

Short Communication

Dietary Glycemic Index, Glycemic Load, and Risk of Incident Breast Cancer in Postmenopausal Women

Carolyn R. Jonas,¹ Marjorie L. McCullough,
Lauren R. Teras, Kimberly A. Walker-Thurmond,
Michael J. Thun, and Eugenia E. Calle

Department of Epidemiology and Surveillance Research, American Cancer Society, Atlanta, Georgia 30329-4251

Abstract

Insulin and insulin-like growth factor-I (IGF-I) are associated with increased risk of breast cancer in several studies. Circulating concentrations of insulin increase with dietary consumption of high glycemic index foods, which, in turn, may influence IGF-I levels or activity, but the relevance of such dietary patterns for breast cancer risk is unclear. We investigated whether consumption of carbohydrates with high dietary glycemic index would predict risk of postmenopausal breast cancer among 63,307 United States women in the Cancer Prevention Study II Nutrition Cohort. From baseline in 1992, participants 40–87 years of age and free from cancer and diabetes, were followed for 5 years; 1442 incident breast cancer cases were documented. Diet was assessed at baseline by a validated 68-item food frequency questionnaire from which we calculated dietary glycemic index and glycemic load. Dietary glycemic index and load were not associated with increased risk of postmenopausal breast cancer (rate ratio = 1.03; 95% confidence interval, 0.87–1.22 and rate ratio = 0.90; 95% confidence interval, 0.76–1.08, respectively) after adjustment for multiple breast cancer risk factors. Associations were not modified by body mass index, physical activity, hormone use, or stage of disease. Future evaluations of glycemic index and breast cancer risk may be strengthened by longer follow-up, more complete dietary information, and measurement of plasma insulin and IGF-I levels.

Introduction

Although steroid sex hormones, especially estrogen, are most strongly implicated in the development of breast cancer (1–4), dysregulation of the peptide hormones, insulin and IGF-I,² may also affect risk (5–12). Several case-control studies and two

cohort studies have reported associations between breast cancer risk, and fasting and nonfasting insulin or IGF-I levels (7–12). Both peptides are known mitogens for human breast cancer cells (5, 6). The relation of insulin and IGF-I physiological activity is suggested by both human and animal studies that show that fasting plasma insulin concentrations are inversely correlated with IGF binding protein-1 levels, which increase bioavailable IGF-I (13–16). Thus, dietary patterns that promote elevated plasma insulin (transiently by diet or by underlying insulin resistance), and hypothetically IGF-I activity, may be expected to increase the risk of breast cancer.

The composition of dietary carbohydrate is a major determinant of postprandial blood glucose concentrations, and resultant fluctuations in circulating insulin. The glycemic response induced by carbohydrate intake and subsequent demand for insulin secretion can be classified by the glycemic index of foods (17, 18). Consumption of high glycemic index foods for short time periods (<6 weeks) has been associated with higher postprandial plasma insulin concentrations in healthy adults (19, 20), as well as increased fasting insulin concentrations in obese, insulin-resistant adults (21). Prolonged intake of high glycemic index diet patterns were positively associated with the onset of type II diabetes in normal weight and obese adults in population-based studies (22, 23). Two recent case-control studies have reported ~30% higher breast cancer risk among women with the highest intake of sweet food items or high dietary glycemic load compared with those with lowest intake of high glycemic index foods (24, 25). We prospectively evaluated the association between breast cancer risk and diets containing a high glycemic load and index in postmenopausal women in the CPS II Nutrition Cohort.

Materials and Methods

Study Cohort and Follow-Up. Women in this analysis were selected from the 97,787 female participants in the CPS II Nutrition Cohort (hereafter referred to simply as the Nutrition Cohort), a prospective study of cancer incidence and mortality among 184,192 United States men and women. The Nutrition Cohort, begun by the American Cancer Society in 1992, is a subgroup of the CPS II mortality cohort, which was launched in 1982 using American Cancer Society volunteers to enroll ~1.2 million men and women in all 50 states (26). Members of the CPS II cohort who resided in 21 states with population-based state cancer registries were invited to participate in the Nutrition Cohort, as described in detail elsewhere (26).

The participants were 50–74 years of age in 1992, when they completed a 10-page self-administered questionnaire that included information on demographic, medical, behavioral, environmental, occupational, and dietary factors. A follow-up questionnaire was sent to cohort members in September 1997 through August 1998 to update information and to ascertain newly diagnosed cancers. For living cohort members, the response rate was ~91%. We excluded from the analysis women who were lost to follow-up from 1992 to 1997–1998 ($n =$

Received 12/7/01; revised 2/25/03; accepted 3/4/03.

The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.

¹ To whom requests for reprints should be addressed, at Epidemiology and Surveillance Research, American Cancer Society, National Home Office, 1599 Clifton Road NE, Atlanta, GA, 30329-4251. Phone: (404) 377-9139; Fax: (404) 327-6450; E-mail: jonasclyn@aol.com.

² The abbreviations used are: IGF, insulin-like growth factor; CPS II, Cancer Prevention Study II; BMI, body mass index; FFQ, food frequency questionnaire; RR, risk ratio; CI, confidence interval; OR, odds ratio.

7,581), who at baseline reported prevalent breast or other cancer ($n = 11,602$) or history of diabetes ($n = 4,148$), or who were not postmenopausal ($n = 4,851$). Also excluded were women who did not meet the *a priori* criteria of daily energy intake in the range of 550–3,500 kcal/day or who left ≥ 10 of the 68 questions (15% of items) on the diet questionnaire blank ($n = 6,298$). After all of the exclusions, the final analytic cohort consisted of 63,307 women. As assessed at baseline in 1992, the majority of participants were white (97.9%), elderly (mean age 62.5 ± 6.1 years), and educated at high school level or higher (95.1%). Those excluded were not different from those who remained with regard to age, weight gain, BMI, reproductive history, and education.

Dietary Assessment. Usual dietary intake over the past year was assessed at baseline using a semiquantitative 68-item FFQ, which is a modification of the brief “Health Habits and History Questionnaire” developed by Block *et al.* (27). Daily nutrient intake was estimated from the FFQ using the “Health Habits and History Questionnaire” diet analysis software DIETSYS, Version 3.8a (27). As assessed previously in this cohort, median validity and reproducibility for nutrients and food groups on the FFQ correlations were 0.58 and 0.69, respectively (28).

Total daily dietary glycemic load and glycemic index values were derived from food intake reported on the FFQ. The glycemic index value of a specific food represents a ratio measure for the incremental increase in blood glucose after its consumption relative to that induced by a standard food, white bread (18). Glycemic index (GI) values for individual food items were added to the nutrient database using published data of glycemic responses measured using standardized analytic methods (18, 29). In the case of multiple line items on the Block FFQ, we estimated GI for each food and assigned the line item the weighted average of GI values based on prevalence of estimated population consumption of those items (18, 30). The glycemic load of the total diet was calculated by summing across all food items the products of: (a) glycemic index for that food; (b) grams of carbohydrate per serving of that food; and (c) number of daily servings. To derive a score for total dietary glycemic index, the dietary glycemic load of the total diet was divided by total daily carbohydrate intake in grams (22). Dietary glycemic load and index were evaluated to examine a quantitative measure of the glucose response induced by total daily carbohydrate intake and a score reflecting the relative proportion of high glycemic index foods composing the diet, respectively. To control for energy intake, measures of dietary glycemic index and load were adjusted for total energy using the residuals method (31).

Case Ascertainment. This analysis included a total of 1,442 incident breast cancer cases diagnosed after return of the baseline questionnaire through August 31, 1997. The majority of incident cases were initially identified by self-report on the 1997–1998 follow-up questionnaire and then verified by obtaining medical records or through linkage with state registries when complete medical records could not be obtained ($n = 1,164$). Verified incident breast cancer cases also included those identified during confirmation of any cancer diagnosis but not self-reported ($n = 38$). Pilot work linking the Nutrition Cohort members to four state cancer registries indicated that the ability of our respondents to accurately report a past diagnosis of cancer is very high (sensitivity = 0.93, specificity >0.99 ; Ref. 32). Therefore, we included in this analysis self-reported breast cancers for which confirmed diagnosis information had not yet been obtained ($n = 213$). A few incident cases ($n = 27$) were also identified through automated linkage of the cohort with the

National Death Index (33). For these cases, the death certificate listed breast cancer as a primary or contributory cause of death (International Classification of Diseases, Ninth Revision, codes 174.0–174.9) during the interval from the date of enrollment in 1992 or 1993 and August 31, 1997.

For analysis by stage of disease, the 1,158 breast cancer cases for whom we had information on stage from medical records or state registry linkage were classified by general summary stage into one of three groups. Cases were grouped as *in situ* (stage I, $n = 174$), localized (stage II, $n = 762$), or regional by direct extension, regional to lymph node, regional by direct extension and lymph node, and distant/systemic disease (stage III, $n = 222$).

Statistical Analysis. We used Cox proportional hazards modeling to examine the association of dietary glycemic index and dietary glycemic load with breast cancer incidence while adjusting for other potential risk factors. All of the Cox models were stratified on single year of age at enrollment. Multivariate models included other risk factors and confounders, including age at menarche (<12 , 13, or ≥ 14 years), age at menopause (<45 , 45– <50 , 50– <54 , or ≥ 54 years), number of live births (nulliparous, 1–2 births, or ≥ 3 births), age at first live birth (nulliparous, <20 , 20–24, 25–29, or ≥ 30 years), hormone replacement therapy (never, current, or former), oral contraceptive use (ever or never), family history of breast cancer in a mother or sister (yes or no), personal history of breast cysts (yes or no), education (less than high school, high school graduate, some college, or college graduate), BMI [weight (kg)/height (m^2) (<22 , 22– <25 , 25– <27 , 27– <30 , or ≥ 30), adult weight gain from age 18 (≤ 10 , 10–25, 26–42, or >42 pounds), location of body weight gain by self-report (chest/waist, chest/waist/other, or other than chest/waist), height (<63 , 63– <64 , 64– <66 , or ≥ 66 inches), physical activity as assessed by metabolic equivalent energy expenditure units (METs) for exercise (34; MET-hours per week <7 , 7– <15 , 15– <25.5 , or ≥ 25.5), total energy (quintiles), diethylstilbestrol use (ever or never), alcohol use (none, <1 , 1, or >1 drink/day), race (white, black, or other), and smoking status (never, current, or former). Total energy (quintiles) was included, consistent with the residual method of energy adjustment (31). Other nondietary and dietary factors (*i.e.*, fat, fiber intake) were considered but were not confounders in the multivariate models.

To test for effect modification by the potential confounders described above, interaction terms between dietary glycemic index (or load) tertiles and each other risk factor were included in multivariate models. Also, we evaluated whether the association between dietary glycemic index or load and breast cancer risk varied by follow-up time. The likelihood ratio test was used to test for significance (35).

Results

The estimated dietary glycemic load was nearly twice as high in the top compared with the bottom quintile of intake (Table 1). High dietary glycemic load was associated with higher daily intakes of total carbohydrate, total fiber, fiber from grains, fiber from fruits and vegetables, fruit servings per day, vegetable servings per day, and lower intake of total dietary fat. Dark breads, white bread or rolls, and spaghetti represented the top food contributors to the daily glycemic load in this cohort. Glycemic load was inversely associated with BMI, adult weight gain, smoking, and alcohol consumption, and was positively associated with physical activity and multivitamin use (Table 1). In contrast, high dietary glycemic index was associated with higher total fat and slightly lower plant food, fiber, and alcohol

Table 1 Age-standardized baseline characteristics according to quintiles of glycemic load and index among postmenopausal women in CPS II Nutrition Survey cohort

Variable	Quintile of glycemic load			Quintile of glycemic index		
	1	3	5	1	3	5
Quintile mean score	83	115	147	65	74	85
BMI ≥ 30 (%) ^{a,b}	16.2	14.6	10.5	12.3	14.6	15.2
Adult weight gain >40 lb (%) ^c	27.2	24.9	18.8	22.6	26.4	26.7
Regular physical activity (%) ^d	22.6	24.2	27.8	27.1	24.7	20.9
Hormone replacement therapy never user (%)	40.8	39.4	38.8	37.1	39.4	42.9
Oral contraceptive never user (%)	59.2	61.4	63.0	58.8	61.3	63.6
Nonsmoker (%)	44.2	57.0	60.0	50.5	55.8	53.9
Nondrinker (%)	32.5	46.2	57.7	37.3	46.8	52.5
Daily multivitamin user (%)	28.5	33.0	37.5	37.8	30.9	27.7
Daily dietary intake (Mean \pm SE)						
Dietary glycemic index ^e	70.4 \pm 0.1	74.3 \pm 0.1	78.7 \pm 0.1	—	—	—
Dietary glycemic load ^e	—	—	—	101 \pm 0.2	116 \pm 0.2	127 \pm 0.2
Total energy (kcal)	1348 \pm 4.1	1375 \pm 4.2	1382 \pm 4.1	1341 \pm 4.0	1370 \pm 4.0	1354 \pm 4.1
Total carbohydrate (g) ^e	119 \pm 0.1	155 \pm 0.1	187 \pm 0.1	156 \pm 0.2	155 \pm 0.3	150 \pm 0.1
Total fat (g) ^e	60 \pm 0.1	49 \pm 0.1	36 \pm 0.1	44 \pm 0.1	49 \pm 0.1	53 \pm 0.1
Protein (g) ^e	52 \pm 0.1	54 \pm 0.1	55 \pm 0.1	58 \pm 0.1	53 \pm 0.1	51 \pm 0.1
Total fiber (g) ^e	8.4 \pm 0.03	11.3 \pm 0.03	14.5 \pm 0.03	11.7 \pm 0.03	11.6 \pm 0.03	10.4 \pm 0.03
Fiber from grains (g) ^e	2.6 \pm 0.01	4.0 \pm 0.01	5.4 \pm 0.01	3.5 \pm 0.02	4.1 \pm 0.02	4.2 \pm 0.02
Fiber from vegetable, fruits (g) ^e	4.8 \pm 0.02	6.3 \pm 0.03	7.9 \pm 0.03	7.2 \pm 0.02	7.6 \pm 0.03	5.2 \pm 0.03
Alcohol (g)	11.5 \pm 0.09	3.3 \pm 0.09	1.6 \pm 0.09	7.7 \pm 0.09	4.1 \pm 0.10	3.3 \pm 0.09
Vegetable serv/day	1.7 \pm 0.01	2.0 \pm 0.01	2.4 \pm 0.01	2.2 \pm 0.01	2.1 \pm 0.01	1.8 \pm 0.01
Fruit serv/day	1.3 \pm 0.01	2.0 \pm 0.01	2.7 \pm 0.01	2.1 \pm 0.01	2.1 \pm 0.01	1.6 \pm 0.01

^a Percentages adjusted to the age distribution of the study population.

^b BMI [weight/(height²)].

^c Adult weight gain is defined as difference of reported weight at age 18 and weight in 1992.

^d Regular physical activity represented as highest quartile of MET score.

^e Energy-adjusted intake.

Table 2 Breast cancer incidence according to quintiles of dietary glycemic load and index in post-menopausal women, CPS II Nutrition Survey, 1992–1997

	Quintiles of energy-adjusted glycemic load					P for trend	Quintiles of energy-adjusted glycemic index					P for trend
	1 (lowest)	2	3	4	5 (highest)		1 (lowest)	2	3	4	5 (highest)	
No. cases	304	287	305	292	254		314	300	278	269	281	
Total person-years of follow-up	55871	57489	55414	53719	54772		59000	59221	49877	54198	54968	
Age-adjusted RR ^a	1.00	0.92	1.01	1.00	0.86	0.267	1.00	0.96	1.06	0.95	1.00	0.947
95% CI		0.78–1.08	0.87–1.19	0.86–1.18	0.73–1.02			0.82–1.12	0.90–1.24	0.81–1.12	0.86–1.19	
Multivariate-adjusted RR ^b	1.00	0.94	1.05	1.05	0.90	0.679	1.00	0.97	1.06	0.98	1.03	0.706
95% CI		0.80–1.11	0.89–1.24	0.88–1.24	0.76–1.08			0.82–1.13	0.90–1.25	0.83–1.15	0.87–1.22	

^a Adjusted for age at interview.

^b Adjusted for age at interview, age at menarche, age at menopause, number of live births, age at first live birth, hormone replacement therapy, oral contraceptive use, family history of breast cancer in a mother or sister, personal history of breast cysts, education, BMI, adult weight gain from age 18, location of body weight gain, height, physical activity, energy, diethylstilbestrol use, alcohol use, race, and smoking status.

intakes. In addition, dietary glycemic index was positively associated with BMI and adult weight gain, and negatively associated with physical activity and multivitamin use (Table 1).

We found no evidence of increased risk for breast cancer associated with high dietary glycemic load (RR = 0.90; 95% CI, 0.76–1.08; highest *versus* lowest quintile) or glycemic index (RR = 1.03; 95% CI, 0.87–1.22; highest *versus* lowest quintile; Table 2). The lack of association between dietary glycemic load or index and incident breast cancer did not change when controlling for other risk factors for breast cancer, or correlated dietary factors, or when excluding total energy intake. The association with dietary glycemic load or index was not significantly modified by BMI, physical activity, hormone replacement therapy use, or other covariates, with one exception. A significant interaction was observed for weight gain and

glycemic load (for highest glycemic load: RR = 0.98; 95% CI, 0.76–1.26 among women with <15 lb weight gain; RR = 0.76; 95% CI, 0.59–0.98 with 15–35 lb weight gain; RR = 1.12; 95% CI, 0.88–1.44 with >35 lb weight gain; *P* < 0.036), but no meaningful trends or patterns were observed. In the analysis limited to verified breast cancer cases, there was no significant association of dietary glycemic load or index by stage at diagnosis.

Discussion

During the first 5 years of follow-up for this large prospective study, dietary glycemic load and index were not associated with breast cancer risk in postmenopausal women. In addition, the null associations were not modified by degree of obesity, which itself leads to insulin resistance and elevated circulating insulin

concentrations (36). Other physiological factors known to influence insulin sensitivity and plasma insulin levels, such as physical activity and smoking, did not modify the association.

Our findings are in contrast to two previous case-control studies evaluating dietary intake patterns characteristic of high glycemic responses (24, 25). A positive association of high dietary glycemic load (OR, 1.5) and index (OR, 1.4) with postmenopausal breast cancer risk was described in a large hospital-based case-control study (25). Another case-control study evaluated early stage disease in premenopausal women only; high intake of refined carbohydrate food items modestly increased risk (OR, 1.3; Ref. 24). The lack of association of dietary patterns proposed to increase insulin and potentially IGF-I levels (13–16) in our cohort of postmenopausal women is not incongruent with studies demonstrating insulin and IGF-I associations only with premenopausal, and modest or no associations only with postmenopausal breast cancer (8–10, 37). Furthermore, it is possible that an association will not be found among disease-free older women (*e.g.*, we excluded women with diabetes at baseline) who are potentially less susceptible to these dietary influences.

Strengths of this study include its prospective design, large size, and ability to examine breast cancer by stage. This study extends findings from available case-control studies by evaluating high glycemic diet patterns and breast cancer risk prospectively with adequate power, while controlling for various potential confounding factors. Furthermore, we found that the relationship between glycemic load or index and breast cancer risk did not differ by breast cancer stage. This does not appear to support the hypotheses that these dietary factors may have a stronger role in advanced cases by influencing the growth-promoting effects of insulin and IGF-I on breast tumor cells (5).

A potential limitation of our study is the ability of the brief 68-item FFQ to capture the true range of total dietary glycemic load or index, which may be restricted by the limited variety of low and high glycemic index food items. Associations between glycemic load and index, and breast cancer would be expected to be attenuated by random measurement error. In addition, other dietary and behavioral factors, which are known to modify the glycemic response to foods consumed, are not easily assessed by our FFQ. These include food processing or preparation, specific mixtures of food items consumed, and the frequency, timing, and size of meals in relation to daily physical activity. However, reported intake on the FFQ produced estimates for glycemic load and index that were similar in range and variation to values reported in other large cohorts, which were positively predictive of other chronic disease states in those cohorts (22, 23, 38). Although there is some evidence in our data that glycemic load and index are differentially associated with other risk factors, including BMI, weight gain, and physical activity, and, thus, may be measuring different dietary qualities, neither were related to breast cancer risk. Our relatively short follow-up period of 5 years may not have allowed an effect of diet to emerge.

Clinical and observational studies show that prolonged consumption of high glycemic index foods contribute to increased fasting and postprandial insulin levels (19–21), and promote the onset of type II diabetes mellitus in healthy adults (22, 23). Several prospective and case-control studies have demonstrated independent and positive associations of fasting and nonfasting plasma insulin, and IGF-I concentrations and breast cancer risk (7–12). The limited epidemiological data available provide little support for a link between carbohydrate intake and IGF-I levels in women (39). Future evaluations of dietary glycemic effects would be strengthened by measure-

ment of plasma insulin and IGF-I levels and their relation to postmenopausal breast cancer in this cohort.

In summary, dietary patterns proposed to promote hyperinsulinemia and potentially IGF activity did not appear to increase risk of postmenopausal breast cancer, at least during this 5-year follow-up. A central role of hormonal mechanisms in the etiology of breast cancer is well established. However, the influence of environmental or dietary factors on metabolic or endocrine profiles that ultimately affect breast cancer risk is not well understood. Additional studies are needed to more clearly describe the link between these blood hormone levels and breast cancer risk, and to characterize the lifestyle and physiological factors that determine plasma insulin and IGF-I levels.

Acknowledgments

We thank Dr. Heather Spencer Feigelson for comments in manuscript preparation and Andrea Robertson for programming assistance.

References

- Clemons, M., and Goss, P. Estrogen and the risk of breast cancer. *N. Engl. J. Med.*, 344: 276–285, 2001.
- Kelsey, J. L., Gammon, M. D., and John, E. M. Reproductive factors and breast cancer. *Epidemiol. Rev.*, 15: 636–647, 1993.
- Collaborative Group on Hormonal Factors in Breast Cancer. Breast cancer and hormone replacement therapy: collaborative reanalysis of data from 51 epidemiological studies of 52,705 women with breast cancer and 108,411 women without breast cancer. *Lancet*, 350: 1047–1059, 1997.
- Folsom, A. R., Kaye, S. A., Prineas, R. J., Potter, J. D., Gapstur, S. M., and Wallace, R. B. Increased incidence of carcinoma of the breast associated with abdominal adiposity in postmenopausal women. *Am. J. Epidemiol.*, 131: 794–803, 1990.
- Papa, V., Pezzina, V., Costantino, A., Belfiore, A., Ghiuffrida, D., Frittitta, L., Vannelli, G. B., Brand, R., Goldfine, I. D., and Vigneri, R. Elevated insulin receptor content in human breast cancer. *J. Clin. Investig.*, 86: 1503–1510, 1990.
- Helle, S. I., and Lonning, P. E. Insulin-like growth factors in breast cancer. *Acta Oncol.*, 35(Suppl. 5): 19–22, 1996.
- Bruning, P. F., Bonfrer, J. M. G., van Noord, P. A. H., Hart, A. M., de Jong-Bakker, M., and Nooijen, W. J. Insulin resistance and breast cancer risk. *Int. J. Cancer*, 52: 511–516, 1992.
- Del Giudice, M. E., Fantus, I. G., Ezzat, S., McKeown-Eyssen, G., Page, D., and Goodwin, P. J. Insulin and related factors in premenopausal breast cancer risk. *Breast Cancer Res. Treat.*, 47: 111–120, 1998.
- Hankinson, S. E., Willett, W. C., Colditz, G. A., Hunter, D. J., Michaud, D. S., Deroo, B., Rosner, B., Speizer, F. E., and Pollack, M. Circulating concentrations of insulin-like growth factor-I and risk of breast cancer. *Lancet*, 351: 1393–1396, 1998.
- Bohlke, K., Cramer, D. W., Trichopoulos, D., and Mantzoros, C. S. Insulin-like growth factor-I in relation to premenopausal ductal carcinoma *in situ* of the breast. *Epidemiology*, 9: 570–573, 1998.
- Agurs-Collins, T., Adams-Campbell, L. L., Kim, K. S., and Cullen, K. J. Insulin-like growth factor-I and breast cancer risk in post-menopausal African-American women. *Cancer Detect. Prev.*, 24: 199–206, 2000.
- Yang, G., Lu, G., Jin, F., Dia, Q., Best, R., Shu, X., Chen, J., Pan, X., Shrubsole, M., and Zheng, W. Population-based, case-control study of blood C-peptide level and breast cancer risk. *Cancer Epidemiol. Biomark. Prev.*, 10: 1207–1211, 2001.
- Conover, C. A., Lee, P. D., Kanaley, J. A., Clarkson, J. T., and Jensen, M. D. Insulin regulation of insulin-like growth factor binding protein-1 in obese and nonobese humans. *J. Clin. Endocrinol. Metab.*, 74: 1355–1360, 1992.
- Conover, C. A., and Lee, P. D. Insulin regulation of insulin-like growth factor-binding protein production in cultured HepG2 cells. *J. Clin. Endocrinol. Metab.*, 70: 1062–1067, 1990.
- Kaaks, R. Nutrition, hormones, and breast cancer: Is insulin the missing link? *Cancer Causes Control*, 7: 605–625, 1996.
- Bar, R. S., Boes, M., Clemmons, D. R., Busby, W. H., Sandra, A., Dake, B. L., and Booth, B. A. Insulin differentially alters transcapillary movement of intravascular IGFBP-1, IGFBP-2, and endothelial cell IGF-binding proteins in the rat heart. *Endocrinology*, 127: 497–499.
- Smith U. Carbohydrates, fat and insulin action. *Am. J. Clin. Nutr.*, 59: 686S–689S, 1994.

18. Wolever, T. M. S., and Jenkins, D. J. A. The use of the glycemic index in predicting the blood glucose response to mixed meals. *Am. J. Clin. Nutr.*, *43*: 167–172, 1986.
19. Brand Miller, J. C. Importance of glycemic index in diabetes. *Am. J. Clin. Nutr.*, *59*(Suppl.): 747S–752S, 1994.
20. Holt, S. H. A., Brand Miller, J. C., and Petocz, P. An insulin index of foods: the insulin demand generated by 1000-kJ portions of common foods. *Am. J. Clin. Nutr.*, *66*: 1264–1276, 1997.
21. Periera, M. A., Jacobs, D. R., Pins, J. J., Raatz, S. K., Gross, M. D., Slavin, J. L., and Seaquist, E. R. Effect of whole grains on insulin sensitivity in overweight hyperinsulinemic adults. *Am. J. Clin. Nutr.*, *75*: 848–855, 2002.
22. Salmeron, J., Manson, J. E., Stampfer, M. J., Colditz, G. A., Wing, A. L., and Willett, W. C. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA*, *277*: 472–477, 1997.
23. Salmeron, J., Ascherio, A., Rimm, E. B., Colditz, G. A., Spiegelman, D., Jenkins, D. J., Stampfer, M. J., Wing, A. L., and Willett, W. C. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care*, *20*: 545–550, 1997.
24. Potischman, N., Coates, R. J., Swanson, C. A., Carroll, R. J., Daling, J. R., Brogan, D. R., Gammon, M. D., Midthune, D., Curtin, J., Brinton, L. A. Increased risk of early-stage breast cancer related to consumption of sweet foods among women less than age 45 in the United States. *Cancer Causes Control*, *10*: 937–946, 2002.
25. Augustin, L. S. A., Dal Maso, L., La Vecchia, C., Parpinel, M., Negri, E., Vaccarella, S., Kendall, C. W. C., Jenkins, D. J. A., and Franceschi, S. Dietary glycemic index and glycemic load, and breast cancer risk: a case-control study. *Ann. Oncol.*, *12*: 1533–1538, 2001.
26. Calle, E. E., Rodriguez, C., Jacobs, E. J., Almon, M. L., Chao, A., McCullough, M. L., Feigelson, H. S., and Thun, M. J. The American Cancer Society Cancer Prevention Study II Nutrition Cohort - Rationale, study design, and baseline characteristics. *Cancer (Phila.)*, *94*: 500–511, 2002.
27. Block, G., Hartman, A. M., and Naughton, D. A reduced dietary questionnaire: development and validation. *Epidemiology*, *1*: 58–64, 1990.
28. Flagg, E. W., Coates, R. J., Calle, E. E., Potischman, N., and Thun, M. J. Validation of the American Cancer Society Cancer Prevention Study II Nutrition Survey Cohort Food Frequency Questionnaire. *Epidemiology*, *11*: 462–468, 2000.
29. Foster-Powell, K., and Brand Miller, J. International tables of glycemic index. *Am. J. Clin. Nutr.*, *62*: 871S–893S, 1995.
30. Pennington, J. A. T. Revision of the Total Diet Study food list and diets. *J. Am. Diet Assoc.*, *82*: 166–173, 1983.
31. Willett, W. C., and Stampfer, M. J. Total energy intake: implications for epidemiologic analyses. *Am. J. Epidemiol.*, *24*: 17–27, 1986.
32. Bergmann, M. M., Calle, E. E., Mervis, C. A., Miracle-McMahill, H. L., Thun, M. J., and Heath, C. W. Validity of self-reported cancers in a prospective cohort study in comparison with data from state cancer registries. *Am. J. Epidemiol.*, *147*: 556–562, 1998.
33. Calle, E. E., and Terrell, D. D. Utility of the National Death Index for ascertainment of mortality among Cancer Prevention II participants. *Am. J. Epidemiol.*, *137*: 235–241, 1993.
34. Ainsworth, B. E., Haskell, W. L., Leon, A. S., Jacobs, D. R., Montoye, H. J., Sallis, J. F., and Paffenbarger, R. S. Compendium of physical activities: classification of energy costs of human physical activities. *Med. Sci. Sports Exerc.*, *25*: 71–80, 1993.
35. Kleinbaum, D., Kupper, L., and Morgenstern, H. *Epidemiologic Research: Principles and Quantitative Methods*. New York: Van Nostrand Reinhold Company, pp. 493–496, 1982.
36. Colditz, G. A., Willett, W. C., Stampfer, M. J., Manson, J. E., Hennekens, C. H., Arky, R. A., and Speizer, F. E. Weight as a risk factor for clinical diabetes in women. *Am. J. Epidemiol.*, *132*: 501–513, 1990.
37. Toniolo, P., Bruning, P. F., Akhmedkhanov, A., Bonfrer, J. M. G., Koenig, K. L., Lukanova, A., Shore, R. E., and Zeleniuch-Jacquotte, A. Serum insulin-like growth factor-I and breast cancer. *Int. J. Cancer.*, *88*: 828–832, 2000.
38. Liu, S., Willett, W. C., Stampfer, M. J., Hu, F. B., Franz, M., Sampson, L., Hennekens, C. H., and Manson, J. E. A prospective study of dietary glycemic load, carbohydrate intake, and risk coronary heart disease in US women. *Am. J. Clin. Nutr.*, *71*: 1455–1461, 2000.
39. Holmes, M. D., Pollak, M. N., Willett, W. C., and Hankinson, S. E. Dietary correlates of plasma insulin-like growth factor I and insulin-like growth factor binding protein 3 concentration. *Cancer Epidemiol. Biomark. Prev.*, *11*: 852–861, 2002.

BLOOD CANCER DISCOVERY

Dietary Glycemic Index, Glycemic Load, and Risk of Incident Breast Cancer in Postmenopausal Women

Carolyn R. Jonas, Marjorie L. McCullough, Lauren R. Teras, et al.

Cancer Epidemiol Biomarkers Prev 2003;12:573-577.

Updated version Access the most recent version of this article at:
<http://cebp.aacrjournals.org/content/12/6/573>

Cited articles This article cites 35 articles, 10 of which you can access for free at:
<http://cebp.aacrjournals.org/content/12/6/573.full#ref-list-1>

Citing articles This article has been cited by 17 HighWire-hosted articles. Access the articles at:
<http://cebp.aacrjournals.org/content/12/6/573.full#related-urls>

E-mail alerts [Sign up to receive free email-alerts](#) related to this article or journal.

Reprints and Subscriptions To order reprints of this article or to subscribe to the journal, contact the AACR Publications Department at pubs@aacr.org.

Permissions To request permission to re-use all or part of this article, use this link
<http://cebp.aacrjournals.org/content/12/6/573>.
Click on "Request Permissions" which will take you to the Copyright Clearance Center's (CCC) Rightslink site.