Dietary Glycemic Load and Breast Cancer Risk in the Women's Health Study

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Abstract

A diet with a high glycemic load (GL) may contribute to a metabolic environment that enhances tumorigenesis. Little is known, however, about whether high glycemic diets increase breast cancer risk in women. We examined the associations between baseline measurements of dietary GL and overall glycemic index (GI) and subsequent breast cancer in a cohort of 39,876 women, ages 45 years or older, participating in the Women's Health Study. During a mean of 6.8 years of follow-up there were 946 confirmed cases of breast cancer. We found no association between dietary GL [multivariable-adjusted relative risk (RR), 1.01; confidence interval (CI), 0.76–1.35, comparing extreme quintiles; *P* for trend = 0.96] or overall GI (corresponding RR, 1.03; CI, 0.84–1.28; *P* for trend = 0.66) and breast cancer risk in the cohort as a whole. Exploratory analyses stratified by baseline measurements of menopausal status, physical activity, smoking history, alcohol use, and history of diabetes mellitus, hypertension, or hypercholesterolemia showed no significant associations, except in the subgroup of women who were premenopausal and reported low levels of physical activity (GL multivariable-adjusted RR, 2.35; CI, 1.03–5.37; *P* for trend = 0.07; GI multivariable-adjusted RR, 1.56; CI, 0.88–2.78; *P* for trend = 0.02, comparing extreme quintiles). Although we did not find evidence that a high glycemic diet increases overall breast cancer risk, the increase in risk in premenopausal women with low levels of physical activity suggests the possibility that the effects of a high glycemic diet may be modified by lifestyle and hormonal factors. Prospective studies of a larger sample size and longer duration are warranted to confirm our findings.

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Introduction

Breast cancer is the most commonly diagnosed invasive cancer in women (1). In the United States, breast cancer follows lung cancer as a leading cause of cancer mortality and will be responsible for an estimated 39,800 deaths in 2003 (2). Risk is thought to be largely influenced by factors related to hormone exposure, some of which exert their effects relatively early in a woman's life (2, 3). Many studies have examined associations between diet and breast cancer, and although no strong dietary risk factors have been identified, fruit and vegetable intake may be weakly protective (4), and alcohol consumption may increase risk, especially when folic acid intake is low (5, 6).

The glycemic potential of a diet high in refined-carbohydrate has long been of interest in the management of type 2 diabetes mellitus, but there is growing recognition that consumption of a diet with a high glycemic load (GL) may have adverse effects in the nondiabetic population as well. In 1992, Bruning *et al.* (7) found evidence of insulin resistance in breast cancer cases compared with controls and in the mid-1990s, Kazer (8) hypothesized that insulin-like growth factor 1 may be an important factor in this relationship. Giovannucci and McKeown-Eyssen (9, 10) further developed the insulin resistance hypothesis, but in relation to colon cancer, suggesting that hyperinsulinemia and insulin resistance may act as tumor promoters. They noted that dietary and lifestyle risk factors for developing insulin resistance, such as physical inactivity, obesity, and positive energy balance, were risk factors for developing cancer, and suggested that chronic hyperinsulinemia may create an unfavorable metabolic environment that facilitates carcinogenesis. Both insulin and insulin-like growth factor 1 are anabolic, stimulating mitosis and proliferation and inhibiting apoptosis in both normal and cancer cells of the breast (11, 12). Also, insulin and insulin-like growth factor 1 stimulate the synthesis of sex steroids and decrease concentrations of their binding proteins, which may increase risk of breast cancer, especially in premenopausal women (11, 13–15), although not all studies have supported this finding (16).

Many factors influence how rapidly carbohydrates are digested and absorbed, and hence what their glycemic and insulinemic effects will be (17). The glycemic index (GI) was introduced in 1981 as a way to rank foods according to their measured effect on blood glucose response (18). The GI of a food is based on portions that contain a fixed amount of carbohydrate (generally 50 g) rather than on portions that are typically consumed (19). A related measure, the GL, is calculated using both the GI of a food as well as the actual amount of carbohydrate consumed in a portion (20). We hypothesize that a diet with a high dietary GL and high overall GI increases a woman's risk of developing breast cancer.

Subjects and Methods

Study Population. The Women's Health Study includes 39,876 women who were 45 years or older at baseline in

1993–1995 and who had no history of coronary heart disease, cerebrovascular disease, or cancer, other than nonmelanoma skin cancer. The study was designed as a randomized trial to evaluate the balance of benefits *versus* risks of taking aspirin, vitamin E, and β-carotene to reduce the risk of cardiovascular disease and cancer. The β-carotene treatment was terminated in January 1996, after several randomized trials reported null or harmful effects of β-carotene supplementation on cardiovascular disease risk (21). This study was conducted according to the ethical guidelines of Brigham and Women's Hospital.

Assessment of Dietary Variables. A 131-item semiquantitative food frequency questionnaire (SFFQ) was sent to participants at baseline. The SFFQ listed common serving sizes for each food and asked participants to report how often they consumed a serving of that food, on average, over the previous year. There were nine categories of response: never or less than once per month, 1–3 times per month, once per week, 2–4 times per week, 5–6 times per week, once per day, 2–3 times per day, 4–5 times per day, and ≥6 times per day. Nutrient values for items on the SFFQ were obtained from United States Department of Agriculture materials and information from manufacturers; GI values were obtained primarily from the tables compiled by Foster-Powell and Brand-Miller (22). Details of calculating dietary GL and overall GI have been described elsewhere (23). Briefly, the GL for each food item on the SFFQ was calculated by multiplying the GI of the food by the number of carbohydrate grams in a serving of that food. The dietary GL for each participant was estimated by multiplying the GL for each reported food item by the participant's frequency of consumption, then summing overall foods. The overall GI for each participant was calculated by dividing the participant's dietary GL by the total grams of carbohydrate consumed. This variable is a weighted average of the GI of the foods consumed (the weights are the carbohydrate grams) and is an indicator of the average GI of the carbohydrate consumed. Glucose was used as the standard in calculating GI and GL values.

The SFFQ was validated for nutrients against multiple diet records in a similar population of women participating in the Nurses' Health Study and was found to be reasonably well correlated with the diet records (mean energy-adjusted correlation for the nutrients measured was $r = 0.62$; Ref. 24). The validity and physiological relevance of dietary GL as assessed by food frequency questionnaires is supported by several studies. In a cross-sectional study of healthy postmenopausal women, dietary GL was positively associated with plasma triacylglycerol concentrations (geometric mean, 0.98 and 1.75 mmol/liter, for the lowest and highest quintiles, respectively, of GL, P for trend < 0.001) and negatively associated with high-density lipoprotein-cholesterol concentrations (geometric mean, 1.50 and 1.34 μmol/liter, for the lowest and highest quintiles, respectively, of GL, P for trend $= 0.03$; Ref. 23). The positive dose-response relations between dietary GL and plasma lipid profiles observed in these epidemiological data were consistent with findings from controlled metabolic experiments and, thus, provide objective evidence that our SFFQ provided sensitive measures of both the quality and quantity of carbohydrate intake, and that measurement error, although inevitably present, did not preclude our ability to detect important associations between dietary GL and subsequent occurrence of breast cancer. Dietary GL has also been found to be associated with increased concentrations of high-sensitivity C-reactive protein, a marker of systemic inflammation and risk factor for ischemic heart disease (25). In prospective cohort studies, GL was associated with increased coronary heart disease risk in women and with increased diabetes mellitus risk in both men and women (20, 26, 27).

Women were excluded from these analyses if their SFFQ contained more than 70 blanks or if their reported daily total energy intake was less than 2514 kJ or greater than 14,665 kJ. These exclusions left a cohort of 38,446 women. Study participants completed baseline and run-in questionnaires regarding demographic variables, health habits, physical activity, and medical history. Follow-up questionnaires were administered yearly.

Assessment of Physical Activity. Energy (kJ) expended each week in physical activity was estimated from the reported amount of time spent during the past year in eight groups of recreational activities: walking or hiking; jogging; running; bicycling; aerobic exercise or aerobic dance; lower-intensity exercise; racquet sports; or lap swimming, and from how many flights of stairs climbed daily. Each group of activities, including stair climbing, was assigned a multiple of resting metabolic rate (MET score), which was multiplied by the woman's estimated resting metabolic rate (4.2 kJ/kg body weight) and by the hours per week engaged in the activity. These values were summed to obtain an estimate of weekly energy expenditure from recreational activities and stair climbing for each woman (28). The validity of physical activity assessment from self-administered questionnaires has been demonstrated in a random sample from a large population study of nurses, using past-week recalls and 7-day diaries as the referents. The correlations obtained were 0.79 for the recalls and 0.62 for the diaries (29).

Breast Cancer Ascertainment. Women were asked to report new diagnoses of major illnesses, including breast cancer. Diagnoses were confirmed by an Endpoints Committee that reviewed relevant records, including pathology reports, and determined how to classify the cancer. Only the first occurrence of breast cancer was considered an end point. Each cancer was classified as either *in situ* or invasive, and its hormone receptor status was recorded as estrogen receptor positive or negative and/or progesterone receptor positive or negative

Data Analysis. We categorized dietary GL and overall GI into quintiles of intake and used Cox proportional hazards models to estimate relative risks while controlling for age (years), body mass index, baseline alcohol use (never/rarely, 1–3 drinks/month, 1–6 drinks/week, ≥ 1 drink/day), baseline smoking status (never, current, past), age at menarche (≤10, 11, 12, 13, 14, ≥15), age at first pregnancy (never, <20, 20–24, 25–20, ≥30), number of pregnancies lasting 6 months or longer (0, 1, 2, 3, 4, ≥5), history of using oral contraceptives for 2 months or more (yes, no), use of postmenopausal hormones (never, past, current), family history of breast cancer (mother or sister diagnosed at age ≤60), and physical activity (tertiles of kJ expended weekly in recreational activity and stair climbing). In addition to these variables, we controlled for total energy (kJ), total fat (g), total fiber (g), and folate (μg) in one set of models and for total energy (kJ), folate (μg), and intake of fruits and vegetables (servings/day), whole grains (servings/day), and red meat intake (servings/day) in another set of models. To test for trend, we assigned the dietary GL or overall GI quintile median value to each subject in that quintile. To determine whether the relationships between foods with a high GL and breast cancer risk were consistent with the dietary GL models, we examined quartiles of intake of refined grain, whole grain, and total grain, and servings per day of cold cereal, dark bread, potatoes, and soft drinks, in both age-adjusted and multivariable-adjusted models. We repeated the dietary GL and overall GI analyses restricting the outcome to invasive cases only and again re-

Table 1 Baseline distributions of breast cancer risk factors by quintiles of energy-adjusted glycemic load (GL) in the Women's Health Study

	Quintile of energy-adjusted GL					*P*
	1 (n = 7689)	2 (n = 7689)	3 (n = 7690)	4 (n = 7689)	5 (n = 7689)	
GL (median)	92	106	117	127	143	
Overall GI[a] (mean within GL quintile)	50 ± 3	52 ± 3	53 ± 3	54 ± 3	55 ± 3	<0.0001[b]
Mean age (yr)	53.5 ± 6.7	53.6 ± 6.8	53.9 ± 7.0	54.2 ± 7.1	54.4 ± 7.4	<0.0001[b]
Postmenopausal at baseline (%)	52.4	53.3	54.0	56.2	57.4	<0.0001[c]
Mean BMI[a]	26.7 ± 5.4	26.3 ± 5.0	26.1 ± 5.0	25.7 ± 4.8	25.2 ± 4.7	<0.0001[b]
Current or past smoker (%)	60.8	51.6	47.0	43.7	41.7	<0.0001[c]
Alcohol use (%)						<0.0001[c]
Rarely/never	32.9	40.2	43.1	48.5	59.1	
1–3 drinks/mo	10.5	12.8	14.4	14.2	14.0	
1–6 drinks/wk	34.0	35.3	33.9	31.8	23.6	
≥1 drink/day	22.6	11.8	8.5	5.4	3.2	
Physical activity (mean kJ expended per wk)	3493 ± 4773	3806 ± 4893	4104 ± 4884	4318 ± 5312	4555 ± 5510	<0.0001[b]
Breast cancer in mother or sister at age <60 (%)	6.0	6.0	6.0	6.2	6.0	0.96[c]
Hormone replacement therapy use (%)						0.0012[c]
Current use (at baseline)	39.9	41.4	42.1	43.1	42.4	
Past use only	10.4	10.3	9.6	9.9	10.9	
Never	49.4	48.2	48.0	46.9	46.5	
Age at menarche (%)						0.33[c]
≤10 yr	8.6	8.2	8.5	7.9	8.0	
11 yr	16.8	16.4	16.3	16.0	15.3	
12 yr	27.8	28.6	29.3	28.2	28.0	
13 yr	29.2	28.8	28.1	29.0	29.2	
14 yr	10.0	10.2	10.6	11.1	11.2	
≥15 yr	7.5	7.7	7.0	7.8	8.2	
Oral contraceptive use (ever used for ≥2 mo)	72.4	71.1	68.8	68.1	65.3	<0.0001[c]
Age at first pregnancy lasting ≥6 months (%)						<0.0001[c]
Not applicable	12.3	10.3	11.0	12.1	11.9	
<20 yr	10.5	9.2	8.6	9.0	9.3	
20–24 yr	44.4	45.2	45.1	43.3	42.2	
25–29 yr	22.5	24.7	24.3	24.7	25.1	
≥30 yr	9.4	9.8	9.9	10.2	10.5	
Pregnancies lasting ≥6 mo (%)						0.0002[c]
0	13.3	11.3	12.4	13.0	13.1	
1	9.4	9.0	8.8	8.4	9.5	
2	29.8	29.6	28.9	28.9	30.0	
3	23.4	25.5	24.4	24.4	23.0	
4	13.4	13.9	13.9	13.9	13.6	
≥5	10.2	10.2	11.1	11.0	10.5	
History of diabetes mellitus (%)	3.8	2.6	2.5	2.1	1.7	<0.0001[c]
History of hypertension (%)	27.8	26.1	25.4	25.1	24.5	<0.0001[c]
History of hypercholesterolemia (%)	27.6	28.7	28.7	29.0	33.3	<0.0001[c]
Screening mammogram reported at baseline (%)	91.0	92.3	93.0	93.3	92.1	<0.0001[c]

[a] GI, glycemic index; BMI, body mass index.
[b] *P* for a test for linear trend.
[c] *P* for a test of independence.

stricting to cases that were either estrogen receptor positive and/or progesterone receptor positive.

We hypothesized *a priori* that the potential effect of a high dietary GL or high overall GI diet may be modified by factors that are associated with hormone status or insulin resistance. To explore this possibility, we conducted analyses stratified by baseline measurements of menopausal status (postmenopausal, premenopausal/uncertain), physical activity (tertiles of kJ expended in recreational activity and stair climbing), body mass index (<25, ≥25), smoking status (never, past/current), alcohol use (≤3 drinks/month, 1–6 drinks/week, ≥1 drink/day), and baseline medical history that may influence dietary changes (history of diabetes mellitus, hypertension, or hypercholesterolemia *versus* no history). Because the effect of physical activity may be influenced by menopausal status, we examined dietary GL and overall GI intake while stratifying on physical activity and menopausal status simultaneously. We used SAS (version 8, SAS Institute Inc., Cary, NC) to analyze these data.

Results

Mean follow-up time for this cohort was 6.8 years (262,750 person-years were accrued), during which 946 cases of breast cancer were confirmed. Of these, 753 cases were invasive and 492 cases were estrogen receptor positive and/or progesterone receptor positive. The mean dietary GL for this cohort was 117; mean overall GI was 53. Dietary GL quintile medians ranged from 92 to 143 (Table 1). Compared with the rest of the cohort, women in the highest dietary GL quintile were older, were more likely to be postmenopausal at baseline, had a lower body mass index, smoked less, drank less alcohol, expended more energy in physical activity, were more likely to have used

Table 2 Baseline nutrient and food group intake by quintiles of energy-adjusted glycemic load (GL) in the Women's Health Study

Nutrient or food group	Quintile of energy-adjusted GL					P^a
	1	2	3	4	5	
Energy (kJ/day)	7104 ± 2327	7340 ± 2268	7366 ± 2185	7267 ± 2142	7028 ± 2239	<0.0001
Fat (g/day)	69 ± 11	63 ± 8	58 ± 8	54 ± 8	46 ± 9	<0.0001
Protein (g/day)	89 ± 16	85 ± 12	82 ± 12	79 ± 11	71 ± 12	<0.0001
Carbohydrate (g/day)	177 ± 20	205 ± 12	222 ± 12	237 ± 13	267 ± 22	<0.0001
Alcohol (g/day)	9 ± 14	5 ± 7	4 ± 6	3 ± 5	2 ± 4	<0.0001
Fiber (g/day)	16 ± 4	18 ± 5	19 ± 5	20 ± 6	22 ± 8	<0.0001
Folate (μg/day)	383 ± 219	409 ± 212	432 ± 215	450 ± 221	468 ± 242	<0.0001
Fruits and vegetables (svg[b]/day)	5.2 ± 2.9	5.8 ± 3.0	6.1 ± 3.1	6.4 ± 3.2	6.7 ± 3.8	<0.0001
Red meat (svg/day)	1.0 ± 0.7	0.8 ± 0.5	0.7 ± 0.5	0.6 ± 0.4	0.4 ± 0.4	<0.0001
Whole grain (svg/day)	0.99 ± 0.93	1.25 ± 1.03	1.46 ± 1.11	1.61 ± 1.24	1.75 ± 1.46	<0.0001
Refined grain (svg/day)	1.81 ± 1.25	2.18 ± 1.39	2.28 ± 1.41	2.33 ± 1.45	2.26 ± 1.49	<0.0001
Total grain (svg/day)	2.79 ± 1.58	3.43 ± 1.74	3.74 ± 1.78	3.95 ± 1.90	4.02 ± 2.04	<0.0001
Cold cereal (svg/day)	0.20 ± 0.28	0.32 ± 0.32	0.38 ± 0.35	0.44 ± 0.38	0.50 ± 0.56	<0.0001
Dark bread (svg/day)	0.51 ± 0.66	0.64 ± 0.76	0.75 ± 0.85	0.84 ± 0.94	0.90 ± 1.05	<0.0001
Potatoes (svg/day)	0.29 ± 0.23	0.32 ± 0.24	0.34 ± 0.24	0.34 ± 0.25	0.34 ± 0.33	<0.0001
Soft drinks (svg/day)	0.06 ± 0.19	0.09 ± 0.25	0.11 ± 0.30	0.16 ± 0.41	0.32 ± 0.80	<0.0001

[a] *P* for a test for linear trend.
[b] svg, serving(s).

hormone replacement therapy, were more likely to have a baseline medical history of hypercholesterolemia, and were less likely to have a medical history of hypertension or diabetes mellitus. Women in the lowest dietary GL quintile were less likely than the rest of the cohort to have ever had a screening mammogram. Risk factors relating to parity also differed between dietary GL quintiles. Carbohydrate, fiber, folate, fruit and vegetable, refined grain, whole grain, cereal, dark bread, and soft drink intake increased as dietary GL increased; fat, protein, alcohol, and red meat intake decreased (Table 2). Although dietary composition differed, total energy intake was lower in quintiles one and five than in the middle quintiles.

We found no evidence of increased breast cancer risk in the cohort as a whole with either increasing dietary GL or increasing overall GI (Table 3). The multivariable-adjusted relative risk (RR) comparing the highest to lowest quintile of dietary GL was 1.01 [confidence interval (CI), 0.76–1.35]; for overall GI, the corresponding RR was 1.03 (CI, 0.84–1.28). Including the food group variables in the models did not appreciably change the results. We did not observe an increase in risk with intake of foods with a high GL, except for dark bread intake, with which there was a suggestion of a modest increased risk with borderline significance (data not shown).

Restricting the analyses to invasive cases, the multivari-

Table 3 Relative risk [95% confidence interval (CI)] of breast cancer diagnosed anytime after baseline according to quintiles of energy-adjusted dietary glycemic load and quintiles of energy-adjusted overall glycemic index

	No. of cases	Quintile of intake					*P* for trend
		1	2	3	4	5	
All women							
Glycemic load							
Age-adjusted risk	946	1.00	1.04 (0.85–1.27)	0.98 (0.80–1.20)	0.95 (0.78–1.17)	1.07 (0.88–1.31)	0.70
Multivariable-adjusted risk[a]	897	1.00	0.97 (0.78–1.20)	0.94 (0.74–1.18)	0.90 (0.70–1.16)	1.01 (0.76–1.35)	0.96
Glycemic index							
Age-adjusted risk	946	1.00	0.88 (0.71–1.07)	0.96 (0.78–1.17)	0.97 (0.79–1.18)	1.06 (0.87–1.29)	0.39
Multivariable-adjusted risk[a]	897	1.00	0.86 (0.70–1.07)	0.96 (0.78–1.18)	0.93 (0.76–1.15)	1.03 (0.84–1.28)	0.66
Premenopausal women							
Glycemic load							
Age-adjusted risk	354	1.00	0.86 (0.62–1.18)	0.81 (0.59–1.13)	0.88 (0.63–1.21)	0.98 (0.71–1.34)	0.92
Multivariable-adjusted risk[a]	338	1.00	0.87 (0.62–1.24)	0.93 (0.64–1.36)	1.02 (0.68–1.54)	1.27 (0.79–2.03)	0.27
Glycemic index							
Age-adjusted risk	354	1.00	0.68 (0.48–0.98)	1.04 (0.76–1.44)	0.89 (0.64–1.25)	1.24 (0.91–1.70)	0.07
Multivariable-adjusted risk[a]	338	1.00	0.64 (0.44–0.93)	1.06 (0.76–1.48)	0.88 (0.62–1.26)	1.29 (0.92–1.81)	0.06
Postmenopausal women							
Glycemic load							
Age-adjusted risk	589	1.00	1.16 (0.90–1.51)	1.10 (0.85–1.43)	1.00 (0.76–1.30)	1.15 (0.89–1.49)	0.58
Multivariable-adjusted risk[a]	559	1.00	1.04 (0.79–1.38)	0.96 (0.71–1.30)	0.86 (0.62–1.18)	0.90 (0.63–1.31)	0.40
Glycemic index							
Age-adjusted risk	589	1.00	1.00 (0.78–1.28)	0.91 (0.71–1.18)	1.02 (0.79–1.30)	0.95 (0.74–1.23)	0.75
Multivariable-adjusted risk[a]	559	1.00	0.99 (0.77–1.28)	0.90 (0.69–1.16)	0.97 (0.74–1.26)	0.89 (0.67–1.17)	0.39

[a] Multivariable model was adjusted for age, body mass index, alcohol, smoking, age at menarche, age at first pregnancy, number of pregnancies, oral contraceptive use, postmenopausal hormone use, family history of breast cancer, physical activity, total energy, energy-adjusted total fat, energy-adjusted total fiber, and energy-adjusted folate.

Table 4 Multivariable-adjusted[a] relative risk [95% confidence interval (CI)] of breast cancer diagnosed anytime after baseline according to quintiles of energy-adjusted glycemic load stratified by physical activity and by menopausal status and physical activity simultaneously

	No. of cases	Quintile of glycemic load					*P* for trend
		1	2	3	4	5	
All women, by tertile kJ expended in physical activity							
Lowest tertile physical activity	311	1.00	1.25 (0.88–1.78)	1.12 (0.75–1.66)	1.14 (0.74–1.75)	1.24 (0.75–2.04)	0.53
Middle tertile physical activity	305	1.00	0.92 (0.63–1.34)	0.70 (0.46–1.07)	0.84 (0.54–1.29)	1.00 (0.61–1.65)	>0.99
Highest tertile physical activity	281	1.00	0.72 (0.47–1.09)	0.98 (0.65–1.46)	0.74 (0.47–1.16)	0.77 (0.46–1.29)	0.39
Premenopausal women, by tertile kJ expended in physical activity							
Lowest tertile physical activity	119	1.00	1.60 (0.91–2.84)	1.52 (0.79–2.91)	1.62 (0.79–3.34)	2.35 (1.03–5.37)	0.07
Middle tertile physical activity	120	1.00	0.93 (0.50–1.72)	0.77 (0.39–1.54)	1.02 (0.50–2.09)	1.48 (0.66–3.33)	0.28
Highest tertile physical activity	99	1.00	0.35 (0.17–0.71)	0.67 (0.36–1.27)	0.61 (0.31–1.23)	0.49 (0.21–1.16)	0.22
Postmenopausal women, by tertile kJ expended in physical activity							
Lowest tertile physical activity	192	1.00	1.07 (0.68–1.69)	0.93 (0.56–1.54)	0.91 (0.53–1.56)	0.84 (0.45–1.57)	0.50
Middle tertile physical activity	185	1.00	0.93 (0.58–1.50)	0.69 (0.40–1.17)	0.75 (0.43–1.30)	0.79 (0.42–1.51)	0.40
Highest tertile physical activity	182	1.00	1.18 (0.68–2.05)	1.41 (0.81–2.44)	0.95 (0.51–1.75)	1.12 (0.57–2.21)	0.97

[a] Multivariable model was adjusted for age, body mass index, alcohol, smoking, age at menarche, age at first pregnancy, number of pregnancies, oral contraceptive use, postmenopausal hormone use, family history of breast cancer, physical activity, total energy, energy-adjusted total fat, energy-adjusted total fiber, and energy-adjusted folate.

able-adjusted RR comparing extreme quintiles of dietary GL was 0.96 (CI, 0.70–1.33; *P* for trend = 0.63) and for GI was 1.06 (CI, 0.84–1.34; *P* for trend = 0.55). Restricting to cases that were either estrogen receptor positive or progesterone receptor positive, the RR comparing extreme quintiles of dietary GL was 0.89 (CI, 0.60–1.33; *P* for trend = 0.33) and for GI was 1.01 (CI, 0.75–1.36; *P* for trend = 0.95). Again, the RRs did not change appreciably when the food group variables were included in the models.

Estimated risk was somewhat increased in premenopausal women (GL multivariable-adjusted RR, 1.27; CI, 0.79–2.03, comparing extreme quintiles) but not in postmenopausal women (Table 3). Risk was also weakly elevated in women in the lowest tertile of physical activity and the highest quintile of GL intake (multivariable-adjusted RR, 1.24; CI, 0.75–2.04; Table 4). Examining strata of menopausal status and exercise simultaneously, risk was increased in women who were premenopausal at baseline and who were in the lowest tertile of physical activity (multivariable-adjusted RR, 2.35; CI, 1.03–5.37; Table 4). For overall GI, the multivariable-adjusted RR was 1.56 (CI, 0.88–2.78; *P* for trend = 0.02, comparing extreme quintiles).

There was no association between increasing dietary GL or overall GI and breast cancer risk in the body mass index or smoking subgroups (data not shown). Examining risk separately within strata of alcohol use, there was a small increase in risk, although not statistically significant, with high dietary GL or overall GI in women who drank little or no alcohol (GL multivariable-adjusted RR, 1.22; CI, 0.81–1.85, comparing extreme quintiles, *P* for trend = 0.30), but not in women who drank one or more drinks per week. Risk increased slightly with high dietary GL in women who reported a history of diabetes, hypertension, or hypercholesterolemia at baseline (multivariable-adjusted RR, 1.25; CI, 0.81–1.93, comparing extreme quintiles, *P* for trend = 0.53).

We tested for the presence of multiplicative interaction between dietary GL and each of the stratification variables; none of the *P*s were significant at the conventional $\alpha = 0.05$ level, perhaps because of a lack of statistical power.

Discussion

We found no overall association between dietary GL or overall GI and breast cancer incidence in this cohort of women ages 45 or older and followed for ~7 years. Results from previous studies have been mixed. A prospective cohort study of postmenopausal American women reported an RR of 0.90 (CI, 0.76–1.08, comparing extreme quintiles of GL; *P* for trend = 0.68), and a corresponding RR of 1.03 (CI, 0.87–1.22; *P* for trend = 0.71) for GI (30). Two case-control studies, however, reported positive associations between GI or dietary GL measures and breast cancer risk. Augustin *et al.* (in 2001; Ref. 31) report an odds ratio of 1.34 (CI, 1.10–1.61, comparing extreme quintiles of GL; *P* for trend = <0.01) in a large study of Italian women. Levi *et al.* (in 2002; Ref. 32) examined the association between overall GI and breast cancer in a hospital-based case–control study and found an odds ratio of 1.25 (CI, 0.83–1.87, comparing extreme tertiles; *P* for trend = 0.39), although they found no association between dietary GL and breast cancer.

The dietary and lifestyle factors that we examined are highly interrelated and difficult to measure accurately. Our findings may be biased by unmeasured confounders as well as by residual confounding from poorly measured dietary and lifestyle variables. Dietary information was collected only at baseline, reflecting the previous year's intake. It is uncertain whether changes in diet during the follow-up period influenced breast cancer risk. Another potential source of bias is mammogram use in the study population. Women in the lowest quintile of dietary GL were least likely to have had a screening mammogram before enrollment in the study. If women with undiagnosed breast cancer are more likely to have a low dietary GL diet, risk estimates could be biased away from the null.

High dietary GL and overall GI were weakly associated with increased breast cancer risk in premenopausal women, although this increase was not seen in premenopausal women who reported high levels of physical activity. Although alcohol intake has been associated with an increased risk of breast cancer (5), we found a small increase in risk in nondrinkers, but not in drinkers, who had a high glycemic diet. Evidence is mixed, but some studies suggest that moderate intake of alcohol may weakly improve insulin sensitivity (33). Our finding that breast cancer risk is somewhat increased with increasing dietary GL in women who had been diagnosed with hypertension, hypercholesterolemia, or diabetes at baseline, suggests that lifestyle or metabolic factors associated with these conditions may amplify the effects of a high glycemic diet. An alternative explanation is that women with a history of these conditions are

more likely to have dramatically changed their diets as a consequence of their diagnoses, and that changes in dietary intakes were not fully captured by the dietary questionnaire. Because of power limitations, we were unable to examine these conditions separately. We cannot rule out the possibility that these results are chance associations found because of the multiple comparisons we made and are not the reflection of a causal relationship between dietary GL, dietary GI, and breast cancer.

In this cohort, dietary GL is positively associated with reported physical activity. If the effect of a high dietary GL diet is modified by physical inactivity, then any residual confounding by physical activity within strata would be expected to bias the risk estimates toward the null, implying that true risk may be greater than our estimates. A previous study of exercise and breast cancer in this group of women found an inverse association between energy expended in physical activity and breast cancer risk, although the association was stronger in postmenopausal women than in the cohort as a whole (premenopausal women were not examined separately; Ref. 28).

In conclusion, in this prospective cohort study we did not find evidence that dietary GL or overall GI increases overall breast cancer risk. However, we did find an increase in risk in women who were premenopausal or of uncertain menopausal status at baseline and were in the lowest tertile of reported physical activity, suggesting that the effects of a high glycemic diet may be modified by interrelated lifestyle and hormonal factors. Future prospective studies of larger sample size and longer duration are warranted to confirm our findings.

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