The Journal of Nutrition
Nutritional Epidemiology

Dietary Energy Density and Postmenopausal Breast Cancer Incidence in the Cancer Prevention Study II Nutrition Cohort[1,2]

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Abstract

Background: Dietary energy density (ED) is a measure of diet quality that estimates the amount of energy per unit of food (kilocalories per gram) consumed. Low-ED diets are generally high in fiber and fruits and vegetables and low in fat. Dietary ED has been positively associated with body mass index (BMI) and other risk factors for postmenopausal breast cancer.

Objective: We evaluated the associations of total dietary ED and energy-dense (high-ED) foods with postmenopausal breast cancer incidence.

Methods: Analyses included 56,795 postmenopausal women from the Cancer Prevention Study II Nutrition Cohort with no previous history of breast or other cancers and who provided information on diet, lifestyle, and medical history in 1999. Multivariable-adjusted breast cancer incidence rate ratios (RRs and 95% CIs) were estimated for quintiles of total dietary ED and for the consumption of high-ED foods in Cox proportional hazards regression models.

Results: During a median follow-up of 11.7 y, 2509 invasive breast cancer cases were identified, including 1857 estrogen receptor-positive and 277 estrogen receptor-negative tumors. Median dietary ED was 1.5 kcal/g (IQR: 1.3–1.7 kcal/g). After adjusting for age, race, education, reproductive characteristics, and family history, high compared with low dietary ED was associated with a statistically significantly higher risk of breast cancer (RR for fifth quintile compared with first quintile: 1.20; 95% CI: 1.05, 1.36; *P*-trend = 0.03). The association between the amount of high-ED foods consumed and breast cancer risk was not statistically significant. We observed no differences by estrogen receptor status or effect modification by BMI, age, or physical activity.

Conclusion: These results suggest a modest positive association between total dietary ED and risk of postmenopausal breast cancer. *J Nutr* 2016;146:2045–50.

Keywords: breast cancer, energy density, diet, obesity, postmenopausal women

Introduction

Breast cancer is the most frequently diagnosed cancer among American women. By the end of 2016, there will be ~245,000 incident invasive cases diagnosed, and ~40,000 women will die from breast cancer (1). Breast cancer is a heterogeneous disease. For example, differences in risk factors, clinical characteristics, responses to treatments, and prognoses have been observed among subtypes determined by the estrogen receptor (ER)[5] (2–4). Among prospective cohort studies, tumors that express the ER (~70–80% ER+) have been more strongly associated with hormone-related influences than ER− tumors (~20–30% ER−) (4–6).

Established risk factors for postmenopausal breast cancer include reproductive characteristics, hormonal therapies containing estrogen and progestin, alcohol consumption, and factors related to energy balance, including physical activity, obesity, and adult weight gain (7). For dietary components, such as dietary fiber and total fat, the World Cancer Research Fund (WCRF)/American Institute for Cancer Research (AICR) (8, 9) concluded that there was no convincing evidence for associations with breast cancer incidence and mortality. Nevertheless, diet continues to be an active area of research, with more studies focusing on overall dietary patterns and considering whether risks may differ by other attributes (e.g., ER status or other tumor characteristics) (10–16).

Dietary energy density (ED) is a relatively new measure of diet quality that estimates the amount of energy per unit of food

[1] The authors reported no funding received for this study.
[2] Author disclosures: TJ Hartman, SM Gapstur, MM Gaudet, R Shah, WD Flanders, Y Wang, and ML McCullough, no conflicts of interest.
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[5] Abbreviations used: AICR, American Institute for Cancer Research; CPS-II, Cancer Prevention Study II; ED, energy density; ER, estrogen receptor; $Q_{5v.1}$, fifth quintile compared with first quintile; WCRF, World Cancer Research Fund.

Manuscript received May 9, 2016. Initial review completed June 9, 2016. Revision accepted August 4, 2016.
First published online September 14, 2016; doi:10.3945/jn.116.234344.

(kilocalories per gram) consumed. ED can be calculated for individual foods, meals, and total diet (17). A low-ED diet pattern is generally high in fruits and vegetables and fiber and low in fat (large weight with less energy contribution) (17). We recently reported that dietary ED was positively associated with measures of body fat and established obesity-related markers for cancer in a cross-sectional, nationally representative sample of US adults (18). These findings support WCRF/AICR's judgment that consuming high-ED food increases, whereas low-ED decreases, the risk of weight gain, overweight, and obesity and thereby might be associated with cancer risk (8). On average, individuals consume a similar weight of food daily; thus, replacing high-ED foods with low-ED foods should encourage weight control and could ultimately reduce the risk of weight-related cancers later in life (19–21). Other aspects of a high-ED diet pattern may also influence cancer risk. For example, ED was positively associated with measures of breast density among young women independent of weight status (22). This may be very important because women with a high breast density have a 4–6-fold increase in breast cancer risk (23).

No prospective study, to our knowledge, has evaluated the association between consuming energy-dense foods and breast cancer risk. Moreover, no study, to our knowledge, has evaluated the association between total dietary ED, perhaps a better indicator of overall diet quality than the frequency of consuming energy-dense foods, and breast cancer. Our primary objective was to examine associations of total dietary ED and high-ED foods with invasive breast cancer incidence. Because BMI is positively associated with postmenopausal cancer risk and could potentially be on the causal pathway between a high-ED dietary pattern and risk, we also explored whether BMI explains or modifies a potential association between ED and breast cancer risk. Last, we also assessed whether associations differed by age, physical activity, and ER status.

Methods

Cohort description. Women in this study were drawn from the CPS-II (Cancer Prevention Study II) Nutrition Cohort, a prospective study of cancer incidence and mortality that was established by the American Cancer Society in 1992 and includes ~98,000 women (24). The nutrition cohort is a subset of the larger CPS-II mortality study initiated by the American Cancer Society in 1982. Participants in the nutrition cohort were recruited from 21 states and were aged 50–74 y at enrollment when they completed a survey on demographic, medical, dietary, and lifestyle characteristics. All living members have received follow-up questionnaires every 2 y since 1997 to update exposure information and to ascertain newly diagnosed cancers. All aspects of the CPS-II Nutrition Cohort have been reviewed and approved by the Emory University Institutional Review Board.

Follow-up for this analysis began in 1999 when participants completed and returned a comprehensive FFQ (24–26) and was calculated from the date of receipt of this FFQ until the date of invasive breast cancer diagnosis, death, or until June 30, 2011, whichever came first. Of the 73,640 CPS-II Nutrition Cohort participants who completed the 1999 FFQ, 1744 were lost to follow-up, and exclusions were made for women who reported a history of any cancer before 1999 (except nonmelanoma skin cancer) (n = 13,624), with a menopausal status of perimenopausal, premenopausal, or unknown (n = 189); unverified self-reported breast cancers (n = 26); or an invalid diagnosis date (n = 6). We also excluded women with implausible dietary data [very low (<600 kcal/d) or very high (>3500 kcal/d) total energy intakes or missing complete sections of the FFQ (n = 1256)], leaving a final analytic sample of 56,795.

Breast cancer case ascertainment. Cases included invasive breast cancer cases diagnosed between January 1999 and July 2011. Most breast cancer diagnoses were identified through self-report on follow-up questionnaires and then verified via medical records or linkage with state registries or computerized linkage with the National Death Index (n = 2451) (97.7%); however, some were listed as a primary or contributory cause of death on their death certificate and were identified through linkage with the National Death Index only (n = 58) (2.3%) (27). Tumor clinical characteristics, when available (e.g., ER status), were obtained from state registries or abstracted from medical records and were available for 2134 cases (85%).

Assessment of dietary intake. Diet was assessed in 1999 with the use of a modified 152-item Willett FFQ. Participants were asked how often on average (never to 6 servings/d) they consumed a specific portion of foods and beverages over the previous year. The food energy (kilocalories), weight (grams), and nutrient content of foods and beverages were determined with the use of a nutrient database from Harvard University that included composition values from the USDA and supplemented with other sources. No standardized method exists, to our knowledge, for selecting foods and beverages to include in the ED calculation; however, Johnson et al. (28) recommended using foods only and controlling for beverage energy when it is an important confounder. Most studies that have observed associations between dietary ED and disease status have done so with the use of food-only ED (28). We calculated total dietary ED from foods only and computed ED for individual foods. We also created a total quantity of high-ED foods consumed by summing the consumption of individual foods with EDs ≥2.25 (>225 kcal/100 g) (e.g., desserts, candy, buttered or regular microwave popcorn, chips, breakfast quick breads, peanut butter, jam, mayonnaise and other salad dressings, higher-fat meats, etc.) (29). Nuts, seeds, wheat germ, and olive oil met the criteria for high-ED foods but were excluded because according to WCRF/AICR guidelines relatively unprocessed energy-dense foods such as these may provide valuable nutrients and have not been shown to contribute to weight gain when consumed as part of typical diets (29).

Statistical analysis. Statistical analyses were performed with the use of SAS version 9.2 (SAS Institute). We calculated Spearman correlation coefficients between continuous variables of total dietary ED and the quantity of high-ED foods consumed and BMI (in kg/m^2) and selected dietary variables [e.g., total energy intake (kilocalories per day)]. Total dietary ED and high-ED food consumption were categorized into quantiles (quintiles or quartiles) of intake based on the overall distribution in the cohort, with the lowest quantile serving as the referent. Multivariable-adjusted breast cancer incidence rate ratios (RRs and 95% CIs) were estimated for categories of ED in Cox proportional hazards regression models, with the lowest category as the referent. The associations between breast cancer risk and total dietary ED and quantity of high-ED foods consumed were evaluated in models that adjusted for age, race/ethnicity, educational status, age at menarche, age at first birth and parity, age at menopause, family history of breast cancer, and hormone replacement therapy use. Final models were evaluated with and without BMI as a categorical variable. Several other potential covariates did not appreciably contribute to model fit or interpretation and thus were not included in the final models. These variables included adult weight gain, waist circumference, smoking status, menstrual cycle regularity, oral contraceptive use, physical activity, sitting time, total energy intake and energy intake from beverages, alcohol consumption, history of benign breast disease, and recent mammography. Tests of linear trends were conducted in final multivariable models by assigning the median value from each quintile of ED and modeling this value as a continuous variable. The Cox proportional hazards assumption was tested by modeling multiplicative interaction terms between ED variables and time. We evaluated interactions by BMI, age, and physical activity with ED by including each individual factor and its cross-product term with the ED quintile in separate multivariable models with the use of the likelihood ratio test. We also evaluated whether the associations between total dietary ED or high-ED foods (modeled as quartiles because of the small numbers of ER− cases) and postmenopausal breast cancer risk differed by ER status. For these analyses, we used joint Cox proportional hazards models (30) and censored women when they were diagnosed with breast cancer with the ER status that was not the outcome of the particular analysis. Results from 2-sided chi-square tests were considered statistically significant at $P < 0.05$.

Results

During a median follow-up of 11.7 y, 2509 breast cancer cases were identified; 2134 had information on ER status (85% cases). Among tumors with a known receptor status, 1857 (87%) were ER+ and 277 (13%) were ER−. Baseline participant characteristics are presented by category of total dietary ED in **Table 1**. Median dietary ED was 1.5 kcal/g (IQR: 1.3–1.7 kcal/g). Women who consumed higher-ED diets were more likely to be heavier, to have a larger waist circumference, and to have experienced greater adult weight gain (i.e., from age 18 y to baseline) than those who consumed lower-ED diets. They were also more likely to be current smokers and less physically active. As expected, women who consumed higher-ED diets tended to have diets that were also higher in total energy and fat but lower in fiber.

Spearman correlation coefficients between total dietary ED with total energy (kilocalories), fat (percentage of energy), and fiber (g/1000 kcal) were 0.15, 0.49, and −0.70, respectively (all $P < 0.05$; data not presented). In contrast, Spearman correlation coefficients between the quantity of high-ED foods consumed with total energy (kilocalories), fat (percentage of energy), and fiber (g/1000 kcal) were 0.75, 0.32, and −0.32, respectively (all $P < 0.05$; data not presented). The correlation between total dietary ED with the quantity of high-ED foods was 0.49; neither measure was highly correlated with BMI (0.10 for total dietary ED and 0.09 for the quantity of high-ED foods).

The association between total dietary ED consumption and postmenopausal breast cancer risk is shown in **Table 2**. Without adjusting for BMI, there was a statistically significant positive association between total ED and risk [RR for fifth quintile

TABLE 1 Characteristics of eligible CPS-II Nutrition Cohort participants[1]

		Quintiles of dietary energy density, kcal/g				
	Overall	<1.23	1.23 to <1.38	1.38 to <1.52	1.52 to <1.71	≥1.71
n	56,795	10,914	11,491	11,147	11,803	11,440
Lifestyle characteristics						
Age, y	68.5 ± 6.2	69.2 ± 6.2	68.8 ± 6.2	68.6 ± 6.2	68.2 ± 6.2	67.9 ± 6.2
BMI, kg/m^2	25.8 ± 5.0	25.1 ± 4.7	25.5 ± 4.8	25.8 ± 5.1	26.1 ± 5.1	26.5 ± 5.3
Height, inches	64.5 ± 2.5	64.4 ± 2.6	64.6 ± 2.5	64.6 ± 2.5	64.6 ± 2.5	64.6 ± 2.5
Waist circumference, cm	86.2 ± 12.9	84.2 ± 12.7	85.3 ± 12.6	86.2 ± 12.9	86.9 ± 12.8	88.4 ± 13.3
Adult weight gain, kg	13.8 ± 12.6	11.6 ± 12.0	12.9 ± 12.2	13.9 ± 12.7	14.6 ± 12.7	15.9 ± 13.2
Caucasians, %	97.6	96.2	97.8	97.9	98.1	98.1
≥High school graduate, %	95.1	95.1	95.5	95.5	95.0	94.5
Cigarette smoking, %						
Never	50.5	51.6	51.2	50.7	50.4	48.6
Current	4.5	2.0	3.0	3.9	5.3	8.2
Former	37.7	38.7	38.2	38.0	37.4	36.4
Aged <12 y at menarche, %	19.4	21.8	20.0	19.2	18.6	17.6
Nulliparous, %	7.3	7.4	7.1	6.8	7.4	7.7
Aged ≥50 y at menopause, %	52.6	53.8	53.1	52.5	52.3	51.3
HRT use, %						
Never	27.8	27.3	26.8	27.5	26.9	30.6
Current ERT only	25.7	25.7	26.8	26.1	26.2	23.8
Former ERT only	11.4	11.9	11.3	11.4	10.8	11.6
Current combined HRT	19.4	18.7	19.4	19.2	20.6	18.9
Former combined HRT	4.5	4.6	4.4	4.4	4.7	4.2
Family history of breast cancer, %	17.3	17.7	17.4	17.5	16.7	17.5
Recent mammography, %						
Never	2.2	1.9	1.9	1.8	2.1	3.1
≤2 y	88.9	90.2	90.4	89.6	88.4	85.9
>2 y	8.1	7.1	7.0	7.9	8.6	9.9
Physical activity (MET-h/wk),[2] %						
No activity	5.3	4.2	4.3	4.7	5.5	7.9
>0 to <17.5	63.9	56.6	61.8	64.9	66.6	69.3
≥17.5	28.7	37.3	31.9	28.4	25.7	20.6
Daily dietary intake						
Total energy, kcal/d	1613 ± 492	1492 ± 452	1580 ± 465	1616 ± 481	1656 ± 493	1715 ± 537
Beverage energy, kcal/d	251 ± 151	245 ± 149	252 ± 147	254 ± 147	255 ± 150	251 ± 160
Fat, % energy	30.2 ± 6.7	25.5 ± 5.8	28.4 ± 5.6	30.2 ± 5.8	32 ± 6.0	34.8 ± 6.6
Saturated fat, % energy	9.8 ± 2.7	8 ± 2.2	9.1 ± 2.2	9.8 ± 2.3	10.5 ± 2.4	11.6 ± 2.7
Fiber, g/1000 kcal	11.4 ± 3.1	14.8 ± 3.1	12.4 ± 2.3	11.2 ± 2.1	10.2 ± 2.0	8.7 ± 2.0
Alcohol, g/d	7.3 ± 16.7	6.7 ± 13.9	7.2 ± 15.9	7.6 ± 17.3	7.5 ± 16.9	7.2 ± 19.2

[1] Values are means ± SDs unless otherwise indicated. Percentages may not sum because of rounding or missing values for exposure. CPS-II, Cancer Prevention Study II; ERT, estrogen replacement therapy; HRT, hormone replacement therapy; MET-h, metabolic equivalent task hours.
[2] METs are defined for each type of exercise-related physical activity as a multiple of METs of sitting quietly for 1 h.

TABLE 2 Association between dietary energy density and the incidence of invasive breast cancer overall and by ER status among 56,795 women in the CPS-II Nutrition Cohort[1]

Dietary energy density,[2] kcal/g	Cases, *n*	Age	Multivariable[3]	Multivariable + BMI	Multivariable + total energy
Overall breast cancer					
<1.23	438	1.00	1.00	1.00	1.00
1.23 to <1.38	539	1.16 (1.03, 1.32)	1.17 (1.03, 1.33)	1.16 (1.02, 1.32)	1.17 (1.03, 1.32)
1.38 to <1.52	489	1.09 (0.96, 1.24)	1.11 (0.97, 1.26)	1.09 (0.96, 1.24)	1.10 (0.97, 1.25)
1.52 to <1.71	517	1.09 (0.96, 1.24)	1.11 (0.98, 1.26)	1.09 (0.96, 1.24)	1.10 (0.97, 1.25)
≥1.71	526	1.16 (1.02, 1.31)	1.20 (1.05, 1.36)	1.17 (1.03, 1.33)	1.18 (1.04, 1.35)
P-trend		0.11	0.03	0.09	0.06
By ER status[4]					
ER+					
<1.27	420	1.00	1.00	1.00	
1.27 to <1.45	514	1.16 (1.02, 1.32)	1.17 (1.03, 1.33)	1.16 (1.02, 1.31)	
1.45 to <1.65	447	1.04 (0.91, 1.18)	1.05 (0.92, 1.21)	1.04 (0.91, 1.19)	
≥1.65	476	1.07 (0.94, 1.22)	1.11 (0.97, 1.27)	1.08 (0.95, 1.24)	
P-trend		0.67	0.56	0.56	
ER−					
<1.27	58	1.00	1.00	1.00	
1.27 to <1.45	72	1.18 (0.83, 1.67)	1.18 (0.84, 1.67)	1.17 (0.83, 1.66)	
1.45 to <1.65	65	1.07 (0.75, 1.52)	1.09 (0.76, 1.55)	1.07 (0.75, 1.52)	
≥1.65	82	1.31 (0.94, 1.84)	1.35 (0.97, 1.90)	1.32 (0.94, 1.85)	
P-trend		0.16	0.14	0.14	

[1] Values are multivariable-adjusted RRs (95% CIs) unless otherwise indicated. CPS-II, Cancer Prevention Study II; ER, estrogen receptor; HRT, hormone replacement therapy.
[2] Categorized into quintiles for overall breast cancer and quartiles for stratified analyses by ER status.
[3] Adjusted for age, education, race/ethnicity, age at menarche, age at first birth/parity, age at menopause, family history of breast cancer, and HRT use.
[4] *P* value for heterogeneity by ER status = 0.64.

compared with first quintile ($Q_{5v.1}$): 1.20; 95% CI: 1.05, 1.36; *P*-trend = 0.03]. Adjusting for BMI attenuated the associations, although confidence limits for the comparisons of the fifth to the first quintiles did not cross 1.0 (RR for $Q_{5v.1}$: 1.17; 95% CI: 1.03, 1.33; *P*-trend = 0.09). In models that adjusted for BMI there were no statistically significant interactions by age, physical activity, or BMI. As shown in Table 2, in stratified analyses associations for total ED with breast cancer risk were not statistically significant for either ER+ or ER− cases. Differences between risk subtypes were also not statistically significant.

The association between the quantity of high-ED foods consumed and postmenopausal breast cancer risk is shown in **Table 3**. Both with and without adjusting for BMI, the quantity of high-ED foods consumed was not significantly associated with a higher risk of breast cancer (RR for $Q_{5v.1}$: 1.06; 95% CI: 0.93, 1.21 and RR for $Q_{5v.1}$: 1.09; 95% CI: 0.96, 1.24, respectively). Adding total energy intake to the model also had little effect on the results (data not shown). Associations for high-ED foods with breast cancer risk were not statistically significant for either ER+ or ER− cases (data not shown) and did not differ by ER status.

Discussion

In this large prospective cohort, women who consumed high-ED diets were at modestly higher risk for postmenopausal breast cancer during >10 y of follow-up. Additional adjustment for BMI, which may be on the causal pathway, slightly attenuated this association. Overall, risk estimates were heightened beginning with the second quintile and were fairly stable across the remaining upper quintiles. There was no effect modification by BMI, age, or physical activity, and results did not differ by ER status. In analyses to assess the risk of greater high-ED food intake, risk estimates tended to be positive but not statistically significant.

TABLE 3 Association between quantity of energy-dense food and incidence of invasive breast cancer among 56,795 women in the CPS-II Nutrition cohort[1]

	Quintiles of energy-dense food quantities, g/d					
	<114	114 to <149	149 to <186	186 to <237	≥237	*P*-trend
Cases, *n*	457	507	515	543	487	
Model						
Age	1.00	1.11 (0.98, 1.26)	1.12 (0.99, 1.27)	1.18 (1.05, 1.34)	1.07 (0.94, 1.21)	0.31
Multivariable[2]	1.00	1.10 (0.97, 1.25)	1.13 (0.99, 1.28)	1.18 (1.04, 1.34)	1.09 (0.96, 1.24)	0.19
Multivariable + BMI	1.00	1.10 (0.97, 1.25)	1.12 (0.98, 1.27)	1.16 (1.03, 1.32)	1.06 (0.93, 1.21)	0.40

[1] Values are multivariable-adjusted RRs (95% CIs) unless otherwise indicated.
[2] Adjusted for age, education, race/ethnicity, age at menarche, age at first birth/parity, age at menopause, family history of breast cancer, and hormone replacement therapy use.

The epidemiologic evidence for a relation between a diet high in ED and breast cancer risk is limited (31), and no previous study to our knowledge has specifically examined total dietary ED. Chandran et al. (31) evaluated the association between consuming energy-dense foods and breast cancer in a population-based case-control study, stratifying by race, age, and ER status. In European American postmenopausal women only (n = 366 cases and 316 controls), a statistically significant increased breast cancer risk (OR for fourth quartile compared with first quartile: 2.95; 95% CI: 1.66, 5.22; P-trend = 0.001) was observed with frequent consumption (>11 compared with ≤3 servings/wk) of energy-dense foods after adjusting for confounders, including BMI. The results were more pronounced among women with ER+ than ER− cancers. In comparison, we found limited evidence for an association between ED foods and risk. Adjusting for total energy intake in the study by Chandran et al. (31) strengthened their results for high-ED foods, whereas adjusting for total energy intake had a minimal impact on the risk estimates in our study. Differences in results between our study and that of Chandran et al. may partly be because of the study design; CPS-II is a prospective study with diet measured before diagnosis, whereas in the Chandran et al. case-control study diet was recalled after case diagnoses. In addition, our analyses included additional high-ED foods (e.g., mayonnaise, butter or margarine).

Dietary ED may play a role in breast cancer risk through a complex interplay of correlated and modifiable dietary factors, including total energy intake, diet composition, and nutrient intakes (32). High-ED diet consumption contributes to increased energy intake and is associated with obesity (18, 33). Insulin insensitivity, chronic inflammation, oxidative stress, and unfavorable effects on growth factor and sex hormone concentrations are metabolic consequences that accompany obesity and are associated with carcinogenesis (34–37). In our study, we observed that high-ED diets were higher in total energy and total and saturated fat but lower in fiber. A controlled weight-maintenance feeding study of 48 women tested the effects of diet composition on a series of sex hormone concentrations (38). In comparison with a high-fat (40% energy), low-fiber (12 g/d) diet, lower-fat (20–25% energy), higher-fiber (40 g/d) diets significantly decreased (−9% to −15%) serum concentrations of sex hormones linked to breast cancer risk (38). Over a woman's lifetime response to a high-ED diet could influence breast cancer risk through the generation of mutagenic metabolites and tissue growth stimulation (39). Last, dietary patterns characterized by higher intakes of refined starches, added sugar, and saturated fats and lower consumption of fruits, vegetables, and fiber lead to lower intakes of antioxidants (e.g., carotenoids) and other potentially anticarcinogenic phytochemicals (8). Several studies have reported inverse associations for plant-based dietary patterns (likely low-ED), defined either with the use of data-driven approaches or a priori indexes, with the risk of ER− breast cancers, but associations with overall breast cancer have been inconsistent (10–16). Nevertheless, diets lacking these constituents may increase DNA damage susceptibility, unchecked cellular proliferation, and systemic inflammation (40–42).

This large prospective study has several strengths. It included a long follow-up time, and many covariates were available for the analysis. Dietary data were collected before diagnosis with the use of a well-characterized instrument designed to assess usual dietary intake and validated with a series of four 1-wk dietary records collected in a demographically similar group of women. Pearson correlation coefficients for comparing energy-adjusted total fat and fiber (dietary ED was not assessed) between the FFQ and means of food records were 0.53 and 0.58, respectively (25, 43). Nevertheless, there are measurement errors associated with all dietary assessment methods, and there were likely measurement errors in the calculation of ED in our study. For example, behavior changes contributing to modest but persistent decreases in dietary ED, such as selecting lower-fat versions of foods or adding vegetables to higher-ED foods (e.g., pizza, sandwiches, other mixed dishes) are challenging to capture with FFQs. We used a single questionnaire to characterize dietary intake to maximize our sample size; however, a subset of the population that also had dietary data collected in 2003 demonstrated stability in dietary ED estimates over time. For example, ~80% of respondents in the highest category of ED (i.e., fifth quintile) in 1999 reported dietary intakes that placed them in either the fourth or fifth quintile in 2003. Residual confounding by BMI or other factors cannot be ruled out. Finally, the CPS-II Nutrition Cohort includes mostly older, white, middle-class women, which has implications for the generalizability of our observations to younger and more diverse populations of women.

In summary, our results provide evidence of a modest positive association between dietary ED and postmenopausal breast cancer risk. To our knowledge, this is the first analysis to examine the association between overall dietary energy density and breast cancer risk. The quality of a wide variety of dietary patterns can be increased through simultaneously reducing saturated fat and increasing fiber and vegetable and fruit intakes. Our data support the value of dietary patterns that incorporate fruits and vegetables and other low-ED foods that may facilitate weight management and reduce the risk of postmenopausal breast cancer.

Acknowledgments

The authors would like to acknowledge the contribution to this study from central cancer registries supported through the Centers for Disease Control and Prevention National Program of Cancer Registries, and cancer registries supported by the National Cancer Institute Surveillance Epidemiology and End Results program. TJH, SMG, and MLM designed the research; SMG, MMG, and YW provided guidance on the data analysis plans; TJH, RS, WDF, and MLM analyzed the data; SMG and MLM provided study oversight; and TJH had primary responsibility for writing the paper. All authors read and approved the final manuscript.

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