.77, 2.36)	
Q3	25	2.84 (1.50, 5.39)	1.03 (0.54, 1.95)	
Q4	32	2.23 (1.10, 4.52)	1.36 (0.71, 2.61)	
Q5	28	3.89 (1.81, 8.34)	1.67 (0.80, 3.46)	
P for trend[4]		0.001	0.216	

[1] ORDET Study, the Hormones and Diet in the Etiology of Breast Tumors Study. Values were adjusted for height, weight, age at menarche, smoking status, education, parity, oral contraceptive use, energy intake, fiber intake, saturated fat intake, and alcohol intake.
[2] Likelihood ratio test on the median intake in each quintile with 1 df.
[3] RRs; 95% CIs in parentheses (all such values).
[4] Test for linear trend was performed by using the median intake in each quintile.

breast cancer associated with GI differed little between premenopausal and postmenopausal women, and in no case were the higher GI quintiles associated with significantly increased risk of breast cancer. By contrast, menopausal status modified the association between dietary GL and breast cancer, as shown by a significant ($P = 0.027$) interaction between GL and menopausal status and a significantly greater risk of breast cancer in the highest GL quintile than in the lowest (RR = 3.89; 95% CI: 1.81, 8.34; *P* for trend = 0.001) in premenopausal women, but no risk difference across GL quintiles for postmenopausal women.

The results of the stratified analysis to assess the effects of BMI on associations of GL and GI with breast cancer risk are shown in **Table 5**. *P* for trend is reported when interactions were significant. There was no evidence that BMI modified the effect of GI on breast cancer risk. However, BMI did modify the association between GL and breast cancer, with a significant ($P = 0.006$) interaction between dietary GL and BMI. For women with normal BMI (ie, <25), the risk of breast cancer increased significantly with GL, and the RR of the highest quintile compared with the lowest was 5.79 (95% CI: 2.60, 12.90; P for trend = 0.001); for women with BMI ≥ 25, GL was unrelated to breast cancer risk.

Second-order interactions between GL or GI, menopausal status, and BMI categories were explored but found not to be significant (data not shown). Spearman correlations between GL and serum glucose and fructosamine in the 379 controls of a previous nested case-control study conducted by our group (30, 31) showed that GL did not correlate with fasting glycemia but correlated significantly with fructosamine ($r = 0.13$, $P < 0.01$).

TABLE 3
Relative risks (RR) of breast cancer in relation to adding 5% of energy from total carbohydrates, carbohydrates from high-glycemic-index (GI) foods and carbohydrates from low-GI foods in Italian women in the ORDET Study[1]

	RR[2] (95% CI)
Total carbohydrates[3]	1.25 (0.94, 1.66)
Carbohydrates from high-GI foods[3]	1.55 (1.07, 2.26)
Carbohydrates from low-GI foods[3]	0.86 (0.55, 1.34)

[1] *n* = 289 breast cancer cases. ORDET Study, the Hormones and Diet in the Etiology of Breast Tumors Study.
[2] Adjusted for height, weight, age at menarche, smoking status, education, oral contraceptive use, parity, and alcohol intake.
[3] Partition model.

DISCUSSION

In the present prospective study, we found that high dietary GL and, to a lesser extent, high dietary GI were significantly associated with a greater risk of breast cancer. This greater risk was evident in 2 groups of women—those in premenopause and those with BMI < 25.

Dietary GI and dietary GL reflect different aspects of carbohydrate intake. GI is a measure of carbohydrate quality in relation to glucose availability and is independent of quantity, whereas GL is a measure of the total glycemic effect and hence is an

TABLE 5
Adjusted relative risks (RR) (and 95% CIs) of breast cancer by energy-adjusted quintile (Q) of glycemic index and glycemic load in Italian women in the ORDET Study, stratified by BMI[1]

	BMI < 25 (n = 147)		BMI ≥ 25 (n = 142)		
	Cases	RR	Cases	RR	P for interaction[2]
	n		*n*		
Glycemic index					0.075
Q1	14	1	26	1	
Q2	28	1.68 (0.88, 3.22)[3]	26	1.20 (0.69, 2.09)	
Q3	32	2.11 (1.11, 4.01)	32	1.30 (0.76, 2.21)	
Q4	35	2.24 (1.19, 4.23)	29	1.19 (0.69, 2.07)	
Q5	38	2.22 (1.18, 4.19)	29	1.11 (0.64, 1.94)	
Glycemic load					0.006
Q1	14	1	30	1	
Q2	27	2.18 (1.10, 4.33)	35	1.28 (0.76, 2.15)	
Q3	32	3.29 (1.64, 6.60)	27	1.10 (0.62, 1.96)	
Q4	29	3.14 (1.50, 6.59)	25	1.20 (0.65, 2.24)	
Q5	45	5.79 (2.60, 12.9)	25	1.31 (0.66, 2.61)	
P for trend[4]		0.001		0.538	

[1] ORDET Study, the Hormones and Diet in the Etiology of Breast Tumors Study. BMI was measured as kg/m^2. Adjusted for height, weight, age at menarche, smoking status, education, parity, oral contraceptive use, energy intake, fiber intake, saturated fat intake, and alcohol intake.
[2] Likelihood ratio test on the median intake in each quintile with 1 df.
[3] 95% CIs in parentheses (all such values).
[4] Test for linear trend was performed by using the median intake in each quintile.

indicator of the insulin demand of the diet. High-glycemic diets are in fact generally associated with greater insulin secretion (33). It is noteworthy that, whereas dietary GI and dietary GL were associated with breast cancer risk, the fraction of energy from carbohydrates was unrelated to that risk. However, when we divided energy obtained from carbohydrates into that from high-GI foods and that from low-GI foods, only the former was significantly associated with breast cancer risk. This finding suggests that the consumption of large quantities of high-GI foods rather than the consumption of high quantities of carbohydrates is linked to the development of breast cancer.

Previous epidemiologic studies have provided conflicting evidence regarding associations between the risk of breast cancer and dietary GI and GL. Our findings are in agreement with case-control studies that found positive associations of breast cancer risk with dietary GL alone (21) and with both dietary GI and GL (15). Another case-control study suggested that high dietary GL and GI increased breast cancer risk, but the associations were not significant (34).

To our knowledge, breast cancer risk in relation to GL and GI has been examined in 8 prospective studies (16–20, 22–24), 3 of which involved only postmenopausal women (18, 20, 23), and 1 of which involved only premenopausal women (16). None of these studies found significant associations between breast cancer risk and dietary GL or GI, but 2 of the studies reported associations of high GL and GI with a greater risk of breast cancer in postmenopausal women (19, 24).

The finding in the present study that a greater risk of breast cancer was related to high dietary GL in premenopausal women but not in postmenopausal women is consistent with the findings of a stratified analysis of 946 breast cancer cases in the Women's Health Study (22). That study found a direct association between GL and breast cancer risk in premenopausal women who reported low levels of physical activity.

In a previous nested case-control study of the ORDET Study cohort, our group found that breast cancer risk increased significantly with increasing serum concentrations of insulin-like growth factor 1 (IGF-1) and glucose in premenopausal women, although insulinemia was not significantly associated with breast cancer risk in these women (30). Other studies also found an association of breast cancer with prediagnostic IGF-1 (in premenopausal women only) (35, 36) and with high plasma concentrations of insulin and C-peptide (36, 37). However, the European Prospective Investigation into Cancer and Nutrition suggested that C-peptide was directly associated with breast cancer risk only after menopause and that, before menopause, there was a hint of an inverse relation (38).

The findings of the present study lead us to suggest that the high GI characteristic of most Western foods may be an important contributor to breast cancer risk, particularly in younger women. The mechanism may involve insulin. Persistently high insulinemia may increase breast cancer risk by several mechanisms, including an alteration of cell cycle kinetics (39) or the inhibition of apoptosis (40) or through a gonadotropic effect (insulin stimulates the synthesis of ovarian androgens) or through metabolic effects on the liver, where insulin inhibits the synthesis of sex hormone–binding globulin and IGF-1–binding proteins 1 and 2, thus increasing the bioavailability of both sex hormones and IGF-1 (36, 37, 41, 42).

A previous nested case-control study by our group in ORDET Study women found that serum fructosamine concentrations tended to be directly associated with breast cancer risk, irrespective of menopausal status (31). In the present study, we investigated the control group from that previous study, and we found that serum fructosamine concentrations correlated with GL. Serum fructosamine is a product of serum protein glycation and a short-term (2–3-wk) indicator of blood glucose concentrations.

An unexpected finding of the present study was that, with stratification by BMI, the increased breast cancer risk of a high-GL diet was stronger for women with BMI < 25 but was not present in those with higher BMI. The lack of an association between GL and breast cancer risk in women with a higher BMI may be due to the fact that, in these women, some of the metabolic effects of high GL are already present because of their adiposity (43–45), and a high-GL diet would not add further risk—in overweight postmenopausal women, adipose tissue is a major site of the estrogen synthesis that is associated with a greater risk of breast cancer (46). Conversely, in women with lower BMI, a highly glycemic diet would greatly increase the risk of breast cancer.

In addition to the prospective design and highly complete follow-up, a major strength of the present study, in comparison with previously published cohort studies, is that we used GI values that had mostly been determined for Italian foods; in fact, specific GIs were available for 96% of the carbohydrate food items present in the FFQ. The FFQ itself had been designed specifically to quantify the food items and preparations typically consumed in Northern Italy. Because the glucose response and, possibly, the insulin response of a food vary with characteristics such as physical form and vegetable variety, the "Italian" GIs we used are likely to be more accurate than those estimated from international food tables.

It is important to note, however, that the glucose and insulin responses to a given food item may be influenced by the other macronutrients, such as protein, that are consumed with the food (47, 48), by the cooking procedure (49, 50), and even by the chewing time (51). Such factors are not easily assessed by an FFQ, even though the FFQ used in the present study included a section on cooking methods and cooking fat content. In contrast, there is a strong indication that the GI of a mixed meal can be predicted consistently from the GI of each individual food item, and that, although fat and protein affect the absolute glycemic response, they do not change the GI rank of foods (52–55). A potential limitation of our study is that the ORDET Study FFQ was not specifically designed to furnish dietary GI and GL, although it was designed to provide estimates of total carbohydrate and total energy intake.

In conclusion, the present study has found a strong association between a highly glycemic diet and the development of breast cancer, particularly in premenopausal women. We also found an unexpected and strong link between high GL and breast cancer in women with BMI < 25, which indicates that further studies in this complex area are needed.

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The authors' responsibilities were as follows—SS and VK: assessed food intakes, contributed to analysis and interpretation of data, and wrote the manuscript; FB, VK, AM, and PM: the conception of the study; FB: developed the FFQ; AE: data collection in the ORDET Study; AE and PC: the follow-up of the cohort; SG: assisted in estimating glycemic index and glycemic load intake; and all authors: reviewed the manuscript. None of the authors had a personal or financial conflict of interest.

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