Original Article

Consumption of Sugar-Sweetened and Artificially Sweetened Beverages and Breast Cancer Survival

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BACKGROUND: The activation of insulin pathways is hypothesized to promote tumor growth and worsen breast cancer survival. Sugar-sweetened beverages (SSBs) can lead to a higher risk of insulin resistance and may affect survival. The authors prospectively evaluated the relation of postdiagnostic SSB and artificially sweetened beverage (ASB) consumption with mortality among women with breast cancer. **METHODS:** In total, 8863 women with stage I through III breast cancer were identified during follow-up of the Nurses' Health Study (NHS; 1980-2010) and Nurses' Health Study II (NHSII; 1991-2011). Women completed a validated food frequency questionnaire every 4 years after diagnosis and were followed until death or the end of follow-up (2014 for the NHS and 2015 for the NHSII). Multivariable Cox proportional hazards regression was used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) of breast cancer-specific and all-cause mortality after adjusting for measures of adiposity and other potential predictors of cancer survival. **RESULTS:** With a median follow-up of 11.5 years, 2482 deaths were prospectively documented, including 1050 deaths from breast cancer. Compared with women who had no consumption, women who had SSB consumption after diagnosis had higher breast cancer-specific mortality (>1 to 3 servings per week: HR, 1.31 [95% CI, 1.09-1.58]; >3 servings per week: HR, 1.35 [95% CI, 1.12-1.62]; P_{trend} = .001) and all-cause mortality (>1 to 3 servings per week: HR, 1.21 [95% CI, 1.07-1.37]; >3 servings per week: HR, 1.28 [95% CI, 1.13-1.45]; P_{trend} = .0001). In contrast, ASB consumption was not associated with higher breast cancer-specific or all-cause mortality. Furthermore, replacing 1 serving per day of SSB consumption with 1 serving per day of ASB consumption was not associated with a lower risk of mortality. **CONCLUSIONS:** Higher postdiagnostic SSB consumption among breast cancer survivors was associated with higher breast cancer-specific mortality and death from all causes. ***Cancer* 2021;0:1-12**. © *2021 American Cancer Society*.

KEYWORDS: all-cause mortality, artificially sweetened beverages, breast cancer, breast cancer-specific mortality, sugar-sweetened beverages.

INTRODUCTION

Sugar-sweetened beverages (SSBs), such as soft drinks, fruit-flavored drinks, punches, sports drinks, and energy drinks, are among major sources of added sugar in the American diet and can lead to a higher risk of many conditions, including insulin resistance, obesity, type 2 diabetes, and cardiovascular diseases.[1-6] These conditions may contribute to a poor prognosis among women with breast cancer.[7-14] High levels of insulin at time of diagnosis have been associated with a worse prognosis in nondiabetic women with breast cancer.[15] Insulin treatment in breast cancer survivors with diabetes has been associated with a poorer prognosis.[16,17] Thus, dietary factors that contribute to higher levels of circulating glucose and insulin may affect survival in women with breast cancer. This hypothesis was strengthened by our recent analyses of fruit juice consumption and dietary glycemic load among women with breast cancer in the Nurses' Health Study (NHS) and Nurses' Health Study II (NHSII), in which high consumption of fruit juice and dietary intake with high glycemic load were associated with higher risk of breast cancer-specific and all-cause mortality.[18,19] In addition, high intake of SSBs has been associated with a higher risk of mortality in healthy populations.[20-23] However, it is unclear whether SSB consumption after a breast cancer diagnosis affects

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disease progression and survival. Although caffeine, an ingredient in some soft drinks, may suppress breast cancer tumor growth,[24] play an antidiabetic role,[25,26] and decrease the risk of mortality,[27] survival benefits associated with postdiagnostic caffeinated versus caffeine-free soft drinks remain unclear among patients with breast cancer. Furthermore, individuals usually consider artificially sweetened beverages (ASBs) as healthy alternatives to SSBs; however, a higher risk of mortality has been reported with higher ASB consumption.[22] The safety of ASBs has not been examined in women already diagnosed with breast cancer.

In this regard, we evaluated the associations between SSB and ASB consumption after a diagnosis of breast cancer in relation to breast cancer-specific and all-cause mortality. Furthermore, we estimated the breast cancer-specific and all-cause mortality risk when substituting other beverages for SSBs.

MATERIALS AND METHODS

Study Population

The NHS is an ongoing, prospective cohort study that was created in 1976, with an enrollment of 121,700 female registered nurses, aged 30 to 55 years at inception, residing in 11 states of the United States. The NHSII is an ongoing, prospective cohort study that was created in 1989, with an enrollment of 116,429 female registered nurses, aged 25 to 42 years at inception, residing in 14 states of the United States. Participants were followed through biennial self-administered questionnaires to collect information on health lifestyle and clinical outcomes. We selected women who had a confirmed diagnosis of invasive breast cancer from 1980 to 2010 in the NHS and from 1991 to 2011 in the NHSII. For the current study, we excluded women from the analyses who were missing diet information ≥12 months after diagnosis, those who had a total energy intake <600 or >3500 kcal per day, those who left blank >70 food items on the food frequency questionnaire (FFQ), those who left blank items concerning SSB or ASB on the FFQ, those who were diagnosed with cancer (except nonmelanoma skin cancer) before breast cancer, those who had stage IV disease at diagnosis, and those who were missing information on disease stage. Thus, 8863 women with stage I through III breast cancer were included in the analysis (see Supporting Fig. 1). Completion of the questionnaire was considered to suggest informed consent when the study protocol was approved in 1976 (NHS) and 1989 (NHSII) by the institutional review boards of Brigham and Women's Hospital and the Harvard T.H. Chan School of Public Health (Boston, Massachusetts), and those of participating registries, as required. The studies were conducted in accordance with recognized ethical guidelines (the Declaration of Helsinki).

Assessment of Dietary Intake

In the NHS, participants completed a semiquantitative FFQ with 61 items in 1980, followed by FFQs that were expanded to 116 to 130 items in 1984, 1986, and every 4 years thereafter until 2010. In the NHSII, a similar FFQ of approximately130 items was completed in 1991 and every 4 years thereafter through 2011 (questionnaires are available at http://www.nurseshealthstudy.org/participants/questionnaires). Questionnaire items about SSBs included regular carbonated caffeinated soft drinks, regular carbonated caffeine-free soft drinks, and noncarbonated sweetened beverages (e.g., punch, lemonade, fruit drink, or sugared iced tea). ASBs included carbonated caffeinated low-calorie soft drinks and carbonated caffeine-free low-calorie beverages. Questions included the frequency of consumption over the past year for a standard 355-mL (12-ounce) serving (1 glass, can, or bottle) of each SSB or ASB. For each beverage, there were 9 response categories, ranging from *never or less than once/month* to *6 or more times/day*. Postdiagnostic SSB and ASB consumption data were collected from FFQs completed ≥12 months after diagnosis. The mean time from breast cancer diagnosis to the first postdiagnostic FFQ was 3.3 ± 2.0 years (10th percentile = 1.3 years; 90th percentile = 4.9 years).

To reduce measurement error and within-person variation in the assessment of long-term intake after diagnosis, we calculated the cumulative averages of SSB, ASB, total energy, and alcohol intake from all available FFQs after diagnosis.[28] The FFQ has been extensively validated in our cohorts compared with more detailed methods[29-31] and biomarkers of intake.[31]

Ascertainment of Breast Cancer and Death

Women reported a breast cancer diagnosis through the biennial questionnaires. Then, we requested permission from those women or their next of kin to access medical records and pathology reports to confirm the diagnosis and collect data on treatment and tumor characteristics, including disease stage and ER/progesterone receptor (PR) status. For approximately 70% of women, breast cancer tissue was collected and tumor microarrays were performed to assess tumor characteristics by immunohistochemistry; the details of those assessments are described elsewhere.[32-34] An immunohistochemical staining method was used to determine the status of ER, PR, human epidermal growth factor receptor 2 (HER2), cytokeratin 5/6 (CK5/6), Ki-67, and epidermal growth factor receptor (EGFR) in

tumors. In women for which tumor microarrays were not available, we extracted ER, PR, and HER2 status from their medical records. The following molecular subtypes were determined based on ER, PR, HER2, CK5/6, Ki-67, and EGFR status along with histologic grade: luminal A (ER-positive and/or PR-positive, HER2-negative, and Ki-67–negative [or histologic grade 1 or 2]), luminal B (ER-positive and/or PR-positive, and HER2-positive; or ER-positive, and/or PR-positive, HER2-negative, and Ki-67-positive [or histologic grade 3]), HER2-enriched (ER-negative, PR-negative, and HER2-positive), basal-like (ER-negative, PR-negative, HER2-negative, and CK5/6-positive and/or EGFR-positive), and unclassified tumors that lacked expression for all 5 markers. Insulin receptor (IR) expression in tumors was measured in 2480 women from the NHS using Definiens image analysis software (Tissue Studio, Definiens AG, Munich, Germany).[35]

Deaths were reported by family members or the postal service or were ascertained through a search of the National Death Index. The cause of death was determined by physician review of the death certificate and medical records.

Covariates

By using biennial questionnaires that were returned after breast cancer diagnosis, we obtained data on postdiagnostic body mass index (BMI), physical activity, smoking status, and aspirin use, all of which were updated every 2 or 4 years, if available. Because treatment may affect lifestyle factors, we only collected data that were reported ≥12 months after diagnosis. To minimize chances of reverse causation, cumulative averages of postdiagnostic BMI and physical activity were calculated using 4-year lagged data. Data on prediagnostic BMI were obtained from the last questionnaire that women returned before breast cancer diagnosis. Then, the change in BMI from prediagnosis to postdiagnosis was calculated. Information related to menopausal status, age at menopause, postmenopausal hormone use, and oral contraceptive use was collected from the last biennial questionnaire before diagnosis. In addition, we collected data related to breast cancer characteristics, including age at diagnosis, disease stage, and treatment with radiotherapy, chemotherapy, and hormones from reviewing medical records and supplemental questionnaires.

Statistical Analysis

Women with stage I through III breast cancer were followed from the date of returning the first FFQ after diagnosis until death or until June 1, 2014 for the NHS and June 1, 2015 for the NHSII, whichever occurred first. Deaths from breast cancer and all causes were outcomes of the study.

We combined data from the NHS and NHSII and used stratified Cox proportional hazards regression models to estimate hazard ratios (HRs) and 95% confidence intervals (CIs). Eligible participants were divided into 4 groups based on the number of servings per week of SSB or ASB consumption. We fit 2 models: in model 1, we stratified by cohort and adjusted for age at diagnosis and calendar year of diagnosis. In model 2 (multivariable model), we stratified by cohort and adjusted for age at diagnosis, calendar year of diagnosis, time between diagnosis and first FFQ after diagnosis, calendar year at the start of follow-up of each-2-year questionnaire cycle, postdiagnostic total energy intake, and potential predictors of breast cancer survival, including prediagnostic BMI, prediagnostic to postdiagnostic BMI change, postdiagnostic alcohol consumption, postdiagnostic smoking, postdiagnostic physical activity, postdiagnostic aspirin use, prediagnostic oral contraceptive use, prediagnostic menopausal status, age at menopause, postmenopausal hormone use, race, stage of disease, ER/PR status, radiotherapy, chemotherapy, and hormonal treatment. Women who had unknown menopausal status at the time of diagnosis were categorized in the premenopausal group if they were aged <46 years for smokers or <48 years for never smokers and were categorized in the postmenopausal group if they were aged >54 years for smokers or >56 years for never smokers.[36] For missing covariates, which comprised from less than 1% to 12.6% of total person-years, we used the missing-indicator method. To address the potential confounding role of other dietary factors, we also evaluated the associations after additionally controlling for the postdiagnostic modified Alternate Healthy Eating Index (AHEI) (excluding SSB and alcohol scores) as well as intake of total fruit and vegetable, total red and processed meat, coffee, fruit juice, total protein, dietary glycemic index, or both fruit juice and dietary glycemic load. A restricted cubic spline analysis was used to assess the dose-response relation between SSB consumption and outcomes of interest.[37] In addition, we examined breast cancer-specific and all-cause mortality risk after the cross-classification of participants based on prediagnostic and postdiagnostic SSB intake (high/high, low/high, or high/low compared with low/low). Greater than 1 serving per week of SSB was categorized as high intake.

We estimated the effect of replacing 1 serving per day of SSB consumption with an isovolumetric serving (355 mL) of ASBs, fruit juice, coffee, tea, skim/low-fat milk, whole milk, and water on mortality by simultaneously including these beverage items as continuous variables in

the multivariable model. The HRs and 95% CIs for the substitution effect were derived from the difference between the regression coefficients, variances, and covariances.[38]

Furthermore, we calculated the population-attributable risk percentage (PAR%) and 95% CI using a macro developed by Spiegelman et al[39] to quantify the proportional reductions expected in breast cancer-specific and all-cause mortality if women did not drink SSBs after diagnosis or if all women drank ≤2 servings/month of SSBs after diagnosis. In this model, we set the low-risk category as a reference group for covariates, including cohort, age at diagnosis, calendar year of diagnosis, calendar year at the start of follow-up of each-2-year questionnaire cycle, prediagnostic BMI, prediagnostic to postdiagnostic BMI change, postdiagnostic smoking, postdiagnostic physical activity, postdiagnostic alcohol consumption, postdiagnostic energy intake, postdiagnostic aspirin use, prediagnostic menopausal status, age at menopause, postmenopausal hormone use, stage of disease, ER/PR status, radiotherapy, chemotherapy, and hormonal treatment. Covariates for the PAR analysis were selected using stepwise Cox proportional hazards regression. To estimate the risk difference, we used PROC GENMOD, with NORMAL working distribution and repeated in ID.

Stratified analyses were conducted to evaluate potential effect modification by including IR status (IR-positive/IR-negative), ER status (ER-positive/ER-negative), and molecular subtypes (luminal A/luminal B/HER2-enriched/basal-like). Furthermore, we evaluated the associations stratified by disease stage, postdiagnostic BMI, smoking status, alcohol consumption, and modified AHEI as secondary analyses. *P* values for heterogeneity were calculated using the Wald test. All analyses were conducted using SAS software version 9.4 (SAS Institute) with a 2-sided *P* value < .05.

RESULTS

During a median follow-up of 11.5 years, we documented 2482 deaths from all causes and 1050 deaths from breast cancer among 8863 eligible women who were diagnosed with breast cancer. The mean intake of SSBs after diagnosis was 0.25 serving per day (10th percentile = 0 serving per day; 90th percentile = 0.73 serving per day), and the mean intake of ASBs after diagnosis was 0.49 serving per day (10th percentile = 0 serving per day; 90th percentile = 1.39 servings per day). Women who had higher SSB consumption after diagnosis were younger at the time of diagnosis, more likely to smoke after diagnosis, and reported higher total energy intake (Table 1). They were less likely to be physically active after diagnosis, to use aspirin after diagnosis, and to use oral contraceptives before diagnosis. Women who had higher ASB consumption after diagnosis were younger at the time of diagnosis and had a higher BMI but a lower prevalence of smoking after diagnosis. They were more likely to use oral contraceptives before diagnosis.

SSB and ASB Consumption After Diagnosis and Survival

Postdiagnostic SSB consumption was associated with higher breast cancer-specific mortality (versus no consumption; >1 to 3 servings per week: HR, 1.31 [95% CI, 1.09-1.58]; >3 servings per week: HR, 1.35 [95% CI, 1.12-1.62]; P_{trend} = .001) and all-cause mortality (versus no consumption; >1 to 3 servings per week: HR, 1.21 [95% CI, 1.07-1.37]; >3 servings per week: HR, 1.28 [95% CI, 1.13-1.45]; P_{trend} = .0001) (Table 2). These associations were approximately linear (see Supporting Fig. 2a,b). After additional adjustment for the modified AHEI (excluding SSB and alcohol scores), associations were somewhat attenuated for all-cause mortality but not for breast cancer-specific mortality (Table 2). In addition, we observed similar associations after additional adjustment for intake of fruits and vegetables, total red and processed meat, coffee, fruit juice, total protein, dietary glycemic index, or both fruit juice and dietary glycemic load (see Supporting Table 1). Among women who drank >3 servings per week of SSBs after diagnosis, there were 56.3 additional deaths per 10,000 person-years of follow-up compared with women who did not drink SSBs (risk difference, 56.3 per 10,000 person-years; 95% CI, 26.8-85.8 per 10,000 person-years). The proportional reduction expected in breast cancer-specific mortality was 10.5% (95% CI, −1.0%, 21.7%) if all women did not drink SSBs after diagnosis and was 8.6% (95% CI, 0.4%, 16.8%) if all women drank ≤2 servings per month of SSBs after diagnosis. The PAR% for all-cause mortality was 10.4% (95% CI, 2.5%, 18.1%) if all women did not drink SSBs after diagnosis and was 6.6% (95% CI, 1.0%, 12.2%) if all women drank ≤2 servings per month of SSBs after diagnosis.

The mortality risk did not differ substantially by consumption of postdiagnostic carbonated and noncarbonated SSBs (see Supporting Table 2). Furthermore, both postdiagnostic carbonated caffeinated and caffeine-free soft drinks were associated with higher all-cause mortality risk (see Supporting Table 3).

Postdiagnostic ASB consumption was not associated with a higher risk of breast cancer-specific mortality (versus no consumption; >3 servings per week: HR, 1.02 [95% CI, 0.87-1.19]; P_{trend} = .58) or all-cause mortality (>3 servings per week: HR, 1.08 [95% CI, 0.97-1.20]; P_{trend} = .15) (Table 2).

Associations for postdiagnostic consumption of SSBs and ASBs and breast cancer-specific and all-cause

TABLE 1. Characteristics of Women With Breast Cancer in the combined Nurses' Health Study and Nurses' Health Study II, According to Consumption of Sugar-Sweetened and Artificially Sweetened Beverages Measured From the First Food Frequency Questionnaire After Diagnosis

	SSB Consumption, Servings/Wk				ASB Consumption, Servings/Wk			
Characteristic	No Consumption	>0 to 1	>1 to 3	>3	No Consumption	>0 to 1	>1 to 3	>3
Total no.	4336	2121	1031	1375	3863	1502	936	2562
Mean								
SSB consumption, servings/d	0.0	0.1	0.3	1.3	0.4	0.2	0.2	0.2
ASB consumption, servings/d	0.6	0.4	0.4	0.3	0.0	0.1	0.4	1.5
Coffee consumption, cups/d	1.7	1.7	1.7	1.4	1.6	1.7	1.8	1.6
Total fruit intake, servings/d	1.6	1.6	1.5	1.5	1.6	1.6	1.6	1.5
Total vegetable intake, servings/d	3.2	3.1	3.0	3.0	3.1	3.1	3.0	3.2
Alcohol consumption, g/d	6.3	5.4	5.0	4.6	5.6	5.9	6.2	5.5
Animal fat intake, % energy/d	14.2	14.8	14.7	14.1	13.9	14.4	14.7	15.0
Total fat intake, % energy/d	31.1	30.9	30.4	29.1	30.3	30.5	30.5	31.2
Total energy intake, kcal/d	1596	1729	1816	2016	1724	1679	1715	1749
Modified AHEI score[a]	49.7	47.3	45.4	43.2	48.5	48.1	47.3	46.0
Age at diagnosis, y	59.7	58.4	57.7	56.5	60.1	59.9	59.1	55.5
Body mass index, kg/m^2	26.6	26.4	26.3	26.8	25.6	26.6	26.8	27.9
Physical activity, MET-h/wk	19.3	17.9	16.4	14.4	17.5	18.8	16.7	18.0
Current smokers, %	7	8	10	13	11	8	10	8
Ever used oral contraceptives, %	60	55	54	57	56	57	58	60
Ever used postmenopausal hormone, %	47	49	49	47	48	48	50	47
Current use of aspirin, %	45	43	45	42	43	46	42	44
Premenopausal at diagnosis, %	26	26	27	26	27	27	26	26
Stage of breast cancer, %								
I	61	59	56	59	59	60	61	60
II	29	30	33	31	30	30	29	30
III	10	11	11	10	11	10	10	10
ER status, %								
Positive	78	77	74	76	77	76	77	77
Negative	16	17	20	18	17	18	16	17
Missing	6	6	6	6	6	6	7	6
Treatment, %								
Radiotherapy	57	56	55	55	55	57	57	58
Chemotherapy	45	47	47	47	46	44	45	47
Hormonal treatment	70	68	65	72	69	68	69	71

Abbreviations: AHEI, Alternative Healthy Eating Index; ASB, artificially sweetened beverage; ER, estrogen receptor; MET, metabolic equivalent of task; SSB, sugar-sweetened beverage.
[a]These scores did not include sugar-sweetened beverage or alcohol scores.

mortality remained similar when SSBs and ASBs were mutually adjusted for each other. For SSBs, compared with no consumption, the association of consumption with breast cancer-specific mortality was as follows: the HR was 1.33 (95% CI, 1.11-1.61) for women consuming >1 to 3 servings per week and 1.36 (95% CI, 1.13-1.65) for those consuming >3 servings per week (P_{trend} = .0007); for all-cause mortality, versus no consumption, the HR was 1.23 (95% CI, 1.09-1.38) for women consuming >1 to 3 servings per week and 1.31 (95% CI, 1.15-1.48) for those consuming >3 servings per week (P_{trend} < .0001).

To examine changes in intake from the last FFQ reported before diagnosis to the FFQs reported after diagnosis, we cross-classified prediagnostic and postdiagnostic intake. Compared with women who reported low prediagnostic and low postdiagnostic SSB consumption, breast cancer-specific mortality was higher among those who had low prediagnostic and high postdiagnostic SSB consumption (HR, 1.25; 95% CI, 1.04-1.50) and among those who had high prediagnostic and high postdiagnostic SSB consumption (HR, 1.33; 95% CI, 1.12-1.58). We did not observe a significantly increased risk among women who had high prediagnostic and low postdiagnostic intake (Table 3). Associations were similar for all-cause mortality (Table 3).

Replacing 1 serving per day of SSB consumption with an isovolumetric serving (355 mL) of ASBs, fruit juice, skim/low-fat milk, or whole milk was not associated with changes in the risk of breast cancer-specific or all-cause mortality (Fig. 1). However, replacing 1 serving per day of SSB consumption with an isovolumetric serving of coffee or tea was associated with 18% and 15% lower risk of breast cancer-specific mortality,

TABLE 2. Postdiagnostic Consumption Levels of Sugar-Sweetened and Artificially Sweetened Beverages in Relation to Mortality After Breast Cancer Diagnosis (n = 8863) in the Nurses' Health Study and Nurses' Health Study II[a]

	Consumption Level: HR (95% CI)				
	No Consumption	>0 to 1 Serving/Wk	>1 to 3 Servings/Wk	>3 Servings/Wk	P_{Trend}
SSBs					
Breast cancer-specific mortality					
No. of deaths	358	306	185	201	
Person-years	35,936	31,541	17,002	16,622	
Model 1	1.00	0.88 (0.76-1.03)	0.99 (0.83-1.18)	1.17 (0.98-1.39)	.01
Model 2	1.00	1.07 (0.92-1.26)	1.31 (1.09-1.58)	1.35 (1.12-1.62)	.001
Model 2 + modified AHEI	1.00	1.07 (0.92-1.26)	1.30 (1.08-1.57)	1.34 (1.11-1.62)	.002
All-cause mortality					
No. of deaths	809	781	440	452	
Person-years	35,936	31,541	17,002	16,622	
Model 1	1.00	1.07 (0.96-1.18)	1.13 (1.00-1.26)	1.32 (1.17-1.48)	<.0001
Model 2	1.00	1.09 (0.99-1.21)	1.21 (1.07-1.37)	1.28 (1.13-1.45)	.0001
Model 2 + modified AHEI	1.00	1.07 (0.97-1.19)	1.17 (1.04-1.32)	1.22 (1.07-1.38)	.003
ASBs					
Breast cancer-specific mortality					
No. of deaths	394	208	117	331	
Person-years	34,354	19,709	15,066	31,971	
Model 1	1.00	0.85 (0.72-1.01)	0.63 (0.51-0.77)	0.90 (0.77-1.04)	.61
Model 2	1.00	0.97 (0.82-1.15)	0.82 (0.66-1.01)	1.02 (0.87-1.19)	.58
Model 2 + modified AHEI	1.00	0.97 (0.82-1.16)	0.81 (0.66-1.01)	1.01 (0.86-1.18)	.68
All-cause mortality					
No. of deaths	905	526	340	711	
Person-years	34,354	19,709	15,066	31,971	
Model 1	1.00	0.98 (0.88-1.09)	0.87 (0.77-0.99)	1.05 (0.95-1.16)	.19
Model 2	1.00	1.04 (0.93-1.16)	0.89 (0.79-1.02)	1.08 (0.97-1.20)	.15
Model 2 + modified AHEI	1.00	1.04 (0.93-1.16)	0.89 (0.78-1.02)	1.06 (0.95-1.18)	.29

Abbreviations: AHEI, Alternate Healthy Eating Index; ASBs, artificially sweetened beverages; HR, hazard ratio; SSBs, sugar-sweetened beverages.
[a]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 food frequency questionnaire (year), calendar year at the start of follow-up of each-2-year questionnaire cycle, prediagnostic body mass index (<20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, 30.0 to <35.0, or ≥35.0 kg/m^2, or missing), body mass index change after diagnosis (no change [≥−0.5 to ≤0.5 kg/m^2], decrease [<−0.5 kg/m^2], increase [>0.5 to 2.0 kg/m^2], increase [>2.0 kg/m^2], or missing), postdiagnostic smoking (never, past, current 1-14 cigarettes per day, current 15-24 cigarettes per day, current ≥25 cigarettes per day, or missing), postdiagnostic physical activity (<5.0, 5.0 to <11.5, 11.5 to <22.0, or ≥22.0 metabolic equivalent of task hours per week, or missing), oral contraceptive use (ever, never), postdiagnostic alcohol consumption (<0.15, 0.15 to <2.0, 2.0 to <7.5, or ≥7.5 g/day), postdiagnostic total energy intake (quintiles, kcal/day), prediagnostic menopausal status, age at menopause, and postmenopausal hormone use status (premenopausal; postmenopausal, aged <50 years at menopause, and never used postmenopausal hormones; postmenopausal, aged <50 years at menopause, and past postmenopausal hormone use; postmenopausal, aged <50 years at menopause, and current postmenopausal hormone use; postmenopausal, aged ≥50 years at menopause, and never used postmenopausal hormones; postmenopausal, aged ≥50 years at menopause, and past postmenopausal hormone use; postmenopausal, aged ≥50 years at menopause, and current postmenopausal hormone use; or missing), postdiagnostic aspirin use (never, past, current, or missing), race (non-Hispanic White or other), stage of disease (I, II, or III); estrogen receptor/progesterone receptor (ER/PR) status (ER/PR-positive, ER-positive and PR-negative, ER/PR-negative, or missing), radiotherapy (yes, no, or missing), chemotherapy (yes, no, or missing), and hormonal treatment (yes, no, or missing).

respectively. Replacing 1 serving per day of SSB consumption with an isovolumetric serving of coffee, tea, or water was associated with 19%, 17% and 9% lower risk of all-cause mortality, respectively.

We also examined whether the associations of SSBs and ASBs with mortality differed by tumor IR status, ER status, or molecular subtypes. We observed stronger associations between postdiagnostic SSB consumption and all-cause mortality among women who had IR-negative tumors compared with those who had IR-positive tumors (P for heterogeneity = .04) (Table 4). The association between SSB or ASB consumption and mortality did not differ by ER status (Table 4) or molecular subtypes (Table 5).

Sensitivity Analyses

We examined associations with the first postdiagnostic measure of SSB consumption rather than cumulative updating (see Supporting Table 4). There was a high correlation between first postdiagnostic SSB consumption and the cumulative average of postdiagnostic SSB consumption ($r = 0.90$), and the results were similar to those provided Table 2. We also evaluated the associations with simple updates of dietary intake (see Supporting Table 5) as well as accounting for left truncation time since diagnosis (see Supporting Table 6). The results were very similar across several different analytic approaches.

Higher SSB consumption was associated with higher breast cancer-specific and all-cause mortality risk

TABLE 3. Changes in Sugar-Sweetened Beverage Consumption From Prediagnosis to Postdiagnosis in Relation to Mortality After Breast Cancer Diagnosis (n = 8490)[a]

	Postdiagnostic SSB Consumption			
	≤1 Serving/Wk		>1 Servings/Wk	
	No. of Deaths/ Person-Years	HR (95% CI)	No. of Deaths/ Person-Years	HR (95% CI)
Breast cancer-specific mortality				
Prediagnostic SSB Consumption				
≤1 Serving/Wk	504/52,846	1.00	157/14,329	1.25 (1.04-1.50)
>1 Servings/Wk	122/11,299	1.00 (0.81-1.22)	206/17,426	1.33 (1.12-1.58)
All-cause mortality				
Prediagnostic SSB Consumption				
≤1 Serving/Wk	1244/52,846	1.00	405/14,329	1.15 (1.02-1.29)
>1 Servings/Wk	251/11,299	0.98 (0.85-1.12)	437/17,426	1.22 (1.08-1.36)

Abbreviation: HR, hazard ratio; SSB, sugar-sweetened beverage.

[a]Models were stratified by cohort and adjusted for age at diagnosis (year), calendar year of diagnosis, time between diagnosis and first food frequency questionnaire (year), calendar year at the start of follow-up of each-2-year questionnaire cycle, prediagnostic body mass index (<20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, 30.0 to <35.0, and ≥35.0 kg/m^2, or missing), body mass index change after diagnosis (no change [≥−0.5 to ≤0.5 kg/m^2], decrease [<−0.5 kg/m^2], increase [>0.5 to 2.0 kg/m^2], increase [>2.0 kg/m^2], or missing), postdiagnostic smoking (never, past, current 1-14 cigarettes per day, current 15-24 cigarettes per day, current ≥25 cigarettes per day, or missing), postdiagnostic physical activity (<5.0, 5.0 to <11.5, 11.5 to <22.0, and ≥22.0 metabolic equivalent of task hours per week, or missing), oral contraceptive use (ever, never), postdiagnostic alcohol consumption (<0.15, 0.15 to <2.0, 2.0 to <7.5, or ≥7.5 g/day), postdiagnostic total energy intake (quintiles, kcal/day), prediagnostic menopausal status, age at menopause, and postmenopausal hormone use status (premenopausal; postmenopausal, aged <50 years at menopause, and never used postmenopausal hormones; postmenopausal, aged <50 years at menopause, and past postmenopausal hormone use; postmenopausal, aged <50 years at menopause, and current postmenopausal hormone use; postmenopausal, aged ≥50 years at menopause, and never used postmenopausal hormones; postmenopausal, aged ≥50 years at menopause, and past postmenopausal hormone use; postmenopausal, aged ≥50 years at menopause, and current postmenopausal hormone use; or missing), postdiagnostic aspirin use (never, past, current, or missing), race (non-Hispanic White or other), stage of disease (I, II, or III), estrogen receptor/progesterone receptor (ER/PR) status (ER/PR positive, ER positive and PR negative, ER/PR negative, or missing), radiotherapy (yes, no, or missing), chemotherapy (yes, no, or missing), and hormonal treatment (yes, no, or missing).

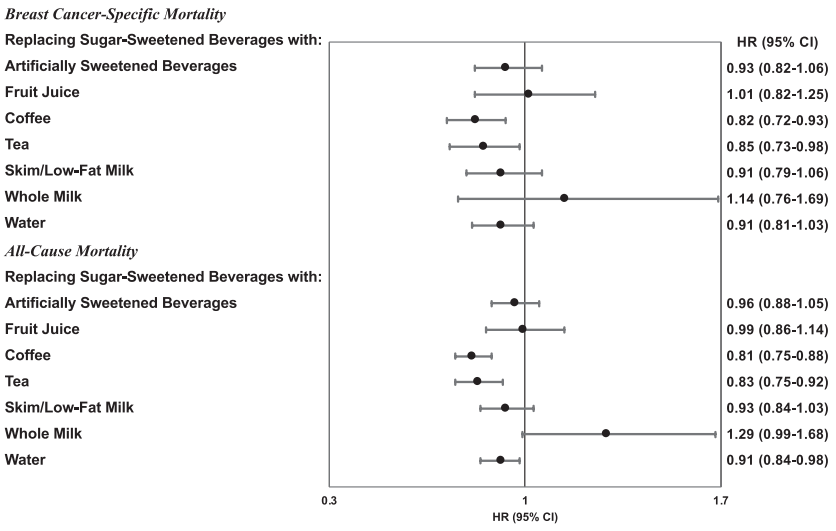

Figure 1. Multivariable hazard ratios (HRs) and 95% confidence intervals for breast cancer-specific and all-cause mortality associated with replacement of sugar-sweetened beverages by other beverages.

among women with stage I or II breast cancer. However, there was no significant interaction (see Supporting Table 7). Higher SSB consumption was associated with a higher breast cancer-specific mortality risk among women who had a postdiagnostic BMI ≥25 kg/m^2 (versus no consumption; >3 servings per week: HR, 1.46; 95% CI, 1.14-1.86), but not among those who had a postdiagnostic BMI <25 kg/m^2 (versus no consumption; >3 servings per week: HR, 1.15; 95% CI, 0.85-1.54; *P* for heterogeneity = .05) (see Supporting Table 8). High

TABLE 4. Postdiagnostic Consumption Levels of Sugar-Sweetened and Artificially Sweetened Beverages in Relation to Mortality After Breast Cancer Diagnosis in the Nurses' Health Study and Nurses' Health Study II, Stratified by Insulin Receptor (n = 2480) and Estrogen Receptor (n = 8322) Status

		Consumption Level: HR (95% CI)					
	No. of Deaths	No Consumption	>0 to 1 Serving/Wk	>1 to 3 Servings/Wk	>3 Servings/Wk	P_{Trend}	$P_{Heterogeneity}$
SSBs							
Breast cancer-specific mortality							
IR status							
IR positive	172	1.00	1.20 (0.81-1.79)	1.32 (0.83-2.08)	1.11 (0.65-1.91)	.83	
IR negative	212	1.00	0.74 (0.51-1.08)	0.91 (0.59-1.41)	1.43 (0.93-2.18)	.01	.32
ER status							
ER positive	755	1.00	1.12 (0.93-1.34)	1.26 (1.00-1.57)	1.39 (1.11-1.72)	.005	
ER negative	209	1.00	0.86 (0.58-1.27)	1.65 (1.11-2.45)	1.75 (1.15-2.67)	.001	.64
All-cause mortality							
IR status							
IR positive	457	1.00	1.13 (0.89-1.44)	1.20 (0.91-1.59)	1.07 (0.77-1.47)	.86	
IR negative	543	1.00	0.91 (0.72-1.14)	1.04 (0.80-1.36)	1.52 (1.16-1.99)	.0001	.04
ER status							
ER positive	1817	1.00	1.10 (0.98-1.24)	1.19 (1.03-1.37)	1.37 (1.19-1.58)	<.0001	
ER negative	440	1.00	1.19 (0.92-1.55)	1.64 (1.22-2.21)	1.55 (1.14-2.10)	.009	.66
ASBs							
Breast cancer-specific mortality							
IR status							
IR positive	172	1.00	1.35 (0.89-2.04)	0.82 (0.48-1.39)	0.72 (0.47-1.10)	.03	
IR negative	212	1.00	1.02 (0.68-1.53)	1.10 (0.69-1.74)	1.13 (0.79-1.61)	.49	.02
ER status							
ER positive	755	1.00	0.92 (0.75-1.12)	0.78 (0.60-1.00)	0.98 (0.82-1.18)	.78	
ER negative	209	1.00	1.06 (0.72-1.55)	1.00 (0.62-1.61)	1.08 (0.74-1.57)	.74	.61
All-cause mortality							
IR status							
IR positive	457	1.00	1.12 (0.87-1.44)	0.75 (0.54-1.03)	0.87 (0.67-1.14)	.16	
IR negative	543	1.00	1.07 (0.83-1.38)	1.13 (0.87-1.48)	1.23 (0.98-1.55)	.08	.02
ER status							
ER positive	1817	1.00	0.98 (0.86-1.11)	0.87 (0.74-1.01)	1.06 (0.94-1.19)	.20	
ER negative	440	1.00	1.26 (0.97-1.64)	1.15 (0.84-1.57)	1.06 (0.81-1.39)	.84	.56

Abbreviation: ASBs, artificially sweetened beverages; ER, estrogen receptor; HR, hazard ratio; IR, insulin receptor; SSBs, sugar-sweetened beverages.

[a]Models were stratified by cohort and adjusted for age at diagnosis (year), calendar year of diagnosis, time between diagnosis and first food frequency questionnaire (year), calendar year at the start of follow-up of each-2-year questionnaire cycle, prediagnostic body mass index (<20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, 30.0 to <35, and ≥35.0 kg/m^2, or missing), body mass index change after diagnosis (no change [≥−0.5 to ≤0.5 kg/m^2], decrease [<−0.5 kg/m^2], increase [>0.5 to 2,0 kg/m^2], increase [>2.0 kg/m^2], or missing), postdiagnostic smoking (never, past, current 1-14 cigarettes per day, current 15-24 cigarettes per day, current ≥25 cigarettes per day, or missing), postdiagnostic physical activity (<5.0, 5.0 to <11.5, 11.5 to <22.0, or ≥22.0 metabolic equivalent of task hours per week, or missing), oral contraceptive use (ever, never), postdiagnostic alcohol consumption (<0.15, 0.15 to <2.0, 2.0 to <7.5, or ≥7.5 g/day), postdiagnostic total energy intake (quintiles, kcal/day), prediagnostic menopausal status, age at menopause, and postmenopausal hormone use status (premenopausal; postmenopausal, aged <50 years at menopause, and never used postmenopausal hormones; postmenopausal, aged <50 years at menopause, and past postmenopausal hormone use; postmenopausal, aged <50 years at menopause, and current postmenopausal hormone use; postmenopausal, aged ≥50 years at menopause, and never used postmenopausal hormones; postmenopausal, aged ≥50 years at menopause, and past postmenopausal hormone use; postmenopausal, aged ≥50 years at menopause, and current postmenopausal hormone use; or missing), postdiagnostic aspirin use (never, past, current, or missing), race (non-Hispanic White or other), stage of disease (I, II, or III), estrogen receptor/progesterone receptor (ER/PR) status (ER/PR positive, ER positive and PR negative, ER/PR negative, or missing), radiotherapy (yes, no, or missing), chemotherapy (yes, no, or missing), and hormonal treatment (yes, no, or missing). Analyses for ER status were not adjusted for ER/PR status.

TABLE 5. Postdiagnostic Consumption Levels of Sugar-Sweetened and Artificially Sweetened Beverages in Relation to Mortality After Breast Cancer Diagnosis in the Nurses' Health Study and Nurses' Health Study II, Stratified by Molecular Subtypes of Breast Cancer (n = 5270)[a]

		Consumption Level: HR (95% CI)					
	No. of Deaths	No Consumption	>0 to 1 Serving/Wk	>1 to 3 Servings/Wk	>3 Servings/Wk	P_{Trend}	$P_{Heterogeneity}$
SSBs							
Breast cancer-specific mortality							
Luminal A	305	1.00	1.16 (0.86-1.56)	1.32 (0.92-1.89)	1.61 (1.13-2.29)	.009	
Luminal B	153	1.00	0.90 (0.59-1.37)	1.19 (0.73-1.95)	0.96 (0.57-1.63)	.93	
HER2-enriched	45	1.00	1.14 (0.40-3.23)	2.51 (0.72-8.67)	1.95 (0.55-6.87)	.30	
Basal-like	45	1.00	0.90 (0.29-2.82)	1.21 (0.39-3.74)	5.58 (1.85-16.88)	.0004	.88
All-cause mortality							
Luminal A	793	1.00	1.04 (0.86-1.24)	1.21 (0.97-1.50)	1.42 (1.13-1.78)	.0009	
Luminal B	341	1.00	1.05 (0.79-1.38)	1.09 (0.78-1.53)	1.07 (0.76-1.51)	.73	
HER2-enriched	83	1.00	0.88 (0.45-1.72)	1.16 (0.51-2.60)	1.15 (0.50-2.68)	.63	
Basal-like	99	1.00	1.62 (0.78-3.35)	1.59 (0.75-3.36)	2.50 (1.16-5.42)	.04	.74
ASBs							
Breast cancer-specific mortality							
Luminal A	305	1.00	0.82 (0.59-1.12)	0.79 (0.54-1.15)	0.73 (0.54-0.98)	.08	
Luminal B	153	1.00	1.25 (0.77-2.03)	0.96 (0.54-1.69)	1.23 (0.82-1.84)	.40	
HER2-enriched	45	1.00	0.76 (0.26-2.19)	1.70 (0.49-5.93)	0.30 (0.08-1.08)	.06	
Basal-like	45	1.00	0.90 (0.29-2.74)	0.96 (0.25-3.61)	1.20 (0.46-3.14)	.56	.25
All-cause mortality							
Luminal A	793	1.00	0.93 (0.77-1.13)	0.81 (0.64-1.03)	0.98 (0.81-1.18)	.91	
Luminal B	341	1.00	1.14 (0.82-1.59)	1.22 (0.87-1.72)	1.36 (1.03-1.81)	.04	
HER2-enriched	83	1.00	0.86 (0.43-1.72)	1.34 (0.60-2.96)	0.52 (0.24-1.16)	.14	
Basal-like	99	1.00	1.13 (0.56-2.28)	1.09 (0.49-2.40)	1.49 (0.79-2.82)	.19	.33

Abbreviations: ASBs, artificially sweetened beverages; HER2, human epidermal growth factor receptor 2; HR, hazard ratio; SSBs, sugar-sweetened beverages.

[a]Models were stratified by cohort and adjusted for age at diagnosis (year), calendar year of diagnosis, time between diagnosis and first food frequency questionnaire (year), calendar year at the start of follow-up of each-2-year questionnaire cycle, prediagnostic body mass index (<20.0, 20.0 to <22.5, 22.5 to <25.0, 25.0 to <30.0, 30.0 to <35, and ≥35.0 kg/m^2, or missing), body mass index change after diagnosis (no change [≥−0.5 to ≤0.5 kg/m^2], decrease [<−0.5 kg/m^2], increase [>0.5 to 2,0 kg/m^2], increase [>2.0 kg/m^2], or missing), postdiagnostic smoking (never, past, current 1-14 cigarettes per day, current 15-24 cigarettes per day, current ≥25 cigarettes per day, or missing), postdiagnostic physical activity (<5.0, 5.0 to <11.5, 11.5 to <22.0, or ≥22.0 metabolic equivalent of task hours per week, or missing), oral contraceptive use (ever, never), postdiagnostic alcohol consumption (<0.15, 0.15 to <2.0, 2.0 to <7.5, or ≥7.5 g/day), postdiagnostic total energy intake (quintiles, kcal/day), prediagnostic menopausal status, age at menopause, and postmenopausal hormone use status (premenopausal; postmenopausal, aged <50 years at menopause, and never used postmenopausal hormones; postmenopausal, aged <50 years at menopause, and past postmenopausal hormone use; postmenopausal, aged <50 years at menopause, and current postmenopausal hormone use; postmenopausal, aged ≥50 years at menopause, and never used postmenopausal hormones; postmenopausal, aged ≥50 years at menopause, and past postmenopausal hormone use; postmenopausal, aged ≥50 years at menopause, and current postmenopausal hormone use; or missing), postdiagnostic aspirin use (never, past, current, or missing), race (non-Hispanic White or other), stage of disease (I, II, or III), radiotherapy (yes, no, or missing), chemotherapy (yes, no, or missing), and hormonal treatment (yes, no, or missing).

consumption of SSBs was associated with higher risk of breast cancer-specific and all-cause mortality among both never smokers and ever smokers (see Supporting Table 9). Furthermore, the associations between postdiagnostic SSB or ASB consumption and mortality did not differ by alcohol consumption (see Supporting Table 10) or modified AHEI after diagnosis (see Supporting Table 11).

DISCUSSION

The current large, prospective study with long time follow-up demonstrated that higher SSB consumption after breast cancer diagnosis was associated with higher breast cancer-specific and overall mortality risk among breast cancer survivors. These findings are similar to what Malik et al. observed in a prior analysis among cancer-free women using the NHS data.[21] In contrast, higher ASB consumption was not associated with higher breast cancer-specific or all-cause mortality risk among women with breast cancer. Replacing SSBs with an isovolumetric serving of ASBs, fruit juice, skim/low-fat milk, or whole milk was not associated with lower mortality risk. Replacement of SSBs with an isovolumetric serving of coffee or tea was associated with a lower risk of breast cancer-specific mortality, and replacement with coffee, tea, or water was associated with a lower risk of overall mortality.

High SSB consumption increases postprandial blood glucose and insulin levels.[40] Substantial evidence suggests a possible link between hyperglycemia and hyperinsulinemia and a poorer breast cancer prognosis.[7,8,13] In nondiabetic women with breast cancer,[15] high levels of circulating insulin (>13 μIU/mL) before breast cancer treatment were associated with worse disease progression. Hyperglycemia increases tumor cell migration, which affects cancer survival.[41] In addition, increased insulin secretion in response to glucose acts as a growth factor and results in tumor growth.[42] Thus, the elevation in postprandial glucose associated with SSB consumption may affect tumor cell growth. However, our results were significant after adjusting for dietary glycemic index or glycemic load. Overweight and obesity also have been associated with a poorer breast cancer prognosis,[9,10] and because SSB consumption is associated with weight gain,[43] it could further increase the risk of breast cancer mortality by this pathway. Our results were significant when we adjusted for prediagnostic BMI and postdiagnostic weight change, However, we observed higher risk of mortality among women with overweight or obesity. Further confirmatory studies are warranted.

Finally, we observed that replacing SSBs with coffee, tea, or water was associated with a lower risk of mortality. However, substituting other low-calorie or high-calorie beverages, including ASBs, fruit juice, skim/low-fat milk, or whole milk, for SSBs was not associated with significantly improved survival. Our recent study among breast cancer survivors showed that higher coffee consumption after diagnosis was associated with lower breast cancer and all-cause mortality, and higher tea consumption after diagnosis was associated with lower all-cause mortality.[21] Replacing SSBs or fruit juice with water, coffee, tea, ASBs, or low-fat milk also was associated with lower weight gain among healthy participants.[44] In addition, replacing SSBs with coffee was associated with lower risk of diabetes.[5] Given the biologic link between obesity and diabetes, and poor breast cancer outcomes,[9-12] changing beverage drinking patterns by replacing SSBs with water, coffee, or tea and reducing SSB consumption may be a potentially practical strategy to reduce mortality among women with breast cancer.

Evaluating cumulative SSB and ASB consumption every 4 years from self-reported dietary intake before and after diagnosis as well as the large number of breast cancer survivors, with medical confirmation of cancer end points and long duration of follow-up, are strengths of our study. In addition, we controlled for a comprehensive list of key predictors of breast cancer survival, including lifestyle factors and extensive medical history.

Potential limitations of our study need to be considered. Despite controlling for several factors that may affect the association between SSB or ASB consumption and survival, we cannot rule out the possibility of residual confounding in our observational study. In addition, the NHS and NHSII participants were predominately non-Hispanic White and educated. Women with higher SSB consumption tended to have unhealthy dietary intake and lifestyle habits, which could overestimate the association between SSB consumption and mortality. However, adjusting for lifestyle factors resulted in stronger associations with breast cancer-specific mortality. Furthermore, the mean time from breast cancer diagnosis to the first postdiagnostic FFQ was 3.3 years, and we were not able to look at survival shortly after diagnosis.

In this study, we observed that higher SSB consumption after a breast cancer diagnosis was associated with greater breast cancer-specific and all-cause mortality. Replacing SSBs with coffee, tea, or water may help women with early stage breast cancer to improve life expectancy. Given our findings and other evidence,[21] it is prudent for practitioners and public health officials to promote limiting or eliminating SSB consumption to reduce breast cancer mortality in the United States and worldwide. Further research is needed to understand the pathways driving these associations.

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CONFLICT OF INTEREST DISCLOSURES

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AUTHOR CONTRIBUTIONS

Maryam S. Farvid: Study concept and design, statistical analysis, interpretation of data, funding acquisition, writing–original draft, critical revision of the article for important intellectual content, and approval of the final version for submission. **Nicholas D. Spence:** Interpretation of data, critical revision of the article for important intellectual content, and approval of the final version for submission. **Bernard A. Rosner:** Statistical analysis, interpretation of data, critical revision of the article for important intellectual content, and approval of the final version for submission. **Wendy Y. Chen:** Interpretation of data, critical revision of the article for important intellectual content, and approval of the final version for submission. **A. Heather Eliassen:** Interpretation of data, critical revision of the article for important intellectual content, funding acquisition, and approval of the final version for submission. **Walter C. Willett:** Interpretation of data, critical revision of the article for important intellectual content, funding acquisition, and approval of the final version for submission. **Michelle D. Holmes:** Interpretation of data, critical revision of the article for important intellectual content, and approval of the final version for submission.

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