Research Article

Cancer Prevention Research

Consumption of Sugars, Sugary Foods, and Sugary Beverages in Relation to Adiposity-Related Cancer Risk in the Framingham Offspring Cohort (1991–2013)

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Abstract

Background: Higher sugar consumption may increase cancer risk by promoting insulin-glucose dysregulation, oxidative stress, hormonal imbalances, and excess adiposity. This prospective study investigates the association between dietary sugars (fructose and sucrose) and sugary foods and beverages in relation to combined and site-specific (breast, prostate, colorectal) adiposity-associated cancers.

Methods: The analytic sample consisted of 3,184 adults, aged 26–84 years, from the Framingham Offspring cohort. Diet data were first collected between 1991 and 1995 using a food frequency questionnaire. Intakes of fructose, sucrose, sugary foods, and sugary beverages (fruit juice and sugar-sweetened beverages) were derived. Participants were followed up until 2013 to ascertain cancer incidence; 565 doctor-diagnosed adiposity-related cancers, including 124 breast, 157 prostate, and 68 colorectal cancers occurred. Multivariable-adjusted Cox proportional hazards models were used to evaluate associations. Tests for interaction with BMI and waist circumference were conducted.

Results: No associations were observed between fructose, sucrose, sugary food consumption, and combined incidence of adiposity-related cancers or the examined site-specific cancers. While total consumption of sugary beverages was not associated with site-specific cancer risk, higher intakes of fruit juice were associated with 58% increased prostate cancer risk (HR: 1.58; 95% CI, 1.04–2.41) in multivariable-adjusted models. In exploratory stratified analyses, higher sugary beverage intakes increased overall adiposity-related cancer risk by 59% in participants with excessive central adiposity (HR: 1.59; 95% CI, 1.01–2.50; $P_{trend} = 0.057$).

Conclusions: In this cohort of American adults, higher sugary beverage consumption was associated with increased cancer risk among participants with central adiposity.

Impact: These analyses suggest that avoiding sugary beverages represents a simple dietary modification that may be used as an effective cancer control strategy. *Cancer Prev Res; 11(6); 347–58. ©2018 AACR.*

Introduction

Consumption of sugars is increasing worldwide (1) and is a key contributing factor for obesity and associated noncommunicable diseases (2, 3). Dietary sugars encompass both naturally present and added sugars. Naturally present sugars include fructose in fruits and fruit juice as well as lactose in dairy products. Added sugars are introduced to food products during production and processing and have been linked in the scientific literature to chronic disease etiology (1). Added sugars are in the form of sucrose or table sugar, made by processing sugar cane and sugar beets, and high-fructose corn syrup (HFCS), synthesized from corn and sold in two main forms: one has 42% fructose and the other has 55% fructose (4). On the basis of nationally representative data from 2013, 68% of available packaged foods and beverages purchased by U.S. households contain these caloric sweeteners (1).

High sugar consumption due to excessive intakes of calorically sweetened foods and beverages has been linked to overweight and obesity, which can promote cancer through adiposity-related mechanisms including insulin resistance, hyperinsulinemia, increased bioavailability of

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doi: 10.1158/1940-6207.CAPR-17-0218

steroid hormones, oxidative stress, and inflammation (5). These metabolic shifts create an environment that promotes tumor initiation and growth. Beyond their influence on body adiposity, high intakes of sugars have also been shown to independently promote chronic activation of the insulin signaling pathway as well as elevation of markers of oxidative stress and inflammation, which collectively increase cancer risk (6). However, the impact of dietary sugars and their food and beverage sources on cancer risk, particularly adiposity-related cancers, is not well characterized in longitudinal studies (7).

Adiposity-related cancers are cancers that are clearly or possibly linked to overweight and obesity and encompass the most common cancers including gastrointestinal, female, genitourinary, reticuloendothelial system (blood, bone, and spleen), and the thyroid gland cancers (8, 9). These cancers are lifestyle-related and are hypothesized to be avertable through modifications in nutrition and physical activity (7). Therefore, deciphering the impact of sugars on adiposity-related cancers is essential to disrupt the adiposity and cancer link using dietary approaches.

Much of the existing literature on dietary sugars and cancer is derived from case–control studies and is suggestive that sugars, sugary foods, and sugary beverages may be linked to higher risk of certain cancers (7, 10, 11). The World Cancer Research Fund (WCRF) and American Institute for Cancer Research's (AICR) Second Expert Report (7) concludes that there is "limited suggestive" epidemiologic evidence so far that sugars, primarily fructose and sucrose, are associated with risk of colorectal cancer, but that evidence from prospective cohort studies is sparse for other cancer sites. Another issue that has received renewed attention is whether fructose and sucrose have a differential impact on cancer. Sucrose, commonly referred to as table sugar, is composed of both glucose and fructose (12). Fructose levels can vary widely from 42% to 90% of sugar in some HFCS to up to 65% in some the most popular sugary beverages (12, 13). Fructose, which is metabolized differently than glucose in the liver, may have unique adverse effects (12, 14).

An additional knowledge gap is the limited evidence investigating the associations between sugary foods and beverages in relation to the risk of most common cancers. The WCRF/AICR expert panel report emphasized the importance of investigating nutrients in conjunction with their food sources in relation to cancer risk, because evidence on food, nutrition, and cancer is generally most persuasive and usefully synthesized to public health and clinical guidelines for foods rather than individual nutrients (7).

We used data from the prospective Framingham Heart Study (FHS) Offspring cohort to assess the relationship between dietary sugars and adiposity-related cancer risk within a sample of American adults. We hypothesized that higher intakes of sugars and their food and beverage sources will be associated with higher cancer risk. In this study, we focused on total fructose and sucrose intakes, given their documented role in obesity and potential to influence cancer risk, and on sugary foods and beverages, as a surrogate for added sugar intake, in relation to combined incidence of adiposity-related cancers and three of the most common site-specific cancers in the United States: breast, prostate, and colorectal cancers.

Materials and Methods

Study cohort

The FHS is a multi-generational prospective cohort study that was initiated in 1948–1953 in Framingham, MA (15). The Framingham Offspring (FOS) cohort represents the second familial generation of the FHS and consists of the children of the original cohort and their spouses ($n = 5{,}124$ adults; ref. 15). This cohort was initiated in 1971–1975, and clinical exams to collect medical and lifestyle data were conducted, on average, every 4 years and are currently ongoing. The collection of dietary data in the FOS was first initiated in 1991–1995 during the fifth clinical examination. At this clinical exam, there were 3,799 participants, out of which 3,418 had available diet data. Therefore, this was considered the baseline examination for these analyses.

The analytic dataset included participants with valid diet data at exam 5. Although diet data was available at subsequent clinical exams, for these analyses, diet data was used from exam 5 only, because a previous study on trends in carbohydrate consumption in the aging FOS cohort did not reveal any clinically significant changes over time (16). Dietary data was considered valid if reported energy intakes were within the ranges of 600–4,000 and 600–4,200 kcal/day for women and men, respectively, and if participants left <13 blanks on the FFQ. On the basis of these criteria, there were 3,320 participants with valid dietary data. Participants with a history of adiposity-related cancer at or prior to exam 5 ($n = 134$) and pregnant women at exam 5 ($n = 2$) were also excluded. The final analytic dataset included 3,184 participants, aged 26–84 years (mean age: 55.4 years). Written informed consent was obtained from all FHS participants. All research activities were consistent with the Declaration of Helsinki and the ethical standards of New York University's Institutional Review Board (IRB #10-7319).

Dietary assessment

Habitual dietary intake during the previous 12 months was assessed at exam 5 using the validated semiquantitative 126-item Harvard FFQ (17). The FFQ was mailed to study participants for completion prior to the clinical exam, but participants were subsequently asked to bring the completed questionnaire with them to their appointment for review by trained personnel to ensure accuracy.

The FFQ consisted of a list of foods with standard serving sizes. Participants selected their frequency of consumption for the various foods from 9 frequency categories, ranging from never or <1 serving/month to >6 servings/day. Nutrient intakes were computed by multiplying the frequency of consumption of each unit of food by the nutrient content of the specified portion using the US Department of Agriculture nutrient database (17). Participants also reported use of dietary supplements on the FFQ. This FFQ has been validated in numerous population groups for both nutrients and foods (17–19). Intakes of fructose and sucrose, sugary foods and beverages were derived from the FFQ.

Total fructose and sucrose intake variables (g/day) were derived from the FFQ and were already present in the FHS diet files. Sugary food intake (servings/week) was computed as the sum of dairy dessert, grain dessert, sugary breakfast snack, candy, and chocolate intakes. Sugary beverage intake (servings/week) was computed as the sum of fruit juice and sugar-sweetened beverage (SSB) intakes. Fruit juice was defined as the intake of apple juice or apple cider, orange juice, grapefruit juice, and other juice. SSBs included intakes of Cola (Coke, Pepsi and other cola) with sugar, Cola without caffeine, non-cola soft drink and punch, lemonade, or other noncarbonated fruit drinks. In general, one serving of SSB was equivalent to 360 mL (12 fl oz), while one serving of fruit juice was equivalent to 180 mL (6 fl oz).

Cancer case ascertainment

The primary outcome of interest for this study is combined incidence of adiposity-related cancers. Cancers were considered adiposity-related if identified by the American Cancer Society or the National Cancer Institute as clearly or possibly linked to overweight and obesity (8, 9). Therefore, cancers of the gastrointestinal tract, reticuloendothelial system, female reproductive tracts, genitourinary organs, and the thyroid gland were considered adiposity-related in these analyses (8, 9). The secondary outcomes in this study were breast, prostate, and colorectal cancers to examine whether the associations are stronger for some cancers compared with others.

The FHS cancer files include confirmed primary cancers with information on cancer type and date of diagnosis obtained from the patient's medical record. Cancer cases were ascertained using pathology reports. However, less than 5% of diagnoses were based solely on death certificates or clinical reports without pathology reports. Self-reported or suspected diagnoses not confirmed by pathology reports were excluded. Cancer coding was done using the World Health Organization ICD-O system (20). The FHS cancer database continues to be regularly updated from pathology reports as participants are examined, and cancer data are released, on average, every two years. A total of 699 primary adiposity-related cancers occurred in the FOS, but after excluding participants with a history of adiposity-related cancer at or prior to exam 5, a total of 565 primary adiposity-related cancer cases were included. Female cancers ($n = 162$) included breast, ovarian, endometrial, and cervical cancers. Gastrointestinal cancers ($n = 102$) included esophageal, colorectal, gastric, liver, gallbladder, and pancreatic cancers. Genitourinary cancers ($n = 220$) included prostate, bladder and renal cancers. Cancers of the reticuloendothelial system ($n = 65$) included all cancers of the blood, bone, and spleen. The most prevalent cancers in the FOS were breast ($n = 124$), prostate ($n = 157$), and colorectal cancers ($n = 68$), consistent with the most prevalent cancers in the U.S. population (21).

Assessment of covariates

Demographic and anthropometric variables. Age was reported at every exam. Anthropometric measures including height and weight were obtained by trained personnel at all study exams and used to compute body mass index (BMI). Waist circumference (WC) was measured to assess central adiposity. Participants were classified as "normal," "overweight," and "obese" if their BMI was <25, 25–29.9, $\geq$30 kg/m^2, respectively (22). Men and women with WC >40 and >35 inches, respectively, were considered "at risk" (23).

Medical history variables. Participants' history of chronic diseases was ascertained on the basis of the presence or absence of diabetes and CVD at or prior to exam 5. In particular, participants were considered to have diabetes if their fasting blood glucose was greater or equal to 126 mg/dL or if they were receiving diabetes treatment. Similarly, they were considered to have CVD as described previously by FHS (24). Among women, menopausal status was assessed using a standardized medical history questionnaire, and hormone therapy (HT) use was ascertained by a physician at the fifth clinical exam.

Lifestyle variables. Smoking, alcohol use and physical activity level were self-reported during in-person interviewing. Participants were classified as current, former or nonsmokers. Alcohol consumption in ounces/week was assessed using responses to three open-ended questions that queried the number of 1.5-oz cocktails, 12-oz glasses (or cans) of beer, and 4-oz glasses of wine that participants consumed, on average, per week (25). Habitual physical activity levels were assessed by asking participants to report the number of hours per week they spent resting or engaging in various activities ranging from sleep to heavy activity and computing a physical activity index (PAI), as previously published in FHS (26).

Statistical analysis

Clinical and lifestyle characteristics of the FOS cohort at exam 5 were examined across the quintiles of sugary food and beverage intake using general linear models procedure. Cox proportional hazards regression models

were used to estimate the HRs and 95% confidence intervals (CI) for the hypothesized associations between dietary sugars and their food and beverage sources in relation to adiposity-related cancers in the main analyses and also in relation to breast, prostate, and colorectal cancers in exploratory analyses.

For the main analysis with adiposity-related cancers combined, fructose and sucrose variables were categorized into quintiles, while sugary food and beverage variables were categorized into quintiles, quartiles, or tertiles as appropriate depending on the distribution and intake ranges for these variables. For site-specific analyses, all variables were categorized into tertiles, given the limited number of site-specific cancers. In all analyses, individuals in the lowest tertile/quartile/quintile were considered the referent category. Age- and multivariable-adjusted HR were reported. Multivariable regression models for all cancer outcomes were adjusted *a priori* for established risk factors of cancer including age, sex, smoking, alcohol, and energy (7). In the analyses for the breast cancer, we further adjusted relevant cancer risk factors including menopausal status, hormone therapy (HT), age at menopause, and number of live births (7). In analyses for colorectal cancer, we further adjusted for total fiber and for red and processed meat intake (7).

Other variables that are potential confounders including preexisting conditions (CVD and diabetes), antioxidant supplement use, physical activity and fruit and vegetable, fat, and diet soda intake were tested in the models. These covariates were retained in the final model if they changed HRs by >10%. Models were also fitted with and without BMI and WC to determine whether they are confounders or modify the association of dietary sugars with adiposity-related cancers. However, additional adjustment for BMI, WC, chronic diseases (CVD and diabetes), physical activity, antioxidant use, percentage energy from fat, diet soda, and fruit and vegetable intake did not alter findings in any model. *P* values for linear trends across the quintile categories of the exposure variables, in the main analyses with adiposity-related cancers, were computed using the test for linear contrast. The calculated P_{trend} is the *P* value for a test of linear trend in a linear regression model with continuous variables. Participants who were lost to follow-up or died from other causes were censored.

To investigate whether BMI, a measure of total body adiposity, and WC, a measure of central adiposity, modify the impact of sugars on adiposity-related cancers, interactions with BMI and WC were tested, and if present, stratified analyses by WC ("normal" versus "at risk") and BMI ("normal" versus "overweight and obese") were conducted. Given that adiposity-related cancers were defined as cancers linked to both overweight and obesity, we evaluated the interactions by BMI for normal versus overweight and obese individuals. At exam 5, 65.0% of

Table 1. Participant characteristics at exam 5 by quintiles of total sugary food and beverage consumption ($N = 3{,}184$)[a]

Characteristics	<9.9 servings/wk ($n = 644$) Percentage/ mean (SD)	9.9–15.8 servings/wk ($n = 633$) Percentage/ mean (SD)	15.8–22.2 servings/wk ($n = 635$) Percentage/ mean (SD)	22.2–32.4 servings/wk ($n = 636$) Percentage/ mean (SD)	>32.4 servings/wk ($n = 636$) Percentage/ mean (SD)	*P*
Age (y)	53.8 (9.2)	55.3 (9.4)	53.8 (9.6)	55.0 (10.2)	53.8 (10.1)	0.004
Female (%)	62.3%	57%	55.1%	49.2%	41.5%	<0.0001
Education (y)	13.6 (2.5)	13.9 (2.3)	14.3 (2.7)	14.2 (2.6)	14.3 (2.8)	<0.0001
Physical LC Activity	34.4 (5.9)	34.4 (5.6)	34.8 (6.4)	34.8 (6.0)	35.5 (6.9)	0.010
BMI (kg/m^2)[b]	27.4 (5.2)	27.6 (5.1)	27.5 (4.9)	27.0 (4.5)	27.4 (4.9)	0.295
Waist circumference (inches)	36.0 (6.0)	36.7 (5.6)	36.5 (5.4)	36.3 (5.4)	37.0 (5.6)	0.078
Smoking status (%)						
Current smoker	22.4%	20.2%	17.2%	19.1%	18.0%	<0.0001
Former smoker	49.4%	44.7%	39.3%	42.0%	40.9%	
Never smoker	28.2%	35.1%	43.5%	38.9%	41.0%	
Antioxidant use (%)[c]	33.1%	37.3%	34.7%	40.7%	35.4%	0.050
Postmenopausal women (%)	61.4%	64.7%	64.5%	66.6%	62.9%	0.683
HT use (%)[b]	12.4%	12.7%	10.4%	10.7%	5.7%	0.0002
Diet						
Total calories (kcal)	1385.6 (437.5)	1610.0 (472.4)	1806.0 (464.1)	2044.7 (492.8)	2499.4 (586.9)	<0.0001
Total carbohydrates (%kcal)	46.7 (8.8)	49.2 (8.1)	51.3 (7.7)	52.3 (7.4)	54.8 (7.8)	<0.0001
Total protein (%kcal)	18.9 (3.7)	17.7 (3.2)	17.1 (2.7)	15.9 (2.5)	14.5 (2.6)	<0.0001
Total fat (%kcal)	27.5 (6.7)	27.3 (6.1)	27.0 (5.6)	27.7 (5.5)	27.5 (6.0)	0.243
Fruits and vegetables (servings/d)	3.5 (2.6)	3.5 (2.1)	3.8 (2.3)	3.9 (2.1)	3.9 (2.4)	0.002
Legumes (servings/wk)	2.1 (2.0)	2.3 (1.9)	2.4 (1.8)	2.5 (1.9)	2.8 (2.3)	<0.0001
Whole grains (servings/d)	1.0 (1.1)	1.2 (1.2)	1.2 (1.1)	1.3 (1.3)	1.4 (1.5)	<0.0001
Refined grains (servings/d)	1.8 (1.4)	1.9 (1.5)	2.1 (1.5)	2.4 (1.7)	3.0 (2.2)	<0.0001
Red and processed meat (servings/wk)	4.0 (3.5)	4.8 (3.9)	5.0 (3.7)	5.9 (4.5)	6.7 (5.5)	<0.0001
Alcohol (oz/wk)	2.9 (4.0)	2.0 (4.1)	2.3 (3.5)	2.5 (4.0)	2.1 (3.4)	0.001

[a]Characteristics of the FOS cohort at exam 5 were examined across the quintiles of sugary food and beverage intake using general linear models procedure.
[b]BMI, body mass index; HT, hormone therapy.
[c]Antioxidant supplements included vitamins A, C, E, selenium, and beta-carotene.

participants were either overweight or obese, of whom 24.2% were in the obese category. Similarly, interactions with sex, smoking status ("ever" versus "never"), and physical activity ("high or moderate" versus "low") were also examined due to their impact on cancer risk, which may cause the risk estimates to vary (7). A multiplicative term was introduced for these potential interactions in each model. A $P < 0.1$ was considered significant, and if

Table 2. Adjusted HRs (95% CI) for adiposity-related cancers and site-specific cancers by quintile/tertile categories of fructose and sucrose ($n = 3{,}184$)

Fructose (% kcal)	Quintile/Tertile 1	Quintile/Tertile 2	Quintile/Tertile 3	Quintile 4	Quintile 5	p-trend
Adiposity-related cancers ($n = 565$)[a]						
No. at risk (no. with outcome)	*651 (100)*	*627 (129)*	*654 (105)*	*617 (118)*	*635 (113)*	
Age-adjusted	1.00	1.19 (0.92–1.55)	0.90 (0.69–1.19)	1.07 (0.82–1.40)	1.05 (0.80–1.37)	0.938
Multivariable-Adjusted[e]	1.00	1.21 (0.92–1.58)	0.95 (0.72–1.26)	1.18 (0.90–1.56)	1.09 (0.83–1.44)	0.620
Breast cancer ($n = 124$)[b]						
No. at risk (no. with outcome)	*568 (46)*	*568 (44)*	*553 (34)*	–	–	
Age-adjusted	1.00	0.86 (0.57–1.30)	0.73 (0.47–1.15)	–	–	–
Multivariable adjusted[f]	1.00	0.93 (0.61–1.42)	0.76 (0.48–1.22)	–	–	–
Prostate cancer ($n = 157$)[c]						
No. at risk (no. with outcome)	*502 (50)*	*495 (48)*	*498 (59)*	–	–	
Age-adjusted	1.00	0.94 (0.63–1.39)	1.19 (0.81–1.75)	–	–	–
Multivariable-adjusted[g]	1.00	0.97 (0.65–1.46)	1.25 (0.84–1.85)	–	–	–
Colorectal cancer ($n = 68$)[d]						
No. at risk (no. with outcome)	*1,049 (23)*	*1,076 (22)*	*1,059 (23)*	–	–	
Age-adjusted	1.00	0.89 (0.50–1.61)	0.99 (0.55–1.78)	–	–	–
Multivariable-adjusted[h]	1.00	1.14 (0.62–2.11)	1.51 (0.81–2.82)	–	–	–
Adiposity-related cancers ($n = 656$)[a]						
No. at risk (no. with outcome)	*636 (139)*	*655 (112)*	*626 (101)*	*630 (112)*	*637 (101)*	
Age-adjusted	1.00	0.86 (0.67–1.11)	0.70 (0.54–0.91)	0.80 (0.62–1.03)	0.76 (0.59–98)	0.033
Multivariable-adjusted[e]	1.00	0.91 (0.71–1.18)	0.75 (0.57–98)	0.87 (0.67–1.14)	0.81 (0.61–1.07)	0.148
Breast cancer ($n = 124$)[b]						
No. at risk (no. with outcome)	*555 (45)*	*573 (38)*	*561 (41)*	–	–	
Age-adjusted	1.00	0.80 (0.52–1.24)	0.83 (0.54–1.28)	–	–	–
Multivariable adjusted[f]	1.00	0.87 (0.55–1.35)	0.96 (0.61–1.52)	–	–	–
Prostate cancer ($n = 157$)[c]						
No. at risk (no. with outcome)	*491 (57)*	*510 (59)*	*494 (41)*	–	–	
Age-adjusted	1.00	0.86 (0.60–1.24)	0.71 (0.48–1.07)	–	–	–
Multivariable-adjusted[g]	1.00	0.84 (0.57–1.24)	0.70 (0.45–1.08)	–	–	–
Colorectal cancer ($n = 68$)[d]						
No. at risk (no. with outcome)	*1,048 (32)*	*1,081 (17)*	*1,055 (19)*	–	–	
Age-adjusted	1.00	0.47 (0.26–0.84)	0.58 (0.33–1.02)	–	–	–
Multivariable-adjusted[h]	1.00	0.65 (0.35–1.21)	0.87 (0.46–1.64)	–	–	–

[a]For adiposity-related and colorectal cancers quintile cutoffs for fructose (% kcal) were: Q1: <3.3%, Q2: 3.3%–4.4%, Q3: 4.4%–5.6%, Q4: 5.6%–7.2%, Q5: >7.2%; and for sucrose (% kcal): Q1: <6.6%, Q2: 6.6%–8.5%, Q3: 8.5%–10.1%, Q4: 10.1%–12.6%, Q5: >12.6%.

[b]For breast cancers, tertile cutoffs for fructose (% kcal) were: T1: <4.1%, T2: 4.1%–6.0%, T3: >6.0%; and for sucrose (% kcal): T1: <7.9%, T2: 7.9%–10.8%, T3: >10.8%.

[c]For prostate cancers, tertile cutoffs for fructose (% kcal) were: T1: <4.0%, T2: 4.0%–6.1%, T3: >6.1%; and for sucrose (% kcal): T1: <7.7%, T2: 7.7–10.8, T3: >10.8%.

[d]For colorectal cancers, tertile cutoffs for fructose (% kcal) were: T1: <4.0%, T2: 4.0%–6.0%, T3: >6.0%; and for sucrose (% kcal): T1: <7.8%, T2: 7.8–10.8, T3: >10.8%.

[e]Models were adjusted for age, sex, smoking, alcohol, and energy. Additional adjustment for BMI, waist circumference, chronic diseases (CVD and diabetes), physical activity, antioxidant use, percentage energy from fat, and fruit and vegetable intake did not alter these findings.

[f]Models were adjusted for age, smoking, alcohol, energy, menopausal status, age at menopause, hormone therapy use and number of live births. Additional adjustment for BMI, waist circumference, chronic diseases (CVD and diabetes), physical activity, antioxidant use and percentage energy from fat did not alter these findings.

[g]Models were adjusted for age, sex, smoking, alcohol, energy. Additional adjustment for BMI, waist circumference, chronic diseases (CVD and diabetes), physical activity, antioxidant use, percentage energy from fat did not alter these findings.

[h]Models were adjusted for age, sex, smoking, alcohol, energy, fiber intake and red and processed meat intake. Additional adjustment for BMI, waist circumference, chronic diseases (CVD and diabetes), physical activity, antioxidant use, and percentage energy from fat did not alter these findings.

present, results were reported separately in subgroups with the caveat of limited power. All analyses were conducted using SAS version 9.3 (SAS Institute).

Results

Characteristics of the study population

Demographic, clinical, and dietary characteristics of the study population across the quintiles of total sugary food and beverage consumption (servings/week) were evaluated and are shown in Table 1. The mean age increased between the first and fourth quintile of intake from 53.8 to 55 years, but decreased to 53.8 in the fifth quintile ($P = 0.004$). Similarly, the number of years of education increased 13.6 to 14.3 years ($P < 0.0001$), as did the PAI from 34.4 to 35.5 ($P = 0.01$), representing high levels of physical activity in all categories of intake. However, the percentage of females (62.3%–41.5%; $P < 0.0001$) and women who reported HT use decreased across the quintiles (12.4%–5.7%; $P = 0.0002$). The percentage of current, former, and never smokers varied significantly across the categories of sugary food and beverage intake ($P < 0.0001$). In general, the percentage of never and former smokers was higher among participants who reported lower sugary food and beverage intakes. In contrast, there were no significant differences in BMI, WC, antioxidant supplement use, and in the proportion of postmenopausal women across the quintiles of sugary food and beverage consumption ($P \geq 0.05$).

We also characterized their dietary intakes by quintile of sugary food consumption. Participants in the highest quintile reported higher energy (2,499 kcal vs. 1,386 kcal) and carbohydrate intakes (54.8% vs. 46.7%) and lower protein intakes (14.5% vs. 18.9%) compared with those in the lowest quintile ($P < 0.0001$). There were no statistically significant differences in fat intakes ($P = 0.243$). In general, participants with higher sugary food and beverage consumption reported higher intakes of fruits and vegetables, legumes, red and processed meat, whole, and refined grains ($P < 0.0001$). However, they reported significantly lower intakes of alcohol (2.1 vs. 2.9 ounces/week; $P = 0.001$).

Fructose and sucrose in relation to risk of adiposity-related cancers and site-specific cancers

Fructose and sucrose intakes were not significantly associated with combined incidence of adiposity-related cancers in models adjusted for age, sex, energy, smoking, and alcohol (Table 2). Similarly, in secondary analyses, there were no significant associations between fructose and sucrose consumption in relation to risk of any of the site-specific cancers in multivariable-adjusted models. There were no significant interactions by BMI or physical activity ($P \geq 0.159$). A statistically significant multiplicative interaction was observed for WC ($P \leq 0.094$) and smoking status ($P \leq 0.081$) with fructose and sucrose and for sex with sucrose ($P = 0.002$). However, stratified analyses by WC, smoking status, and sex did not reveal any significant associations.

Sugary foods and beverages and overall adiposity-related cancer risk

In analyses evaluating total and types of sugary foods and beverages in relation to cancer risk, null results were observed for adiposity-related cancers in multivariable-adjusted models (Table 3). There were no significant interactions by BMI or physical activity ($P \geq 0.140$). A statistically significant multiplicative interaction was observed for sex ($P \leq 0.021$), WC ($P \leq 0.03$), and smoking status ($P \leq 0.066$). Stratified analyses by sex and smoking status did not reveal any significant associations. However, in stratified analyses by WC, among participants with excessive central adiposity (WC >40 and >35 inches for men and women, respectively), sugary beverage consumption in the fifth compared with the first quintile was associated with 59% higher risk of adiposity-related cancers in models adjusted for age, sex, energy, alcohol, smoking, and BMI (HR: 1.59; 95% CI, 1.01–2.50; $P_{trend} = 0.057$).

Sugary foods and beverages and site-specific cancer risk

In exploratory analyses for site-specific cancers, there was no significant association between total and types sugary foods in relation to the risk of breast, prostate, and colorectal cancers in multivariable-adjusted models (Table 4). Similarly, for total consumption of sugary beverages, null findings were observed for breast, prostate, and colorectal cancers in multivariable-adjusted models (Table 5). However, when types of sugary beverages were examined, SSB consumption was not significantly associated with site-specific cancer risk in multivariable-adjusted models, but intakes of fruit juice in the highest (>7 beverages/week) versus lowest tertile (<2 beverages/week) were associated with 58% higher prostate cancer risk in models adjusted for age, energy, alcohol, and smoking (HR: 1.58; 95% CI, 1.04–2.41).

Discussion

This prospective cohort study uniquely investigates the associations of dietary fructose and sucrose in conjunction with total and type of sugary foods and beverages with overall and site-specific adiposity-related cancer risk within a sample of U.S. adults. Our findings do not support an association between fructose and sucrose in relation to adiposity-related cancers. Sugary foods were not associated with the risk of any cancer. However, in exploratory stratified analyses, total consumption of sugary beverages was associated with 59% higher risk of adiposity-related cancers in participants with excessive central adiposity. Although total consumption of sugary beverages was not associated with risk of the examined site-specific cancers, higher consumption fruit juice was associated with a 58%

Table 3. Age- and multivariable-adjusted Hazard Ratios (95% Confidence Intervals) for combined incidence of adiposity-related cancers ($n = 565$) by sugary food and beverage (servings/week) categories[a]

	No. at risk (no. with outcome)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[j]
Sugary foods[b]			
<4.7	638 (111)	1.00	1.00
4.7–8.4	628 (122)	1.13 (0.88–1.47)	1.15 (0.89–1.50)
8.4–12.9	651 (114)	0.90 (0.69–1.17)	0.92 (0.70–1.21)
12.9–20.3	636 (118)	0.94 (0.73–1.22)	1.00 (0.75–1.33)
>20.3	631 (100)	0.86 (0.66–1.13)	0.84 (0.60–1.17)
P_{trend}		0.111	0.200
Dairy desserts[c]			
<0.5	1,746 (303)	1.00	1.00
0.5–1	612 (121)	1.20 (0.99–1.41)	1.22 (0.98–1.51)
>1	817 (139)	0.87 (0.68–1.08)	0.82 (0.66–1.02)
P_{trend}		0.058	0.076
Grain desserts[d]			
<0.9	739 (140)	1.00	1.00
0.9–2.4	576 (100)	0.88 (0.68–1.14)	0.91 (0.70–1.18)
2.4–4.4	601 (108)	0.95 (0.74–1.22)	0.99 (0.76–1.28)
4.4–8	632 (105)	0.80 (0.62–1.03)	0.85 (0.65–1.11)
>8	636 (112)	0.95 (0.74–1.22)	1.03 (0.78–1.37)
P_{trend}		0.492	0.985
Sugary breakfast snacks[e]			
<0.9	739 (131)	1.00	1.00
0.9–1.9	628 (101)	0.98 (0.76–1.28)	1.04 (0.80–1.36)
1.9–3.5	572 (110)	1.08 (0.83–1.39)	1.13 (0.87–1.46)
3.5–6.9	621 (123)	1.06 (0.83–1.36)	1.14 (0.88–1.48)
>6.9	624 (100)	0.80 (0.62–1.04)	0.82 (0.62–1.09)
P_{trend}		0.228	0.358
Chocolate and candy[f]			
<0.5	1,241 (241)	1.00	1.00
0.5–1.9	990 (155)	0.89 (0.83–1.10)	0.88 (0.72–1.09)
>1.9	950 (169)	0.95 (0.79–1.22)	0.99 (0.80–1.23)
P_{trend}		0.747	0.945
Sugary drinks[g]			
<1.9	657 (101)	1.00	1.00
1.9–5.5	629 (105)	1.05 (0.79–1.37)	1.10 (0.83–1.45)
5.5–8	642 (121)	1.07 (0.82–1.40)	1.09 (0.83–1.42)
8–13	632 (110)	1.03 (0.78–1.35)	1.05 (0.79–1.39)
>13	624 (128)	1.24 (0.96–1.62)	1.28 (0.97–1.70)
P_{trend}		0.165	0.171
Fruit juice[h]			
<0.9	627 (106)	1.00	1.00
0.9–3	707 (115)	0.80 (0.61–1.05)	0.84 (0.64–1.11)
3–6.9	553 (90)	0.90 (0.68–1.19)	0.91 (0.68–1.21)
6.9–8.4	647 (123)	0.94 (0.73–1.23)	0.96 (0.73–1.25)
>8.4	649 (131)	1.02 (0.79–1.32)	1.05 (0.80–1.38)
P_{trend}		0.484	0.463
SSB[i]			
0	1,136 (207)	1.00	1.00
0–0.9	559 (103)	1.02 (0.80–1.29)	0.99 (0.78–1.26)
0.9–3.5	764 (117)	0.86 (0.68–1.08)	0.84 (0.66–1.06)
>3.5	724 (138)	1.05 (0.84–1.30)	1.00 (0.79–1.27)
P_{trend}		0.937	0.663

[a]Quintiles, quartiles or tertiles of intake were compared depending on the distribution of intakes.

[b]Sugary foods included sherbet/ice milk, ice cream, muffins/biscuits, pancakes/waffles, chocolate, candy bars, candy without chocolate, cookies, brownies, doughnuts, cake, sweet roll, pie, jams/jellies. For doughnuts, muffins, pancakes and waffles, brownies, sweet rolls, and cookies, the serving size in the FFQ was one standard unit. For chocolate and candy, it was one standard bar and for pies and cakes, it was one standard slice.

[c]Dairy desserts included sherbet/ice milk, and ice cream.

[d]Grain desserts included cookies, doughnuts, cakes, sweet rolls, and pies.

[e]Sugary breakfast snacks included muffins/biscuits, jams/jellies, doughnuts, pancakes/waffles.

[f]Candy and chocolate included chocolate, candy bars and candy without chocolate.

increase in prostate cancer risk in secondary analyses within this cohort.

There is limited suggestive evidence from case–control studies that sugars are linked to a modest increase in colorectal cancer risk (7, 27). More recent case–control evidence is also suggestive that higher sugar intakes may be associated with elevated risk for female cancers (11, 28). However, our null findings are consistent with previous evidence from prospective studies. Most studies on sucrose in relation to cancer risk have reported null results (reviewed in ref. 29). Evidence was more mixed for fructose, as some studies were suggestive of a detrimental impact of up to >2-fold higher cancer risk (30–32) while others reported no association (33–35). Evidence on sugary foods and beverages in relation to adiposity-related cancers is limited (32, 36–40) with results ranging from no association for fruit juice, SSBs and sugary foods in some studies (36–38) to up to 2-fold higher cancer risk for SSBs in American, European, and Asian cohorts (32, 37, 39, 40).

One potential explanation for our null results on dietary sugars in relation to adiposity-related cancers is the level of sugar consumption in the FOS cohort. In a previous report in this cohort (16), at exam 5, total sugar intake represented approximately 18% of total energy intake (sucrose ~10% and fructose ~5% kcal). The mean intake of soft drinks and soda was 2 servings/week and that of fruit juice and drinks was 6.6 drinks/week. Detailed information on mean sugar intakes in the US is limited. However, data from USDA's 1989–1991 and 1994–1996 Continuing Survey of Food Intakes by Individuals showed that soft drinks and soda are top contributors to total caloric intake in the United States (41, 42). Moreover, 1977–2004 NHANES data reported mean fructose intakes of approximately 7.6% kcal among adults aged 60 and above (43). These findings indicate that sugar intakes in the FOS population may have been lower than in the general population, which may explain, at least in part, the observed null associations and may limit the generalizability of study findings.

In site-specific analyses, our null findings for sucrose in relation to the risk of breast, prostate, and colorectal cancer are also consistent with the majority of existing prospective studies (reviewed in ref. 29). While our null findings on fructose in relation to breast cancer are consistent with previous studies (34, 35), evidence on fructose and colorectal cancer is mixed (30, 31, 33). One study using the Iowa Women's Health Study cohort reported no

[g]Total sugary drinks include sugar sweetened beverages and fruit juice.

[h]Fruit juice includes apple juice/cider, orange juice, grapefruit juice and other juice.

[i]Sugar-sweetened beverages include regular sugar-sweetened soda and fruit drinks (lemonade and punch). Regular sugar-sweetened soda include cola soft drinks (with and without caffeine) and non-cola soft drink.

[j]Models were adjusted for age, sex, energy, smoking, and alcohol. Additional adjustment for BMI, waist circumference, chronic diseases (CVD and diabetes), physical activity, antioxidant use, percentage energy from fat and fruit and vegetable intake did not alter these findings.

Table 4. Age- and multivariable-adjusted HRs (95% CI) for risk of site-specific cancers by sugary food (servings/week) categories[a]

	Breast cancer ($n = 124$)[h]			Prostate cancer ($n = 157$)[i]			Colorectal cancer ($n = 68$)[j]		
	No. at risk (no. with outcome)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[k]	No. at risk (no. with outcome)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[l]	No. at risk (no. with outcome)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[m]
Sugary foods[b]									
Tertile 1	559 (43)	1.00	1.00	504 (50)	1.00	1.00	1,051 (23)	1.00	1.00
Tertile 2	574 (40)	0.85 (0.55–1.30)	0.88 (0.56–1.39)	497 (57)	1.09 (0.75–1.60)	1.12 (0.75–1.66)	1,087 (26)	1.11 (0.64–1.93)	1.30 (0.74–2.31)
Tertile 3	556 (41)	0.86 (0.56–1.32)	1.06 (0.64–1.78)	494 (50)	1.02 (0.69–1.52)	1.00 (0.62–1.62)	1,046 (16)	0.63 (0.33–1.19)	0.76 (0.35–1.67)
Dairy desserts[c]									
Tertile 1	1,013 (77)	1.00	1.00	733 (79)	1.00	1.00	1,746 (36)	1.00	1.00
Tertile 2	163 (11)	0.87 (0.46–1.64)	0.81 (0.42–1.58)	292 (33)	1.20 (0.80–1.81)	1.18 (0.78–1.78)	612 (16)	1.33 (0.74–2.41)	1.40 (0.77–2.56)
Tertile 3	506 (35)	0.83 (0.561.25)	0.92 (0.61–1.38)	468 (45)	0.78 (0.54–1.13)	0.74 (0.50–1.10)	817 (16)	0.77 (0.43–1.41)	0.80 (0.42–1.51)
Grain desserts[d]									
Tertile 1	565 (43)	1.00	1.00	499 (58)	1.00	1.00	1,136 (27)	1.00	1.00
Tertile 2	564 (47)	1.01 (0.67–1.53)	1.11 (0.72–1.72)	506 (43)	0.71 (0.48–1.05)	0.71 (0.47–1.08)	1,016 (22)	0.88 (0.50–1.54)	1.06 (0.60–1.90)
Tertile 3	560 (34)	0.74 (0.47–1.16)	0.84 (0.51–1.38)	490 (56)	1.10 (0.76–1.60)	1.12 (0.73–1.72)	1,032 (19)	0.76 (0.42–1.38)	0.91 (0.46–1.79)
Sugary breakfast snacks[e]									
Tertile 1	492 (44)	1.00	1.00	499 (42)	1.00	1.00	1,144 (25)	1.00	1.00
Tertile 2	595 (42)	0.82 (0.54–1.26)	0.88 (0.57–1.38)	494 (68)	1.67 (1.14–2.45)	1.64 (1.10–2.44)	1,003 (26)	1.21 (0.70–2.10)	1.45 (0.82–2.57)
Tertile 3	602 (38)	0.69 (0.45–1.07)	0.74 (0.45–1.19)	502 (47)	0.98 (0.64–1.49)	0.94 (0.60–1.48)	1,037 (17)	0.65 (0.35–1.22)	0.78 (0.40–1.55)
Chocolate and candy[f]									
Tertile 1	656 (44)	1.00	1.00	585 (69)	1.00	1.00	1,241 (31)	1.00	1.00
Tertile 2	469 (34)	1.16 (0.74–1.82)	1.32 (0.83–2.10)	417 (42)	0.90 (0.61–1.32)	0.89 (0.60–1.32)	990 (23)	1.12 (0.70–2.19)	1.08 (0.62–1.90)
Tertile 3	561 (46)	1.24 (0.82–1.87)	1.44 (0.93–2.24)	493 (46)	0.88 (0.61–1.28)	0.85 (0.56–1.28)	950 (14)	0.80 (0.44–1.60)	0.74 (0.37–1.46)

[a]Tertiles of intake were compared.

[b]Sugary foods included sherbet/ice milk, ice cream, muffins/biscuits, pancakes/waffles, chocolate, candy bars, candy without chocolate, cookies, brownies, doughnuts, cake, sweet roll, pie, jams/jellies. For doughnuts, muffins, pancakes and waffles, brownies, sweet rolls and cookies, the serving size in the FFQ was one standard unit. For chocolate and candy, it was one standard bar and for pies and cakes, it was one standard slice.

[c]Dairy desserts included sherbet/ice milk, and ice cream.

[d]Grain desserts included cookies, doughnuts, cakes, sweet rolls, and pies.

[e]Sugary breakfast snacks included muffins/biscuits, jams/jellies, doughnuts, pancakes/waffles.

[f]Candy and chocolate included chocolate, candy bars and candy without chocolate.

[h]For breast cancers tertile cutoffs (servings/week) were as follows for sugary foods: T1: <6.5, T2: 6.5–13.8, T3>13.8; for dairy desserts: T1: <0.5, T2: 0.5–0.9, T3: >0.9; for grain desserts: T1: <1.5, T2: 1.5–4.9, T3: >4.9 for sugary breakfast snacks: T1: <1.4, T2: 1.4–3.9, T3: >3.9; for candy and chocolate: T1: <0.5, T2: 0.5–1.9, T3: >1.9.

[i]For prostate cancers tertile cutoffs (servings/week) were as follows for sugary foods: T1: <7.9, T2: 7.9–16.3, T3: >16.3; for dairy desserts: T1: <0.5, T2: 0.5–1.0, T3: >1.0; for grain desserts: T1: <1.9, T2: 1.9–6.0, T3: >6.0; for sugary breakfast snacks: T1: <1.9, T2: 1.9–4.9, T3: >4.9; for candy and chocolate: T1: <0.5, T2: 0.5–1.5, T3: >1.5.

[j]For colorectal cancers tertile cutoffs (servings/week) were as follows for sugary foods: T1: <7.1, T2: 7.1–14.9, T3: >14.9; for dairy desserts: T1: <0.5, T2: 0.5–0.9, T3: >0.9; for grain desserts: T1: <1.9, T2: 1.9–5.5, T3: >5.5; for sugary breakfast snacks: T1: <1.5, Q2: 1.5–4.4; T3: >4.4; for candy and chocolate: T1: <0.5, T2: 0.5–1.9, T3: >1.9.

[k]Models were adjusted for age, energy, smoking, alcohol, menopausal status, age at menopause, hormone therapy and number of live births. Additional adjustment for BMI, waist circumference, chronic diseases (CVD and diabetes), education, physical activity, antioxidant use, percentage energy from fat and fruit and vegetable intake did not alter these findings.

[l]Models were adjusted for age, energy, smoking, and alcohol. Additional adjustment for BMI, waist circumference, chronic diseases (CVD and diabetes), education, physical activity, antioxidant use, percentage energy from fat and fruit and vegetable intake did not alter these findings.

[m]Models were adjusted for age, sex, smoking, alcohol, energy, fiber intake and red and processed meat intake. Additional adjustment for BMI, waist circumference, chronic diseases (CVD and diabetes), education, physical activity, antioxidant use, percentage energy from fat and fruit and vegetable intake did not alter these findings.

association (33), whereas two studies were indicative of a detrimental impact of 37% to 2-fold increased colorectal cancer risk with higher fructose consumption (30, 31). In one (31) of these studies (30, 31), associations were only significant among men. However, we were unable to investigate associations by sex due to the limited number of colorectal cancers in these exploratory analyses.

Epidemiologic evidence addressing the association between sugary drinks and cancer is limited and has focused primarily on colorectal cancer as an outcome. Pooled estimates from a recent meta-analysis demonstrated null associations between sugar-sweetened soft drinks and colon cancer (44). However, a study investigating cancer prevention guidelines in relation to breast cancer showed that adherence to the recommendation to reduce intake of sugary beverages was protective against breast cancer risk (45). This study is one of the early reports on sugary food and beverage consumption in relation to prostate cancer risk. We documented an increase in prostate cancer risk with higher intakes fruit juice, which increased prostate cancer risk by 58%. Only one previous Swedish study evaluated sugary beverages in relation to prostate cancer and reported null results for fruit juice, although approximately 40% higher risk of symptomatic but not total prostate cancer was observed for higher SSB intakes (46). This is inconsistent with our finding of a detrimental impact of fruit juice and the null results observed for SSB in relation to prostate cancer risk.

Although fruit juice may be a source of fiber, vitamins, and minerals with cancer-protective properties (7), fruit juice provides more calories than the whole fruit and consumed varieties may be calorically sweetened (1).

Table 5. Age- and multivariable-adjusted HRs (95% CI) for risk of site-specific cancers by sugary beverage (servings/week) categories[a]

	Breast cancer ($n = 124$)[e]			Prostate cancer ($n = 157$)[f]			Colorectal cancer ($n = 68$)[g]		
	No. at risk (no. with cancer)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[h]	No. at risk (no. with cancer)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[i]	No. at risk (no. with cancer)	Age-adjusted HR (95% CI)	Multivariable-adjusted HR (95% CI)[j]
Sugary drinks[b]									
Tertile 1	595 (48)	1.00	1.00	522 (42)	1.00	1.00	1,067 (17)	1.00	1.00
Tertile 2	526 (33)	0.78 (0.50–1.22)	0.76 (0.48–1.19)	476 (60)	1.29 (0.87–1.93)	1.26 (0.84–1.90)	1,058 (31)	1.89 (1.04–3.43)	2.07 (1.12–3.82)
Tertile 3	568 (43)	1.02 (0.67–1.54)	1.00 (0.65–1.57)	497 (55)	1.35 (0.91–2.03)	1.36 (0.88–2.09)	1,059 (20)	1.13 (0.59–2.17)	1.39 (0.68–2.82)
Fruit juice[c]									
Tertile 1	576 (47)	1.00	1.00	500 (38)	1.00	1.00	1,097 (20)	1.00	1.00
Tertile 2	622 (36)	0.65 (0.42–1.01)	0.66 (0.43–1.02)	519 (57)	1.37 (0.91–2.06)	1.34 (0.88–2.04)	1,120 (24)	1.12 (0.62–2.03)	1.21 (0.66–2.22)
Tertile 3	490 (41)	1.02 (0.67–1.56)	1.03 (0.67–1.62)	476 (62)	1.59 (1.06–2.38)	1.58 (1.04–2.41)	966 (24)	1.35 (0.74–2.46)	1.66 (0.88–3.12)
SSB[d]									
Tertile 1	717 (50)	1.00	1.00	419 (45)	1.00	1.00	1,136 (27)	1.00	1.00
Tertile 2	565 (47)	1.23 (0.82–1.84)	1.21 (0.80–1.83)	450 (43)	1.28 (0.88–1.86)	1.26 (0.86–1.85)	1,015 (19)	0.77 (0.43–1.40)	0.76 (0.41–1.41)
Tertile 3	406 (27)	1.06 (0.66–1.69)	1.04 (0.64–1.71)	626 (69)	1.08 (0.72–1.62)	1.06 (0.69–1.63)	1,032 (22)	0.91 (0.51–1.60)	0.96 (0.51–1.82)

[a]Tertiles of intake were compared.
[b]Sugary drinks include sugar sweetened beverages and fruit juice.
[c]Fruit juice includes apple juice/cider, orange juice, grapefruit juice and other juice.
[d]Sugar-sweetened beverages include regular sugar-sweetened soda and fruit drinks (lemonade and punch).
[e]For breast cancers, tertile cutoffs (servings/week) were as follows for sugary drinks: T1: <3.5, T2: 3.5–8.4, T3: >8.4; fruit juice: T1: <1.5, T2: 1.5–7.0, T3: >7.0; SSB: T1: 0, T2: 0–1, T3: >1.
[f]For prostate cancers, tertile cutoffs (servings/week) were as follows for sugary drinks: T1: <5.5, T2: 5.5–10.4, T3: >10.4; fruit juice: T1: <2.0, T2: 2.0–7.0, T3: >7.0; SSB: T1: 0.5, T2: 0.5–3.5, T3: >3.5.
[g]For colorectal cancers, tertile cutoffs (servings/week) were as follows for sugary drinks: T1: <4.0, T2: 4.0–9.4, T3: >9.4; fruit juice: T1: <1.9, T2: 1.9–7.0, T3: >7.0; SSB: T1: <0.5, T2: 0.5–3.5, T3: >3.5.
[h]Models were adjusted for age, energy, smoking, alcohol, menopausal status, age at menopause, hormone therapy use and number of live births. Additional adjustment for BMI, waist circumference, chronic diseases (CVD and diabetes), education, physical activity, antioxidant use, percentage energy from fat, and diet soda intake did not alter these findings.
[i]Models were adjusted for age, energy, smoking, and alcohol. Additional adjustment for BMI, waist circumference, chronic diseases (CVD and diabetes), education, physical activity, antioxidant use, percentage energy from fat, and diet soda intake did not alter these findings.
[j]Models were adjusted for age, sex, smoking, alcohol, energy, fiber intake and red and processed meat intake. Additional adjustment for BMI, waist circumference, chronic diseases (CVD and diabetes), education, physical activity, antioxidant use, percentage energy from fat, and diet soda intake did not alter these findings.

While the FFQ used in this study may have queried participants about 100% fruit juice intake, they may have reported intakes of both 100% and calorically sweetened fruit juice varieties that were commercially available during the study period. The role of fruit juice in cardio-metabolic health is controversial with some evidence suggestive of a detrimental impact (1, 2), particularly on weight gain, a cancer risk factor (7). Furthermore, it is notable that in this cohort, participants consumed most of their sugary beverages as fruit juice with 75% of men reporting consumption levels of $\geq$1 serving per day. In contrast, approximately 25% of men did not consume SSB, while 75% of men reported consuming $\leq$5 SSBs/week. Therefore, the null findings for SSB may be attributed, at least in part, to the limited range of SSB intakes in this cohort, which may have reduced the ability to detect an association.

Sugary beverages can increase prostate cancer risk by promoting insulin–glucose dysregulation, oxidative stress, inflammation, and increasing adiposity and its associated steroid hormone imbalances, which collectively increase cancer risk (6, 47). In this cohort, BMI and WC did not increase across the categories of sugary food and beverage consumption ($P \geq 0.078$). Furthermore, adjustment for both BMI and WC did not alter our findings. Beyond these mechanisms, sugary beverages may uniquely increase prostate cancer risk, because malignant prostate cancer cells, in addition to using passive glucose transporters as shown in long-standing research (48), can utilize glucose from sodium-dependent glucose transporters (49). Consequently, sugars may have a particularly pronounced impact on malignant prostate cells, thereby increasing prostate cancer risk. However, it should be noted that this finding of a detrimental effect on prostate cancer risk may be due to chance given the number of multiple comparisons that were conducted in these exploratory analyses.

We uniquely reported that sugary beverages increase adiposity-related cancer risk among men and women with WC >40 and 35 inches, respectively, suggesting that calorically sweetened beverages may be particularly detrimental to the health of individuals with excessive central adiposity. Interactions between body composition and sugar intake in the context of cancer risk have been previously evaluated in few studies (31, 32, 50). In analyses within the Nurses' Health Study and Health Professionals Follow Up Study cohorts, associations between fructose or sucrose and cancer were stronger among women and men with BMI $\geq$ 25 (31, 50). In contrast, associations between SSB and endometrial cancer risk were not modified by BMI (32), but were stronger among women with higher central adiposity (11). Consistently with these findings, associations between SSB and adiposity-related cancers did not vary BMI in this study, although stronger associations were

observed among participants with WC >35 and >40 inches, respectively, suggesting that central body adiposity may play a role. These findings need to be confirmed in a larger sample size to clarify the role of central adiposity in modifying these associations.

Interpretation of our findings is subject to some caveats. One limitation of our study is the measurement error associated with self-reported sugar intakes, which are particularly prone to misreporting (51, 52). This may have resulted in random misclassification of sugar intakes. Moreover, the FFQ may not have captured the full range of sugar food sources, particularly added sugars in processed foods and condiments, which may have resulted in underestimation of sugar intakes and likely attenuated the associations toward the null (52, 53). However, a comparison of the Harvard FFQ with 1-week diet records reported moderate to strong correlation coefficients of 0.51 for sweets, desserts, SSB, and fruit drinks and of 0.76 for fruit juice (53). Nevertheless, the measurement error associated with self-reported sugars intake may explain the lack of consistency in the epidemiologic evidence on the association between sugars and cancer (54). To address this issue, future studies may benefit from the use of 24-hour urinary sucrose and fructose as predictive biomarkers for total sugar intake and a calibration equation for the biomarker that provides an unbiased measure of sugars intake (54).

An additional limitation of this study was the inability to examine the effects of naturally occurring versus added sugars, because the FFQ does not adequately assess added sugar intake, the lack of a comprehensive sugar database in general, and the variation in sugar content of processed foods along with the inability to capture that variation using the FFQ. Consequently, the FHS diet file does not have variables for naturally occurring versus added sugars. However, we did evaluate intakes of sugary foods and beverages as a proxy for added sugar intake, as these would be the primary sources of added sugar in the diet. Furthermore, data on diet and other covariates was used from the baseline examination for this analysis (exam 5), which may not capture changes over time or during a critical period in the adult life course. However, a previous report in this population showed only modest changes in carbohydrate intake over time (16), therefore it is not likely that the use of baseline diet data significantly altered associations.

Another limitation of this study is the limited power for site-specific and stratified analyses. Effect size of the association between sugar and cancer (as with most dietary exposures) may be moderate. Therefore, due to the sample size and small number of site-specific cancers, we may have had limited power to detect an association. Findings from these exploratory analyses may also be due to chance given the number of multiple comparisons. Moreover, the possibility of residual confounding by unknown factors, despite our adjustment for a variety of dietary and lifestyle factors, cannot be ruled out. Finally, our study sample consisted of middle-aged, Caucasian adults; this limits the generalizability of our results to other populations for which associations between diet and cancer may vary. Nonetheless, the strengths of our study include the use of the comprehensive dietary, lifestyle, and clinical data collected in the FHS. Diet data was collected using a FFQ with documented validity and reproducibility for assessing habitual intakes (53). Trained personnel obtained anthropometric measures; and cancer cases were doctor-diagnosed. Finally, the prospective cohort design and long follow-up duration are unique strengths of this study.

In summary, in this prospective cohort study of American adults, findings were suggestive that higher intakes of sugary beverages are associated with increased risk of adiposity-related cancers, among participants with excessive central adiposity. Among types of sugary beverages, consumption of >7 servings of fruit juice per week (>1 serving/day) was associated with increased risk of prostate cancer, the most prevalent non-skin cancer among men (21), in exploratory analyses. Because sugary beverages currently account for almost 50% of added sugar intakes in the United States (55), dietary advice on cancer recommending the replacement of these calorically sweetened, nutrient-poor beverages with drinks that do not contain added sugars, such as water, may be beneficial as a cancer control strategy, particularly for high-risk individuals. Furthermore, implementing targeted initiatives represents an essential public health frontier, as a range of synergetic clinical and public awareness measures are needed to reduce intakes of sugary beverages and the associated chronic disease burden in the United States.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Authors' Contributions

Conception and design: N. Makarem, Y. Lin, N. Parekh
Development of methodology: N. Makarem, Y. Lin
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): P. Jacques, N. Parekh
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): N. Makarem, Y. Lin, P. Jacques, R.B. Hayes, N. Parekh
Writing, review, and/or revision of the manuscript: N. Makarem, E.V. Bandera, Y. Lin, P. Jacques, R.B. Hayes, N. Parekh
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): N. Makarem, N. Parekh
Other (experience and expertise with the dietary data used for this study): P. Jacques

Acknowledgments

The Framingham Heart Study is conducted and supported by the National Heart, Lung, and Blood Institute (NHLBI) in

collaboration with Boston University (Contract No. N01-HC-25195). Funding support for the Framingham Food Frequency Questionnaire datasets was provided by ARS Contract #53-3k06-5-10, ARS Agreement #'s 58-1950-9-001, 58-1950-4-401, and 58-1950-7-707. This manuscript was not prepared in collaboration with investigators of the Framingham Heart Study and does not necessarily reflect the opinions or views of the Framingham Heart Study, Boston University, or NHLBI.

This study was supported by the American Cancer Society Research Scholar Grant (#RSG-12-005-01-CNE) awarded (to N. Parekh). The American Cancer Society had no role in the design and analysis of the study or in the writing of this article.

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Received July 17, 2017; revised January 2, 2018; accepted April 12, 2018; published first April 19, 2018.

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