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Original Contribution

Low-Carbohydrate Diets, Dietary Approaches to Stop Hypertension-Style Diets, and the Risk of Postmenopausal Breast Cancer

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The authors prospectively examined the association between the Dietary Approaches to Stop Hypertension diet score, overall, animal-based, and vegetable-based low-carbohydrate-diet scores, and major plant food groups and the risk of postmenopausal breast cancer in 86,621 women in the Nurses' Health Study. Diet scores were calculated by using data from up to 7 food frequency questionnaires, with follow-up from 1980 to 2006. The authors ascertained 5,522 incident cases of breast cancer, including 3,314 estrogen receptor-positive (ER+) cancers and 826 estrogen receptor-negative (ER−) cancers. After adjustment for potential confounders, the Dietary Approaches to Stop Hypertension diet score was associated with a lower risk of ER− cancer (relative risk comparing extreme quintiles = 0.80, 95% confidence interval: 0.64, 1.01; *P* trend = 0.02). However, this was largely explained by higher intakes of fruits and vegetables. The authors also observed an inverse association between risk of ER− cancer and the vegetable-based, low-carbohydrate-diet score (corresponding relative risk = 0.81, 95% confidence interval: 0.65, 1.01; *P* trend = 0.03). High total fruit and low-protein vegetable intakes were associated with a lower risk of ER− cancer (relative risk comparing extreme quintiles = 0.71, 95% confidence interval: 0.55, 0.90; *P* trend = 0.005). No association was found between ER+ tumors and fruit and vegetable intakes. A diet high in fruits and vegetables, such as one represented by the Dietary Approaches to Stop Hypertension diet score, was associated with a lower risk of ER− breast cancer. In addition, a diet high in plant protein and fat and moderate in carbohydrate content was associated with a lower risk of ER− cancer.

breast neoplasms; diet; nutrition assessment

Abbreviations: CI, confidence interval; DASH, Dietary Approaches to Stop Hypertension; ER, estrogen receptor; ER−, estrogen receptor-negative; ER+, estrogen receptor-positive; FFQ, food frequency questionnaire; PR−, progesterone receptor-negative; PR+, progesterone receptor-positive; RR, relative risk.

Recent data on the use of whole-diet approaches to evaluate the association between diet and breast cancer risk have suggested that adherence to a prudent or healthy eating pattern reduced the risk (1, 2). Such patterns are usually characterized by high intakes of fruits, vegetables, whole grains, and lean meats. However, patterns are identified a posteriori and only reflect existing eating patterns in the population. Using preestablished diet quality scores, we have previously shown that several diets that emphasized plant foods were associated with a lower risk of estrogen receptor-negative (ER−) postmenopausal breast cancer (3). Although we additionally observed an inverse association between combined intake of vegetables and legumes and ER− tumors, results for fruit and vegetable intakes from other studies were less consistent; however, many of those studies did not conduct separate analyses by the estrogen receptor status of the tumors (4).

The Dietary Approaches to Stop Hypertension (DASH) diet emphasizes the intake of plant foods and is promoted by the US Department of Agriculture as a healthy eating pattern for the general public (5). This diet encourages the eating of plant proteins, fruits and vegetables, and a moderate amount of low-fat dairy products and limiting sugary foods and sodium. Dietary scores that reflect adherence to a DASH-style diet have been linked to a lower risk of colorectal cancer (6, 7). However, this score has not been evaluated in relation to breast cancer risk.

On the other hand, breast cancer development may, like colon cancer, also be mediated by the mitotic effect of insulin and insulin-like growth factors (8). Low-carbohydrate diets might have a low glycemic load, but they can vary greatly because they can be either plant-based or animal-based. Their potential to influence breast cancer development also has not been evaluated.

In the present analysis, we prospectively examined the association among the DASH score, low-carbohydrate diets (overall, animal-based, and plant-based), and the risk of postmenopausal breast cancer in a large ongoing cohort. In addition, we explored the association between major plant food-group contributors to these diets and their associations with breast cancer. Because we have previously noted differences in association when stratifying by estrogen receptor status (3), we also separately analyzed estrogen receptor-positive (ER+) tumors and ER− tumors.

MATERIALS AND METHODS

Study population

The Nurses' Health Study is a cohort study established in 1976 that consists of 121,700 female nurses who were aged 30–55 years and living in 11 US states at the time of study entry (9). Questionnaires are sent biennially to collect medical, lifestyle, and other health-related information. In 1980, participants completed a 61-item food frequency questionnaire (FFQ). This questionnaire was expanded to include 116 items in 1984, and similar FFQs were sent in 1986, 1990, 1994, 1998, and 2002.

For the present analysis, we used 1980 as the baseline when the first dietary data were collected. We included women who completed the 1980 FFQ with fewer than 10 missing items and who had plausible total energy intakes (calculated from the FFQ; between 500 kcal/day and 3,500 kcal/day) (10). After excluding those with a history of cancer ($n = 3{,}101$) (except nonmelanoma skin cancer), we included 86,620 women for whom we had follow-up data from 1980 through 2006. This study was approved by the institutional review board of the Brigham and Women's Hospital, Boston, Massachusetts.

Dietary assessment

Self-administered semiquantitative FFQs were designed to assess participants' average food intakes over the preceding year. A standard portion size and 9 possible consumption frequency categories, from "never or <1/month" to "6+ times per day," were given for each food. Total energy and nutrient intakes were calculated by summing up data from all foods. Previous validation studies revealed reasonably good correlations between energy-adjusted nutrients assessed by the FFQ and multiple food records completed over the preceding year (10).

The computation of low-carbohydrate-diet scores has been previously described in detail (11). Briefly, percentages of energy from fat, protein, and carbohydrates were divided evenly into 11 categories according to percentiles. For fat and protein, participants in the highest category received 10 points for that macronutrient, participants in the next category received 9 points, and so forth. For carbohydrates, the lowest intake category received 10 points and the highest received zero points. We summed the fat, protein, and carbohydrate scores to create the overall low-carbohydrate-diet score, which ranged from 0 to 30. In addition, we also created a vegetable low-carbohydrate-diet score, which was based on the percent of energy from carbohydrates, vegetable protein, and vegetable fat, and an animal low-carbohydrate-diet score, which was based on the percent of energy from carbohydrates, animal protein, and animal fat. Thus, each participant was given overall, animal, and vegetable scores.

The DASH score has previously been described in detail (12). Briefly, it consists of 8 components featured in the DASH diet (13): high intakes of fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains and low intakes of sodium, sweetened beverages, and red and processed meats. For each component, we classified women into quintiles according to their intake ranking. Component scores for fruits, vegetables, nuts and legumes, low-fat dairy products, and whole grains were used to determine the women's quintile rankings. For example, those whose intakes were in quintile 1 were assigned 1 point and those whose intakes were in quintile 5 were assigned 5 points. For sodium, red and processed meats, and sweetened beverages, low intakes were desired. Therefore, those in the lowest quintile were given a score of 5 points and those in the highest quintile were given a score of 1 point. We then summed up the component scores to obtain an overall DASH score, ranging from 8 to 40.

Case ascertainment

When a participant self-reported a breast cancer diagnosis in a biennial questionnaire, we contacted her for permission to obtain and review pathology records to confirm the diagnosis and obtain staging, hormone receptor status, and other relevant information. We only included incidents of invasive breast cancer in the present study. Deaths were reported by the postal service, family members, or the National Death Index. In the present study, we included only postmenopausal breast cancer cases to reduce the number of potential differences in etiology.

Covariate assessment

Body mass index was calculated from weight reported on each biennial questionnaire and height reported on the first questionnaire. Smoking status and average number of cigarettes smoked, regular intake of a multivitamin, history of benign breast disease, menopausal status, and use of postmenopausal hormone therapy were assessed every 2 years. Data on parity and age at first birth were collected several times during follow-up. Data on hours per week of vigorous activities were collected in 1980, 1982, and 1984. Leisure-time physical activity level was measured 7 times, beginning in 1986, by using validated questions about 10

Table 1. Age-Standardized Baseline (1980) Characteristics and 1994 Dietary Intake, by Quintile of Low-Carbohydrate-Diet Score, Nurses' Health Study, 1980–2006

Characteristic	Overall Diet Score			Animal-Based Diet Score			Vegetable-Based Diet Score		
	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5	Quintile 1	Quintile 3	Quintile 5
Body mass index[a]	24.1	24.5	24.9	24.1	24.5	24.9	24.7	24.5	24.2
Current smoking, %	28	28	32	27	28	32	30	28	30
Physical activity level, hours/week	3.0	3.1	2.9	3.0	3.1	2.9	3.0	3.0	3.0
Postmenopausal hormone use, %	9.9	10.6	11.3	9.6	10.5	11.7	11.4	10.4	10.4
Family history of breast cancer, %	6.1	6.4	6.3	6.3	6.6	6.3	6.0	6.3	6.5
Energy intake, kcal	1,443	1,725	2,082	1,751	1,745	1,682	1,715	1,737	1,767
Alcohol intake, g	3	6	6	3	6	5	3	5	6
Carbohydrate intake, % of energy intake	63.4	52.2	43.8	63.6	52.7	43.1	59.1	52.9	47.9
Animal protein intake, % of energy intake	10.8	13.2	14.7	9.3	13.1	16.7	13.6	13.2	11.9
Vegetable protein intake, % of energy intake	6.2	5.4	4.8	6.5	5.4	4.6	4.9	5.5	6.0
Animal fat intake, % of energy intake	10.4	15.7	20.9	9.4	15.3	22.4	14.7	15.9	15.3
Vegetable fat intake, % of energy intake	11.1	13.5	15.4	13.3	13.7	12.5	8.9	12.8	18.9
Saturated fat intake[b], g	12	17	22	12	17	22	15	17	18
Monounsaturated fat intake[b], g	15	20	25	16	20	24	16	20	25
Polyunsaturated fat intake[b], g	7	9	11	8	9	10	7	9	11
Trans fat intake[b], g	1.8	2.4	2.7	2.0	2.3	2.6	1.8	2.4	2.7
Fiber intake[b], g	23	19	16	24	19	16	19	19	19
Glycemic load[b]	136	109	90	137	110	88	125	111	100
Fruit, servings/day	2.9	2.4	2.1	3.4	2.4	1.7	3.1	2.5	1.9
Low-protein vegetables[c], servings/day	3.3	3.5	3.7	3.9	3.5	3.1	3.2	3.6	3.8

[a] Weight (kg)/height (m)^2.

[b] Data were energy adjusted using the residual method of Willett (10).

[c] Does not include legumes or nuts.

common activities. The numbers were then summed and used to calculate metabolic equivalent hours (14). Height data were collected at baseline. We also obtained weight at age 18 years during follow-up. Data on family history of breast cancer were collected several times during follow-up.

Statistical analysis

We used Cox proportional hazard models to assess the association among the DASH score, the 3 low-carbohydrate-diet scores, and the risk of postmenopausal breast cancer during follow-up. Person-years of follow-up were counted from the age in months at the return date of the baseline questionnaire until the age in months at the date of diagnosis of breast cancer, age at date of death, or age at end of follow-up, whichever came first. In addition, we separately analyzed data on ER+ and ER− tumors. We did not stratify by progesterone receptor status because we did not observe substantial differences in results. Women were categorized into quintiles of low-carbohydrate-diet scores or DASH diet score. To reduce random within-person variation and to best represent long-term dietary intake, we calculated cumulative averages of the diet scores from our repeated FFQs (15). For example, the diet score in 1980 was used to predict breast cancer incidence between 1980 and 1984, the average score from 1980 to 1984 was used to predict incidence from 1984 to 1986, and so forth, with cumulative dietary information used for the entire follow-up duration.

In multivariate analyses, we adjusted for age (continuous), physical activity level (quintiles), body mass index (5 categories), energy intake (quintiles), alcohol intake (4 categories), smoking (5 categories), multivitamin use (yes vs. no), family history of breast cancer (yes vs. no), history of benign breast disease (yes vs. no), weight change since 18 years of age (7 categories), and menopausal status and use of postmenopausal hormone replacement therapy (14 categories), with updated information at each 2-year questionnaire cycle. We also adjusted for adult height (4 categories) and body mass index at 18 years of age (4 categories).

In addition, we explored the association between the major categories of plant foods and the incidence of ER− tumors.

Table 2. Age-Standardized Baseline Characteristics and 1994 Dietary Intake, by Quintile of Dietary Approaches to Stop Hypertension Score, Nurses' Health Study, 1980–2006

Characteristic	Quintile 1	Quintile 2	Quintile 3	Quintile 4	Quintile 5
Body mass index[a]	24.6	24.6	24.5	24.5	24.2
Current smoking, %	40	34	29	25	20
Physical activity, hours/week	2.6	2.8	3.0	3.1	3.4
Postmenopausal hormone use, %	9.1	10.3	10.6	11.2	11.2
Family history of breast cancer, %	5.6	6.2	6.4	6.8	6.5
Energy intake, kcal	1,665	1,661	1,723	1,783	1,827
Alcohol intake, g	5	5	5	5	4
Carbohydrate intake, % of energy intake	48.6	50.5	52.8	54.6	58.2
Animal protein intake, % of energy intake	13.1	13.1	13.1	13.1	12.6
Vegetable protein intake, % of energy intake	4.6	5.1	5.5	5.7	6.3
Animal fat intake, % of energy intake	19.6	17.4	15.6	14.2	11.6
Vegetable fat intake, % of energy intake	13.6	13.7	13.4	13.1	12.8
Saturated fat intake[b], g	21	19	17	16	13
Monounsaturated fat intake[b], g	23	22	20	19	17
Polyunsaturated fat intake[b], g	10	9	9	9	8
Trans fat intake[b], g	3.0	2.7	2.3	2.1	1.7
Fiber intake[b], g	14	17	19	21	25
Glycemic load[b]	105	107	111	114	120
Fruit, servings/day	1.4	1.9	2.4	2.9	3.5
Low-protein vegetables[c], servings/day	2.2	2.8	3.4	4.0	4.9

[a] Weight (kg)/height (m)^2.
[b] Data were energy adjusted using the residual method of Willett (10).
[c] Does not include legumes or nuts.

Because we have previously reported results on the vegetable component of the Alternate Healthy Eating Score (combined intake of vegetables and legumes) (3), we separated the vegetable category into low-protein vegetables (i.e., excluding beans and peas) and legumes (beans and peas). In that analysis, we also examined intakes of total fruits, nuts, and whole grains. Because intake of whole grains was not measured in the 1980 FFQ, we used the follow-up duration of 1984–2006 for this item. Statistical analysis was conducted using SAS, version 9.1 (SAS Institute, Inc., Cary, North Carolina). All *P* values are 2-sided.

RESULTS

During 26 years of follow-up, we ascertained 5,522 incident cases of postmenopausal breast cancer. Of these, 3,314 were ER+ tumors, 826 were ER− tumors, and 1,382 were not classified. At baseline, women with a higher overall and animal low-carbohydrate-diet scores tended to have higher body mass indexes and were more likely to be smokers (Table 1). On the other hand, women with higher vegetable low-carbohydrate-diet scores or DASH scores tended to be leaner (Tables 1 and 2). In addition, those with higher DASH scores were less likely to be smokers and were more likely to have higher levels of physical activity. Because of the long follow-up period, we presented dietary intake information in 1994, as that reflects intake at approximately the midpoint of the follow-up period. Higher alcohol intake was observed among women with higher low-carbohydrate-diet scores. However, the difference in the percent of energy from carbohydrates and glycemic load was less pronounced between extreme quintiles of the vegetable low-carbohydrate-diet score than other 2 low-carbohydrate-diet scores. Women with higher DASH scores consumed more energy, with a large portion of the energy intake from carbohydrates, fruits, and vegetables and less energy from animal fat or protein.

After adjustment for potential confounders, neither the low-carbohydrate-diet scores (Table 3) nor the DASH scores (Table 4) were associated with overall incidence of breast cancer or ER+ breast cancer. This was true even if we stratified by ER+/progesterone receptor-positive (PR+) tumors and ER+/progesterone receptor-negative (PR−) tumors (data not shown). However, for ER− tumors, an inverse association was observed for both the vegetable low-carbohydrate-diet score (relative risk (RR) comparing the fifth quintile with the first quintile = 0.81, 95% confidence interval (CI): 0.65, 1.01; *P* trend = 0.03) and the DASH score (RR comparing extreme quintiles = 0.80, 95% CI: 0.64, 1.01; *P* trend = 0.02). We then further stratified by ER− tumors by progesterone receptor status. Comparing

Table 3. Relative Risk of Incident Breast Cancer, by Quintile of Low-Carbohydrate-Diet Score, Nurses' Health Study, 1980–2006

Type of Cancer	Quintile 1	Quintile 2	95% CI	Quintile 3	95% CI	Quintile 4	95% CI	Quintile 5	95% CI	*P* Trend
Total breast cancer										
Overall low-carbohydrate-diet score										
No. of cases	1,078	1,155		1,126		1,105		1,058		
Age- and energy-adjusted analyses	1	1.05	0.96, 1.14	1.05	0.97, 1.14	1.02	0.94, 1.11	1.06	0.97, 1.15	0.32
Multivariate analysis[a]	1	1.02	0.93, 1.11	1.01	0.93, 1.10	0.98	0.90, 1.06	1.02	0.93, 1.11	0.92
Animal low-carbohydrate-diet score										
No. of cases	1,084	1,157		1,083		1,110		1,088		
Age- and energy-adjusted analyses	1	1.08	1.00, 1.18	1.03	0.94, 1.12	1.05	0.97, 1.14	1.08	0.99, 1.18	0.16
Multivariate analysis[a]	1	1.04	0.96, 1.13	0.97	0.89, 1.05	0.98	0.90, 1.07	1.02	0.94, 1.11	0.91
Vegetable low-carbohydrate-diet score										
No. of cases	1,112	1,116		1,124		1,078		1,092		
Age- and energy-adjusted analyses	1	0.99	0.91, 1.08	0.99	0.91, 1.08	0.98	0.90, 1.06	1.00	0.92, 1.09	0.88
Multivariate analysis[a]	1	0.96	0.88, 1.04	0.95	0.87, 1.03	0.93	0.85, 1.01	0.95	0.87, 1.03	0.16
Estrogen receptor-positive tumors										
Overall low-carbohydrate-diet score										
No. of cases	633	687		670		705		623		
Age- and energy-adjusted analyses	1	1.06	0.95, 1.18	1.06	0.95, 1.19	1.11	1.00, 1.24	1.05	0.94, 1.18	0.15
Multivariate analysis[a]	1	1.01	0.90, 1.12	1.01	0.90, 1.12	1.04	0.93, 1.16	1.01	0.90, 1.13	0.61
Animal low-carbohydrate-diet score										
No. of cases	615	698		667		695		643		
Age- and energy-adjusted analyses	1	1.15	1.03, 1.28	1.11	1.00, 1.24	1.16	1.04, 1.29	1.13	1.01, 1.26	0.06
Multivariate analysis[a]	1	1.08	0.97, 1.20	1.02	0.92, 1.14	1.05	0.94, 1.18	1.05	0.93, 1.17	0.78
Vegetable low-carbohydrate-diet score										
No. of cases	655	669		671		637		686		
Age- and energy-adjusted analyses	1	1.00	0.90, 1.12	1.00	0.90, 1.12	0.98	0.88, 1.09	1.07	0.96, 1.19	0.47
Multivariate analysis[a]	1	0.95	0.85, 1.06	0.94	0.84, 1.05	0.91	0.81, 1.01	0.99	0.89, 1.10	0.47
Estrogen receptor-negative tumors										
Overall low-carbohydrate-diet score										
No. of cases	161	173		176		160		157		
Age- and energy-adjusted analyses	1	1.06	0.86, 1.32	1.10	0.89, 1.37	1.00	0.80, 1.24	1.06	0.85, 1.32	0.77
Multivariate analysis[a]	1	1.04	0.84, 1.29	1.08	0.87, 1.34	0.97	0.78, 1.21	1.06	0.85, 1.33	0.73
Animal low-carbohydrate-diet score										
No. of cases	167	181		145		162		172		
Age- and energy-adjusted analyses	1	1.11	0.90, 1.37	0.90	0.72, 1.13	1.01	0.81, 1.25	1.12	0.90, 1.39	0.75
Multivariate analysis[a]	1	1.09	0.88, 1.35	0.89	0.71, 1.11	0.99	0.79, 1.23	1.13	0.91, 1.41	0.75

Vegetable low-carbohydrate-diet score										
No. of cases	172	171		176		166		142		
Age- and energy-adjusted analyses	1	1.00	0.81, 1.24	0.99	0.80, 1.22	0.99	0.79, 1.22	0.83	0.67, 1.04	0.06
Multivariate analysis[a]	1	0.98	0.79, 1.21	0.96	0.77, 1.18	0.94	0.76, 1.17	0.81	0.65, 1.01	0.03

Abbreviation: CI, confidence interval.

[a] Adjusted for age, energy intake, multivitamin use, smoking, body mass index, height, weight at 18 years of age, weight change since 18 years of age, family history of breast cancer, benign breast disease, physical activity level, alcohol intake, and menopausal hormone use.

extreme quintiles of the DASH score for ER−/PR− tumors (698 cases), we found that the relative risk was 0.83 (95% CI: 0.65, 1.07; *P* trend = 0.11) and the corresponding comparison for the vegetable low-carbohydrate-diet score yielded a relative risk of 0.83 (95% CI: 0.65, 1.06; *P* trend = 0.06). For ER−/PR+ tumors (94 cases), the relative risk comparing extreme quintiles of DASH score was 0.65 (95% CI: 0.31, 1.37; *P* trend = 0.14), and the same comparison for the vegetable low-carbohydrate-diet score yielded a relative risk of 0.88 (95% CI: 0.44, 1.76; *P* trend = 0.68).

Among plant food categories, we observed a significant inverse association between fruit intake and low-protein vegetable intake and ER− tumors when comparing those in the fifth quintile with those in the first (RR = 0.71, 95% CI: 0.55, 0.92; *P* trend = 0.01 and RR = 0.76, 95% CI: 0.60, 0.95; *P* trend = 0.048, respectively) (Table 5). When these 2 categories were combined, the relative risk of ER− tumors was 0.71 (95% CI: 0.55, 0.90; *P* trend = 0.005) when comparing the extreme quintiles. When we added nuts and legumes to the combination (i.e., nongrain plant foods), the relative risk did not improve appreciably. A major difference between the DASH score and the vegetable low-carbohydrate-diet score is the dairy component in the DASH score. No association was observed between intakes of all dairy, low-fat dairy, or high-fat dairy and ER+ breast cancer or ER− breast cancer.

When we included nongrain plant foods into the regression model with the DASH score, the inverse association with ER− tumors was attenuated and no longer statistically significant. However, when we included nongrain plant foods into the regression model with the vegetable low-carbohydrate score, the inverse association for the vegetable score was essentially unchanged (data not shown). Separate analyses focusing on components of the vegetable low-carbohydrate score showed that none of the components was associated with ER− tumors on their own (data not shown).

DISCUSSION

In up to 26 years of follow-up, we observed a significant inverse association between a high DASH score or high vegetable low-carbohydrate-diet score and the risk of ER− breast cancer but not of ER+ cancer. We broadened our approach in the present analysis to examine plant groups, as they contribute up to 50% of the points in the DASH score, and we noted a lower risk of ER− tumors with higher intakes of fruits and vegetables. The limited influence of estrogen on the development of ER− tumors or differences in etiology might allow for easier detection of predictors (16).

Studies that used statistical procedures to identify existing dietary patterns suggested a small reduction in overall breast cancer risk with greater consumption of plant foods, moderate consumption of lean animal protein, and low consumption of red and processed meats and refined grains (1). We have previously noted a lower risk of ER− breast cancer in women with higher Alternate Healthy Eating scores, Recommended Food scores, and Alternate Mediterranean

Table 4. Relative Risk of Incident Breast Cancer, by Quintile of Dietary Approaches to Stop Hypertension Score, Nurses' Health Study, 1980–2006

Type of Cancer	Quintile 1	Quintile 2	95% CI	Quintile 3	95% CI	Quintile 4	95% CI	Quintile 5	95% CI	*P* Trend
Total breast cancer										
No. of cases	975	1,009		1,125		1,147		1,266		
Age- and energy-adjusted analyses	1	0.92	0.84, 1.00	0.97	0.89, 1.06	0.97	0.89, 1.06	0.97	0.89, 1.05	0.71
Multivariate analysis[a]	1	0.90	0.82, 0.99	0.95	0.87, 1.04	0.95	0.87, 1.04	0.97	0.89, 1.06	0.98
Estrogen receptor-positive tumors										
No. of cases	573	605		673		715		752		
Age- and energy-adjusted analyses	1	0.94	0.84, 1.06	0.99	0.88, 1.11	1.03	0.92, 1.15	0.98	0.87, 1.09	0.87
Multivariate analysis[a]	1	0.91	0.81, 1.02	0.95	0.84, 1.06	0.98	0.88, 1.10	0.96	0.85, 1.08	0.89
Estrogen receptor-negative tumors										
No. of cases	166	162		162		156		181		
Age- and energy-adjusted analyses	1	0.87	0.70, 1.08	0.82	0.66, 1.02	0.80	0.64, 1.00	0.83	0.66, 1.02	0.03
Multivariate analysis[a]	1	0.85	0.68, 1.06	0.80	0.64, 1.00	0.77	0.61, 0.97	0.80	0.64, 1.01	0.02

Abbreviation: CI, confidence interval.

[a] Adjusted for age, energy intake, multivitamin use, smoking, body mass index, height, weight at 18 years of age, weight change since 18 years of age, family history of breast cancer, benign breast disease, physical activity level, alcohol intake, and menopausal hormone use.

Diet scores, all of which favor higher consumption of plant foods (3). In the present analysis, the inverse association between the DASH score and ER− tumors appeared to be largely explained by intake of plant foods. Previously, we found that higher consumption of combined vegetables and legumes as part of the Alternate Healthy Eating score was also associated with a lower risk of ER− tumors (3). In the present analysis, we found an inverse association between intakes of total fruits and low-protein vegetables and ER− tumors. A previous analysis in this cohort showed an inverse association between yellow/orange vegetables and ER− tumors (3). In the Black Women's Health Study, total vegetable consumption, in particular consumption of carrots, was associated with a lower risk of ER−/PR− tumors (17). Similar results for total fruits and vegetables were also seen in a Danish cohort (18).

Both insulin-like growth factor-1 and insulin might have a proliferative effect on breast cancer cells (8). Lower levels of adiponectin (19, 20), a marker for insulin sensitivity and metabolic syndrome (21), have been implicated in the risk of breast cancer. Although currently the literature mostly shows no association among glycemic index, carbohydrate intake, and ER− cancer (22–24), a direct association has also been seen (25). Similarly, current literature on antioxidant intake as a predictor of breast cancer is also mixed (4, 26). However, this does not preclude the possibility that the inverse association we observed with the vegetable low-carbohydrate diet score is mediated by these pathways. In addition, our findings also concur with the current literature, which suggests that a plant-based diet in combination with lower intakes of red and processed meat and refined grains is associated with lower risk of breast cancer (1). On the other hand, we did not find an association between breast cancer and whole grains, which is consistent with the overall null results in current literature on whole grains (27), or cereal fiber (22, 28, 29).

Our repeated assessment of dietary intake allowed us to take into account dietary changes during the follow-up period. Because of the large cohort size and long follow-up period, we had a sufficient number of ER− cancer cases for analysis. However, because diet and lifestyle information were self-reported, some level of misclassification could not be avoided. In addition, our scoring algorithm for the DASH score was not intended to precisely measure the food group specified in the DASH diet. Our low-carbohydrate-diet scores were also not designed to reflect any of the popular low-carbohydrate diets. However, we believe that our scoring algorithm accurately captured the principles of these diets.

In conclusion, high DASH scores and high vegetable low-carbohydrate diet scores, both of which are characterized by higher intakes of plant foods, are associated with a lower risk of ER− breast cancer. Plant-based diets have been shown to reduce the risk of cardiovascular disease (12, 30) and diabetes (31). Data from our study, as well as from studies by others (1), suggest an additional benefit of reducing the risk of ER− breast cancer. Because ER− tumors tend to be more aggressive and have fewer treatment options than ER+ tumors (32), it is of special importance to identify prevention strategies.

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Table 5. Multivariate[a] Relative Risk of Estrogen Receptor-Negative Breast Cancer, by Quintile of Plant Food Intake, Nurses' Health Study, 1980–2006

Type of Food	Quintile 1	Quintile 2	95% CI	Quintile 3	95% CI	Quintile 4	95% CI	Quintile 5	95% CI	*P* Trend
Total fruit										
Median intake, servings/day	0.9	1.8		2.9		4.2		7.1		
No. of cases of breast cancer	155	148		190		202		132		
Multivariate relative risk	1	0.84	0.66, 1.05	1.00	0.80, 1.25	1.02	0.82, 1.28	0.71	0.55, 0.92	0.01
Juices										
Median intake, servings/day	0.1	0.3		0.7		1.8		2.9		
No. of cases of breast cancer	161	150		177		168		171		
Multivariate relative risk	1	0.90	0.72, 1.12	0.95	0.76, 1.18	0.93	0.75, 1.17	0.95	0.76, 1.19	0.43
Low-protein vegetables[b]										
Median intake, servings/day	1.2	2.0		2.7		3.7		6.5		
No. of cases of breast cancer	168	168		166		158		167		
Multivariate relative risk	1	0.86	0.69, 1.07	0.79	0.64, 0.99	0.70	0.55, 0.88	0.76	0.60, 0.95	0.048
Total fruits and low-protein vegetables										
Median intake, servings/day	2.6	4.5		6.4		8.6		13.4		
No. of cases of breast cancer	166	146		188		178		149		
Multivariate relative risk	1	0.75	0.60, 0.94	0.92	0.74, 1.14	0.85	0.68, 1.07	0.71	0.55, 0.90	0.005
Nuts										
Median intake, servings/day	0.04	0.1		0.2		0.4		0.9		
No. of cases of breast cancer	164	153		180		183		147		
Multivariate relative risk	1	0.92	0.73, 1.14	1.01	0.81, 1.25	0.99	0.79, 1.23	0.78	0.62, 0.99	0.11
Legumes										
Median intake, servings/day	0.1	0.1		0.2		0.2		0.4		
No. of cases of breast cancer	149	184		154		170		170		
Multivariate relative risk	1	1.11	0.89, 1.38	0.99	0.78, 1.24	0.98	0.78, 1.23	1.00	0.79, 1.26	0.38
Whole grains[c]										
Median intake, g/day	4.5	10.1		15.1		21.3		32.8		
No. of cases of breast cancer	138	123		138		140		161		
Multivariate relative risk	1	0.82	0.64, 1.05	0.88	0.69, 1.12	0.85	0.67, 1.09	0.96	0.75, 1.23	0.83
Nongrain plant foods[d]										
Median intake, servings/day	3.0	5.1		7.1		9.4		14.4		
No. of cases of breast cancer	173	150		183		171		150		
Multivariate relative risk	1	0.73	0.58, 0.91	0.85	0.68, 1.06	0.77	0.61, 0.97	0.66	0.52, 0.85	0.003

[a] Adjusted for age, energy intake, multivitamin use, smoking, body mass index, height, weight at 18 years of age, weight change since 18 years of age, family history of breast cancer, benign breast disease, physical activity level, alcohol intake, and menopausal hormone use.
[b] Includes all vegetables except legumes and potatoes.
[c] Follow-up between 1984 and 2006 because the 1980 food frequency questionnaire did not provide adequate information on these foods.
[d] Total fruits, vegetables, nuts, and legumes.

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