

Sugar-Sweetened Soda Consumption and Total and Breast Cancer Mortality: The Western New York Exposures and Breast Cancer (WEB) Study

Nadia Koyratty¹, Susan E. McCann², Amy E. Millen¹, Jing Nie¹, Maurizio Trevisan³, and Jo L. Freudenheim¹



ABSTRACT

Background: There is growing evidence of an association between sugar-sweetened beverages (SSB) and increased risk of mortality in various populations. However, SSB influence on mortality among patients with breast cancer is unknown.

Methods: We assessed the relationship between sugar-sweetened soda and both all-cause and breast cancer mortality among women with incident, invasive breast cancer from the Western New York Exposures and Breast Cancer Study. Breast cancer cases were followed for a median of 18.7 years, with ascertainment of vital status via the National Death Index. Frequency of sugar-sweetened soda consumption was determined via dietary recall using a food frequency questionnaire. Cox proportional hazards, adjusting for relevant variables, were used to estimate HRs and 95% confidence intervals (CI).

Results: Of the 927 breast cancer cases, 386 (54.7%) had died by the end of follow-up. Compared with never/rarely sugar-

sweetened soda drinkers, consumption at ≥ 5 times per week was associated with increased risk of both total (HR = 1.62; 95% CI, 1.16–2.26; $P_{\text{trend}} < 0.01$) and breast cancer mortality (HR = 1.85; 95% CI, 1.16–2.94; $P_{\text{trend}} < 0.01$). Risk of mortality was similarly increased among ER-positive, but not ER-negative patients; among women with body mass index above the median, but not below the median; and among premenopausal, but not postmenopausal women for total mortality only.

Conclusions: Reported higher frequency of sugar-sweetened soda intake was associated with increased risks of both total and breast cancer mortality among patients with breast cancer.

Impact: These results support existing guidelines on reducing consumption of SSB, including for women with a diagnosis of breast cancer.

Introduction

Breast cancer is the most common incident cancer and the second leading cause of cancer mortality among women in the United States (1). With improved early detection and treatment, the number of breast cancer survivors has grown to more than 3.1 million currently in the United States alone (2). Given the ever-increasing number of patients with breast cancer, understanding the factors related to reduced mortality following a breast cancer diagnosis is critically important. Although dietary changes are potentially modifiable practices that can be implemented by patients with cancer, there is much that remains unknown regarding the relationship, if any, between dietary factors and cancer mortality (3).

One dietary component of potential importance is sugar-sweetened beverages (SSB), which groups together carbonated sugar-sweetened soda, sports or energy drinks, sweetened waters, teas, coffees, and all other beverages containing added caloric sweeteners such as high-fructose corn syrup (HFCS), sucrose, glucose, honey, molasses, and even fruit-juice concentrate (4). According to the Global Burden of Disease 2017 Risk Collaborators, worldwide consumption of SSB has

increased drastically in the past few decades (5). Although the WHO recommends limiting sugar consumption to $\leq 10\%$ of total energy intake, consumption in the U.S. population generally exceeds that guideline (6). Among the many types of SSB available, sugar-sweetened soda is among the top sources of added sugars and calories in the diet of Americans, but contributes little else nutritionally (7). In fact, in the U.S. population, added sugars contribute about 11% to 17% of daily energy intake, with sugar-sweetened soda contributing about a third of the total added sugar intake (7, 8).

There is considerable evidence of an association of a range of health problems associated with excessive intake of SSB or high sugar diets; these include cardiometabolic diseases, including weight gain, type 2 diabetes, and cardiovascular diseases (CVD; refs. 9, 10). In addition, there is mixed evidence of their association with cancer (11–13), including for breast cancer (14, 15); with some studies indicating increased risk of incident cancer (12, 14), whereas others indicate no or inverse associations (13, 15).

With regard to mortality, SSB consumption has also been identified as one of the primary contributors to increases in total attributable deaths and disability adjusted life years (DALY) globally between 1990 and 2017 (5). Recently, some studies have suggested positive associations between higher intakes of SSB and total mortality in groups suffering from cancers (16, 17) and among general disease-free populations (13, 18–23), but others have found no significant associations (24, 25). There is less evidence regarding all-cancer mortality and cancer-specific mortality in relation to SSB (10, 13, 19, 21, 23, 25). To our knowledge, the Nurses' Health Study (NHS) is the only study that reports on SSB and breast cancer mortality. In the NHS, there was a trend toward increased breast cancer mortality associated with increased SSB intake (HR = 1.09; 95% CI, 1.00–1.18; $P_{\text{trend}} = 0.02$; ref. 20). However, there is no study on this association specifically within a cohort of patients with breast cancer.

¹Department of Epidemiology and Environmental Health, School of Public Health and Health Professions, University at Buffalo, Buffalo, New York. ²Division of Cancer Prevention and Population Sciences, Department of Cancer Prevention and Control, Roswell Park Comprehensive Cancer Center, Buffalo, New York. ³Health Sciences, Vin University, Hanoi, Vietnam.

Corresponding Author: Nadia Koyratty, Department of Epidemiology and Environmental Health, University at Buffalo, State University of New York, 270 Farber Hall, Buffalo, NY 14214. E-mail: bibinadi@buffalo.edu

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Given the suggestive evidence that SSBs consumption may increase the risk of breast cancer incidence (26–28) and mortality (20), understanding their possible impact on breast cancer prognosis is potentially significant. Sugar-sweetened soda is the most heavily-consumed SSB type in all age groups of the U.S. population and functions as a good proxy for high intakes of added sugars (29); we therefore report here on the association between reported sugar-sweetened soda intake with total and breast cancer mortality in a population-based study of women diagnosed with incident, primary, invasive breast cancer in Western New York.

Materials and Methods

Study population

The Western New York Exposures and Breast Cancer (WEB) Study was a population-based case-control study in Erie and Niagara counties, conducted between 1996 and 2001. For this project, we only used data regarding the breast cancer cases ($N = 1,170$). A more detailed description of the study design and methods is available elsewhere (30–32). WEB Study breast cancer cases were women ages 35 to 79 years at the time of interview, diagnosed with primary, histologically-confirmed, incident, invasive breast cancer, identified by nurse case finders in all the major hospitals in the study region. Of the eligible cases, 72% agreed to participate. Our analyses are limited to women with complete information on sugar-sweetened soda consumption ($n = 28$ excluded) and relevant covariates. In addition, to minimize confounding, those who had diabetes at baseline enrolment were excluded ($n = 76$) because their consumption of sugar-sweetened soft drinks was different from those without diabetes ($P < 0.05$). Breast cancers diagnosed at stage 0 non-invasive ($n = 144$) were also excluded. This led to a final sample size of 927 breast cancer cases for our analyses. Written informed consent was obtained from all participants; the study was approved by the institutional review boards of the State University of New York, University at Buffalo, and participating hospitals.

Data collection

Assessment of consumption of sugar-sweetened soda

We define sugar-sweetened soda as regular carbonated SSB, not including fruit juices, sports drinks, coffees, teas, or flavoured waters. A modified version of the Health Habits and History food frequency questionnaire (FFQ) was used to assess usual dietary intake in the 12 to 24 months prior to diagnosis of breast cancer (33). Participants were asked to recall how often, on average, they consumed sugar-sweetened soda (i.e., not diet soda), using a nine-level categorical frequency scale ranging from (i) rarely/never, (ii) once a month, (iii) two to three times per month, (iv) once a week, (v) twice a week, (vi) three to four times per week, (vii) five to six times per week, (viii) once a day to (ix) ≥ 2 times per day. We collapsed these nine categories into four groups as follows: (i) rarely/never, (ii) \leq one time per week, (iii) two to four times per week, and (iv) \geq five times per week. Although, the FFQ queried about serving sizes of sugar-sweetened soda during intake, we do not account for this information in our analyses since more than 40% of the participants were missing portion size information.

Assessment of survival

Vital status of breast cancer cases participating in the WEB study was determined from the National Death Index (NDI) through December 31, 2018. We used the International Classification of Diseases, Tenth revision (ICD-10), to systematically identify cause of death. Total mortality was defined as death from any cause, whereas

breast cancer mortality was attributed if breast cancer was specifically identified as the underlying cause of death. Participants' contribution to person-time survival was calculated as the number of months of follow up from date of diagnosis until date of death or until the end of follow-up on December 31, 2018, whichever occurred first.

Covariate measurement

Recalls from the FFQ were also used to estimate energy intake (daily kilocalories), fruit intake (daily grams), vegetable intake (daily grams), dietary fiber (daily grams), alcohol consumption over the previous 12 to 24 months (ever/never), and other nutrient intakes. Data were also collected by trained interviewers during in-person computer-assisted interviews at baseline on demographics (age at diagnosis, race/ethnicity, education), smoking history (lifetime pack years), reproductive history (age at first birth, age at menarche, menopausal status, age at menopause, parity, ever hormone replacement therapy), and physical activity (metabolic hours per week) obtained from all forms of recreational, work- and chore-related activities performed by participants in the week prior to the interview. All participants who reported a prior physician-diagnosed history of angina, stroke, heart attack (myocardial infarction, transient ischemic heart attack), atrial fibrillation, rheumatoid heart disease, and aortic aneurism were classified as having CVD. History of physician-diagnosed high blood pressure, high blood cholesterol, and high blood glucose were similarly reported by participants. Body mass index (BMI) at baseline was calculated as weight (kg) divided by the square of height (m^2). Height and weight were measured by trained interviewers using a standardized protocol (34). Clinical characteristics of tumors from women with breast cancer [cancer stage at diagnosis, estrogen-receptor (ER) status, progesterone-receptor (PR) status] were obtained from baseline medical charts reviewed by trained nurses. During the interview, the women were also asked about the planned or prior treatments for their incident breast cancer including queries regarding surgery, radiation, and chemotherapy.

Statistical analyses

Descriptive statistics for demographic, personal, and reproductive characteristics of those who died and those who remained alive until the end of the follow-up period were compared. We used T tests for the mean and SD of continuous and normally distributed variables. For non-normal continuous variables, we present the median and interquartile range and made comparisons using the Wilcoxon rank-sum test. Frequencies and percentages are reported for categorical variables and we used the Chi-square test for group comparisons.

Hazard ratios (HR) and the respective 95% confidence intervals (CI) for total and breast cancer mortality were estimated with Cox proportional hazards regression models. We included covariates in the model that altered the unadjusted HRs by 10% or more, as well as other covariates based on *a priori* knowledge of risk factors for breast cancer survival. The covariates examined included age, race, education, smoking, physical activity, BMI, age at first birth, parity, age at menopause, age at menarche, menopausal status, energy intake, dietary fiber intake, fruit intake, vegetable intake, sodium intake, fat intake, vitamin supplement intake, alcohol consumption, stage at diagnosis, ER status, PR status, radiotherapy, chemotherapy, hormone replacement therapy, high blood pressure, high blood cholesterol, high blood glucose and baseline CVD diagnosis. Our final models were adjusted for age (years), race (white/black), education (years), smoking (life pack years), physical activity (metabolic hours per week), cancer stage (stage I (the reference group), stage II, stages III/IV, stage unknown), BMI (kg/m^2), alcohol intake (ever/never), energy intake

(Kcal/day), ER status [ER positive (the reference group), ER negative, ER unknown], baseline CVD diagnosis (no/yes), high blood pressure (no/yes), high blood cholesterol (no/yes), vegetable intake (g/day), fruit intake (g/day), and dietary fiber (g/day). The proportional hazards assumption was tested for all models and was found to hold in all analyses. We also assessed whether there was a trend in risk for total and breast cancer mortality across frequencies of sugar-sweetened soda consumption using the Wald Chi-square test for trend.

We examined associations stratified by menopausal status (postmenopausal and premenopausal), ER status (ER positive and ER negative) and BMI (< median BMI and \geq median BMI). Product terms were used to test for the interaction between sugar-sweetened soda intake and menopausal status, ER status, and BMI. In addition, because the probability that terminal cancer and its treatments may affect diet and that diet would be unlikely to affect the survival outcome at later stages, we carried out sensitivity analyses by excluding women who died within 1 year of diagnosis ($n = 6$). Results remained unchanged and we present the HR from the complete sample. We also performed an analysis excluding participants with reported daily energy intake of less than 500 calories or more than 5,000 calories ($N = 2$) and those who had missing energy intake information ($n = 18$). The point estimates were not affected and we present results with the complete sample and after imputing the missing energy intake information. All analyses were conducted using SAS for Windows version 9.4.

Results

Descriptive characteristics of breast cancer cases from the WEB study included in our analyses are shown in **Table 1**. Total follow-up time from the date of diagnosis ranged from 8.9 to 262 months, with a median survival time of 224 months. Of the included 927 women diagnosed with primary, incident, invasive breast cancer, 386 (41.6%) had died by the end of the follow-up period at December 31, 2018. Breast cancer deaths accounted for 39.6% of all deaths ($n = 153$). Compared with women who survived to the end of the follow-up period, those who died were on average, older, more likely to be postmenopausal, smoked more, were at higher cancer stage at diagnosis, had higher BMI, consumed less fruits and vegetables, were less physically active, were less likely to be alcohol drinkers and were more likely to have had cardiovascular disease, high blood pressure, and high blood cholesterol. Mortality did not differ by age at menarche, age at menopause, hormone therapy use, tumor ER or PR status, age at first childbirth, race, family history of breast cancer, energy intake, dietary fiber intake, or fat intake. Among the participants who died, there was a somewhat higher percentage of women who reported high frequency of sugar-sweetened soda consumption compared with the women who remained alive. The frequency of diet soda consumption also differed by survival status ($P = 0.03$) and by sugar-sweetened soda consumption frequency ($P < 0.01$).

Compared with those who rarely or never drank sugar-sweetened soda, reported consumption at ≥ 5 times per week was associated with increased breast cancer mortality (HR = 1.85; 95% CI, 1.16–2.94; $P_{\text{trend}} < 0.01$) and total mortality (HR = 1.62; 95% CI, 1.16–2.26; $P_{\text{trend}} < 0.01$; **Table 2**). As part of our sensitivity analyses, we ran additional models that included treatment for the breast cancer such as chemotherapy and radiation therapy. The results were similar (total mortality: HR = 1.49; 95% CI, 1.06–2.08; $P_{\text{trend}} = 0.02$; breast cancer mortality: HR = 1.78; 95% CI, 1.11–2.85; $P_{\text{trend}} < 0.01$). Similarly, including diet soda consumption as a covariate in the models did not

change our measures of associations (total mortality: HR = 1.46; 95% CI, 1.05–2.04; $P_{\text{trend}} = 0.02$; breast cancer mortality: HR = 1.65; 95% CI, 1.01–2.68; $P_{\text{trend}} = 0.03$).

Tests for interactions were not significant for BMI ($P = 0.65$), menopausal status ($P = 0.13$), or ER status ($P = 0.89$). In analyses stratified by menopausal status (**Table 3**), associations were stronger among the pre- than the postmenopausal women for breast cancer mortality but not total mortality. In analyses stratified by ER status, women with ER-positive breast cancer had higher risk of both total (HR = 1.65; 95% CI, 1.10–2.50; $P_{\text{trend}} = 0.02$) and breast cancer mortality (HR = 2.41; 95% CI, 1.31–4.46; $P_{\text{trend}} < 0.01$) with increasing frequency of sugar-sweetened soda consumption, whereas among those who were ER-negative, associations for total mortality and breast cancer mortality included the null. In BMI-stratified analyses, among women with BMI above the median, higher sugar-sweetened soda intake was associated with increased risks of total mortality (HR = 1.87; 95% CI, 1.21–2.89; $P_{\text{trend}} < 0.01$) and breast cancer mortality (HR = 2.02; 95% CI, 1.05–3.90; $P_{\text{trend}} = 0.03$). The associations were not significant for women with BMI below the median.

Discussion

In this study of women with primary, incident, histologically-confirmed, invasive breast cancer, we found a dose-response trend of increasing risk for both total mortality and breast cancer mortality with higher consumption frequency of sugar-sweetened, non-diet soda ($P_{\text{trend}} < 0.01$ for both), after adjusting for age, race, education, smoking, physical activity, cancer stage, BMI, menopausal status, alcohol intake, energy intake, ER status, baseline CVD, high blood pressure, high blood cholesterol, vegetable intake, fruit intake, dietary fiber. With higher frequency of sugar-sweetened soda consumption, there was increased risk of total and breast cancer mortality among women with ER positive ($P_{\text{trend}} < 0.01$), but not ER-negative tumors ($P_{\text{trend}} > 0.05$), with BMI above the median ($P_{\text{trend}} < 0.05$), but not below the median BMI ($P_{\text{trend}} > 0.05$) and for premenopausal women ($P_{\text{trend}} < 0.05$); for postmenopausal women, there was increased risk for breast cancer mortality ($P_{\text{trend}} = 0.03$), but not total mortality ($P_{\text{trend}} = 0.07$).

To our knowledge, this is the first study specifically among patients with breast cancer regarding the association between sugar-sweetened soda and mortality. Among patients with upper aerodigestive tract cancer (16) and colon cancer (17), SSB consumption has been found to be positively associated with increased risk of all-cause mortality. Among cohorts initially free from any cancer, such as European Prospective Investigation into Cancer and Nutrition (EPIC; ref. 23), Health Professionals Follow-up Study (HPFS; ref. 20), NHS (20), Vitamins and Lifestyle Study (VLS; ref. 19), and the Singapore Chinese Health Study (SCHS; ref. 25), the association of SSB with all-cause or cancer-specific mortality have been less consistent. For instance, VLS, HPFS, and NHS all reported significantly higher risk of all-cause and cancer mortality, whereas EPIC reported higher risk for all-cause mortality, but not for cancer mortality and SCHS reported higher risk for cancer mortality, but not for all-cause mortality. Of these five studies, only NHS reported on breast cancer-specific mortality. They found increased risk of breast cancer death with increasing SSB intake. Findings likely differ primarily because of the consumption patterns in these different populations or based on the definition of SSB in each study and the SSB parameterization used in the statistical analyses.

Sugar-sweetened soda, as part of the SSB group, are among the leading sources of added sugars in the American diet, irrespective of age (7, 8, 29, 35). High intake of sugar-sweetened soda, in the quantities

Table 1. Sugar-sweetened soda and breast cancer prognosis - WEB study: descriptive characteristics by mortality status ($N = 927$).

Covariates	Total	Alive	Dead	P^a
<i>N</i> (%)	927 (100)	541 (58.4)	386 (41.6)	
White (<i>n</i> , %)	856 (92.3)	503 (93.0)	353 (91.5)	0.39
Age (years) ^{b,c}	57.7 (11.3)	54.5 (9.6)	62.4 (11.9)	<0.01
Education (years) ^{b,c}	13.5 (2.6)	13.9 (2.5)	13.0 (2.6)	<0.01
Lifetime smoking (life pack years) ^{d,e}	0.1 (18.3)	0.2 (14.2)	2.1 (23.5)	<0.01
Physical activity (METH/week) ^d	235.5 (14.8)	236.8 (16.0)	234.5 (14.3)	<0.01
BMI (kg/m ²) ^{b,c}	28.4 (6.4)	27.8 (6.2)	29.3 (6.5)	<0.01
Age at first childbirth (<i>n</i> , %)				0.97
Nulliparous	160 (17.3)	91 (16.8)	69 (17.9)	
<24 years old	272 (29.3)	161 (29.8)	111 (28.8)	
24 to 27 years old	266 (28.7)	155 (28.7)	111 (28.8)	
>27 years old	229 (24.7)	134 (24.8)	95 (24.6)	
Post-menopause (<i>n</i> , %) ^c	653 (70.4)	342 (63.2)	311 (80.6)	<0.01
Energy intake (kcal/d) ^{b,f}	1,446 (683)	1,532 (571.5)	1,564.4 (697.3)	0.45
Dietary fiber (g/day) ^{b,f}	11.4 (6.8)	12.3 (5.6)	11.7 (5.5)	0.12
Vegetable intake (g/day) ^{d,f}	56.8 (57.5)	59.2 (56.7)	52.7 (57.0)	0.04
Fruit intake (g/day) ^{d,f}	94 (148.8)	100.1 (157.4)	88.2 (114.0)	0.02
Saturated fat (g/day) ^{d,f}	20.7 (14.5)	20.7 (13.7)	20.6 (14.9)	0.26
Polysaturated fatty acids (g/day) ^{d,f}	8.9 (7.1)	8.8 (7.1)	9.2 (7.1)	0.18
Ever alcohol consumption (<i>n</i> , %) ^f	470 (50.7)	297 (54.9)	173 (44.8)	<0.01
Stage at diagnosis (<i>n</i> , %) ^c				<0.01
Stage I	444 (47.9)	295 (54.5)	149 (38.6)	
Stage II	284 (30.6)	155 (28.7)	129 (33.4)	
Stage III/IV	56 (6.0)	14 (2.6)	42 (10.9)	
Unknown	143 (15.4)	77 (14.2)	66 (17.1)	
ER status (<i>n</i> , %)				0.69
Negative	259 (27.9)	153 (28.3)	106 (27.5)	
Positive	615 (66.3)	360 (66.5)	255 (66.0)	
Unknown	53 (5.7)	28 (5.2)	25 (6.5)	
PR status (<i>n</i> , %)				0.28
Negative	326 (37.8)	183 (36.3)	143 (39.9)	
Positive	536 (62.2)	321 (63.7)	215 (60.1)	
Unknown	65 (7.0)	37 (7.0)	28 (7)	
Radiation therapy (<i>n</i> , %)	488 (53.3)	305 (57.1)	183 (48.0)	<0.01
Chemotherapy (<i>n</i> , %)	400 (44.2)	236 (44.3)	164 (44.0)	0.93
Hormone replacement therapy (<i>n</i> , %) ^c	381 (41.1)	221 (40.9)	160 (41.5)	0.85
Family history of breast cancer (<i>n</i> , %) ^c	181 (19.5)	113 (20.9)	68 (17.6)	0.45
Prior benign breast disease (<i>n</i> , %) ^c	325 (35.6)	205 (38.6)	120 (31.4)	0.03
High blood pressure (<i>n</i> , %) ^c	301 (32.5)	138 (25.5)	163 (42.2)	<0.01
High blood cholesterol (<i>n</i> , %) ^c	314 (33.9)	164 (30.3)	150 (38.9)	<0.01
High blood glucose (<i>n</i> , %) ^c	21 (2.3)	14 (2.6)	7 (1.8)	0.44
Baseline CVD (<i>n</i> , %) ^c	212 (22.9)	100 (18.5)	112 (29.0)	<0.01
Sugar sweetened soda (<i>n</i> , %) ^f				0.07
Never/rarely	480 (51.8)	290 (53.6)	190 (48.2)	
≤ once per week	201 (21.7)	123 (22.7)	78 (20.2)	
2–4 times per week	133 (14.4)	74 (13.7)	59 (15.3)	
≥5 times per week	113 (12.2)	54 (10.0)	59 (15.3)	
Underlying causes of death (<i>n</i> , %)				
All cancer mortality			211 (54.7)	
Breast cancer mortality			153 (39.6)	
CVD mortality			76 (19.7)	
Other causes			99 (25.7)	

^a P value displayed compares patients with breast cancer who were alive and those who died; comparison of means by t test, of medians by Kruskal–Wallis test, and of frequencies by chi-square test.

^bMean (SD).

^cAt baseline interview at the time of breast cancer diagnosis.

^dMedian (interquartile range).

^eLifetime considered from any smoking start age.

^fMeasured as dietary recall via FFQ in the 12 to 24 months prior to breast cancer diagnosis.

Table 2. Association between sugar-sweetened soda and mortality among WEB study breast cancer cases (*N* = 927).

Frequency of consumption	Rarely/never (<i>n</i> = 480)	≤1 time per week (<i>n</i> = 201)	2–4 times per week (<i>n</i> = 133)	≥5 times per week (<i>n</i> = 113)	<i>P</i> _{trend}
Total mortality (<i>N</i> = 386)	190	78	59	59	
Age-adjusted	Ref.	1.04 (0.80–1.35)	1.41 (1.05–1.89)	2.01 (1.49–2.70)	<0.01
Multivariable-adjusted ^a	Ref.	1.00 (0.76–1.31)	1.26 (0.92–1.72)	1.62 (1.16–2.26)	<0.01
Breast cancer mortality (<i>N</i> = 153)	63	27	29	34	
Age-adjusted	Ref.	1.02 (0.65–1.61)	1.71 (1.10–2.66)	2.38 (1.56–3.64)	<0.01
Multivariable-adjusted ^a	Ref.	0.93 (0.58–1.47)	1.49 (0.93–2.39)	1.85 (1.16–2.94)	<0.01

^aMultivariable-adjusted: age (years), race (white/black), education (years), smoking (life pack years), physical activity (metabolic hours/week), cancer stage [stage I (the reference group), stage II, stage III/IV, stage unknown], BMI (kg/m²), menopausal status (premenopausal/postmenopausal), alcohol intake (ever/never), energy intake (Kcal/day), ER status [ER positive (the reference group), ER negative, ER unknown], baseline CVD (no/yes), high blood pressure (no/yes), high blood cholesterol (no/yes), vegetable intake (g/day), fruit intake (g/day), dietary fiber (g/day).

Table 3. Association between sugar-sweetened soda and mortality stratified by menopausal status, ER status, and BMI.

Frequency of consumption	Rarely/never (<i>n</i> = 480)	≤1 time per week (<i>n</i> = 201)	2–4 times per week (<i>n</i> = 133)	≥5 times per week (<i>n</i> = 113)	<i>P</i> _{trend}
Premenopause (<i>N</i> = 274)^a					
Total deaths (<i>N</i> = 75)	21	20	16	18	
Total mortality (HR, 95% CI)	Ref	1.76 (0.94–3.31)	1.96 (0.96–4.00)	3.21 (1.53–6.73)	<0.01
Breast cancer deaths (<i>N</i> = 56)	18	13	12	13	
Breast cancer mortality (HR, 95% CI)	Ref	1.33 (0.63–2.79)	1.55 (0.68–3.50)	2.64 (1.14–6.15)	0.02
Postmenopause (<i>N</i> = 653)^a					
Total deaths (<i>N</i> = 311)	169	58	43	41	
Total mortality (HR, 95% CI)	Ref	0.83 (0.61–1.14)	1.08 (0.76–1.55)	1.42 (0.97–2.08)	0.07
Breast cancer deaths (<i>N</i> = 97)	45	14	17	21	
Breast cancer mortality (HR, 95% CI)	Ref	0.71 (0.38–1.32)	1.48 (0.81–2.69)	1.81 (1.02–3.23)	0.03
ER-positive (<i>N</i> = 615)^b					
Total deaths (<i>N</i> = 255)	137	48	32	38	
Total mortality (HR, 95% CI)	ref	0.83 (0.59–1.16)	1.16 (0.77–1.75)	1.65 (1.10–2.50)	0.02
Breast cancer deaths (<i>N</i> = 91)	41	15	15	20	
Breast cancer mortality (HR, 95% CI)	Ref	0.90 (0.49–1.66)	1.51 (0.80–2.85)	2.41 (1.31–4.46)	<0.01
ER-negative (<i>N</i> = 259)^b					
Total deaths (<i>N</i> = 106)	43	26	22	15	
Total mortality (HR, 95% CI)	Ref	1.41 (0.84–2.35)	1.35 (0.75–2.46)	0.94 (0.46–1.89)	0.95
Breast cancer deaths (<i>N</i> = 57)	21	12	13	11	
Breast cancer mortality (HR, 95% CI)	Ref	1.01 (0.47–2.15)	1.50 (0.69–3.24)	1.14 (0.50–2.64)	0.65
BMI < Median (<i>N</i> = 463)^c					
Total deaths (<i>N</i> = 167)	81	40	24	22	
Total mortality (HR, 95% CI)	Ref	0.92 (0.62–1.36)	0.77 (0.47–1.27)	1.27 (0.75–2.15)	0.52
Breast cancer deaths (<i>N</i> = 74)	30	16	13	15	
Breast cancer mortality (HR, 95% CI)	Ref	0.90 (0.48–1.68)	1.04 (0.51–2.14)	1.75 (0.84–3.64)	0.12
BMI ≥ Median (<i>N</i> = 464)^c					
Total deaths (<i>N</i> = 219)	109	38	35	37	
Total mortality (HR, 95% CI)	Ref	1.04 (0.71–1.52)	1.70 (1.13–2.55)	1.87 (1.21–2.89)	<0.01
Breast cancer deaths (<i>N</i> = 79)	33	11	16	19	
Breast cancer mortality (HR, 95% CI)	Ref	0.95 (0.47–1.90)	1.91 (1.00–3.66)	2.02 (1.05–3.90)	0.03

^aInteraction between sugar-sweetened soda consumption and menopausal status prior to stratification: *P* = 0.13.

All models were adjusted for age (years), race (white/black), education (years), smoking (life pack years), physical activity (metabolic hours/week), cancer stage [stage I (the reference group), stage II, stage III/IV, stage unknown], BMI (kg/m²), alcohol intake (ever/never), energy intake (Kcal/day), ER status [ER positive (the reference group), ER negative, ER unknown], baseline CVD (no/yes), high blood pressure (no/yes), high blood cholesterol (no/yes), vegetable intake (g/day), fruit intake (g/day), dietary fiber (g/day).

^bInteraction between sugar-sweetened soda consumption and ER status prior to stratification: *P* = 0.89.

All models were adjusted for age (years), race (white/black), education (years), smoking (life pack years), physical activity (metabolic hours/week), cancer stage [stage I (the reference group), stage II, stage III/IV, stage unknown], BMI (kg/m²), menopausal status (premenopausal/postmenopausal), alcohol intake (ever/never), energy intake (Kcal/day), baseline CVD (no/yes), high blood pressure (no/yes), high blood cholesterol (no/yes), vegetable intake (g/day), fruit intake (g/day), dietary fiber (g/day).

^cInteraction between sugar-sweetened soda consumption and BMI prior to stratification: *P* = 0.65.

All models were adjusted for age (years), race (white/black), education (years), smoking (life pack years), physical activity (metabolic hours/week), cancer stage [stage I (the reference group), stage II, stage III/IV, stage unknown], BMI (kg/m²), menopausal status (premenopausal/postmenopausal), alcohol intake (ever/never), energy intake (Kcal/day), ER status [ER positive (the reference group), ER negative, ER unknown], baseline CVD (no/yes), high blood pressure (no/yes), high blood cholesterol (no/yes), vegetable intake (g/day), fruit intake (g/day), dietary fiber (g/day).

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consumed by many in the United States, has been associated with weight gain and high adiposity (36–38), both of which are well-established risk factors for cancers, particularly postmenopausal breast cancer (39, 40) and for reduced survival after breast cancer diagnosis (41–43). BMI was associated with both sugar-sweetened soda consumption frequency ($P = 0.04$) and with mortality status ($P < 0.01$) in our WEB population. In analyses stratified by BMI, those with BMI \geq median ($\sim 27 \text{ kg/m}^2$) had higher risks for both total and breast cancer mortality, whereas the HR were much smaller and did not reach statistical significance for those with BMI less than the median. Although this difference in the mortality risks between BMI groups may be indicative of its role as a potential effect measure modifier in the association between sugar-sweetened soda consumption and mortality, there was no significant interaction.

Postmenopausal women had significantly higher BMI compared with premenopausal women ($P < 0.01$). We found increased risk of breast cancer mortality ($P_{\text{trend}} = 0.03$) with higher frequency of sugar-sweetened soda consumption among postmenopausal women with breast cancer, even with adjustment for BMI. However, we did not find an association with total mortality in this older group. Although we also found significantly higher risks of total and breast cancer mortality among premenopausal women, the number of women in this group in the WEB study are small and CIs for the HR were wide. We know of no other study on this association between sugar-sweetened soda and breast cancer mortality with data stratified by menopausal status.

Another mechanism by which sugar-sweetened soda may promote carcinogenesis and potentially affect prognosis after breast cancer diagnosis, is through glycemic response (44). With the large quantities of sucrose and fructose that make up sugar-sweetened soda, these beverages have the highest glycemic load in comparisons to other foods or drinks (45, 46). Their contribution to high concentrations of glucose and insulin may lead to hyperinsulinemia, impaired glucose tolerance, and higher circulating insulin-like growth factor (IGF) levels (47–49); all of which have been associated with higher risk of breast cancer through enhanced tumor development and tumor cell migration (28, 50–56). Hyperglycemia after sugar-sweetened soda consumption also induces oxidative stress (57, 58). Most sugar-sweetened soda contain large amounts of fructose from the sweetening agent, HFCS, which can produce advanced glycation end-products, found to contribute to the development and progression of cancers in nonhuman studies (28, 59). In a prospective cohort, patients with breast cancer in the United States with higher prediagnostic blood glucose were found to have lower overall survival (60). In another cohort of nonmetastatic patients with breast cancer, all-cause mortality was associated with high fasting blood glucose level. In the Health, Eating, Activity and Lifestyle (HEAL) Study of Breast Cancer Prognosis cohort, there was a nonsignificant trend toward higher all-cause and breast cancer mortality risks associated with high glycemic index and glycemic loads (61).

When the association between mortality and sugar-sweetened soda was stratified by ER-status among the WEB breast cancer cases, there were higher risks for both total mortality and breast cancer mortality for women with ER positive, but not ER negative tumors. To our knowledge, there are no other studies that have examined this association in a cohort of patients with breast cancer stratified by ER status. Additional research, accounting for adequate statistical power, should be performed to investigate the interaction between SSB intake and ER status in the association with mortality among women with breast cancer.

These results need to be considered in the context of the strengths and limitations of the study. As an observational study, we made every effort to control for other possible variables that might affect the associations under investigation, but residual confounding cannot be entirely ruled out. Another limitation of these findings is the single measure of diet used as exposure measure; participants were asked to recall their usual dietary intake in the 12 to 24 months prior to the breast cancer diagnosis. The effect of diet on breast cancer survival is likely to be a complex combination of prediagnostic and postdiagnostic consumption (62, 63); we did not have dietary data following diagnosis or during follow-up. Women in the WEB study may have changed their diet following their breast cancer diagnosis, potentially with changes toward a healthier diet and lifestyle, perhaps including reduced sugar-sweetened soda intake (62). If this change did occur, it would likely have attenuated the observed associations.

Another limitation in the examination of sugar-sweetened soda is the potential underestimation of total sugar intake which is considered the primary dietary culprit in SSB for poor survival post breast cancer diagnosis. Because of the nature of the questionnaire, we could not isolate individual types of sugar-containing beverages, such as juices, teas, coffees, sports drinks, or flavored waters. However, since sugar-sweetened soda makes up the majority of all SSB consumption (29), our reported associations are most likely underestimates of the true associations. It is also important to note that high frequency of sugar-sweetened soda consumption is not an isolated feature of the diet, but is usually part of an unhealthy diet pattern. In our analyses, we attempted to adjust for overall diet quality, by adjusting for fruit, vegetable, and dietary fiber. Results remained similar to models not including diet quality variables. In addition, because sugar-sweetened nondiet soda is perceived as an unhealthy choice, the information provided by the WEB participants may not be completely accurate due to social desirability bias. We would not expect the bias to be differential between those who remained alive and those who died because diet information was collected prior to the outcome occurrence. All these sources of error would likely result in an underestimation of the actual intake of sugar-sweetened soda and an underestimation of the true association between sugar-sweetened soda and mortality in this population.

This study also has multiple strengths. We used data from a large-scale population-based series of incident, histologically-confirmed breast cancer cases. In addition, where other studies have focused on the general disease-free population, we specifically focused on a population of patients with breast cancer and survivors. Survival was ascertained prospectively from the time of enrolment, using the NDI, which has been widely utilized and validated for mortality studies (64). Furthermore, we had a relatively long follow-up time that is adequate for survival studies (median: 224; range: 8.88–262 months). Finally, comparisons of descriptive characteristics between women who died with those still alive at the end of the follow-up period identified expected risk factors associated with mortality, suggesting that our sample is representative of the general population of patients with breast cancer.

In summary, our study contributes to the current growing evidence of mortality risk associated with the consumption of SSB. Our findings suggest that higher frequency of consumption of sugar-sweetened soda is associated with greater risk of both total mortality and breast cancer mortality among women diagnosed with incident invasive breast cancer. Overall, even though we cannot infer causality from this study, our findings coupled with the nutritional knowledge that sugar-

sweetened soda is a nutrient-poor beverage option, having a high contribution of unnecessary added sugars to the diet, support recommendations for their reduced consumption, even among patients with breast cancer and survivors.

Authors' Disclosures

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Authors' Contributions

N. Koyratty: Formal analysis, writing—original draft, writing—review and editing. **S.E. McCann:** Conceptualization, writing—review and editing. **A.E. Millen:** Writing—review and editing. **J. Nie:** Data curation, software. **M. Trevisan:** Writing—review and

editing. **J.L. Freudenheim:** Conceptualization, resources, supervision, funding acquisition, methodology, writing—review and editing.

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