Annals of Oncology **12**: 1533–1538, 2001.

Original article

Dietary glycemic index and glycemic load, and breast cancer risk: A case-control study

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Summary

Background: Certain types of carbohydrates increase glucose and insulin levels to a greater extent than others. In turn, insulin may raise levels of insulin-like growth factors, which may influence breast cancer risk. We analyzed the effect of type and amount of carbohydrates on breast cancer risk, using the glycemic index and the glycemic load measures in a large case-control study conducted in Italy.

Patients and methods: Cases were 2569 women with incident, histologically-confirmed breast cancer interviewed between 1991 and 1994. Controls were 2588 women admitted to the same hospital network for a variety of acute, non-neoplastic conditions. Average daily glycemic index and glycemic load were calculated from a validated 78-item food frequency questionnaire.

Results: Direct associations with breast cancer risk emerged for glycemic index (odds ratio, OR for highest vs. lowest quintile = 1.4; P for trend < 0.01) and glycemic load (OR = 1.3; $P < 0.01$). High glycemic index foods, such as white bread, increased the risk of breast cancer (OR = 1.3) while the intake of pasta, a medium glycemic index food, seemed to have no influence (OR = 1.0). Findings were consistent across different strata of menopausal status, alcohol intake, and physical activity level.

Conclusions: This study supports the hypothesis of moderate, direct associations between glycemic index or glycemic load and breast cancer risk and, consequently, a possible role of hyperinsulinemia/insulin resistance in breast cancer development.

Key words: breast cancer, carbohydrate, case-control study, glycemic load

Introduction

Diets with a high glycemic index (GI) or glycemic load (GL) are associated with high consumption of refined carbohydrates, which are quickly absorbed and are capable of elevating blood glucose to a greater extent than slow-release carbohydrates such as legumes and whole grains [1, 2]. Both indices give an indirect measure of dietary insulin demand. It has been hypothesized that high insulin levels could be the unifying mechanism for the risk of several Western chronic diseases [3–5]. Dietary GI and GL have been directly associated with colorectal cancer risk [6] as well as other chronic conditions such as type II diabetes [7, 8], coronary heart disease [9] and obesity [10]. However, their influence on breast cancer risk has not been investigated.

A role of diets with a high glycemic response and chronic hyperinsulinemia on breast cancer risk has been suggested [11, 12]. Among dietary factors that affect insulin levels, starch has been directly associated with breast cancer risk in many studies [13–17]. In an Italian case-control study, direct associations have been found between breast cancer risk and intake of starch and energy [17]. Conversely, inverse associations emerged from intake of vegetables, pulses, [18, 19], dietary fibre [20], and polyunsaturated-to-saturated (P/S) fat ratio [17].

A possible role of insulin in breast carcinogenesis is also suggested from non-dietary factors. Positive associations with breast cancer have been reported on hyperinsulinemia [21, 22], diabetes [23, 24], body mass index (BMI) in postmenopausal but not premenopausal women [25–27], and for serum concentrations of insulin-like growth factor-1 (IGF-1) [28–30].

Since different starchy foods elicit different glycemic and insulinemic responses, we decided to evaluate the possible differential effects of carbohydrate-rich foods on breast cancer risk by GI and GL measurements.

Patients and methods

A multicentre case-control study on breast cancer was conducted between June 1991 and April 1994 in six Italian areas: the Provinces of Pordenone and Gorizia in North eastern Italy, the urban areas of Milan and Genoa, the Provinces of Forlì, in the North of the country, Latina in central Italy, and the urban area of Naples in the South.

Cases were women with incident histologically-confirmed breast cancer, diagnosed no more than one year before the interview and with no previous diagnosis of cancer at any site. Overall, 2569 women aged 23–74 years (median age 55) were included. Controls were patients with no history of cancer, admitted to hospitals within the same catchment areas of those where cases were identified. Eligible diagnoses were acute, non-neoplastic, non-gynaecological conditions, unrelated to hormonal or digestive tract diseases, or associated with long-term modifications of diet. They included 2588 women, aged 20–74 years (median age 56), belonging to the following diagnostic categories: trauma, mostly fractures and sprains (22%), other orthopaedic disorders, such as lower-back pain and disc disorders (33%), acute surgical conditions (15%), eye diseases (18%), and other miscellaneous disorders, such as ear, nose, and throat, skin and dental conditions (12%). Cases were frequency matched to controls according to age in quinquennia and area of residence. Approximately 4% of cases and controls approached for interview during their hospital stay refused to participate.

The same structured questionnaire and coding manual were used in each centre, and all interviewers were centrally trained and routinely supervised. Checking data for consistency and reliability was also centrally conducted. The questionnaire included information on socio-demographic characteristics, such as education, occupation and socio-economic indicators, lifelong smoking habits, physical activity at various ages, anthropometric measures before diagnosis, weight at various ages, a problem-oriented personal medical history, and family history of selected cancers. Also included was menstrual and reproductive history, history of use of oral contraceptives, hormone replacement treatment, and female hormone-containing drugs for other indications. Dietary habits were investigated through an interviewer-administered food frequency questionnaire (FFQ) that included 78 items. This questionnaire was used to assess the subjects' dietary habits during the two years prior to cancer diagnosis or hospital admission (for controls). The assessment included total energy, average weekly frequency of consumption of foods or food groups, as well as complex recipes. Satisfactory reproducibility [31, 32] and validity [33] of the FFQ have been reported. To compute energy and nutrient intake, an Italian food-composition database was used [34].

The GI is a ranking of carbohydrate foods based on the post-prandial blood glucose response which is expressed as a percent of the response to an equivalent amount of available carbohydrate from a reference food (e.g., white bread or glucose) [41]. We expressed GI as a percentage of the glycemic response elicited by white bread as a standard food. For each case and control subject, we calculated average daily GI by summing the products of the carbohydrate content per serving, for each food or recipe, times the average number of servings of that food per week, times its GI, all divided by the total amount of available weekly carbohydrate intake [35, 36]. A score for the daily average GL was computed as the GI, but without dividing by the total amount of carbohydrates. However, for these calculations we used the carbohydrate content of 50 foods or recipes, since 28 foods or recipes, chiefly meat, cheese, and fish-based dishes contained a negligible amount of carbohydrates [34]. With respect to GI values, we primarily used international tables [36]. In order to take into account Italian cooking habits (e.g., pasta 'al dente'), Italian sources were used for a few local recipes [37]. Food items for which a GI had not been determined were assigned the GI of the nearest comparable food (e.g., tangerines were assigned the GI of oranges).

Odds ratios (ORs) and the corresponding 95% confidence intervals (95% CI) for quintiles of GI and GL were computed using unconditional multiple logistic regression models [38]. The regression equations included terms for age, study centre, years of education, occupational physical activity, history of diabetes, oral contraceptive use, parity, menopausal status, number of daily meals, intakes of fibre, alcohol and energy. Adjustment for energy was made using the residuals method [39]. GI and GL were also introduced as continuous variables, and the units were expressed in increments of 5 and 50, respectively. To test heterogeneity between premenopausal and postmenopausal women, we compared differences between the likelihood of the model estimating a common OR and that estimating a specific OR for each group to the chi-square distribution, with 1 (number of groups minus one) degree of freedom.

Table 1. Distribution of 2569 cases of breast cancer and 2588 controls[a] by age group, years of education, parity, menopausal status, alcohol intake and occupational physical activity. Italy, 1991–1994.

Characteristic	Cases		Controls		χ^2 (heterogeneity)[b] P-value
	No.	%	No.	%	
Age group (yrs)					
<35	87	3.4	140	5.4	
35–44	383	14.9	332	12.8	
45–54	772	30.1	694	26.8	
55–64	799	31.1	802	31.0	
$\geqslant 65$	528	20.6	620	24.0	
Education (yrs)					
<7	1259	49.3	1569	61.2	
7–11	714	28.0	642	25.0	109.88
$\geqslant 12$	582	22.8	354	13.8	$P<0.01$
Parity (number of births)					
Nulliparae	401	15.6	380	14.7	
1	584	22.8	494	19.1	
2	968	37.7	909	35.2	
3	406	15.8	489	18.9	48.73
$\geqslant 4$	207	8.1	314	12.1	$P<0.01$
Menopausal status					
Premenopausal	988	38.5	843	32.6	25.44
Postmenopausal	1578	61.5	1745	67.4	$P<0.01$
Alcohol intake (drinks per week)					
0	771	30.0	913	35.3	
1–6	569	22.2	510	19.7	
7–13	525	20.4	498	19.2	16.84
$\geqslant 14$	704	27.4	667	25.8	$P<0.01$
Occupational physical activity					
Low	878	34.2	801	31.0	
Medium	1311	51.0	1321	51.0	17.64
High	380	14.8	466	18.0	$P<0.01$

[a] Some figures do not add up to the total because of some missing values.
[b] Cochran-Mantel-Haenszel χ^2, adjusted for centre and age.

Results

Table 1 shows the distribution of breast cancer cases and controls according to age and selected characteristics. Cases were significantly more educated than controls. They also had significantly fewer full-term pregnancies, were more often premenopausal and reported higher alcohol intake, but had lower levels of occupational physical activity.

GI was positively correlated with GL (Pearson correlation coefficient, $r = 0.56$), intake of bread ($r = 0.59$), cakes and sweets ($r = 0.36$), available carbohydrate ($r = 0.40$), cereal fibre ($r = 0.43$) and negatively correlated with fruit ($r = -0.20$) and vegetables ($r = -0.14$). Correlations of GI with other dietary and non-dietary factors were weak (i.e. $|r| < 0.10$).

After a multivariate analysis adjusted for known and suspected risk factors, direct associations with breast cancer risk emerged for GI (OR in highest vs. lowest

Table 2. Odds ratios (ORs) and 95% confidence intervals (CIs)[a] of breast cancer by menopausal status and quintile of energy-adjusted glycemic index and glycemic load score. Italy, 1991–1994.

	Quintile					χ^2_1 (trend); *P*-value	Continuous
	1[b]	2	3	4	5		
Glycemic index							
Upper limit	69.6	73.1	75.7	78.9	–		per 5 units × day
Prenopausal	1	1.44 (1.06–1.96)	1.34 (0.98–1.83)	1.58 (1.16–2.15)	1.37 (1.00–1.89)	3.91; $P = 0.05$	1.09 (1.00–1.19)
Postmenopausal	1	1.13 (0.91–1.41)	1.30 (1.04-1.62)	1.09 (0.87-1.36)	1.40 (1.12-1.75)	6.12; $P = 0.01$	1.10 (1.03–1.17)
All cases	1	1.21 (1.02–1.45)	1.29 (1.08–1.54)	1.23 (1.03–1.47)	1.36 (1.14–1.64)	9.26; $P < 0.01$	1.09 (1.04–1.15)
Glycemic load score							
Upper limit	140	173	204	248	–		per 50 units × day
Premenopausal	1	1.01 (0.74–1.37)	0.90 (0.66–1.23)	1.25 (0.91–1.72)	1.24 (0.90–1.70)	2.98; $P = 0.08$	1.11 (0.98–1.26)
Postmenopausal	1	1.10 (0.87–1.38)	1.39 (1.10–1.76)	1.40 (1.11–1.77)	1.46 (1.15–1.86)	13.3; $P < 0.01$	1.13 (1.03–1.24)
All cases	1	1.05 (0.88–1.26)	1.19 (0.99–1.43)	1.30 (1.08–1.57)	1.34 (1.10–1.61)	13.2; $P < 0.01$	1.10 (1.02–1.19)

[a] Adjusted for age, study centre, years of education, occupational physical activity, meal frequency, alcohol consumption, fibre and energy intake, history of diabetes, oral contraceptive use, parity, and menopausal status (when appropriate).
[b] Reference category.

Table 3. Odds ratios (ORs) and 95% confidence intervals (CIs)[a] of breast cancer by menopausal status and quintile of intake of bread, pasta, and sugar spoons. Italy, 1991–1994.

Food	Quintile					χ^2_1 (trend); *P*-value	Continuous
	1[b]	2	3	4	5		
Bread[c]							
Upper limit[d]	7.75	14	16	22.5	–		per 50 g × day
Premenopausal	1	1.17 (0.83–1.65)	1.04 (0.75–1.44)	1.22 (0.87–1.70)	1.30 (0.91–1.85)	1.87; $P = 0.17$	1.04 (0.95–1.12)
Postmenopausal	1	1.14 (0.90–1.44)	1.19 (0.96–1.47)	1.24 (0.99–1.56)	1.35 (1.05–1.74)	5.72; $P = 0.02$	1.11 (1.05–1.18)
Pasta[e]							
Upper limit[d]	3	4.25	5.5	6.75	–		per 50 g × day
Premenopausal	1	1.11 (0.80–1.54)	0.99 (0.71–1.37)	0.99 (0.71–1.39)	0.97 (0.68–1.37)	0.25; $P = 0.61$	1.03 (0.83–1.28)
Postmenopausal	1	0.97 (0.78–1.21)	1.02 (0.81–1.28)	1.29 (1.02–1.63)	1.07 (0.84–1.35)	2.37; $P = 0.12$	1.09 (0.94–1.26)
Sugar spoons[f]							
Upper limit[d]	7	17	28	45	–		per 10 g × day
Premenopausal	1	1.45 (1.03–2.03)	1.61 (1.13–2.29)	1.54 (1.11–2.13)	1.42 (1.01–2.00)	2.84; $P = 0.09$	1.03 (0.97–1.10)
Postmenopausal	1	1.39 (1.11–1.74)	1.25 (0.98–1.60)	1.60 (1.26–2.02)	1.27 (0.99–1.64)	4.48; $P = 0.03$	1.02 (0.97–1.08)

[a] Adjusted for age, study centre, years of education, occupational physical activity, meal frequency, alcohol consumption, fibre and energy intake, history of diabetes, oral contraceptive use, and parity.
[b] Reference category.
[c] Includes also crackers, polenta, and pizza.
[d] Servings per week.
[e] Includes also rice, lasagne, and tortellini.
[f] Includes also honey, jam, and candies.

quintile = 1.4; 95% CI: 1.1–1.6) and GL (OR = 1.3; 95% CI: 1.1–1.6) (Table 2). Associations of GL, but not GI, with breast cancer were apparently stronger in postmenopausal (OR = 1.5; 95% CI: 1.2–1.9) than premenopausal women (OR = 1.2; 95% CI: 0.9–1.7) and χ^2 for heterogeneity between premenopausal and postmenopausal women was 3.83 ($P = 0.05$) for GL and 10.12 ($P < 0.01$) for GI.

The risk of breast cancer was related to consumption of refined carbohydrate foods with typically high GI values such as white bread, particularly in postmenopausal women (OR = 1.4, 95% CI: 1.1–1.7, in highest quintile), while intake of pasta, a medium GI food, did not affect the risk of breast cancer regardless of menopausal status (Table 3). A less clear association of breast cancer with sugar, a medium-high GI food, emerged.

We further assessed the relationship between GL and breast cancer risk by analyzing for two separate strata of alcohol intake and physical activity. Neither variable seemed to substantially modify the unfavourable effect of high GL diets (Table 4).

Discussion

The present study shows moderate direct associations between dietary GI or GL and breast cancer risk (OR = 1.4, 1.3, respectively) after adjustment for known risk

Table 4. Odds ratios (ORs) and 95% confidence intervals (CIs)[a] of breast cancer by strata of selected variables and quintile of energy-adjusted glycemic load. Italy, 1991–1994.

	Quintile					χ^2_1 (trend); *P*-value
	1[b]	2	3	4	5	
Upper limit	140	173	204	248	–	
Alcohol intake						
< 7 drinks per week	1	1.06 (0.80–1.42)	1.18 (0.89–1.55)	1.38 (1.04–1.81)	1.25 (0.95–1.65)	5.22; $P = 0.02$
⩾ 7 drinks per week	1	1.00 (0.79–1.27)	1.11 (0.86–1.43)	1.14 (0.87–1.48)	1.40 (1.06–1.86)	5.42; $P = 0.02$
Occupational physical activity						
Low-Medium	1	1.09 (0.89–1.33)	1.21 (0.99–1.48)	1.32 (1.07–1.62)	1.35 (1.09–1.66)	10.7; $P < 0.01$
High	1	0.88 (0.56–1.40)	1.16 (0.73–1.86)	1.28 (0.82–2.00)	1.36 (0.86–2.16)	3.24; $P = 0.07$

[a] Adjusted for age, study centre, years of education, meal frequency, fibre and energy intake, oral contraceptive use, parity, history of diabetes, menopausal status, alcohol consumption and occupational physical activity when appropriate.
[b] Reference category.

factors such as socio-demographic variables, oral contraceptive use, parity, menopausal status, history of diabetes, physical activity, number of meals, intake of fibre, alcohol and energy.

The main sources of carbohydrates in the Italian population were bread and pasta (20.5% and 13.4% of total carbohydrate intake, respectively) [40]. No association was observed with pasta, a food with a medium GI, in either premenopausal or postmenopausal women, while a positive association emerged with the main refined carbohydrate source such as white bread, characterized by a high GI. In general, the effect of the major carbohydrate foods does not change with menopausal status. Carbohydrate foods consumed in isoglucidic amounts produce different glycemic and insulinemic responses, depending upon the nature of the food and the type, and extent of food processing [2]. The glycemic index captures the qualitative differences among carbohydrate-rich foods [41] while the glycemic load is a measure of both quality and quantity of carbohydrates consumed, and thus represents a measure of dietary insulin demand.

Western lifestyles, characterized by low physical activity, obesity, high dietary energy and refined carbohydrate intake, have been suggested to increase breast cancer risk by raising blood levels of bioavailable estrogen and other hormones including insulin, and related growth factors [42].

Insulin and insulin-like growth factor-1 (IGF-1) are powerful negative regulators of sex hormone-binding globulin (SHBG) synthesis *in vitro*, and they may stimulate breast cancer proliferation in several ways [42, 43]. Insulin has been shown to have high affinity with the IGF-1 receptor that, when stimulated, results in mitogenic and anti-apoptotic effects on mammary cell lines [42, 44].

Epidemiologic evidence suggests a promoting effect of hyperinsulinemia [21, 22] and of IGF-1 on breast carcinogenesis [28–30, 45–47] as well as on other cancer sites, suggesting a systemic effect of these growth factors [5, 43]. Direct associations have also been found between IGF-1 and other recognized risk factors for breast cancer, such as breast density [48], and adult height, a surrogate measure of growth factor activity, and breast cancer risk [27, 49].

The associations between GI or GL and breast cancer risk were somewhat higher and significantly stronger in postmenopausal than in premenopausal women. Similarly, other epidemiological observations identified high body weight as a risk factor in postmenopausal, but not in premenopausal women [25–27]. It has been suggested that obesity, determined by a positive energy balance, may affect subsequent breast cancer risk [11] through an increase in female and growth hormones (e.g. estrogen, insulin, IGF-1) and ultimately in mammary gland mass [50]. Body fat is indeed the main site of estrogen synthesis when the ovaries cease its production, and it is also directly associated with high circulating insulin levels [51]. Diets with elevated GL, by increasing insulin secretion, in the long run, may worsen the effect of a high estrogenic environment. Some evidence also suggests that IGF-1 is more strongly associated with breast cancer risk in premenopausal than in postmenopausal women, where both these groups were studied [28, 30, 52]. A possible effect of premenopausal IGF-1 concentrations on the risk of breast cancer after menopause cannot, however, be ruled out.

Alcohol consumption has been associated with an increased risk of breast cancer [53] and decreased risk of diabetes [54], possibly through its effects on blood glucose and insulin levels. In the present study, however, we found no difference in the relationship between GL and breast cancer risk in separate strata of alcohol intake, suggesting that alcohol intake does not significantly modify the effect of GL. Physical inactivity is a risk factor for both hyperinsulinemia/insulin resistance and for breast cancer [11, 55]. In our study, however, physical activity level did not modify the impact of high GL diets.

As in most case-control studies, recall and selection biases are possible [38]. However, awareness of any dietary hypotheses in breast cancer etiology, most notably the one concerning an adverse effect of refined carbohydrates, was limited in the Italian population

when the study was conducted (early 1990s). While it is possible that dietary habits of hospital controls may have differed from those of the general population, great attention was paid to minimize bias by excluding all control subjects with conditions that might have been associated with special dietary habits (e.g. diabetes mellitus, cardiovascular diseases, etc.). Moreover, interviewing all subjects in a hospital setting may have allowed greater comparability of dietary history between cases and controls, and adjustment for total energy intake should have controlled for potential over- and under-reporting. Participation among eligible patients was practically complete and the catchment areas for cases and controls were comparable. Current GI estimates also have some limitations. Some of them derive from small samples, and their variability is unclear [35, 36]. Statistics on the average GI and GL in the general Italian population are not available. However, intake of bread and pasta, foods that give the highest contribution to GI and GL in the Italian diet in our control subsets [40], were similar to those reported in the general population [56].

The greatest strength of this study is due to its uniquely large dataset, which allowed reasonably precise risk estimates. Other strengths include consistency of findings, when major diagnostic categories of controls were used separately, and reliance on a validated food frequency questionnaire [32, 33].

In conclusion, this study found modest but positive associations between GI or GL and breast cancer risk, thus supporting a role of hyperinsulinemia in breast carcinognesis. Further studies including analysis of potential biological markers of breast cancer risk would therefore contribute to a better understanding of the mechanisms of action underlying the adverse effect of diets, particularly of refined carbohydrate-rich diets.

Acknowledgements

This work was supported by a contribution from the Italian Association for Research on Cancer, Milan, Italy.

The authors wish to thank Drs Attilio Giacosa, Maurizio Montella, Ettore Conti, and Prof. Dino Amadori for their help in study coordination, and Mrs Luigina Mei for editorial assistance.

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Received 23 March 2001; accepted 7 June 2001.

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