Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study1–3

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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/m2), the increased risk of dietary GI 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).


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 glycaemia 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.

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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 total carbohydrate intake and 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 of 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

<table>
<thead>
<tr>
<th>Quintile of energy-adjusted GI</th>
<th>Quintile of energy-adjusted GL</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>Q1</td>
</tr>
<tr>
<td>Dietary GI (mg/d) 51.9 ± 0.03</td>
<td>Dietary GL (g/d) 51.9 ± 0.03</td>
</tr>
<tr>
<td>Protein (%) of energy/d 17.6 ± 0.07</td>
<td>Carbohydrate (%) of energy/d 46.7 ± 0.18</td>
</tr>
<tr>
<td>Fat (%) of energy/d 35.4 ± 0.14</td>
<td>Fat (%) of energy/d 35.4 ± 0.14</td>
</tr>
<tr>
<td>Carbohydrate (g/d) 7.6 ± 0.08</td>
<td>Fiber (% of energy/d) 7.6 ± 0.08</td>
</tr>
<tr>
<td>Fiber from vegetables (g/d) 4.3 ± 0.04</td>
<td>Fiber from vegetables (g/d) 4.3 ± 0.04</td>
</tr>
<tr>
<td>Fiber from pulses (g/d) 1.2 ± 0.02</td>
<td>Energy (kcal/d) 1710</td>
</tr>
<tr>
<td>Fiber from cereals (g/d) 6.3 ± 0.08</td>
<td>Total carbohydrate (g/d) 121.5 ± 0.82</td>
</tr>
<tr>
<td>Fiber from potatoes (g/d) 0.62 ± 0.01</td>
<td>Fat (% of energy/d) 35.4 ± 0.14</td>
</tr>
<tr>
<td>Alcohol (%) of energy/d 3.2 ± 0.12</td>
<td>Carbohydrate (% of energy/d) 46.7 ± 0.18</td>
</tr>
<tr>
<td>Energy (kcal/d) 1710</td>
<td>Fats, high-GI carbohydrates, and low-GI carbohydrates by 5%</td>
</tr>
</tbody>
</table>

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 GI 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 GI quintiles. Women in the highest GI quintile also were more educated, smoked less, and had a very slightly lower BMI than did women in the lowest GI 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 GI quintile had a significantly greater risk of breast cancer than did those in lowest GI 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 (i.e., 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 GI and dietary GI with breast cancer risk are shown in Table 4. 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.

<table>
<thead>
<tr>
<th>Glycemic Index</th>
<th>Range</th>
<th>Cases</th>
<th>RR*</th>
<th>RR* 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>&lt;53.5</td>
<td>40</td>
<td>0.92 (0.89, 0.95)</td>
<td>0.88 (0.85, 0.91)</td>
</tr>
<tr>
<td>Q2</td>
<td>53.5–54.9</td>
<td>54</td>
<td>1.38 (0.98, 2.23)</td>
<td>1.44 (0.95, 2.17)</td>
</tr>
<tr>
<td>Q3</td>
<td>55.0–56.1</td>
<td>64</td>
<td>1.69 (1.13, 2.51)</td>
<td>1.62 (1.08, 2.42)</td>
</tr>
<tr>
<td>Q4</td>
<td>56.2–57.5</td>
<td>64</td>
<td>1.70 (1.14, 2.53)</td>
<td>1.62 (1.08, 2.44)</td>
</tr>
<tr>
<td>Q5</td>
<td>&gt;=57.5</td>
<td>67</td>
<td>1.68 (1.13, 2.49)</td>
<td>1.57 (1.04, 2.36)</td>
</tr>
</tbody>
</table>

For trend: 0.010 0.040

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.

<table>
<thead>
<tr>
<th>Source of Carbohydrates</th>
<th>RR* 95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total Carbohydrates</td>
<td>1.25 (0.94, 1.66)</td>
</tr>
<tr>
<td>Carbohydrates from high-GI foods</td>
<td>1.55 (1.07, 2.26)</td>
</tr>
<tr>
<td>Carbohydrates from low-GI foods</td>
<td>0.86 (0.55, 1.34)</td>
</tr>
</tbody>
</table>

For trend: 0.001 0.001

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.

<table>
<thead>
<tr>
<th>Glycemic Index</th>
<th>Premenopausal women (n = 146)</th>
<th>Postmenopausal women (n = 128)</th>
<th>P for interaction</th>
</tr>
</thead>
<tbody>
<tr>
<td>Q1</td>
<td>18</td>
<td>1</td>
<td>0.251</td>
</tr>
<tr>
<td>Q2</td>
<td>30</td>
<td>1.38 (0.77, 2.49)</td>
<td>1.18 (0.64, 2.16)</td>
</tr>
<tr>
<td>Q3</td>
<td>35</td>
<td>1.89 (1.06, 3.39)</td>
<td>1.26 (0.70, 2.26)</td>
</tr>
<tr>
<td>Q4</td>
<td>27</td>
<td>1.31 (0.71, 2.42)</td>
<td>1.61 (0.91, 2.84)</td>
</tr>
<tr>
<td>Q5</td>
<td>36</td>
<td>1.82 (1.01, 3.27)</td>
<td>1.12 (0.62, 2.02)</td>
</tr>
</tbody>
</table>

For trend: 0.001 0.216

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

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).
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 GI alone (21) and with both dietary GI and GL (15). Another case-control study suggested that a diet with high GI characteristic of most Western foods may be an important contributor to 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 GI or GL, 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 GI 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 intake; and all authors: reviewed the manuscript. None of the authors had a personal or financial conflict of interest.

REFERENCES


