American Journal of Epidemiology
Published by the Johns Hopkins Bloomberg School of Public Health 2008.

Vol. 169, No. 4
DOI: 10.1093/aje/kwn347
Advance Access publication December 18, 2008

Original Contribution

Dietary Glycemic Index, Glycemic Load, and Risk of Cancer: A Prospective Cohort Study

Stephanie Materese George, Susan T. Mayne, Michael F. Leitzmann, Yikyung Park, Arthur Schatzkin, Andrew Flood, Albert Hollenbeck, and Amy F. Subar

Initially submitted May 13, 2008; accepted for publication October 3, 2008.

Previous studies have provided limited evidence for a harmful effect of high glycemic index and dietary glycemic load on cancer. The authors analyzed associations among glycemic index, glycemic load, and risk of cancer in women and men in the National Institutes of Health–AARP Diet and Health Study. Published glycemic index values were assigned to 225 foods/food groups. Glycemic load was calculated by multiplying the glycemic index, carbohydrate content, and intake frequency of individual foods reported on a food frequency questionnaire. From 1995 through 2003, the authors identified 15,215 and 33,203 cancer cases in women and men, respectively. Cox proportional hazards models were used to estimate multivariate relative risks and 95% confidence intervals. For women and men, respectively, the relative risks for total cancer for high versus low glycemic index were 1.03 ($P_{trend} = 0.217$) and 1.04 ($P_{trend} = 0.012$) and, for glycemic load, were 0.90 ($P_{trend} = 0.024$) and 0.93 ($P_{trend} = 0.01$). Associations with total cancer held only among the overweight for glycemic index and among those of healthy weight for glycemic load. These findings suggest that glycemic index and glycemic load are not strong predictors of cancer incidence. The direction and small magnitude of associations might be explained by the manner in which high glycemic index and glycemic load track with overall diet and lifestyle patterns.

diet; glycemic index; neoplasms; prospective studies

Abbreviations: CI, confidence interval; CSFII, Continuing Survey of Food Intakes by Individuals; NIH, National Institutes of Health; RR, relative risk; USDA, US Department of Agriculture.

A 20-fold variation (1) in the risk of many cancers across geographic regions suggests complex interactions of nonmodifiable (i.e., age, genetic susceptibility) and modifiable (i.e., diet, physical activity) factors (2). Environmental exposures such as diet might be important in the etiologies of different cancers and could play a key role in cancer prevention (2). There has been some suggestion that 2 dietary characteristics associated with carbohydrate intake—glycemic index and dietary glycemic load—may play a role in cancer etiology, but their precise contribution to cancer risk is unclear (3).

The *glycemic index* is a quantitative assessment of foods based on postconsumption blood glucose levels (4, 5); it is expressed as a percentage of the response to an equivalent carbohydrate portion of a reference food (white bread or glucose) (6). Higher rates of carbohydrate absorption lead to higher rises in blood glucose and higher resulting glycemic index values (4). Glycemic index of the diet is approximately a weighted average of the glycemic index of each food consumed. *Glycemic load* is the product of the glycemic index of a food and the carbohydrate content of the portion size, divided by 100. Because glycemic load takes into account the amount of intake and the carbohydrate content (7), it may be a better measure than glycemic index to characterize the glycemic effect of the diet.

Diets of high glycemic index or glycemic load might increase cancer risk via high circulating blood glucose, increased insulin demand, and bioavailability of insulin-like growth factor-1 (4). During the 2.5- to 3-hour period following consumption, glucose is more completely absorbed

Correspondence to Dr. Amy F. Subar, 6130 Executive Boulevard, MSC 7344, EPN 4005, Bethesda, MD 20892-7344 (e-mail: subara@mail.nih.gov).

from high (e.g., white bread) versus low (e.g., nuts/seeds) glycemic index foods (8). Further, for a given amount of carbohydrate, high glycemic index foods trigger a greater insulin response than do low glycemic index foods. Metabolic studies have suggested that carbohydrates with a high glycemic index increase insulin demand and the risk of insulin resistance and hyperinsulinemia (9–13). Insulin has both direct and indirect mitogenic properties. Chronically elevated concentrations of insulin could increase the risk of cancer by stimulating signaling pathways in the cells that promote tumor development and progression. Elevated insulin also downregulates the level of insulin-like growth factor binding proteins 1 and 2, thereby increasing the bioactivity and bioavailability of insulin-like growth factor-1 (14). High levels of unbound circulating insulin-like growth factor-1 could also be related to tumor promotion and progression (14–16). Moreover, insulin-like growth factor-1 regulates sex hormone binding globulin synthesis in vitro and may increase the bioavailability and levels of unopposed circulating estrogen in the body, which may increase the risk of hormone-related cancers (17, 18).

The primary objective of this analysis was to investigate whether glycemic index and glycemic load are related to increased risk of developing a first primary cancer in a prospective cohort of women and men aged 50 years or older, after controlling for potential confounders. We explored the effects of glycemic index and glycemic load for all major cancers. Our hypothesis was that high glycemic index and high glycemic load are associated with increased risk of total cancer and insulin- or hormone-related cancers.

MATERIALS AND METHODS

Study population

The National Institutes of Health (NIH)–AARP Diet and Health Study has been described previously (19). Briefly, the study was initiated in 1995–1996 with the mailing of a self-administered questionnaire to 3.5 million AARP members aged 50–71 years from 6 US states (California, Florida, Louisiana, New Jersey, North Carolina, and Pennsylvania) and 2 metropolitan areas (Atlanta, Georgia, and Detroit, Michigan). Among the 617,119 participants who returned questionnaires, the following were excluded from the analysis: 27,552 who skipped substantial portions of the questionnaire, 13,442 who indicated that they were not the intended respondent or did not complete the rest of the questionnaire, 8,127 who had more than 10 recording errors or reported consuming fewer than 10 foods, 829 who requested to be removed from the study, 6 who did not provide information on sex, 179 who were duplicates, and 582 who moved out of the study area or died at baseline, leaving a study population of 566,402 participants.

Among these 566,402 participants, we excluded those who indicated that they were proxies for the intended respondents ($n = 15{,}760$) and who had any prevalent registry-reported cancer except nonmelanoma skin cancer at baseline ($n = 1{,}875$), a self-reported cancer on the baseline questionnaire ($n = 49{,}318$), a self-reported end-stage renal disease at baseline ($n = 997$), and a cancer cause-of-death record and no cancer registry record ($n = 3{,}876$). We further excluded individuals who reported extreme intakes (beyond 2 times the interquartile range of sex-specific Box-Cox log-transformed intake) of total energy ($n = 4{,}382$) to account for erroneous overreporting and underreporting of foods. Given that people with prevalent diabetes are often instructed to consume more low glycemic index foods and may be at greater risk for certain cancers than the general population, an additional exclusion was made for those who self-reported diabetes at baseline ($n = 44{,}017$). After these exclusions, the analytical cohort consisted of 262,642 men and 183,535 women. For separate analyses of cancers of the ovary and uterus, we excluded women who had undergone bilateral oophorectomy ($n = 52{,}499$) or hysterectomy ($n = 95{,}857$) at baseline, respectively.

Cancer ascertainment

Cases were identified through probabilistic linkage with 11 state cancer registry databases, certified by the North American Association of Central Cancer Registries as being 90% complete within 2 years of cancer occurrence (19). The case ascertainment method used in the study showed a 90% detection rate of cancer cases in our cohort (20).

We considered as incident cancer cases only those that were both invasive and the first malignancy diagnosed during the follow-up period (through December 31, 2003), if multiple cancers were diagnosed in the same participant. Cancers were defined by using criteria from the Surveillance, Epidemiology, and End Results Program and the *International Classification of Diseases for Oncology, Third Edition*. For reasons of statistical power, only cancers with more than 50 cases in a sex-combined cohort were considered in site-specific analyses.

Dietary assessment

At baseline, dietary intakes were assessed with a self-administered 124-item food frequency questionnaire that was an earlier grid-based version of the Diet History Questionnaire developed at the National Cancer Institute. Participants reported their usual frequency of intake and portion size over the last 12 months, using 3 predefined categories of portion size and 10 predefined frequency categories ranging from ''never'' to ''6+ times per day'' for beverages and from ''never'' to ''2+ times per day'' for solid foods. The food items, portion sizes, and nutrient database for this food frequency questionnaire were constructed on the basis of Subar et al.'s method (21) by using the US Department of Agriculture (USDA) 1994–1996 Continuing Survey of Food Intakes by Individuals (CSFII).

The methods for deriving and including glycemic index and glycemic load values in the NIH–AARP database are described in detail elsewhere (22). Briefly, values are derived from approximately 4,200 individual foods reported by adults in the 1994–1996 CSFII. This list was condensed into 225 nutritionally similar food groups. Using the published glycemic index values compiled by Foster-Powell et al. (23), we linked glycemic index values (using a scale assuming pure glucose = 100) to each of the individual

CSFII foods in these food groups. The method of linkage was by manual review of the glycemic index table to identify those foods that, in the judgment of the investigators, were the best matches for each of the CSFII foods. In the cases where CSFII foods did not correspond closely to foods with published glycemic index values, we used a series of decision criteria (22) to assign glycemic index values. We then calculated the gender- and serving size-specific glycemic load for each of the 225 food groups using the weighted mean method as described by Subar et al. (21). These glycemic load values were used in the NIH–AARP database to calculate the overall daily glycemic load based on food frequency questionnaire-reported frequency and portion size by gender across all questionnaire items.

In the USDA food composition tables used to compute nutrient values for CSFII, the carbohydrate value includes both available (i.e., digestible) carbohydrate and dietary fiber. Because glycemic load represents the glycemic effect of food and the glycemic effect is inherently a function of the carbohydrate available for digestion and absorption, for the purposes of our glycemic load calculations, we defined *carbohydrate* to be the USDA-based value for grams of carbohydrate per serving minus the USDA value for grams of dietary fiber per serving. Available carbohydrate excludes not only dietary fiber but also resistant starch. However, the USDA tables include most resistant starches in their definition of fiber, so subtracting the USDA-based fiber value from total carbohydrate is a reasonable approach. Failure to remove fiber from the carbohydrate value used in these calculations would result in overestimation of the glycemic load from any food containing fiber or resistant starch.

The validity of the food frequency questionnaire used in the study was evaluated by using 2 nonconsecutive 24-hour recalls in 2,053 participants, and it is described in detail elsewhere (24). When the 26 nutrient constituents examined were adjusted for reported energy intake, the estimated correlations with 24-hour recalls ranged from 0.36 to 0.70 for women and from 0.40 to 0.76 for men (24). Estimated correlations for food frequency questionnaire total carbohydrate intake with 24-hour recall carbohydrate intake were 0.71 for women and 0.64 for men (24).

The baseline questionnaire also queried demographic characteristics, medical history, and lifestyle.

Statistical analysis

Multivariate relative risks and 2-sided 95% confidence intervals were estimated with Cox proportional hazards models by using the SAS PROC PHREG procedure, version 9.1.3 (SAS Institute, Inc., Cary, North Carolina). Person-years of follow-up time were calculated from the date the baseline questionnaire was received and scanned until the date of a cancer diagnosis, death, move out of the registry areas, or end of follow-up, whichever came first. The proportional hazards assumption was evaluated by modeling the interaction terms of time and glycemic load, and no statistically significant interaction was found. Relative risks of cancers were estimated according to sex-specific quintiles of glycemic index and glycemic load based on the distribution of the exposures in the AARP cohort. The test for linear trend across categories of glycemic index or glycemic load was performed by assigning participants the median value of their categories and entering it as a continuous term in a regression model.

All models were adjusted for age, race/ethnicity, education, marital status, body mass index, family history of any cancer, total energy intake, physical activity, smoking, alcohol consumption, and menopausal hormone therapy use among women. For categorical variables, an indicator variable for missing responses in each covariate was created. In multivariate models for bladder, esophagus, head and neck, lung, pancreatic, and all cancers, which are strongly related to smoking, we used a more complex categorical smoking variable that took into account smoking status, time since quitting smoking, and smoking dose.

A priori tests for glycemic load interactions with body mass index (<25, ≥ 25 kg/m^2) were made for total cancer, the 4 most prevalent cancer sites (lung, breast, colorectal, prostate), and cancers potentially related to the insulin/hormonal mechanism (endometrial, pancreatic, non-Hodgkin's lymphoma). If a significant interaction was found for body mass index with any of these sites, a sex/body mass index-stratified analysis was run.

RESULTS

Glycemic index and glycemic load were weakly positively correlated ($r = 0.23$) among women and men. Descriptive characteristics of the study population by sex and quintiles of glycemic index and energy-adjusted glycemic load are provided in Table 1. As compared with their counterparts in quintile 1, women and men in quintile 5 for glycemic index and glycemic load consumed more carbohydrates and less alcohol, and they were less well educated. Women and men in quintile 5 for glycemic index consumed more calories, and they were more likely to be current smokers, married, nonwhite, and overweight. However, women and men in quintile 5 for energy-adjusted glycemic load were less likely to be current smokers and more likely to be a healthy weight and physically active. Women in quintile 5 of glycemic index and glycemic load were less likely to be current users of menopausal hormone therapy.

Tables 2–5 show the associations between glycemic index and glycemic load and cancer risk. Glycemic index was not associated with increased risk of total cancer among women (relative risk (RR) = 1.03; $P_{trend} = 0.217$) but was among men (RR = 1.04; $P_{trend} = 0.012$). Higher glycemic load was associated with decreased risk of total cancer among women (RR = 0.90; $P_{trend} = 0.024$) and men (RR = 0.93; $P_{trend} = 0.01$).

Among women, higher glycemic load was associated with decreased risk of ovarian (RR = 0.48; $P_{trend} = 0.029$), pancreatic (RR = 0.49; $P_{trend} = 0.04$), myeloma (RR = 0.45; $P_{trend} = 0.036$), and liver (RR = 0.18; $P_{trend} = 0.019$) cancers.

Higher glycemic index was associated with a modestly increased risk of colorectal cancer among women (RR = 1.16; $P_{trend} = 0.026$) and men (RR = 1.16; $P_{trend} = 0.007$). Among men, higher glycemic index was associated with an increased risk of stomach (RR = 1.50; $P_{trend} = 0.02$), bladder (RR = 1.29; $P_{trend} = 0.023$), and esophageal

Table 1. Characteristics of Study Participants (Men: $n = 262{,}642$; Women: $n = 183{,}535$) by Quintiles of Glycemic Load and Glycemic Index in the NIH–AARP Diet and Health Study, 1995–2003[a]

	Glycemic Load				Energy-adjusted Glycemic Load				Glycemic Index			
	Men		Women		Men		Women		Men		Women	
	Quintile 1	Quintile 5	Quintile 1	Quintile 5	Quintile 1	Quintile 5	Quintile 1	Quintile 5	Quintile 1	Quintile 5	Quintile 1	Quintile 5
Median glycemic load[b]	68.0	197.2	54.1	163.9					108.4	132.6	87	106.3
Median glycemic index[c]	53.4	55.1	52.7	54.4					49.6	58.5	48.8	58.2
Age, years	62.3	61.4	62.0	61.3	61.8	61.8	61.5	61.6	62.1	61.7	61.9	61.4
White, non-Hispanic, %	92.3	91.0	90.7	84.6	95.3	89.4	92.8	94.3	92.9	90.9	90.5	87.5
College or postcollege, %	69.9	59.6	56.2	49.4	70.3	61.7	57.6	50.8	72.2	56.0	63.2	43.6
Married, %	82.1	85.0	40.8	44.0	82.0	85.8	46.0	42.3	81.3	86.3	41.4	44.9
Body mass index <25, %	26.8	30.4	45.5	40.9	24.8	36.3	43.4	47.3	31.2	30.9	50.2	41.1
Family history of any cancer, %	45.8	46.9	51.0	50.2	47.5	46.5	51.3	50.5	46.4	47.1	50.5	51.1
Current smoker, %	10.0	13.1	16.9	14.9	16.9	9.2	22.3	12.1	7.8	17.0	10.4	21.9
Physical activity ≥5 times/week, %	16.9	25.8	13.9	18.6	18.6	26.3	14.7	18.8	28.0	16.7	23.6	11.0
Alcohol ≥15 g/day, %	29.7	26.0	14.2	8.2	65.5	11.9	33.4	2.6	38.2	18.4	12.6	8.6
Carbohydrates, total g/day	134.2	419.5	108.7	355.0	224.2	364.1	198.6	291.3	258.2	270.8	213.2	221.5
Dietary fiber, g/day	11.6	30.7	9.8	27.3	19.5	25.6	17.7	21.3	25.5	16.2	22.1	13.8
Current menopausal hormone therapy, %			46.0	39.8			45.6	41.5			47.1	40.3
Total energy, kcal/day	1,189.4	3,127.2	893.8	2,475.8	2,349.3	2,386.8	1,849.9	1,804.3	2,029.4	2,099.4	1,499.9	1,651.6

Abbreviation: NIH, National Institutes of Health.

[a] Among men and women, all differences between quintile 5 and quintile 1 were statistically significant at $P < 0.0001$ (χ^2 test for categorical variables; t test for continuous variables).

[b] Glycemic load is the product of the glycemic index of a food and the carbohydrate content of the portion size, divided by 100.

[c] Glycemic index is expressed as a percentage of the blood glucose response to an equivalent carbohydrate portion of a reference food (white bread or glucose).

(RR = 1.50; $P_{trend} = 0.013$) cancers and decreased risk of brain cancer (RR = 0.70; $P_{trend} = 0.043$) and non-Hodgkin's lymphoma (RR = 0.79; $P_{trend} = 0.035$). To better understand the smoking-related glycemic index–cancer associations observed, we stratified the bladder and esophageal cancer findings by smoking status, and both associations disappeared among never smokers (data not shown).

On formal testing of interaction by body mass index in the sex-combined data set in cancers specified a priori, there was evidence that body mass index modified the association between glycemic load and risk of total cancer ($P = 0.002$), endometrial cancer ($P = 0.02$), and prostate cancer ($P < 0.0001$). For total cancer, among those with low body mass index, inverse trends were seen for glycemic load in women (RR = 0.84, 95% confidence interval (CI): 0.73, 0.97; $P_{trend} = 0.013$) and men (RR = 0.81, 95% CI: 0.72, 0.90; $P_{trend} = 0.0002$), but among those with a high body mass index, no trends were seen for women (RR = 0.97, 95% CI: 0.85, 1.11; $P_{trend} = 0.626$) or men (RR = 0.97, 95% CI: 0.90, 1.05; $P_{trend} = 0.414$). Among those with a low body mass index, no trends were seen for glycemic index and total cancer in women (RR = 0.99, 95% CI: 0.92, 1.07; $P_{trend} = 0.977$) or men (RR = 1.04, 95% CI: 0.97, 1.10; $P_{trend} = 0.268$), but among those with a high body mass index, positive trends were seen in women (RR = 1.09, 95% CI: 1.01, 1.17; $P_{trend} = 0.031$) and men (RR = 1.04, 95% CI: 1.00, 1.09; $P_{trend} = 0.029$).

Associations between glycemic load and glycemic index and endometrial cancer were not significant in body mass index-stratified analyses. Associations between glycemic load and prostate cancer were significant among men with a low body mass index (RR = 0.83, 95% CI: 0.71, 0.97; $P_{trend} = 0.033$) but not a high body mass index (RR = 0.95, 95% CI: 0.85, 1.06; $P_{trend} = 0.402$). Associations between glycemic index and prostate cancer were not significant in body mass index-stratified analyses.

DISCUSSION

We hypothesized that diets characterized by a high glycemic index and glycemic load are associated with an increased risk of total cancer, on the basis of previous suggestive findings from cohort studies that indicated harmful effects of glycemic index for premenopausal (25) and postmenopausal (26, 27) breast cancer and of glycemic load for endometrial (28), ovarian (29), and colorectal (30, 31) cancer. However, our findings suggest that glycemic index and glycemic load are not strongly associated with cancer incidence. For total cancer, we found evidence of a slightly increased risk for men who consumed high glycemic index foods, but this quintile 5 confidence interval included 1, and we actually found a modest, decreased risk of total cancer for women and men with high glycemic load diets. Further analyses showed, however, that glycemic index was positively related to total cancer only among women and men with a high body mass index, and glycemic load was inversely related to total cancer only among women and men with a low body mass index.

Our glycemic index data are consistent with an explanation based on the Nurses' Health Study, which suggests that

Table 2. Glycemic Index in Relation to Cancer Incidence Among US Women in the NIH–AARP Diet and Health Study, 1995–2003

Type of Cancer	No. of Events	Multivariate Relative Risks[a] Based on Quintile of Glycemic Index[b]									P_{trend}[c]
		Quintile 1 (Referent) (33.61–50.43)	Quintile 2 (50.44–52.56)		Quintile 3 (52.57–54.39)		Quintile 4 (54.40–56.55)		Quintile 5 (56.56–83.94)		
		Relative Risk	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	
Breast	5,478	1.00	0.97	0.89, 1.05	1.02	0.94, 1.11	1.02	0.94, 1.11	1.05	0.97, 1.15	0.129
Colorectal	1,457	1.00	0.94	0.80, 1.12	1.06	0.90, 1.25	1.08	0.91, 1.27	1.16	0.98, 1.37	0.026
Endometrial	1,041	1.00	0.97	0.80, 1.17	0.91	0.75, 1.10	0.91	0.75, 1.11	0.85	0.70, 1.04	0.094
Non-Hodgkin's lymphoma	605	1.00	0.96	0.74, 1.25	1.05	0.81, 1.36	1.03	0.78, 1.36	0.92	0.70, 1.21	0.680
Melanoma	543	1.00	0.98	0.76, 1.27	1.06	0.82, 1.36	0.99	0.76, 1.29	0.77	0.57, 1.03	0.136
Ovarian	475	1.00	1.12	0.85, 1.48	1.01	0.76, 1.34	0.99	0.74, 1.33	0.90	0.67, 1.23	0.371
Kidney	322	1.00	0.94	0.67, 1.33	0.99	0.70, 1.40	0.88	0.62, 1.26	0.84	0.59, 1.21	0.321
Thyroid	176	1.00	1.01	0.63, 1.61	1.02	0.64, 1.63	1.13	0.71, 1.79	0.92	0.56, 1.50	0.878
Brain	146	1.00	1.75	1.02, 3.00	1.46	0.84, 2.55	1.40	0.80, 2.47	1.26	0.70, 2.28	0.790
Myeloma	157	1.00	0.81	0.50, 1.33	1.03	0.65, 1.64	0.83	0.51, 1.36	0.73	0.43, 1.24	0.294
Stomach	127	1.00	1.06	0.61, 1.84	0.70	0.38, 1.31	1.27	0.74, 2.17	1.12	0.64, 1.97	0.520
Myeloid leukemia	119	1.00	1.33	0.76, 2.33	0.67	0.35, 1.31	1.04	0.58, 1.89	1.28	0.72, 2.28	0.601
Liver	72	1.00	1.91	0.95, 3.87	1.23	0.57, 2.64	0.62	0.25, 1.52	0.95	0.43, 2.10	0.209
Lung[d]	2,288	1.00	1.07	0.93, 1.22	1.01	0.88, 1.16	0.98	0.86, 1.13	1.12	0.98, 1.27	0.210
Pancreas[d]	348	1.00	0.90	0.64, 1.27	1.04	0.75, 1.44	0.90	0.64, 1.26	1.00	0.71, 1.40	0.970
Head and neck[d]	300	1.00	0.88	0.61, 1.28	0.82	0.56, 1.19	0.88	0.61, 1.27	0.94	0.66, 1.34	0.834
Bladder[d]	235	1.00	1.13	0.76, 1.68	0.82	0.53, 1.26	0.96	0.64, 1.45	0.91	0.60, 1.38	0.483
Esophagus[d]	76	1.00	0.95	0.43, 2.08	1.10	0.51, 2.35	1.43	0.70, 2.94	1.27	0.60, 2.67	0.332
All cancers[d]	15,215	1.00	0.99	0.94, 1.04	1.01	0.96, 1.06	0.99	0.94, 1.04	1.03	0.98, 1.09	0.217

Abbreviation: NIH, National Institutes of Health.

[a] Adjusted for age, race/ethnicity (non-Hispanic white, non-Hispanic black, and others), education (less than high school, high school graduate, some college, and college graduate/post graduate), marital status (married, not married), body mass index (<18.5, 18.5–<25, 25–<30, 30–<35, ≥35), family history of any cancer (yes, no), physical activity (never/rarely, 1–3 times/month, 1–2, 3–4, and ≥5 times/week), smoking (never, ≤20 cigarettes/day in the past, >20 cigarettes/day in the past, currently ≤20 cigarettes/day, and currently >20 cigarettes/day), alcohol consumption (0, <5, 5–<15, 15–<30, and ≥30 g/day), total energy intake (log-transformed calories), and menopausal hormone therapy use (never, past, current).

[b] Glycemic index is expressed as a percentage of the blood glucose response to an equivalent carbohydrate portion of a reference food (white bread or glucose).

[c] The test for linear trend across categories was performed by assigning participants the median value of their categories and entering it as a continuous term in the model.

[d] Smoking was adjusted for by using smoking status, time since quitting smoking, and smoking dose.

those of higher body mass index who are inactive are likely to be more susceptible to the carbohydrate quality of the foods they consume because of a strong insulin response to high glycemic index foods (32). However, this explanation does not explain the inverse glycemic load and total cancer associations that we saw in low body mass index women and men. Given the low magnitude and direction of the relative risks observed for glycemic index and glycemic load, respectively, it is possible that these exposures are not directly involved in the etiology of cancer but, rather, track with diet and lifestyle patterns associated with cancer risk.

Site-specific associations for glycemic load in our study were largely null, demonstrating consistency with past cohort study results for postmenopausal breast cancer (25, 33–38), premenopausal breast cancer (26, 35, 38), colorectal cancer (31, 39–43), stomach cancer (44), endometrial cancer (45–47), and pancreatic cancer (regarding results for men) (32, 44, 48–50). A few site-specific associations were significant, although multiple comparisons explain their significance given their exploratory nature, and many disappeared in subanalyses with more careful control for confounders, thus weakening support for the effects of glycemic index and glycemic load.

The inverse glycemic load–ovarian cancer relation that we observed was contrary to findings in the National Breast Screening Study (26). We investigated confounding by oral contraceptive use, but this adjustment strengthened the association, arguing against oral contraceptive use as an explanation for our results. Menopausal hormone therapy use was positively associated with ovarian cancer in the

Table 3. Glycemic Index in Relation to Cancer Incidence Among US Men in the NIH–AARP Diet and Health Study, 1995–2003

Type of Cancer	No. of Events	Multivariate Relative Risks[a] Based on Quintile of Glycemic Index[b]									P_{trend}[c]
		Quintile 1 (Referent) (33.51–51.26)	Quintile 2 (51.27–53.32)		Quintile 3 (53.33–55.04)		Quintile 4 (55.05–57.01)		Quintile 5 (57.02–84.13)		
		Relative Risk	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	
Prostate	15,949	1.00	0.99	0.94, 1.04	1.02	0.98, 1.08	1.05	1.00, 1.10	0.98	0.93, 1.03	0.946
Colorectal	3,031	1.00	0.99	0.89, 1.12	1.01	0.90, 1.14	1.04	0.93, 1.17	1.16	1.04, 1.30	0.007
Advanced prostate	1,656	1.00	0.92	0.79, 1.07	1.00	0.86, 1.16	0.96	0.82, 1.12	0.93	0.79, 1.09	0.509
Melanoma	1,485	1.00	1.07	0.91, 1.25	1.09	0.93, 1.27	1.00	0.85, 1.18	1.07	0.90, 1.27	0.680
Non-Hodgkin's lymphoma	1,114	1.00	0.87	0.72, 1.06	0.96	0.79, 1.16	0.91	0.74, 1.10	0.79	0.65, 0.96	0.035
Kidney	857	1.00	0.99	0.79, 1.23	0.99	0.80, 1.23	1.15	0.93, 1.42	1.05	0.84, 1.31	0.368
Stomach	440	1.00	1.44	1.04, 1.99	1.29	0.93, 1.80	1.54	1.12, 2.12	1.50	1.09, 2.08	0.020
Brain	356	1.00	1.07	0.78, 1.45	0.70	0.50, 0.99	0.98	0.71, 1.34	0.70	0.49, 0.99	0.043
Myeloma	331	1.00	0.92	0.65, 1.30	1.09	0.78, 1.52	1.05	0.75, 1.47	0.85	0.59, 1.23	0.614
Myeloid leukemia	288	1.00	0.99	0.69, 1.41	0.82	0.57, 1.20	1.02	0.72, 1.45	0.70	0.47, 1.03	0.117
Liver	238	1.00	1.73	1.13, 2.63	1.24	0.79, 1.95	1.17	0.74, 1.85	1.62	1.05, 2.48	0.185
Thyroid	153	1.00	1.02	0.62, 1.66	1.19	0.74, 1.92	0.81	0.48, 1.38	0.79	0.46, 1.37	0.300
Lung[d]	3,769	1.00	1.00	0.89, 1.11	1.04	0.93, 1.16	1.00	0.90, 1.11	1.08	0.98, 1.20	0.137
Bladder[d]	1,246	1.00	1.13	0.94, 1.36	1.07	0.89, 1.29	1.04	0.86, 1.25	1.29	1.07, 1.54	0.023
Head and neck[d]	939	1.00	0.96	0.78, 1.17	0.78	0.63, 0.97	0.93	0.76, 1.14	0.91	0.74, 1.11	0.365
Pancreatic[d]	601	1.00	0.97	0.74, 1.27	1.19	0.93, 1.54	1.05	0.81, 1.37	1.19	0.92, 1.55	0.160
Esophagus[d]	425	1.00	1.23	0.89, 1.7	1.03	0.74, 1.44	1.24	0.90, 1.71	1.50	1.10, 2.05	0.013
All cancers[d]	33,203	1.00	1.01	0.98, 1.05	1.02	0.98, 1.05	1.03	1.00, 1.07	1.04	1.00, 1.08	0.012

Abbreviation: NIH, National Institutes of Health.

[a] Adjusted for age, race/ethnicity (non-Hispanic white, non-Hispanic black, and others), education (less than high school, high school graduate, some college, and college graduate/post graduate), marital status (married, not married), body mass index (<18.5, 18.5–<25, 25–<30, 30–<35, ≥35), family history of any cancer (yes, no), physical activity (never/rarely, 1–3 times/month, 1–2, 3–4, and ≥5 times/week), smoking (never, ≤20 cigarettes/day in the past, >20 cigarettes/day in the past, currently ≤20 cigarettes/day, and currently >20 cigarettes/day), alcohol consumption (0, <5, 5–<15, 15–<30, and ≥30 g/day), and total energy intake (log-transformed calories).

[b] Glycemic index is expressed as a percentage of the blood glucose response to an equivalent carbohydrate portion of a reference food (white bread or glucose).

[c] The test for linear trend across categories was performed by assigning participants the median value of their categories and entering it as a continuous term in the model.

[d] Smoking was adjusted for by using smoking status, time since quitting smoking, and smoking dose.

NIH–AARP cohort (51). Although use of menopausal hormone therapy was carefully adjusted for in our multivariate models, since the glycemic load–ovarian cancer relation was not significant among women who never used menopausal hormone therapy, confounding by use of this therapy may be an explanation for this finding. Neither this association nor the glycemic load–pancreatic association in women was significant when we stratified by body mass index or excluded the first 2 years of follow-up.

The positive glycemic index–colorectal cancer and inverse glycemic load–myeloma associations observed in women did not have significant quintile 5 confidence intervals. The positive glycemic index–colorectal cancer association in women and positive glycemic index–stomach cancer association in men disappeared when the analysis was restricted to never smokers. Among men, the positive glycemic index–colorectal cancer association disappeared when stratified by red meat intake and otherwise remained significant only among those with a high body mass index or who had never smoked.

To our knowledge, the remaining site-specific associations have not been previously investigated in cohorts. The positive glycemic index–bladder cancer association among men disappeared when we stratified by smoking and simultaneously controlled for smoking status, dose, and time since quitting smoking, suggesting residual confounding by smoking. The positive glycemic index–esophageal cancer association in men became null when we stratified by red meat and otherwise was significant only among men who had a high body mass index or a high saturated fat intake, or who were former or current smokers. The glycemic load–liver cancer association in women may have been the result of residual confounding, as the association was not present when we restricted the analysis to never smokers.

Table 4. Glycemic Load in Relation to Cancer Incidence Among US Women in the NIH–AARP Diet and Health Study, 1995–2003

Type of Cancer	No. of Events	Multivariate Relative Risks[a] Based on Quintile of Glycemic Load[b]									P_{trend}[c]
		Quintile 1 (Referent) (4.61–66.91)	Quintile 2 (66.92–86.23)		Quintile 3 (86.24–106.20)		Quintile 4 (106.21–135.30)		Quintile 5 (135.31–583.68)		
		Relative Risk	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	
Breast	5,478	1.00	0.97	0.88, 1.06	1.03	0.92, 1.14	0.93	0.82, 1.06	0.96	0.81, 1.12	0.495
Colorectal	1,467	1.00	0.92	0.77, 1.10	0.92	0.75, 1.13	0.81	0.64, 1.03	0.87	0.64, 1.18	0.416
Endometrial	1,041	1.00	1.08	0.87, 1.34	1.08	0.84, 1.39	1.01	0.76, 1.36	1.25	0.86, 1.81	0.270
Non-Hodgkin's lymphoma	605	1.00	0.91	0.66, 1.23	0.90	0.63, 1.27	1.01	0.67, 1.52	0.88	0.51, 1.50	0.816
Ovarian	475	1.00	0.69	0.51, 0.95	0.76	0.53, 1.07	0.73	0.48, 1.09	0.48	0.28, 0.84	0.029
Melanoma	543	1.00	1.29	0.97, 1.71	0.91	0.64, 1.30	1.02	0.68, 1.54	0.85	0.50, 1.46	0.231
Kidney	322	1.00	0.91	0.63, 1.32	0.82	0.53, 1.27	0.78	0.47, 1.30	0.78	0.39, 1.51	0.490
Thyroid	176	1.00	1.15	0.68, 1.95	0.90	0.49, 1.67	0.91	0.45, 1.83	1.07	0.44, 2.61	0.958
Brain	146	1.00	1.17	0.66, 2.07	0.99	0.51, 1.95	1.16	0.54, 2.50	1.11	0.41, 3.04	0.914
Myeloma	157	1.00	1.06	0.63, 1.80	0.92	0.50, 1.70	0.54	0.25, 1.15	0.45	0.17, 1.23	0.036
Stomach	127	1.00	0.81	0.43, 1.52	0.49	0.23, 1.06	1.03	0.48, 2.23	0.67	0.24, 1.90	0.758
Myeloid leukemia	119	1.00	1.66	0.87, 3.16	1.65	0.78, 3.48	1.43	0.58, 3.48	1.55	0.50, 4.86	0.865
Liver	72	1.00	0.57	0.26, 1.26	0.76	0.33, 1.77	0.37	0.13, 1.08	0.18	0.04, 0.79	0.019
Lung[d]	2,288	1.00	0.91	0.79, 1.05	0.88	0.75, 1.03	0.85	0.71, 1.02	0.81	0.64, 1.03	0.133
Pancreas[d]	348	1.00	0.81	0.57, 1.16	0.71	0.47, 1.08	0.70	0.43, 1.12	0.49	0.26, 0.94	0.040
Head and neck[d]	300	1.00	0.68	0.47, 0.99	0.59	0.38, 0.91	0.62	0.38, 1.01	0.63	0.34, 1.19	0.360
Bladder[d]	235	1.00	1.09	0.71, 1.66	0.69	0.41, 1.17	0.99	0.55, 1.77	0.89	0.41, 1.91	0.798
Esophagus[d]	76	1.00	0.92	0.40, 2.13	2.01	0.85, 4.73	1.75	0.61, 4.98	2.18	0.57, 8.32	0.216
All cancers[d]	15,215	1.00	0.97	0.92, 1.03	0.96	0.90, 1.02	0.91	0.85, 0.98	0.90	0.82, 0.99	0.024

Abbreviation: NIH, National Institutes of Health.

[a] Adjusted for age, race/ethnicity (non-Hispanic white, non-Hispanic black, and others), education (less than high school, high school graduate, some college, and college graduate/post graduate), marital status (married, not married), body mass index (<18.5, 18.5–<25, 25–<30, 30–<35, ≥35), family history of any cancer (yes, no), physical activity (never/rarely, 1–3 times/month, 1–2, 3–4, and ≥5 times/week), smoking (never, ≤20 cigarettes/day in the past, >20 cigarettes/day in the past, currently ≤20 cigarettes/day, and currently >20 cigarettes/day), alcohol consumption (0, <5, 5–<15, 15–<30, and ≥30 g/day), total energy intake (log-transformed calories), and menopausal hormone therapy use (never, past, current).

[b] Glycemic load is the product of the glycemic index of a food and the carbohydrate content of the portion size, divided by 100.

[c] The test for linear trend across categories was performed by assigning participants the median value of their categories and entering it as a continuous term in the model.

[d] Smoking was adjusted for by using smoking status, time since quitting smoking, and smoking dose.

At present, there is no current literature to support a rationale for the direction of inverse associations that we observed for glycemic index among men for brain cancer and non-Hodgkin's lymphoma (which became null when we stratified by body mass index).

With almost 500,000 participants, 50,000 cancer cases, and 3,078,866 person-years of follow-up, the NIH–AARP Diet and Health Study is well powered to detect differences in cancer incidence if they truly exist. Follow-up of the cohort based on linkage to cancer registries and mortality databases, with approximately 90% sensitivity for incident cancers (20), reduced the likelihood that our overall results reflected bias due to differential follow-up, and the exposure preceded the onset of cancer enabling us to prevent against recall bias. Moreover, there was a wide range of glycemic load, allowing for sufficient variability in this exposure for a difference to be seen.

Our study is limited, however, by the narrow range of glycemic index values in the NIH–AARP cohort. The majority of glycemic index values centered around the middle of the theoretical range for glycemic index (i.e., 0–100), which may have precluded our ability to detect the effects of different levels of glycemic index unless it is a powerful determinant of disease risk at middle values (52).

Additionally, systematic, multivariate measurement error from imprecise dietary measurement may have occurred (53) and affected the hazard ratios and covariate estimates obtained (54). It is possible that reporting of energy intake differed by body mass index status (55), which was not captured in this study. Despite strong follow-up

Table 5. Glycemic Load in Relation to Cancer Incidence Among US Men in the NIH–AARP Diet and Health Study, 1995–2003

Type of Cancer	No. of Events	Multivariate Relative Risks[a] Based on Quintile of Glycemic Load[b]									P_{trend}[c]
		Quintile 1 (Referent) (7.08–83.20)	Quintile 2 (83.21–106.29)		Quintile 3 (106.30–130.13)		Quintile 4 (130.14–164.43)		Quintile 5 (164.44–740.24)		
		Relative Risk	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	Relative Risk	95% Confidence Interval	
Prostate	15,949	1.00	0.98	0.93, 1.03	0.95	0.90, 1.01	0.97	0.91, 1.04	0.92	0.84, 1.00	0.081
Colorectal	3,031	1.00	0.93	0.83, 1.06	0.88	0.77, 1.01	0.87	0.74, 1.02	0.88	0.72, 1.08	0.346
Advanced prostate	1,656	1.00	0.92	0.78, 1.08	0.78	0.64, 0.94	0.83	0.67, 1.03	0.73	0.56, 0.97	0.050
Melanoma	1,485	1.00	1.08	0.91, 1.29	1.09	0.89, 1.33	0.96	0.76, 1.22	1.01	0.75, 1.37	0.661
Non-Hodgkin's lymphoma	1,114	1.00	1.06	0.85, 1.31	1.07	0.84, 1.37	1.10	0.83, 1.45	1.04	0.72, 1.49	0.966
Kidney	857	1.00	1.1	0.87, 1.38	0.94	0.72, 1.23	0.86	0.63, 1.17	1.05	0.72, 1.55	0.996
Stomach	440	1.00	1.31	0.93, 1.83	1.58	1.09, 2.30	1.49	0.96, 2.30	1.42	0.81, 2.49	0.489
Brain	356	1.00	1.50	1.05, 2.15	1.17	0.76, 1.80	1.20	0.73, 1.96	1.25	0.66, 2.35	0.970
Myeloma	331	1.00	1.51	1.03, 2.22	1.21	0.77, 1.90	1.42	0.86, 2.36	1.67	0.88, 3.17	0.254
Myeloid leukemia	288	1.00	0.93	0.63, 1.39	0.85	0.54, 1.34	0.87	0.52, 1.47	0.95	0.49, 1.85	0.989
Liver	238	1.00	0.70	0.46, 1.06	0.50	0.31, 0.83	0.66	0.38, 1.12	0.47	0.23, 0.95	0.101
Thyroid	153	1.00	1.11	0.66, 1.87	0.81	0.43, 1.53	0.88	0.42, 1.85	1.21	0.48, 3.06	0.684
Lung[d]	3,769	1.00	1.00	0.90, 1.12	0.98	0.87, 1.11	0.88	0.76, 1.01	0.93	0.78, 1.11	0.234
Bladder[d]	1,246	1.00	0.99	0.81, 1.20	1.08	0.87, 1.33	0.93	0.72, 1.19	0.99	0.72, 1.36	0.793
Head and neck[d]	939	1.00	0.88	0.70, 1.10	0.94	0.74, 1.20	0.76	0.57, 1.00	0.76	0.53, 1.08	0.113
Pancreatic[d]	601	1.00	0.98	0.74, 1.29	0.88	0.64, 1.20	0.95	0.67, 1.36	0.67	0.42, 1.08	0.082
Esophagus[d]	425	1.00	0.93	0.67, 1.29	0.80	0.55, 1.16	0.88	0.58, 1.33	0.65	0.38, 1.11	0.122
All cancers[d]	33,203	1.00	0.98	0.95, 1.02	0.96	0.92, 1.00	0.94	0.90, 0.99	0.93	0.87, 0.98	0.010

Abbreviation: NIH, National Institutes of Health.

[a] Adjusted for age, race/ethnicity (non-Hispanic white, non-Hispanic black, and others), education (less than high school, high school graduate, some college, and college graduate/post graduate), marital status (married, not married), body mass index (<18.5, 18.5–<25, 25–<30, 30–<35, ≥35), family history of any cancer (yes, no), physical activity (never/rarely, 1–3 times/month, 1–2, 3–4, and ≥5 times/week), smoking (never, ≤20 cigarettes/day in the past, >20 cigarettes/day in the past, currently ≤20 cigarettes/day, and currently >20 cigarettes/day), alcohol consumption (0, <5, 5–<15, 15–<30, and ≥30 g/day), and total energy intake (log-transformed calories).

[b] Glycemic load is the product of the glycemic index of a food and the carbohydrate content of the portion size, divided by 100.

[c] The test for linear trend across categories was performed by assigning participants the median value of their categories and entering it as a continuous term in the model.

[d] Smoking was adjusted for by using smoking status, time since quitting smoking, and smoking dose.

(mean = 6.89 years) of the cohort at the time of this analysis, our assessment of diet may also not have captured the cancer-relevant period of exposure, given cancer's potential for long latency and our modeling based on median quintiles of dietary glycemic load at baseline, when participants were already aged over 50 years. Our study also characterized glycemic index and glycemic load as individual exposures, because past research suggested that the exposures alone might be surrogate markers of insulin load. Our findings reflect their direct effect on cancer incidence.

To date, few glycemic index and glycemic load analyses have provided evidence of meaningful associations with cancer risk. The small magnitude of the inverse and the positive significant relative risks that we observed suggest that glycemic index and glycemic load might not be as useful in predicting cancer incidence as other chronic diseases. In diabetics (56), low glycemic index and glycemic load predicted better glycemic control in the majority of feeding studies (4, 8, 57–60). An increased risk of non-insulin-dependent diabetes mellitus was seen in the Nurses' Health Study for high versus low glycemic index and glycemic load (61) and in the Health Professionals Follow-Up Study for glycemic index (62). This evidence reveals the importance of these concepts in guiding food choice among diabetics in the context of other nutritional indicators (63). Glycemic load has also been associated with increased risk of coronary heart disease in the Nurses' Health Study (64) and with cardiovascular disease in a Dutch cohort (65). Our findings do not rule out the insulin resistance hypothesis, but rather they suggest that glycemic index and glycemic load are not major contributors to aspects of insulin resistance that might influence cancer risk (66).

In summary, analysis of the NIH–AARP cohort did not provide strong evidence that diets high in glycemic index and glycemic load are associated with cancer incidence. With a widening understanding of the complex interactions

involved in cancer etiology and that food is not consumed in isolation, we believe that identification of the role of glycemic load as part of an overall healthy dietary pattern (67) may enable examination of the broader diet–cancer relation.

ACKNOWLEDGMENTS

Author affiliations: Yale School of Public Health, New Haven, Connecticut (Stephanie Materese George, Susan T. Mayne); Nutritional Epidemiology Branch, Division of Cancer Epidemiology and Genetics, National Cancer Institute, Bethesda, Maryland (Stephanie Materese George, Yikyung Park, Arthur Schatzkin); Institute of Epidemiology and Preventative Medicine, University of Regensburg, Regensburg, Germany (Michael F. Leitzmann); Division of Epidemiology and Community Health, School of Public Health, University of Minnesota, Minneapolis, Minnesota (Andrew Flood); AARP, Washington, District of Columbia (Albert Hollenbeck); and Applied Research Program, Division of Cancer Control and Population Sciences, National Cancer Institute, Bethesda, Maryland (Amy F. Subar).

This research was supported (in part) by the Intramural Research Program of the National Cancer Institute, National Institutes of Health.

The authors thank Sigurd Hermansen and Kerry Grace Morrissey from Westat for study outcomes ascertainment and management and Leslie Carroll at Information Management Services for data support and analysis

Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University. Cancer incidence data from California were collected by the Cancer Surveillance Section, California Department of Health Services. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, state of Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System under contract to the Department of Health. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Medical Center in New Orleans. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, Cancer Epidemiology Services, New Jersey State Department of Health and Senior Services. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. Cancer incidence data from Arizona were collected by the Arizona Cancer Regtistry, Division of Public Health Services, Arizona Department of Health Services. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services. Cancer incidence data from Nevada were collected by the Nevada Central Cancer Registry, Center for Health Data and Research, Bureau of Health Planning and Statistics, State Health Division, state of Nevada Department of Health and Human Services.

The views expressed herein are solely those of the authors and do not necessarily reflect those of the contractor or the Florida Department of Health. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions.

Conflict of interest: none declared.

REFERENCES

1. Wilson S, Jones L, Coussens C, et al, eds. *Cancer and the Environment: Gene-Environment Interaction.* Roundtable on Environment Health Sciences, Research, and Medicine, Board on Health Sciences Policy, Institute of Medicine. Washington, DC: National Academies Press; 2002.
2. Kamangar F, Dores GM, Anderson WF. Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. *J Clin Oncol.* 2006;24(14): 2137–2150.
3. Lock K, Pomerleau J, Causer L, et al. The global burden of disease attributable to low consumption of fruit and vegetables: implications for the global strategy on diet. *Bull World Health Organ*. 2005;83(2):100–108.
4. Augustin LS, Franceschi S, Jenkins DJ, et al. Glycemic index in chronic disease: a review. *Eur J Clin Nutr.* 2002;56(11): 1049–1071.
5. Jenkins DJ, Wolever TM, Taylor RH, et al. Glycemic index of foods: a physiological basis for carbohydrate exchange. *Am J Clin Nutr.* 1981;34(3):362–366.
6. Wolever TM, Vuksan V, Eshuis H, et al. Effect of method of administration of psyllium on glycemic response and carbohydrate digestibility. *J Am Coll Nutr.* 1991;10(4):364–371.
7. Brand-Miller JC, Thomas M, Swan V, et al. Physiological validation of the concept of glycemic load in lean young adults. *J Nutr.* 2003;133(9):2728–2732.
8. Jenkins DJ, Kendall CW, Augustin LS, et al. Glycemic index: overview of implications in health and disease. *Am J Clin Nutr.* 2002;76(1):266S–273S.
9. Brand JC, Colagiuri S, Crossman S, et al. Low-glycemic index foods improve long-term glycemic control in NIDDM. *Diabetes Care*. 1991;14(2):95–101.
10. Fontvieille AM, Rizkalla SW, Penfornis A, et al. The use of low glycaemic index foods improves metabolic control of diabetic patients over five weeks. *Diabet Med.* 1992;9(5): 444–450.
11. Jenkins DJ, Wolever TM, Collier GR, et al. Metabolic effects of a low-glycemic-index diet. *Am J Clin Nutr.* 1987;46(6): 968–975.
12. Wolever TM, Jenkins DJ, Vuksan V, et al. Beneficial effect of a low glycaemic index diet in type 2 diabetes. *Diabet Med.* 1992;9(5):451–458.
13. Wolever TM, Jenkins DJ, Vuksan V, et al. Beneficial effect of low-glycemic index diet in overweight NIDDM subjects. *Diabetes Care*. 1992;15(4):562–564.
14. Biddinger SB, Ludwig DS. The insulin-like growth factor axis: a potential link between glycemic index and cancer. *Am J Clin Nutr.* 2005;82(2):277–278.
15. Giovannucci E. Insulin and colon cancer. *Cancer Causes Control*. 1995;6(2):164–179.

16. Giovannucci E. Nutrition, insulin, insulin-like growth factors and cancer. *Horm Metab Res.* 2003;35(11–12):694–704.
17. Kaaks R. Nutrition, energy balance and colon cancer risk: the role of insulin and insulin-like growth factor-I. *IARC Sci Publ.* 2002;156:289–293.
18. Kaaks R, Lukanova A. Energy balance and cancer: the role of insulin and insulin-like growth factor-I. *Proc Nutr Soc.* 2001; 60(1):91–106.
19. Schatzkin A, Subar AF, Thompson FE, et al. Design and serendipity in establishing a large cohort with wide dietary intake distributions: the National Institutes of Health-American Association of Retired Persons Diet and Health Study. *Am J Epidemiol.* 2001;154(12):1119–1125.
20. Michaud DS, Midthune D, Hermansen S, et al. Comparison of cancer registry case ascertainment with SEER estimates and self-reporting in a subset of the NIH–AARP Diet and Health Study. *J Regist Manag*. 2005;32:70–75.
21. Subar AF, Midthune D, Kulldorff M, et al. Evaluation of alternative approaches to assign nutrient values to food groups in food frequency questionnaires. *Am J Epidemiol.* 2000;152(3): 279–286.
22. Flood A, Subar AF, Hull SG, et al. Methodology for adding glycemic load values to the National Cancer Institute Diet History Questionnaire database. *J Am Diet Assoc.* 2006; 106(3):393–402.
23. Foster-Powell K, Holt SH, Brand-Miller JC. International table of glycemic index and glycemic load values. *Am J Clin Nutr.* 2002;76(1):5–56.
24. Thompson FE, Kipnis V, Midthune D, et al. Performance of a food-frequency questionnaire in the US NIH–AARP (National Institutes of Health-American Association of Retired Persons) Diet and Health Study. *Public Health Nutr.* 2008;11(2):183–195.
25. Sieri S, Pala V, Brighenti F, et al. Dietary glycemic index, glycemic load, and the risk of breast cancer in an Italian prospective cohort study. *Am J Clin Nutr.* 2007;83(4):1160–1166.
26. Silvera SA, Jain M, Howe GR, et al. Dietary carbohydrates and breast cancer risk: a prospective study of the roles of overall glycemic index and glycemic load. *Int J Cancer.* 2005;114(4): 653–658.
27. Lajous M, Boutron-Ruault MC, Fabre A, et al. Carbohydrate intake, glycemic index, glycemic load, and risk of postmenopausal breast cancer in a prospective study of French women. *Am J Clin Nutr.* 2008;87(5):1384–1391.
28. Folsom AR, Demissie Z, Harnack L. Glycemic index, glycemic load, and incidence of endometrial cancer: the Iowa Women's Health Study. *Nutr Cancer.* 2003;46(2): 119–124.
29. Silvera SA, Jain M, Howe GR, et al. Glycaemic index, glycaemic load and ovarian cancer risk: a prospective cohort study. *Public Health Nutr.* 2007;10(10):1076–1081.
30. Higginbotham S, Zhang ZF, Lee IM, et al. Dietary glycemic load and risk of colorectal cancer in the Women's Health Study. *J Natl Cancer Inst.* 2004;96(3):229–233.
31. Michaud DS, Fuchs CS, Liu S, et al. Dietary glycemic load, carbohydrate, sugar, and colorectal cancer risk in men and women. *Cancer Epidemiol Biomarkers Prev.* 2005;14(1): 138–147.
32. Michaud DS, Liu S, Giovannucci E, et al. Dietary sugar, glycemic load, and pancreatic cancer risk in a prospective study. *J Natl Cancer Inst.* 2002;94(17):1293–1300.
33. Giles GG, Simpson JA, English DR, et al. Dietary carbohydrate, fibre, glycaemic index, glycaemic load and the risk of postmenopausal breast cancer. *Int J Cancer.* 2006;118(7): 1843–1847.
34. Higginbotham S, Zhang ZF, Lee IM, et al. Dietary glycemic load and breast cancer risk in the Women's Health Study. *Cancer Epidemiol Biomarkers Prev.* 2004;13(1):65–70.
35. Holmes MD, Liu S, Hankinson SE, et al. Dietary carbohydrates, fiber, and breast cancer risk. *Am J Epidemiol.* 2004; 159(8):732–739.
36. Jonas CR, McCullough ML, Teras LR, et al. Dietary glycemic index, glycemic load, and risk of incident breast cancer in postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2003;12(6):573–577.
37. Nielsen TG, Olsen A, Christensen J, et al. Dietary carbohydrate intake is not associated with the breast cancer incidence rate ratio in postmenopausal Danish women. *J Nutr.* 2005; 135(1):124–128.
38. Cho E, Spiegelman D, Hunter DJ, et al. Premenopausal dietary carbohydrate, glycemic index, glycemic load, and fiber in relation to risk of breast cancer. *Cancer Epidemiol Biomarkers Prev.* 2003;12(11 pt 1):1153–1158.
39. Larsson SC, Giovannucci E, Wolk A. Dietary carbohydrate, glycemic index, and glycemic load in relation to risk of colorectal cancer in women. *Am J Epidemiol.* 2007;165(3): 256–261.
40. Kabat G, Shikany J, Beresford S, et al. Dietary carbohydrate, glycemic index, and glycemic load in relation to colorectal cancer risk in the Women's Health Initiative. *Cancer Causes Control.* 2008;19(10):1291–1298.
41. McCarl M, Harnack L, Limburg PJ, et al. Incidence of colorectal cancer in relation to glycemic index and load in a cohort of women. *Cancer Epidemiol Biomarkers Prev.* 2006; 15(5):892–896.
42. Weijenberg M, Mullie P, Brants H, et al. Dietary glycemic load, glycemic index and colorectal cancer risk: results from the netherlands Cohort Study. *Int J Cancer.* 2008;122(3):620–629.
43. Nothlings U, Murphy SP, Wilkens LR, et al. Dietary glycemic load, added sugars, and carbohydrates as risk factors for pancreatic cancer: the Multiethnic Cohort Study. *Am J Clin Nutr.* 2007;86(5):1495–1501.
44. Larsson SC, Bergkvist L, Wolk A. Glycemic load, glycemic index and carbohydrate intake in relation to risk of stomach cancer: a prospective study. *Int J Cancer.* 2006;118(12): 3167–3169.
45. Larsson SC, Friberg E, Wolk A. Carbohydrate intake, glycemic index and glycemic load in relation to risk of endometrial cancer: a prospective study of Swedish women. *Int J Cancer.* 2007;120(5):1103–1107.
46. Silvera SA, Rohan TE, Jain M, et al. Glycaemic index, glycaemic load and risk of endometrial cancer: a prospective cohort study. *Public Health Nutr.* 2005;8(7):912–919.
47. Cust AE, Slimani N, Kaaks R, et al. Dietary carbohydrates, glycemic index, glycemic load, and endometrial cancer risk within the European Prospective Investigation into Cancer and Nutrition cohort. *Am J Epidemiol.* 2007;166(8):912–923.
48. Johnson KJ, Anderson KE, Harnack L, et al. No association between dietary glycemic index or load and pancreatic cancer incidence in postmenopausal women. *Cancer Epidemiol Biomarkers Prev.* 2005;14(6):1574–1575.
49. Patel AV, McCullough ML, Pavluck AL, et al. Glycemic load, glycemic index, and carbohydrate intake in relation to pancreatic cancer risk in a large US cohort. *Cancer Causes Control*. 2007;18(3):287–294.
50. Silvera SA, Rohan TE, Jain M, et al. Glycemic index, glycemic load, and pancreatic cancer risk (Canada). *Cancer Causes Control.* 2005;16(4):431–436.
51. Lacey JV Jr, Brinton LA, Leitzmann MF, et al. Menopausal hormone therapy and ovarian cancer risk in the National

Institutes of Health-AARP Diet and Health Study Cohort. *J Natl Cancer Inst.* 2006;98(19):1397–1405.
52. Flood A, Peters U, Jenkins DJA, et al. Carbohydrate, glycemic index, and glycemic load and colorectal adenomas in the Prostate, Lung, Colorectal, and Ovarian Screening Study. *Am J Clin Nutr.* 2006;84(5):1184–1192.
53. Bingham SA, Luben R, Welch A, et al. Are imprecise methods obscuring a relation between fat and breast cancer? *Lancet*. 2003;362(9379):212–214.
44. Schatzkin A, Kipnis V. Could exposure assessment problems give us wrong answers to nutrition and cancer questions? *J Natl Cancer Inst.* 2004;96(21):1564–1565.
55. Subar AF, Kipnis V, Troiano RP, et al. Using intake biomarkers to evaluate the extent of dietary misreporting in a large sample of adults: the OPEN Study. *Am J Epidemiol.* 2003;158(1):1–13.
53. Colombani PC. Glycemic index and load—dynamic dietary guidelines in the context of diseases. *Physiol Behav.* 2004; 83(4):603–610.
57. Bell SJ, Sears B. Low-glycemic-load diets: impact on obesity and chronic diseases. *Crit Rev Food Sci Nutr.* 2003;43(4): 357–377.
58. Hung T, Sievenpiper JL, Marchie A, et al. Fat versus carbohydrate in insulin resistance, obesity, diabetes and cardiovascular disease. *Curr Opin Clin Nutr Metab Care*. 2003;6(2):165–176.
59. Ludwig DS. The glycemic index: physiological mechanisms relating to obesity, diabetes, and cardiovascular disease. *JAMA*. 2002;287(18):2414–2423.
60. Wolever TM. Carbohydrate and the regulation of blood glucose and metabolism. *Nutr Rev.* 2003;61(5 pt 2):S40–S48.
61. Salmerón JJ, Manson JJE, Stampfer MMJ, et al. Dietary fiber, glycemic load, and risk of non-insulin-dependent diabetes mellitus in women. *JAMA*. 1997;277(6):472–477.
62. Salmerón JJ, Ascherio AA, Rimm EEB, et al. Dietary fiber, glycemic load, and risk of NIDDM in men. *Diabetes Care*. 1997;20(4):545–550.
63. Venn BJ, Green TJ. Glycemic index and glycemic load: measurement issues and their effect on diet-disease relationships. *Eur J Clin Nutr.* 2007;61(suppl 1):S122–S131.
64. Liu S, Willett WC, Stampfer MJ, et al. A prospective study of dietary glycemic load, carbohydrate intake, and risk of coronary heart disease in US women. *Am J Clin Nutr.* 2000;71(6): 1455–1461.
65. Beulens JWJ, de Bruijne LM, Stolk RP, et al. High dietary glycemic load and glycemic index increase risk of cardiovascular disease among middle-aged women: a population-based follow-up study. *J Am Coll Cardiol.* 2007;50(1):14–21.
66. Strayer L, Jacobs DR Jr, Schairer C, et al. Dietary carbohydrate, glycemic index and glycemic load and the risk of colorectal cancer in the BCDDP cohort. *Cancer Causes Control*. 2007;18(8):853–863.
67. Quatromoni PA, Copenhafer DL, Demissie S, et al. The internal validity of a dietary pattern analysis. The Framingham Nutrition Studies. *J Epidemiol Community Health*. 2002; 56(5):381–388.