Postdiagnostic Dietary Glycemic Index, Glycemic Load, Dietary Insulin Index, and Insulin Load and Breast Cancer Survival

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ABSTRACT

Background: We investigated the associations of postdiagnostic dietary glycemic index (GI), glycemic load (GL), insulin index (II), and insulin load (IL) with breast cancer–specific and all-cause mortality.

Methods: Among 8,932 women with stage I–III breast cancer identified in the Nurses' Health Study (NHS; 1980–2010) and NHSII (1991–2011), we prospectively evaluated the associations between postdiagnostic GI, GL, II, and IL, and breast cancer–specific and all-cause mortality. Participants completed a validated food frequency questionnaire every 4 years after diagnosis.

Results: During follow-up by 2014 in the NHS and 2015 in the NHSII, 2,523 deaths, including 1,071 from breast cancer, were documented. Higher postdiagnostic GL was associated with higher risk of both breast cancer–specific mortality [$HR_{Q5vsQ1} = 1.33$; 95% confidence interval (CI) = 1.09–1.63; $P_{trend} = 0.008$] and all-cause mortality ($HR_{Q5vsQ1} = 1.26$; 95% CI = 1.10–1.45; $P_{trend} = 0.0006$). Higher all-cause mortality was also observed with higher postdiagnostic GI ($HR_{Q5vsQ1} = 1.23$; 95% CI = 1.08–1.40; $P_{trend} = 0.001$), II ($HR_{Q5vsQ1} = 1.20$; 95% CI = 1.04–1.38; $P_{trend} = 0.005$), and IL ($HR_{Q5vsQ1} = 1.23$; 95% CI = 1.07–1.42; $P_{trend} = 0.0003$). The associations were not modified by insulin receptor or estrogen receptor status of the tumor, or body mass index.

Conclusions: We found that higher dietary GL, reflecting postprandial glucose response, after a breast cancer diagnosis was associated with higher risk of breast cancer–specific mortality. Higher dietary GI, GL, II, and IL after a breast cancer diagnosis were associated with higher risk of death from any cause.

Impact: These results suggest that carbohydrate quantity and quality may be important in breast cancer prognosis.

See related commentary by McTiernan, p. 252

Introduction

Insulin is a potent growth factor (1) and substantial evidence suggests that high circulating levels of insulin may contribute to poorer breast cancer prognosis (2). Among breast cancer survivors with diabetes, insulin use was associated with greater risk of both breast cancer recurrence and all-cause mortality (3, 4). In addition, tumors are often nutritionally constrained due to their rapid growth, and high blood glucose levels may promote progression. The type, amount, and digestibility of ingested carbohydrates are major determinants of postprandial blood glucose levels and hence circulating insulin levels (5, 6), which raise the possibility that these sorts of diets could be detrimental to the 3.8 million women living in the United States with breast cancer (7). The glycemic index (GI) is a ranking of specific foods or total diets based on the increase in postprandial glucose for a fixed amount of total carbohydrate, and is thus a measure of carbohydrate quality. The glycemic load (GL) combines the amount of carbohydrate in food or diet and its glycemic index, calculated as the product, and thus most strongly relates to postprandial glucose and insulin responses (6, 8). Some evidence indicates that GI may influence the likelihood of developing breast cancer (9). In a prior analysis in the Nurses' Health Study (NHS) among healthy participants, a high dietary GL was associated with greater all-cause mortality (10), but whether these aspects of diet after breast cancer diagnosis influence survival remains unknown (11). Given most women with breast cancer die from other causes, both breast cancer–specific and overall survival are important.

In addition to carbohydrates, dietary intake of protein and fat can induce insulin secretion (12). Dietary insulin index (II) and insulin load (IL) scores rank energy-containing food items according to the postprandial insulin responses (12). Therefore, using these measures may indicate the role of insulin in breast cancer survival more directly. Studies regarding the impact of II and IL on breast cancer survival, however, are lacking.

Therefore, we examined the associations of postdiagnostic dietary GI, GL, II, and IL with breast cancer survival using repeated dietary assessments in the NHS and the Nurses' Health Study II (NHSII). The availability of prediagnostic dietary data allowed the evaluation of independent associations of diets before and after diagnosis with survival. In addition, we examined these associations by the insulin receptor (IR) and estrogen receptor (ER) status of the tumor.

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Subjects and Methods

Study population

For this analysis, we used data from two ongoing cohort studies: the NHS which was established in 1976 with an enrollment of 121,700 U.S. female registered nurses aged 30 to 55 years and the NHSII, which was initiated in 1989 with an enrollment of 116,429 female registered nurses aged 25 to 42 years. Women were included in survival analyses if we confirmed the diagnosis of breast cancer from 1980 to 2010 in the NHS, and from 1991 to 2011 in the NHSII. We excluded women because of missing diet information at least 12 months after diagnosis, implausible total energy intake (<600 or >3,500 kcal/day), leaving blank more than 70 food items, a cancer diagnosis (except nonmelanoma skin cancer) before breast cancer, stage IV disease at diagnosis, and missing information on disease stage. Thus, we included 8,932 women with breast cancer in the analysis.

Completion of the questionnaire was considered to imply informed consent when the study protocol was approved in 1976 (NHS) and 1989 (NHSII) by the institutional review boards of the Brigham and Women's Hospital (Boston, MA) and Harvard T.H. Chan School of Public Health (Boston, MA), and those of participating registries as required. The studies were conducted in accordance with recognized ethical guidelines (Declaration of Helsinki).

Assessment of dietary intake

In 1980, a 61-item semiquantitative food frequency questionnaire (FFQ) was first administered to the NHS participants. Subsequently, an expanded FFQ with 116 to 130 items was administered in 1984, 1986, and every 4 years thereafter until 2010. In the NHSII, a similar FFQ with approximately 130 items was administered in 1991 and every 4 years thereafter until 2011 (questionnaires available at http://www.nurseshealthstudy.org/participants/questionnaires). In all of these questionnaires, the frequency of consumption over the past year was asked for a specified serving of each food item; multiple-choice responses ranged from "never or less than once/month" to "6 or more times/day."

The GI values for carbohydrate-containing foods, reflecting the increment in postprandial plasma glucose levels relative to the increment after ingestion of the same amount of carbohydrate as glucose, were obtained from a published database (6), supplemented with values derived from direct testing of foods on our questionnaire at Nutrition Center of the University of Toronto (Toronto, Ontario, Canada; Prof. David J. Jenkins). The GL values for foods were calculated by multiplying their GI by the amount of carbohydrate in grams. The total dietary GL for each person was calculated by summing the contributions of all foods consumed (6, 13). The overall dietary GI was determined by dividing the average dietary GL by the total amount of carbohydrate intake (14).

The II values for energy-containing foods were obtained from published database (31 foods; ref. 12), supplemented with values derived from direct testing of foods on our questionnaire (73 foods) at the University of Sydney (Camperdown, New South Wales, Australia; Prof. Jennie Brand-Miller). The II was determined by dividing the area under the insulin response curve for 1,000 KJ of each food item by the area under the insulin response curve for 1,000 KJ of glucose (reference food) (15). For the remaining food items in the FFQ, the II values were recipe-derived, imputed, and calculated. The IL for foods were determined by multiplying their II values by their amounts of energy, and the total IL for each person was calculated by summing the contributions of all foods consumed.

$$IL = \sum[\text{insulin index of food} \times \text{energy content of food (kcal/serving)} \times \text{frequency of food intake (servings/day)}]/100$$

The overall dietary II was determined by dividing the average dietary IL by that person's total energy intake.

$$II = IL \times 100/[\sum(\text{energy content of food(kcal/serving)} \times \text{frequency of food intake (servings/day)}]$$

Nutrient (carbohydrate, protein, fat, and fiber), alcohol, and energy values in foods and beverages were obtained from the Harvard University Food Composition Database. The food composition database was updated every 4 years to account for changes in the food supply. The dietary GI, GL, II, IL, carbohydrate, protein, fat, and fiber were energy-adjusted by using the residuals from the regression of dietary factors on total energy intake (16). First postdiagnostic energy-adjusted GI, GL, II, IL, carbohydrate, protein, fat, and fiber intakes were collected from FFQs completed 12 months or more after diagnosis to avoid assessment during active treatment. To reduce measurement error and within-person variation and capture dietary intake over a long period after diagnosis, the cumulative averages of dietary scores and nutrients were calculated using all available FFQs returned after diagnosis.

Ascertainment of breast cancer and death

Breast cancer diagnoses were self-reported on the biennial questionnaires. After obtaining participants' permission, medical records and pathology reports were reviewed to confirm the diagnosis and abstract information on tumor characteristics, stage of disease, ER and progesterone receptor (PR) status, and other relevant information. Breast cancer tissue was collected for approximately 70% of women with breast cancer. Tumor microarrays (TMA) were constructed to assess tumor characteristics by immunohistochemistry (IHC) (17–20). IHC staining, manually read by a study pathologist, was performed to determine the status of the ER, PR, HER2, cytokeratin 5/6 (CK5/6), and EGFR in the tumor tissue. If TMAs were not assessed, we extracted tumor ER and PR status from medical records. Expression of IR in cytoplasmic and membrane was determined using Definiens image analysis software (Tissue Studio) in the NHS (21). After reporting deaths by family members or the postal service, or searching in the National Death Index, the cause of death was assigned by physician review of the death certificate and medical record. International Classification of Diseases, Eighth Edition (ICD-8) were used to classify breast cancer–specific mortality (ICD-8, 174.0–174.9) and cardiovascular disease (CVD) mortality (ICD-8 390–458 and 795).

Covariates

For this study, we collected data on body mass index (BMI), smoking status, physical activity, and aspirin use that women reported in the biennial follow-up questionnaires at least 12 months after breast cancer diagnosis. To decrease the reverse causation possibility, the cumulative averages of postdiagnostic BMI and physical activity using 4-year lagged data were calculated. We also collected data on BMI that breast cancer patients reported in the last biennial follow-up questionnaire before diagnosis and calculated change in BMI from pre- to postdiagnosis. Data on age at menopause, menopausal status, post menopausal hormone use, and oral contraceptive use were collected from the biennial follow-up questionnaires returned before breast cancer diagnosis. In addition, we obtained information of breast cancer characteristics, including age at diagnosis, calendar year of

diagnosis, stage of disease, ER/PR status, self-reported radiotherapy, chemotherapy, and hormonal treatment from supplemental questionnaires or reviewing medical records.

Statistical analysis

Person-time of follow-up was calculated from the return date of the first FFQ assessed after breast cancer diagnosis to the end of the study period (June 1, 2014, for the NHS and June 1, 2015, for the NHSII) or death, whichever occurred first. The endpoints were breast cancer–specific mortality (follow-up at death from other causes was censored), all-cause mortality, and CVD mortality.

Data from the NHS and NHSII were combined and Cox proportional hazards regression models were used to estimate HRs and 95% confidence intervals (CI). Women with breast cancer were grouped into quintiles of the postdiagnostic cumulative average of GI, GL, II, and IL, as well as carbohydrate, protein, fat, fiber, and energy intake. The quintile median value of each dietary factor was used for tests for trend, modeled this as a continuous variable. Models were stratified by cohort and adjusted for age at diagnosis and calendar year of diagnosis. In multivariable models (model 2), we additionally adjusted for time between diagnosis and first FFQ after diagnosis, calendar year at start of follow-up of each-2-year questionnaire cycle, prediagnostic BMI (<20, 20–<22.5, 22.5–<25, 25.0–<30, 30–<35, ≥35 kg/m^2, missing), BMI change after diagnosis [no change (≥−0.5 to ≤0.5 kg/m^2), decrease (≤0.5 kg/m^2), increase (>0.5–2 kg/m^2), increase (>2 kg/m^2), missing], postdiagnostic smoking (never, past, current 1–14 cigarettes/day, current 15–24 cigarettes/day, current ≥25 cigarettes/day, missing), postdiagnostic physical activity (<5, 5–<11.5, 11.5–<22, ≥22 MET-h/week, missing), prediagnostic oral contraceptive use (ever, never), postdiagnostic alcohol consumption (<0.15, 0.15–<2.0, 2.0–7.5, ≥7.5 g/day), postdiagnostic total energy intake (quintiles, kcal/day), prediagnostic menopausal status, age at menopause, and postmenopausal hormone use (premenopausal, postmenopausal and age at menopause <50 years and never postmenopausal hormone use, postmenopausal and age at menopause <50 years and past postmenopausal hormone use, postmenopausal and age at menopause <50 years and current postmenopausal hormone use, postmenopausal and age at menopause ≥50 years and never postmenopausal hormone use, postmenopausal and age at menopause ≥50 years and past postmenopausal hormone use, postmenopausal and age at menopause ≥50 years and current postmenopausal hormone use, missing), postdiagnostic aspirin use (never, past, current, missing), race (non-Hispanic White, other), stage of disease (I, II, III), ER/PR status (ER/PR positive, ER positive and PR negative, ER/PR negative, missing), radiotherapy (yes, no, missing), chemotherapy (yes, no, missing), and hormonal treatment (yes, no, missing). Women with unknown menopausal status at time of diagnosis were considered premenopausal if they were younger than 46 years for smokers or 48 years for never smokers and were considered postmenopausal if they were older than 54 years for smokers or 56 years for never smokers (22). We replaced missing covariate data with the last value carried forward for continuous variables and missing indicators for categorical variables. To account for a potential role of prediagnostic dietary GI, GL, II, and IL in breast cancer survival, we additionally controlled for prediagnostic indices, calculated from the last FFQ reported before breast cancer diagnosis, in the multivariable models. We also evaluated associations after additionally adjusting for postdiagnostic total fruit and total vegetable intake, and fiber intake. We also performed competing risk analyses for causes of death: breast cancer–specific mortality versus CVD mortality as well as other causes of death using Fine–Gray method (23, 24).

In sensitivity analyses, we used left truncation time since diagnosis model due to variations between participants in the timing of returning their first FFQ after diagnosis. Furthermore, we did complete case method and excluded women with missing covariate information that comprised less than 1% of total person years for postdiagnostic smoking status and BMI before diagnosis, 1.4% for BMI after diagnosis, 7.0% for menopausal status, age at menopause, and postmenopausal hormone use before diagnosis, 5.8% for postdiagnostic aspirin use, 9.3% for postdiagnostic physical activity, 9.9% for ER/PR status, 10.2% for hormonal treatment, 11.6% for radiotherapy, and 12.6% for chemotherapy.

To examine potential effect modification, we evaluated the associations of GI, GL, II, and IL with breast cancer–specific and all-cause mortality among women based on tumor IR status (IR positive vs. IR negative) and ER status (ER positive vs. ER negative) as well as postdiagnostic BMI (<25 vs. ≥25 kg/m^2) and menopausal status at diagnosis (premenopausal vs. postmenopausal). The P value for interaction was calculated using Wald test, and all analyses were conducted using SAS software version 9.4 (SAS Institute) with a two-sided P value of 0.05.

Results

Among 8,932 eligible women diagnosed with breast cancer (8,621 non-Hispanic White and 311 other race/ethnicity), we documented 2,523 deaths (2,443 deaths among non-Hispanic White women and 80 deaths among other race/ethnicity populations), of which 1,071 were due to breast cancer, over a mean of 11.5 years of follow-up from returning first FFQ after diagnosis (up to 30 years of follow-up). On average, women reported 3.6 FFQs after diagnosis (range 1–8). Participants with higher dietary GL or IL tended to smoke less, drink less alcohol, consume less animal fat and protein, and take less aspirin. Participants with higher dietary GL or IL also were less likely to have used oral contraceptives and postmenopausal hormone before diagnosis. Women with higher dietary IL after diagnosis were younger at diagnosis and less likely to be physically active (**Table 1**).

After adjustment for potentially confounding variables, all-cause mortality was significantly higher among women with higher postdiagnostic dietary GI: $HR_{Q5vsQ1} = 1.23$; 95% CI = 1.08–1.40; $P_{trend} = 0.001$ (**Table 2**). However, postdiagnostic dietary GI was not significantly associated with higher risk of breast cancer–specific (**Table 2**) or CVD mortality (Supplementary Table S1).

Postdiagnostic dietary GL was positively associated with breast cancer–specific and all-cause mortality (**Table 2**). Comparing highest versus lowest quintile, GL was associated with a 33% higher breast cancer–specific mortality ($HR_{Q5vsQ1} = 1.33$; 95% CI = 1.09–1.63; $P_{trend} = 0.008$) and a 26% higher all-cause mortality ($HR_{Q5vsQ1} = 1.26$; 95% CI = 1.10–1.45; $P_{trend} = 0.0006$). The associations between GL and breast cancer–specific mortality remained significant after additional adjustment for prediagnostic GL ($HR_{Q5vsQ1} = 1.34$; 95% CI, 1.08–1.66; $P_{trend} = 0.01$), postdiagnostic fruit and vegetable intake ($HR_{Q5vsQ1} = 1.32$; 95% CI, 1.07–1.63, $P_{trend} = 0.01$), and postdiagnostic fiber intake ($HR_{Q5vsQ1} = 1.38$; 95% CI, 1.12–1.70, $P_{trend} = 0.004$). Similar results were observed for all-cause mortality. Postdiagnostic dietary GL was also associated with higher risk of CVD mortality, although this finding did not reach statistical significance (Supplementary Table S1). We found similar results using competing risk models.

Although neither II nor IL after diagnosis was significantly associated with breast cancer–specific mortality, they were associated

Table 1. Age and age-standardized characteristics of 8,932 women with breast cancer in the NHS and NHSII after breast cancer diagnosis, according to postdiagnostic energy-adjusted dietary GL and IL.

	GL					IL				
	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Number of participants	1,792	1,750	1,832	1,804	1,754	1,963	1,730	1,696	1,757	1,786
Mean										
Alcohol consumption, g/day	12.6	6.4	4.3	3.1	2.0	13.6	5.6	3.7	2.8	1.9
Animal fat intake, g/day	33	29	26	24	19	29	28	27	25	23
Total carbohydrate intake, g/day	163	196	213	231	260	174	201	214	228	249
Total protein intake, g/day	78	76	74	72	65	74	75	74	73	69
Total energy intake, kcal/day	1,688	1,754	1,766	1,701	1,677	1,680	1,731	1,760	1,717	1,693
Total fruit intake, servings/day	1.1	1.5	1.6	1.7	1.9	1.4	1.6	1.7	1.7	1.6
Total vegetable intake, servings/day	3.2	3.2	3.2	3.0	2.9	3.6	3.3	3.1	2.9	2.5
Whole grain intake, servings/day	0.7	1.0	1.1	1.2	1.3	0.9	1.0	1.1	1.1	1.2
Refined grain intake, servings/day	1.4	1.7	1.9	1.9	2.1	1.4	1.7	1.9	2.0	2.1
Total red and processed meat intake, servings/day	1.1	0.9	0.8	0.7	0.5	0.9	0.9	0.9	0.8	0.7
Age at diagnosis, years	58.8	59.1	58.9	58.9	57.8	60.1	59.7	59.0	58.4	56.1
BMI, kg/m^2	26.6	26.9	26.6	26.6	25.9	26.0	26.7	26.6	26.8	26.6
Physical activity, MET-hrs/week	18.0	16.9	18.0	17.8	18.0	19.6	18.0	16.8	16.7	17.2
%										
Race (non-Hispanic White)	97	97	96	97	95	96	97	96	97	97
Smoking status										
Never	37	45	48	51	54	37	44	49	53	54
Past	49	45	43	42	39	50	45	42	41	39
Current	14	10	9	7	7	13	11	9	6	7
Ever used oral contraceptives	61	57	58	56	54	62	57	56	54	56
Ever used postmenopausal hormone	48	48	49	48	46	49	48	48	47	47
Aspirin use										
Never	17	17	19	21	25	16	18	18	19	25
Past	33	35	35	36	35	35	33	36	38	34
Current	48	47	45	42	39	47	47	46	42	40
Missing	2	1	1	1	1	2	2	0	1	1
Menopausal status at diagnosis										
Premenopausal	26	26	27	26	26	26	27	26	26	26
Postmenopausal	69	68	68	68	68	69	67	69	68	68
Unknown	5	6	5	6	6	5	6	5	6	6
Stage of breast cancer										
I	61	58	62	59	61	61	59	60	59	60
II	29	31	28	31	30	29	31	30	30	30
III	10	11	10	10	9	10	10	10	11	10
ER status										
Positive	77	75	78	77	77	76	76	75	78	79
Negative	17	18	16	18	17	17	17	18	17	16
Missing	6	7	6	5	6	7	7	7	5	5
Treatment										
Radiotherapy	56	55	57	57	57	56	55	55	56	58
Chemotherapy	43	46	46	49	45	44	44	45	47	47
Hormonal treatment	68	67	71	70	71	68	68	65	70	73

with higher risk of all-cause mortality (HR_{Q5vsQ1} = 1.20; 95% CI = 1.04–1.38; P_{trend} = 0.005 and HR_{Q5vsQ1} = 1.23; 95% CI = 1.07–1.42; P_{trend} = 0.0003, respectively; **Table 2**). CVD mortality was also higher among women with higher dietary II and IL (Supplementary Table S1).

To better understand the observed associations with dietary GI/GL and II/IL, we examined the relation of nutrients contributing to these indices to survival (**Table 3**). Postdiagnostic total carbohydrate intake was associated with higher breast cancer–specific (HR_{Q5vsQ1} = 1.24; 95% CI = 1.01–1.52; P_{trend} = 0.06) and all-cause (HR_{Q5vsQ1} = 1.20; 95% CI = 1.04–1.38; P_{trend} = 0.009) mortality. Higher postdiagnostic total protein intake was associated with lower risk of breast cancer–specific (HR_{Q5vsQ1} = 0.68; 95% CI = 0.56–0.83; P_{trend} = 0.0002) and all-cause (HR_{Q5vsQ1} = 0.80; 95% CI = 0.70–0.91; P_{trend} = 0.0009) mortality, whereas postdiagnostic animal protein intake was associated with lower risk of breast cancer–specific mortality (HR_{Q5vsQ1} = 0.73; 95% CI = 0.60–0.89; P_{trend} = 0.001) and postdiagnostic vegetable protein intake was associated with lower risk of all-cause mortality (HR_{Q5vsQ1} = 0.86; 95% CI = 0.75–0.98; P_{trend} = 0.03). Postdiagnostic total fat and vegetable fat intakes were associated with lower risk of all-cause mortality (HR_{Q5vsQ1} = 0.85; 95% CI = 0.74–0.97; P_{trend} = 0.02 and HR_{Q5vsQ1} = 0.73; 95% CI = 0.63–0.84; P_{trend} < 0.0001, respectively). In addition, high intake of dietary fiber after diagnosis was associated with lower risk of all-cause mortality (HR_{Q5vsQ1} = 0.85; 95% CI = 0.75–0.97; P_{trend} = 0.004).

We did not observe significant differences in associations of GI, GL, II, and IL with mortality based on IR status (**Table 4**). Although trends

Table 2. Postdiagnostic energy-adjusted dietary GI, GL, II, and IL in relation to mortality after breast cancer diagnosis (n = 8,932 women) in the NHS and NHSII.

		Breast cancer–specific mortality			All-cause mortality		
Quintile	Median	Deaths (*N*)	Model 1	Model 2	Deaths (*N*)	Model 1	Model 2
Dietary GI							
1	48.1	178	1	1	395	1	1
2	50.7	193	1.01 (0.82–1.23)	1.00 (0.81–1.23)	475	1.12 (0.98–1.28)	1.09 (0.95–1.25)
3	52.4	215	1.09 (0.89–1.33)	1.21 (0.99–1.48)	518	1.18 (1.04–1.35)	1.20 (1.05–1.37)
4	54.0	228	1.14 (0.93–1.39)	1.14 (0.93–1.39)	541	1.22 (1.07–1.39)	1.17 (1.02–1.33)
5	56.2	257	1.32 (1.09–1.60)	1.16 (0.95–1.41)	594	1.39 (1.22–1.57)	1.23 (1.08–1.40)
P_{trend}			0.002	0.08		<0.0001	0.001
Dietary GL							
1	86.5	199	1	1	446	1	1
2	101.8	210	1.03 (0.84–1.25)	1.10 (0.90–1.34)	472	1.02 (0.89–1.16)	1.07 (0.94–1.22)
3	111.0	213	1.05 (0.86–1.27)	1.16 (0.95–1.42)	529	1.12 (0.99–1.27)	1.19 (1.04–1.35)
4	120.7	194	0.95 (0.78–1.16)	1.12 (0.91–1.38)	498	1.03 (0.90–1.17)	1.15 (1.00–1.31)
5	135.8	255	1.30 (1.07–1.56)	1.33 (1.09–1.63)	578	1.22 (1.08–1.38)	1.26 (1.10–1.45)
P_{trend}			0.02	0.008		0.002	0.0006
Dietary II							
1	35.6	198	1	1	399	1	1
2	40.2	218	1.00 (0.82–1.21)	0.92 (0.75–1.13)	471	1.08 (0.94–1.23)	1.07 (0.93–1.23)
3	42.8	206	0.92 (0.75–1.11)	0.95 (0.77–1.17)	492	1.07 (0.94–1.22)	1.10 (0.96–1.27)
4	45.2	228	1.00 (0.83–1.21)	1.03 (0.83–1.26)	554	1.15 (1.01–1.31)	1.19 (1.04–1.37)
5	48.7	221	0.97 (0.80–1.18)	0.99 (0.80–1.22)	607	1.15 (1.01–1.30)	1.20 (1.04–1.38)
P_{trend}			0.79	0.79		0.02	0.005
Dietary IL							
1	581	204	1	1	445	1	1
2	656	221	0.99 (0.82–1.20)	0.95 (0.78–1.16)	502	1.07 (0.94–1.22)	1.02 (0.89–1.16)
3	698	216	0.96 (0.79–1.17)	0.99 (0.81–1.21)	527	1.09 (0.96–1.24)	1.08 (0.95–1.24)
4	741	224	1.01 (0.83–1.22)	1.12 (0.91–1.37)	553	1.15 (1.02–1.31)	1.23 (1.08–1.41)
5	805	206	1.00 (0.82–1.23)	1.03 (0.83–1.28)	496	1.19 (1.04–1.35)	1.23 (1.07–1.42)
P_{trend}			0.92	0.41		0.004	0.0003

Note: Model 1 was stratified by cohort and adjusted for age at diagnosis (year) and calendar year of diagnosis. Model 2 was stratified by cohort and adjusted for age at diagnosis (year), calendar year of diagnosis, time between diagnosis and first FFQ (year), calendar year at start of follow-up of each-2-year questionnaire cycle, prediagnostic BMI (<20, 20–<22.5, 22.5–<25, 25.0–<30, 30–<35, ≥35 kg/m^2, missing), BMI change after diagnosis [no change (≥−0.5 to ≤0.5 kg/m^2), decrease (≤0.5 kg/m^2), increase (>0.5–2 kg/m^2), increase (>2 kg/m^2), missing], postdiagnostic smoking (never, past, current 1–14/day, current 15–24/day, current ≥25/day, missing), postdiagnostic physical activity (<5, 5–<11.5, 11.5–<22, ≥22 MET-h/week, missing), oral contraceptive use (ever, never), postdiagnostic alcohol consumption (<0.15, 0.15–<2.0, 2.0–7.5, ≥7.5 g/day), postdiagnostic total energy intake (quintiles, kcal/day), prediagnostic menopausal status, age at menopause, and postmenopausal hormone use (premenopausal, postmenopausal and age at menopause <50 years and never postmenopausal hormone use, postmenopausal and age at menopause <50 years and past postmenopausal hormone use, postmenopausal and age at menopause <50 years and current postmenopausal hormone use, postmenopausal and age at menopause ≥50 years and never postmenopausal hormone use, postmenopausal and age at menopause ≥50 years and past postmenopausal hormone use, postmenopausal and age at menopause ≥50 years and current postmenopausal hormone use, missing), postdiagnostic aspirin use (never, past, current, missing), race (non-Hispanic White, other), stage of disease (I, II, III), ER/PR status (ER/PR positive, ER positive and PR negative, ER/PR negative, missing), radiotherapy (yes, no, missing), chemotherapy (yes, no, missing), and hormonal treatment (yes, no, missing).

were not significant for ER-negative breast cancer and significant associations were observed between GL and a higher risk of breast cancer–specific mortality among women with ER-positive breast cancer, there was no significant interaction (**Table 4**).

Except higher risk of breast cancer–specific mortality among women with higher dietary GI before diagnosis, we did not observe significant associations of prediagnostic GL, II, and IL from last FFQ before diagnosis and breast cancer–specific or all-cause mortality (Supplementary Table S2). We also examined GI, GL, II, and IL from just the first FFQ after diagnosis. All associations were weaker but the positive association between high GI and all-cause mortality remained statistically significant (Supplementary Table S3).

We observed higher risk of breast cancer–specific mortality for GL and IL among women with BMI ≥25 kg/m^2. However, there were no significant interactions (Supplementary Table S4). In addition, we observed positive associations with breast cancer–specific mortality for postdiagnostic GI among postmenopausal women and for postdiagnostic GL among premenopausal women. However, there were no significant interactions (Supplementary Table S5).

In sensitivity analyses, we accounted for left truncation time since diagnosis. The findings were similar (Supplementary Table S6).

The findings from complete case methods are presented in Supplementary Table S7. They were similar to what was observed after replacing missing covariate data with using missing indicators for categorical variables.

Discussion

In this analysis combining two large prospective cohorts, higher dietary GL after breast cancer diagnosis was associated with a higher risk of breast cancer–specific mortality. As expected from previous findings among women without breast cancer (10), we also observed a

Table 3. Postdiagnostic energy-adjusted carbohydrate, protein, fat, and fiber intake in relation to mortality after breast cancer diagnosis (n = 8,932 women) in the NHS and NHSII.

		Breast cancer–specific mortality			All-cause mortality		
Quintile	Median g/day	Deaths (*N*)	Model 1	Model 2	Deaths (*N*)	Model 1	Model 2
Total carbohydrate							
1	171.2	207	1	1	467	1	1
2	196.8	234	1.12 (0.93–1.35)	1.17 (0.96–1.41)	510	1.08 (0.95–1.22)	1.10 (0.97–1.25)
3	212.7	183	0.90 (0.74–1.10)	1.02 (0.83–1.26)	484	1.02 (0.90–1.16)	1.13 (0.99–1.29)
4	228.8	209	1.02 (0.84–1.23)	1.17 (0.96–1.44)	525	1.06 (0.94–1.20)	1.16 (1.02–1.33)
5	252.8	238	1.20 (0.99–1.45)	1.24 (1.01–1.52)	537	1.12 (0.98–1.27)	1.20 (1.04–1.38)
P_{trend}			0.18	0.06		0.14	0.009
Total protein							
1	57.4	263	1	1	704	1	1
2	66.3	201	0.73 (0.61–0.88)	0.78 (0.65–0.94)	512	0.78 (0.70–0.88)	0.83 (0.73–0.93)
3	72.2	209	0.76 (0.63–0.91)	0.86 (0.71–1.03)	482	0.78 (0.69–0.88)	0.85 (0.76–0.96)
4	78.5	200	0.73 (0.61–0.88)	0.75 (0.62–0.91)	439	0.76 (0.67–0.86)	0.83 (0.73–0.94)
5	89.0	198	0.75 (0.62–0.91)	0.68 (0.56–0.83)	386	0.77 (0.67–0.87)	0.80 (0.70–0.91)
P_{trend}			0.006	0.0002		<0.0001	0.0009
Animal protein							
1	33.7	241	1	1	627	1	1
2	42.8	198	0.78 (0.65–0.94)	0.88 (0.72–1.06)	522	0.89 (0.80–1.00)	0.94 (0.83–1.06)
3	48.9	216	0.83 (0.69–1.00)	0.96 (0.79–1.16)	488	0.85 (0.76–0.96)	0.94 (0.83–1.06)
4	55.5	204	0.77 (0.64–0.94)	0.83 (0.68–1.00)	448	0.83 (0.74–0.94)	0.89 (0.79–1.01)
5	65.9	212	0.83 (0.68–1.00)	0.73 (0.60–0.89)	438	0.90 (0.79–1.02)	0.92 (0.80–1.04)
P_{trend}			0.07	0.001		0.03	0.12
Vegetable protein							
1	17.5	278	1	1	625	1	1
2	20.4	208	0.74 (0.62–0.89)	0.90 (0.75–1.08)	522	0.82 (0.73–0.92)	0.95 (0.84–1.07)
3	22.7	204	0.76 (0.64–0.91)	0.96 (0.80–1.16)	535	0.88 (0.78–0.99)	0.97 (0.87–1.10)
4	25.2	186	0.73 (0.60–0.88)	0.98 (0.81–1.20)	455	0.79 (0.70–0.89)	0.91 (0.81–1.04)
5	29.8	195	0.83 (0.69–1.01)	0.96 (0.78–1.17)	386	0.76 (0.66–0.86)	0.86 (0.75–0.98)
P_{trend}			0.06	0.87		<0.0001	0.03
Total fat							
1	41.0	219	1	1	576	1	1
2	49.0	210	0.98 (0.81–1.18)	0.97 (0.80–1.18)	555	1.07 (0.95–1.20)	1.02 (0.90–1.14)
3	54.7	226	1.07 (0.89–1.29)	1.08 (0.90–1.31)	526	1.09 (0.96–1.22)	1.05 (0.93–1.18)
4	60.9	217	1.06 (0.88–1.28)	1.02 (0.84–1.24)	484	1.10 (0.98–1.25)	0.97 (0.85–1.09)
5	70.5	199	1.10 (0.90–1.35)	0.94 (0.76–1.15)	382	1.06 (0.92–1.21)	0.85 (0.74–0.97)
P_{trend}			0.25	0.69		0.28	0.02
Animal fat							
1	15.6	192	1	1	488	1	1
2	21.4	192	0.97 (0.79–1.18)	0.92 (0.75–1.13)	495	1.07 (0.94–1.21)	0.99 (0.87–1.12)
3	25.7	194	0.95 (0.78–1.16)	0.87 (0.71–1.06)	488	1.07 (0.95–1.22)	0.99 (0.87–1.12)
4	30.0	224	1.08 (0.89–1.32)	0.96 (0.78–1.17)	531	1.23 (1.09–1.40)	1.05 (0.92–1.19)
5	37.0	269	1.28 (1.06–1.55)	0.95 (0.77–1.16)	521	1.27 (1.11–1.44)	1.03 (0.90–1.18)
P_{trend}			0.003	0.84		<0.0001	0.45
Vegetable fat							
1	18.2	247	1	1	604	1	1
2	23.6	241	1.01 (0.85–1.21)	1.15 (0.96–1.37)	580	1.03 (0.92–1.15)	1.00 (0.89–1.12)
3	27.9	218	0.97 (0.81–1.16)	1.12 (0.93–1.34)	521	1.00 (0.89–1.12)	0.97 (0.86–1.09)
4	32.8	210	0.99 (0.82–1.19)	1.20 (0.99–1.46)	476	0.98 (0.87–1.11)	0.97 (0.86–1.10)
5	42.0	155	0.83 (0.67–1.02)	0.87 (0.70–1.08)	342	0.83 (0.72–0.95)	0.73 (0.63–0.84)
P_{trend}			0.09	0.38		0.009	<0.0001
Total dietary fiber							
1	13.7	258	1	1	607	1	1
2	17.0	216	0.83 (0.70–1.00)	0.97 (0.80–1.16)	523	0.84 (0.75–0.94)	0.94 (0.84–1.06)
3	19.6	205	0.79 (0.66–0.95)	0.98 (0.81–1.19)	508	0.79 (0.71–0.89)	0.95 (0.84–1.07)
4	22.5	191	0.76 (0.63–0.92)	0.90 (0.74–1.10)	451	0.71 (0.63–0.80)	0.82 (0.72–0.93)
5	27.3	201	0.84 (0.69–1.01)	0.95 (0.78–1.16)	434	0.71 (0.63–0.81)	0.85 (0.75–0.97)
P_{trend}			0.05	0.52		<0.0001	0.004

higher risk of all-cause mortality with a diet high in GL after diagnosis. Higher postdiagnostic dietary GI, II, and IL was associated with higher risk of all-cause mortality. Higher risk of CVD mortality was also observed among women with higher dietary GI, GL, II, and IL after diagnosis; however, they did not reach statistical significance. Higher postdiagnostic intake of total carbohydrate was associated with a higher risk of breast cancer–specific and all-cause mortality and, as we have observed previously (25), higher postdiagnostic total protein intake was associated with a lower risk of breast cancer–specific and all-cause mortality. Higher dietary fiber intake after diagnosis was associated with lower risk of all-cause mortality. Prediagnostic dietary GI was associated with higher risk of breast cancer–specific mortality; however, we did not observe any significant associations of prediagnostic GL, II, and IL from last FFQ before diagnosis and breast cancer–specific or all-cause mortality.

High GI/GL diets increase postprandial blood glucose and insulin levels more than low GI/GL diets. Growing evidence suggests that hyperglycemia and hyperinsulinemia may adversely affect breast cancer prognosis (26–28). Elevated pretreatment insulin levels have been suggested as a poor prognostic predictor in nondiabetic women with breast cancer (2). Elevated HbA1C levels have also predicted higher mortality in breast cancer survivors (29). In contrast, fasting 13 or more hours per night was associated with a reduced risk of breast cancer recurrence (30). However, dietary GI and GL were not associated with breast cancer prognosis among 688 breast cancer survivors in the Healthy Eating Activity and Lifestyle (HEAL) study with 6.7 years of follow-up after diagnosis and $n = 106$ total deaths (11). Limitations of that analyses include that diet was assessed with a single questionnaire at baseline, a small number of women with breast cancer were included, and the follow-up was relatively short. The much larger number of women with breast cancer ($n = 8{,}932$) and deaths ($n = 2{,}523$) with repeated assessments of diet (up to eight) after diagnosis of breast cancer during up to 30 years of follow-up, this study provided much greater power to evaluate the effect of postdiagnostic diets on survival among women with breast cancer.

The role of dietary insulin scores in relation to progression of breast cancer has not been evaluated in other studies. In the NHSII, we did not observe significant associations between adolescent or early adulthood dietary II or IL and breast cancer risk (31). In this study, a diet high in IL and II after diagnosis was associated with poorer overall survival, but no associations were observed with breast cancer–specific mortality.

There are at least two general mechanisms that could account for the association with GL and breast cancer–specific mortality: (i) that higher glucose levels provide greater nutrition to tumors, which are usually nutritionally constrained due to their rapid growth and (ii) that higher glucose levels stimulate insulin secretion, and insulin itself is a growth factor. Our observation that GL but not IL was associated with higher breast cancer–specific mortality suggests that the first mechanism may be most important. Moreover, II and IL are complex variables: they are correlated with GI and GL because higher glycemic carbohydrates contribute to both, but II and IL also reflect insulinemic responses to fat and protein. If it is actually high glucose levels that stimulate tumors, then the noncarbohydrate insulinemic components of high II and IL diets could actually reduce glycemic responses. The inverse association seen with protein intake tend to support this mechanistic hypothesis.

Breast cancer survivors are also at greater risk for CVD because of common risk factors (32) as well as side effects of breast cancer adjuvant therapy (33–35), which may contribute to the long-term breast cancer prognosis. Given the higher CVD mortality with diets high in GI, GL, II, IL (although not quite statistically significant in this study), a diet low in GI, GL, II, and IL may be an important strategy to improve overall survival among women with breast cancer.

Advantages of this study include the prospective design, detailed and repeated prospective collection of pre- and postdiagnostic diet and lifestyle information, standardized medical record review of reported breast cancer, and long duration of follow-up. Moreover, the availability of detailed data on many established lifestyle factors in parallel with dietary intake assessment allowed comprehensive control for potential predictors of breast cancer survival.

The potential limitations of our study also need to be noted. Although we made efforts to rule out confounding effects from cancer prognostic and lifestyle factors, residual confounding is still possible due to the use of observational data. We were not able to control for receipt of full treatment course, which may contribute to cancer survival. Because it is a nonrandomized study, the possibility of early extension of disease/recurrence, might influence both risk of death and food choices. The study was limited to White educated women who might have better access to medical care services and high-quality nutrition than many others in the U.S. population. So, the findings may not be generalizable to other racial/ethnic groups. Women with higher GL tended to have healthier risk factor profiles, thus these adjustments had minimal impact on or tended to strengthen associations with glycemic indices. Furthermore, glucose and insulin responses to a food item are influenced by potential interactions among ingested foods as well as other factors such as cooking procedure, so the GI or II from individual food items may not predict insulin response to mixed meals. However, Bao and colleagues (36) have shown that II and GL of individual foods can capture insulin responses to mixed meals.

In conclusion, we found that higher dietary GL, but not GI, IL or II, after a breast cancer diagnosis was associated with greater breast cancer–specific mortality. In addition, diets higher in GI, GL, II, and IL after a breast cancer diagnosis were associated with greater death from any cause. Women with breast cancer may benefit from consuming a diet that reduces postprandial glucose response, which would involve limiting carbohydrates and emphasizing those that are less

Note: Model 1 was stratified by cohort and adjusted for age at diagnosis (year) and calendar year of diagnosis. Model 2 was stratified by cohort and adjusted for age at diagnosis (year), calendar year of diagnosis, time between diagnosis and first FFQ (year), calendar year at start of follow-up of each-2-year questionnaire cycle, prediagnostic BMI (<20, 20–<22.5, 22.5–<25, 25.0–<30, 30–<35, ≥35 kg/m^2, missing), BMI change after diagnosis [no change (≥−0.5 to ≤0.5 kg/m^2), decrease (≤0.5 kg/m^2), increase (>0.5–2 kg/m^2), increase (>2 kg/m^2), missing], postdiagnostic smoking (never, past, current 1–14/day, current 15–24/day, current ≥25/day, missing), postdiagnostic physical activity (<5, 5–<11.5, 11.5–<22, ≥22 MET-h/week, missing), oral contraceptive use (ever, never), postdiagnostic alcohol consumption (<0.15, 0.15–<2.0, 2.0–7.5, ≥7.5 g/day), postdiagnostic total energy intake (quintiles, kcal/day), prediagnostic menopausal status, age at menopause, and postmenopausal hormone use (premenopausal, postmenopausal and age at menopause <50 years and never postmenopausal hormone use, postmenopausal and age at menopause <50 years and past postmenopausal hormone use, postmenopausal and age at menopause <50 years and current postmenopausal hormone use, postmenopausal and age at menopause ≥50 years and never postmenopausal hormone use, postmenopausal and age at menopause ≥50 years and past postmenopausal hormone use, postmenopausal and age at menopause ≥50 years and current postmenopausal hormone use, missing), postdiagnostic aspirin use (never, past, current, missing), race (non-Hispanic White, other), stage of disease (I, II, III), ER/PR status (ER/PR positive, ER positive and PR negative, ER/PR negative, missing), radiotherapy (yes, no, missing), chemotherapy (yes, no, missing), and hormonal treatment (yes, no, missing).

Table 4. Postdiagnostic energy-adjusted dietary GI, GL, II, and IL in relation to breast cancer–specific mortality after breast cancer diagnosis in the NHS and NHSII, stratified by IR (n = 2,501 women, n = 392 breast cancer deaths) and ER status (n = 8,384 women, n = 982 breast cancer deaths).

		IR status				ER status			
Quintile	Median	Deaths (*N*)	IR positive	Deaths (*N*)	IR negative	Deaths (*N*)	ER positive	Deaths (*N*)	ER negative
Dietary GI									
1	48.1	25	1	39	1	134	1	32	1
2	50.7	31	1.09 (0.63–1.89)	32	0.49 (0.30–0.79)	141	1.01 (0.79–1.28)	35	1.22 (0.74–2.02)
3	52.4	45	1.46 (0.87–2.46)	47	0.81 (0.52–1.25)	154	1.21 (0.95–1.53)	44	1.44 (0.89–2.33)
4	54.0	38	0.99 (0.58–1.69)	47	0.67 (0.43–1.04)	160	1.19 (0.94–1.51)	47	1.08 (0.66–1.74)
5	56.2	38	1.03 (0.60–1.76)	50	0.68 (0.43–1.05)	180	1.18 (0.93–1.48)	55	1.19 (0.75–1.90)
P_{trend}			0.84		0.33		0.08		0.69
$P_{interaction}$			0.49				0.65		
Dietary GL									
1	86.5	38	1	49	1	148	1	40	1
2	101.8	37	1.02 (0.64–1.63)	44	0.89 (0.58–1.37)	141	1.01 (0.80–1.28)	48	1.15 (0.75–1.78)
3	111.0	35	0.99 (0.61–1.62)	37	0.84 (0.52–1.33)	166	1.29 (1.02–1.63)	31	0.78 (0.48–1.27)
4	120.7	30	1.04 (0.61–1.76)	43	0.90 (0.57–1.42)	140	1.14 (0.89–1.45)	40	1.07 (0.67–1.71)
5	135.8	37	0.90 (0.54–1.50)	42	1.24 (0.78–1.99)	174	1.29 (1.01–1.63)	54	1.27 (0.81–2.00)
P_{trend}			0.71		0.43		0.03		0.38
$P_{interaction}$			0.13				0.79		
Dietary II									
1	35.6	34	1	39	1	148	1	35	1
2	40.2	33	0.71 (0.43–1.19)	45	0.69 (0.44–1.08)	168	0.97 (0.77–1.22)	37	0.87 (0.53–1.44)
3	42.8	29	0.58 (0.34–1.01)	36	0.56 (0.34–0.93)	136	0.84 (0.65–1.08)	49	1.16 (0.71–1.88)
4	45.2	40	0.93 (0.56–1.56)	49	0.73 (0.45–1.18)	163	0.99 (0.78–1.26)	48	1.06 (0.64–1.74)
5	48.7	41	0.76 (0.44–1.31)	46	0.76 (0.47–1.25)	154	0.93 (0.72–1.19)	44	1.12 (0.68–1.85)
P_{trend}			0.61		0.43		0.62		0.49
$P_{interaction}$			0.33				0.38		
Dietary IL									
1	581	41	1	47	1	150	1	38	1
2	656	37	0.74 (0.46–1.18)	45	0.65 (0.42–1.00)	163	0.98 (0.77–1.23)	37	0.76 (0.47–1.22)
3	698	32	0.61 (0.36–1.02)	49	0.77 (0.50–1.21)	152	0.93 (0.73–1.17)	49	1.10 (0.70–1.75)
4	741	38	0.97 (0.59–1.59)	44	0.81 (0.51–1.29)	163	1.15 (0.90–1.46)	45	1.03 (0.65–1.65)
5	805	29	0.74 (0.42–1.29)	30	0.84 (0.50–1.40)	141	0.96 (0.74–1.25)	44	1.06 (0.65–1.73)
P_{trend}			0.51		0.66		0.84		0.52
$P_{interaction}$			0.25				0.24		

Note: Models were stratified by cohort and adjusted for age at diagnosis (year), calendar year of diagnosis, time between diagnosis and first FFQ (year), calendar year at start of follow-up of each-2-year questionnaire cycle, prediagnostic BMI (<20, 20–<22.5, 22.5–<25, 25.0–<30, 30–<35, ≥35 kg/m^2, missing), BMI change after diagnosis [no change (≥−0.5 to ≤0.5 kg/m^2), decrease (≤0.5 kg/m^2), increase (>0.5–2 kg/m^2), increase (>2 kg/m^2), missing], postdiagnostic smoking (never, past, current 1–14/day, current 15–24/day, current ≥25/day, missing), postdiagnostic physical activity (<5, 5–<11.5, 11.5–<22, ≥22 MET-h/week, missing), oral contraceptive use (ever, never), postdiagnostic alcohol consumption (<0.15, 0.15–<2.0, 2.0–7.5, ≥7.5 g/day), postdiagnostic total energy intake (quintiles, kcal/day), prediagnostic menopausal status, age at menopause, and postmenopausal hormone use (premenopausal, postmenopausal and age at menopause <50 years and never postmenopausal hormone use, postmenopausal and age at menopause <50 years and past postmenopausal hormone use, postmenopausal and age at menopause <50 years and current postmenopausal hormone use, postmenopausal and age at menopause ≥50 years and never postmenopausal hormone use, postmenopausal and age at menopause ≥50 years and past postmenopausal hormone use, postmenopausal and age at menopause ≥50 years and current postmenopausal hormone use, missing), postdiagnostic aspirin use (never, past, current, missing), race (non-Hispanic White, other), stage of disease (I, II, III), ER/PR status (ER/PR positive, ER positive and PR negative, ER/PR negative, missing), radiotherapy (yes, no, missing), chemotherapy (yes, no, missing), and hormonal treatment (yes, no, missing). In ER status analysis, we did not adjust for ER/PR status.

rapidly digested such as whole grains, non-starchy vegetables, nuts, and legumes.

Authors' Disclosures

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Disclaimer

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Authors' Contributions

M.S. Farvid: Conceptualization, formal analysis, visualization, methodology, writing–original draft, writing–review and editing. **R.M. Tamimi:** Conceptualization, resources, data curation, funding acquisition, methodology, writing–review and editing. **E.M. Poole:** Methodology, writing–review and editing. **W.Y. Chen:** Conceptualization, methodology, writing–review and editing. **B.A. Rosner:** Conceptualization, validation, methodology, writing–review and editing. **W.C. Willett:** Conceptualization, resources, data curation, funding acquisition, investigation,

methodology, writing–review and editing. **M.D. Holmes:** Conceptualization, supervision, methodology, writing–review and editing. **A.H. Eliassen:** Conceptualization, resources, data curation, supervision, funding acquisition, investigation, methodology, writing–review and editing.

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