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Dietary Fiber, Glycemic Index, and Glycemic Load in Relation to Breast Cancer in Iran

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ABSTRACT

Background: Habitual consumption of diets with a high glycemic index (GI) and a high glycemic load (GL) may influence breast cancer, but consistent evidence is lacking in this regard.
Objectives: In this hospital-based case-control study, we evaluated the contribution of GI, GL and dietary fiber to the risk of breast cancer in Iran, 2011-2012.
Patients and Methods: Data on lifestyle, diet and family history were collected from the 87 newly diagnosed breast cancer premenopausal patients and 198 five-year age-matched controls. Usual dietary intake was assessed by means of a 168-item semi-quantitative food frequency questionnaire (FFQ), which was interviewer-administered. Dietary average GI and GL were calculated by GI of Iranian food table and international tables of GI and GL values: 2008. Multivariate odds ratios (ORs) and 95% confidence intervals (CIs) for GI and GL intake were adjusted for age and major relevant covariates based on the review of literature.
Results: Mean ± SD GI was 59 ± 17 among control patients and 70 ± 16 among breast cancer cases; the corresponding numbers for GL were 159 ± 45 and 189 ± 44, respectively. The multivariate adjusted comparing the highest tertile of dietary GI and GL with the lowest tertile were 2.11 (95% CI 1.33-3.57; p-test for trend = 0.027) and 2.84 (95% CI 2.93-4.11; p-test for trend = 0.037) respectively with a significant trend. Fiber intake was suggestively inversely associated with breast cancer (OR = 0.79; 95% CI 0.34-0.88; p-test for trend = 0.015).
Conclusions: Our results suggest that high dietary levels of GI and GL and low fiber intake may have unfavorable effects on breast cancer.

▸ *Implication for health policy/practice/research/medical education:*
To reduce the prevalence of breast cancer.

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1. Background

Breast cancer incidence and mortality were reported to be higher among women in developed countries (1). However, Asian developing countries had a lower incidence of breast cancer and it is considered that more deprived subgroups are at much lower risk (2, 3). Prevalence of breast cancer in Iran is estimated to be 0.15% (2).

Multiple factors, including environmental and/or

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genetic factors, could be associated with the pathogenesis of breast cancer (4). Nutritional risk factors for breast cancer have been identified in previous studies (5, 6). Although changes in the quantity and quality of dietary fat have received considerable attention in recent years, the role of carbohydrates is not clearly indicated (7). The glycemic index (GI) is a ranking of carbohydrate-containing foods consumed in isoglucidic amounts, based on the postprandial blood glucose response compared with a standard food, usually glucose or white bread. Since both the quantity and quality of the ingested carbohydrates affect the postprandial glycemic response, an additional measure called glycemic load (GL), is also usually used, which is the product of the GI value and the total carbohydrate content of the portion of food ingested (8). High GI meals contain fast absorbable carbohydrates and result in high blood glucose levels and greater insulin demand (9). Hyperinsulinemia could stimulate the insulin-like growth factor-1 (IGF-1), a cell proliferative hormone associated with increased risk of several cancers (10-13).

Since disease risk is related to insulinemia, sex hormone bioavailability and insulin like growth factor 1, the role of GI and GL have been previously questioned in the etiology of breast cancer. A previous study determined the major dietary patterns among adult women living in Tehran and showed that unhealthy dietary pattern included high consumption of refined grains and sugars (14). Some studies have indicated the association between intake of meals high in dietary GI and GL, and an increased risk of breast cancer (15-19), although the issue remains open to discussion (20, 21).

2. Objectives

Considering the fact that nutrition is coming to the fore as a major environmental factor which may affect breast cancer, we analyzed the association of GI, GL, total fiber and carbohydrate intakes with breast cancer in a case–control study conducted in Iran.

3. Patients and Methods

3.1. Study Design

From February 2011 to March 2012, incident and histologically confirmed cases of breast cancer were identified from hospital records in the three general hospitals of Shahid Beheshti University of Medical Science. All cases were considered for inclusion if breast cancer diagnosis was established less than six months before interview and only if no history of other concomitant cancers was evident. A sample of hospitalized controls was recruited using frequency-matched to cases by age (± 5 years). All were hospitalized for non-neoplastic conditions in the same hospital, were not taking hormone therapy in the three months before recruitment, had not a history of cancer, had not current chronic or acute liver disease, and had not undergone bilateral ovariectomy. Also, control group was consisted of patients admitted to the same hospital as the cases for a wide spectrum of acute non-neoplastic diseases that were unrelated to smoking (i.e. chronic obstructive bronchitis and cardiovascular disease), alcohol abuse (i.e. liver cirrhosis and pancreatitis) or long-term modification of diet. Controls were hospitalized mainly because of the following conditions: traumas, surgical conditions (mostly abdominal such as acute appendicitis and kidney stones), non-traumatic orthopedic conditions (mostly disk disorders and back pain) and miscellaneous diseases (including acute eye, nose, skin and throat disorders).

Cases and controls were interviewed in person by trained professional interviewers. Ethical approval for this study was obtained from Shahid Beheshti University of medical science, Iran. Before enrollment, informed consent was obtained from each volunteer.

3.2. Measurements

Age of diagnosis for cases and age of participants were identified at the time of case and control recruitment. Data collected included demographic information, medical, occupational, and family histories and lifetime smoking of cigarettes.

Weight was measured with subjects standing without shoes on digital scales (Soehnle, Germany) and was recorded to the nearest 100 g. Height was measure while subjects were in a standing position without shoes, using a non-stretch tape meter fixed to a wall and was recorded to the nearest 0.5 cm. Body Mass Index (BMI) was calculated as weight in kilograms divided by height in meters squared at the time of interview.

Dietary information was collected by trained dietitians using a 125-item semi-quantitative food frequency questionnaire (FFQ), which assesses past nutritional intake for a one-year period, generally the year before the interview for controls and the year before diagnosis for cases. The FFQ was used in the first prospective cohort study of cardiovascular risk factors in Iran, Tehran lipid and glucose study (TLGS), and has been validated for multiple diet records for use in epidemiologic studies (22). The FFQ estimates usual dietary intake, providing a measure of the average intake of 168 food items and nutrients, based on a given serving of each food item on a daily (i.e bread), weekly (i.e. rice or meat) or monthly (i.e. fish) basis. We altered the dietary data into average monthly intake for every food item, by assuming one month equal to 30.5 days. Data on individual alcohol consumption were not collected according to cultural barricades; hence, it did not compromise the analysis. Food intakes reported in household measures were converted into grams of food, in order to process the food for analysis with nutritionist IV software (23).

To calculate GL and GI, we used the GI of Iranian food table and international tables of GI and GL values 2008 (24,

25). Because the Iranian Food Table of GI is incomplete, the rest of the meals and soft drinks were analyzed for their GI content using the international tables of GI and GL values: 2008. However, Iranian Food Table of GI was used for some foods (like Iranian bread) that are not listed in the international tables of GI and GL values: 2008. Food items for which a GI had not been reported were attributed to the GI of the nearest comparable food (i.e., tangerines were assigned the GI of oranges) or were calculated by using recipes. Lack of information about the GI of vegetables and legumes was resolved by calculating a mean GI for usually consumed vegetables and legumes in our study. The GI is based on the postprandial blood glucose response compared with white bread. The overall dietary GI was estimated for each participant by calculating the weighted average GI of all food items eaten by using the carbohydrate intake from that item (g/d) as a weighting factor. The resulting value denotes the overall quality of carbohydrate intake for each participant. Meanwhile, the average dietary GL was calculated by multiplying the overall dietary GI by the total amount of carbohydrate, which was then divided by 100. Each unit of GL denotes the equivalent of one gram carbohydrate from glucose (26).

3.3. Statistical Analysis

Chi-square test was used to compare proportions, and analysis of variance was used to compare means to assess the differences of distribution of categorical variables. Results were presented as odds ratios (ORs) and 95% confidence intervals (CIs) compared with the lowest GI and GL category. Age adjusted and multivariable adjusted ORs, including age, BMI, non-carbohydrate energy intake, fruit and vegetable consumption, using oral contraceptive, and smoking and corresponding 95% CIs were estimated by using logistic regression. All P-values were based on two-sided tests and were considered statistically significant if < 0.05. Meanwhile, data were filtered to remove GI, GL, fiber or carbohydrate extreme outliers separately. All analyses were conducted using the Social Sciences statistical software package version 17 (SPSS Inc., Chicago, IL, USA).

4. Results

The study population included 90 premenopausal women with breast cancer and 200 controls. For analysis, five participants were excluded because total energy intake were either > 3 or < 3SD from the mean (n = 2), miss-

Table 1. Selected Demographic Characteristics Among Cases With Breast Cancer and Matched Controls[a].

Characteristic	Cases		Controls		*P* Value
	No.	%	No.	%	
Age					1.00
< 35	43	49	97	49	
≥ 35	44	51	101	51	
BMI					< 0.001
< 25	72	83	91	46	
≥ 25	15	17	107	54	
Smoking history					0.314
Never smoker	23	26	55	28	
Ex-smoker, pack-year < 10	22	25	50	25	
Ex-smoker, pack-year ≥ 10	18	21	40	20	
Current smoker, pack-year < 20	19	22	38	19	
Current smoker, pack-year ≥ 20	5	6	15	8	
Oral contraceptive user					0.031
Yes	56	65	82	41	
No	31	35	116	59	
Number of live births					0.821
< 3	37	43	89	45	
≥ 3	50	57	109	55	
Years of education					0.224
0	25	29	69	35	
1-5	50	57	105	53	
5-11	12	14	24	12	

[a]All statistical tests were two-sided. Chi-square statistics were used to compare proportions.

Table 2. Mean ± Standard Deviation of Dietary Factors Among Cases With Breast Cancer and Matched Controls

Dietary Factors	Cases	Controls	*P* value
Total energy intake, kcal/day	1938.2 ± 732.1	2324.6 ± 477.4	0.089
Carbohydrate, g	263.1 ± 78.2	303.2 ± 87.9	0.062
Glycemic index	70.13 ± 16.72	59.86 ± 17.66	0.007
Glycemic load	189.14 ± 44.63	159 ± 45.19	0.003
Dietary fiber, g	14.2 ± 5.0	39.3 ± 10.7	< 0.001
Protein, g	84.0 ± 42.3	97.9 ± 24.9	0.134
Fat, g	61.5 ± 39.7	79.9 ± 26.8	0.286

Table 3. Odds Ratios (95% Confidence Intervals) for Breast Cancer According to Tertile of Each Dietary Carbohydrate Variable

	Tertile of Intake			
	Tertile 1 (Lowest)	**Tertile 2**	**Tertile 3 (Highest)**	***P* value**
GI				
Number of Case/Control	24/66	28/66	35/66	
Minimally-adjusted OR[a]	1.0	1.39 (0.94-2.32)	2.07 (1.77-3.34)	0.044
Multivariate OR[b]	1.0	1.73 (0.89-2.82)	2.11 (1.33-3.57)	0.027
GL				
Number of Case/Control	22/66	27/66	38/66	
Minimally-adjusted OR[a]	1.0	2.33 (1.93-3.48)	2.22 (1.67-3.15)	0.003
Multivariate OR[b]	1.0	2.14 (1.85-3.32)	2.84 (2.93-4.11)	0.037
Total carbohydrates, g				
Number of Case/Control	27/66	28/66	32/66	
Minimally-adjusted OR[a]	1.0	0.34 (0.14-1.54)	0.55 (0.28-1.26)	0.058
Multivariate OR[b]	1.0	1.77 (0.91-2.45)	1.81 (0.69-3.33)	0.615
Starch, g				
Number of Case/Control	27/66	29/66	31/66	
Minimally-adjusted OR[a]	1.0	0.53 (0.34-1.89)	0.72 (0.56-2.39)	0.465
Multivariate OR[b]	1.0	1.27 (0.55-2.23)	0.59 (0.33-3.25)	0.135
Sugar,.g				
Number of Case/Control	25/66	29/66	33/66	
Minimally-adjusted OR[a]	1.0	1.21 (0.82-2.34)	2.14 (1.89-3.03)	0.029
Multivariate OR[b]	1.0	1.67 (0.78-2.33)	2.29 (1.39-3.04)	0.041
Total fiber, g				
Number of Case/Control	38/66	29/66	20/66	
Minimally-adjusted OR[a]	1.0	0.81 (0.54-1.19)	0.55 (0.33-0.74)	0.006
Multivariate OR[b]	1.0	0.87 (0.71-1.22)	0.79 (0.34-0.88)	0.015

Abbreviations: GI, glycemic index;GL, glycemic load
[a] ORs and 95% CI adjusted for age and sex.
[b] Multivariate ORs and 95% CI adjusted for age, BMI, non-carbohydrate energy intake, fruit and vegetable consumption, using oral contraceptive, and smoking.

ing Body Mass Index (BMI) (n = 1) and poor responses in regard to dietary questions (n = 2), leaving 87 cases with breast cancer and 198 controls for final analysis.

Table 1 shows the distribution of the 87 cases and 198 controls on selected demographic variables and risk factors for breast cancer. The mean age of the cases and controls was 36.5 (SD = 7.9) and 36.8 (SD = 7.1) years, respectively, and their average BMI was 20.1 (SD = 2.9) and 26.3 (SD = 3.9) kg/m2, respectively (*P* value < 0.001). Tobacco consumption and years of education at time of interview were not significantly different between cases and controls (*P* value = 0.314 and 0.224 respectively). Cases used oral contraceptive significantly more than controls (*P* value = 0.031).

The mean intakes of dietary factors by cases and controls are listed in *Table 2*. There were no differences between breast cancer cases and controls in mean values of total energy, fat, starch and protein intakes. Mean ± SD dietary GI and GL levels were significantly higher among breast cancer cases compared to controls (*P* value < 0.05). On the other hand, controls consumed significantly more dietary fiber than their case peers (*P* value < 0.001).

Table 3 shows crude and multivariate ORs (95% CIs) for breast cancer according to the tertile of each dietary carbohydrate variable. The multivariate adjusted comparing of the highest tertile of dietary GI and GL with the lowest tertile were 2.11 (95% CI, 1.33-3.57; p-test for trend = 0.027) and 2.84 (95% CI, 2.93-4.11; p-test for trend = 0.037) respectively, with a significant trend. Mutually adjustment for GL did not noticeably change the observed association of GI with breast cancer risk (p-test for trend = 0.035). Moreover, mutually adjustment for GI did not noticeably change the observed association of GL with breast cancer risk (p-test for trend = 0.045). A protective independent effect was observed for the highest tertile of total fiber intake (OR: 0.79, CI, 0.34-0.88; p-test for trend = 0.015). Sugar was directly associated with breast cancer risk (OR: 2.29, CI, 1.39-3.04; p-test for trend = 0.041). No significant association was observed between carbohydrate intake and breast cancer, with multivariate adjusted ORs of 1.81 (95% CI, 0.69-3.33) for the third tertile compared with the lowest (p-test for trend = 0.615). There were no significant associations or dose–response trends for higher intakes of starch (OR: 0.59, CI, 0.33-3.25; p-test for trend = 0.135). After adjusting for Hormone Replacement Therapy (HRT), Oral Contraceptive Pills (OCP), age at first delivery, age at menarche and physical activity, the significant associations were not changed.

5. Discussion

The present study, based on a valid and detailed FFQ, confirms the existence of a direct relation between GI and GL, and breast cancer risk; while high intake of fiber was associated with a significantly decreased risk of breast cancer.

Results from this hospital-based case-control study support previous cohort studies that provided evidence on increased risk of breast cancer with decreased consumption of refined carbohydrate. Consumption of sweet carbohydrates with high GI or GL and low fiber which are quickly absorbed, are capable of elevating blood glucose and insulin level to a greater amount (16-18, 27).

A few case-control studies were conducted to investigate the link between dietary carbohydrates, GL, or GI and breast cancer (28-30), but most of such studies have not supported the possible link between GI or GL and increased breast cancer risk (19-21, 31-35). However, McCann et al., in subgroup analysis observed a significant reduction in postmenopausal breast cancer risk with high GI and GL pattern scores combined (19).

A high GI or GL diet may increase breast cancer risk through an alteration of cell cycle kinetics (36), the inhibition of apoptosis (37), a gonadotropic effect (insulin stimulates the synthesis of ovarian androgens). Also, the 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) is of great importance (10-13). Dietary fiber may have the potential role to alter inflammatory processes in the tumor microenvironment, as there are already well-known associations of fiber and decreased plasma levels of the inflammatory cytokines IL-6 and TNF-α-R_2, and decreased concentrations of high sensitivity C-reactive protein (38, 39). Moreover, evidence suggests that dietary fiber intake improves breast cancer prognosis by reducing estrogen levels (40). Furthermore, dietary fiber can play a role in modulating insulin resistance through controlling postprandial glucose levels and improving insulin sensitivity (41).

The present study was the first study which evaluated the contribution of GI, GL and fiber to the risk of breast cancer in Iran. The strength of this study is the high participation rate of patients in our research (more than 90%). Studies in developing countries can offer unique opportunities to investigate the association between diet and cancer (42). Also, potential limitations of the study included reliability and validity of the estimation of average GI and GL, which were based on the relatively limited number of food items. Recall bias is unlikely given that the association between food glycemic levels and breast cancer was not evident at the time of interviews, since we registered incident cases. Measurement bias was unavoidable, because of using FFQ to assess dietary intake. This might have led us to underestimate the associations. However, we used a validated FFQ and excluded the participants who were misreporting (under or over reporting) their energy intake. Among the possible limitations of the present study, there is the use of hospital controls, whose may have different dietary habits and lifestyle as compared with the general population (43). However, we excluded control subjects admitted for conditions associated with tobacco smoking or long-term modifications of diet. Moreover, the common hospital settings for cases and controls may have increased comparability of dietary history among subjects and the questionnaire was satisfactorily reproducible and reliable (44). Another limitation of this study is the small sample size. Because of this limitation, we could not report our results by stratification for BMI and waist circumference, so we suggest conducting similar studies with appropriate number of subjects.

Despite such limitations, we have shown that diets with a high GI or GL may increase risk of breast cancer, whereas high consumption of fiber may decrease the risk. In conclusion, our study presents that a high-GI and GL, Low-fiber diet is directly related to increased risk of

breast cancer, supporting the hypothesis that a diet rich in refined cereals and sugar through hyperglycemia and subsequent increase of insulin demand is possibly associated with breast cancer.

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