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Sucrose Intakes and Incident Colorectal Cancer Risk among Women

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Abstract

Background: High sucrose intakes are hypothesized to increase colorectal cancer (CRC) risk by several mechanisms, and sucrose intakes have been consistently positively associated with CRC risk in case-control studies. However, all but one prospective study reported a null sucrose-CRC association. The only prospective study to report a positive association was the Iowa Women's Health Study (IWHS) of 35,221 cancer-free Iowa women, aged 55 – 69 years old at baseline in 1986, after four years of follow up.

Materials and Methods: To address the discrepant findings in the literature, after 26 years of follow up in the IWHS, we updated and expanded on our earlier reported analyses. During follow up through 2012, 1,731 women were diagnosed with CRC. Baseline dietary intakes were assessed with a Willett semiquantitative food frequency questionnaire. We used multivariable Cox proportional hazards regression models to estimate adjusted hazards ratios (HRs) and their 95% confidence intervals (CI).

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Declaration of Interest Statement

None of the authors has a conflict of interest to disclose. The findings and conclusions contained within are those of the authors and do not necessarily reflect positions or policies of the National Cancer Institute or the Wilson P. and Anne W. Franklin Foundation. The National Cancer Institute and the Wilson P. and Anne W. Franklin Foundation had no influence on the analysis and interpretation of the data, the decision to submit the manuscript for publication, or the writing of the manuscript.

Results: For those in the highest relative to the lowest intake quintiles, the adjusted HRs (95% CI) for CRC were 1.04 (0.87–1.23; P_{trend} = 0.59) for sucrose, 1.00 (0.82–1.21; P_{trend} = 0.67) for sucrose-containing foods, and 1.01, (0.83–1.22; P_{trend} = 0.56) for non-dairy sucrose-containing foods, respectively. These findings did not differ substantially by colorectal site or according to categories of selected participant characteristics.

Conclusions: Our findings do not support that intakes of sucrose or sucrose-containing foods are substantially associated with CRC risk among older women.

Keywords

sucrose; colorectal cancer; prospective cohort studies

Introduction

Colorectal cancer (CRC) remains the second leading cause of cancer-related deaths among men and women combined in the United States (1). Dietary and lifestyle factors play an important role in the etiology of CRC (2). Various authors assert that a Western diet, which includes high sucrose intakes, is associated with CRC (3).

Sucrose (“table sugar”) has been hypothesized to increase CRC risk via genotoxicity from compounds from cooked sucrose (4), and effects on gastrointestinal transit time, fecal bile acid concentrations (5), and insulin-like growth factor-I (IGF-I) (3, 6, 7). Sucrose increased biomarkers of colorectal neoplasms in rodent models (4, 8).

In human epidemiologic studies that reported associations of sucrose or sucrose-containing foods with colorectal neoplasm (3, 5, 9–19) although eight of eight case-control studies reported positive associations (9–16), four (3, 17–19) of five prospective cohort studies (3, 5, 17–19) reported null associations and only one (5) reported a positive association. The one study that reported a positive association with colon cancer was the Iowa Women’s Health Study (IWHS), a prospective cohort study of 35,216 cancer-free women at baseline in 1986. After follow up through 1990, 212 cases were identified; the relative risks (RR) for CRC with higher total sucrose, sucrose-containing foods, and non-dairy sucrose-containing foods were 1.45, 1.74, and 2.00, respectively. Since 1990, study participants have been followed another 22 years (through 2012), and a total of 1,731 incident CRC cases were identified.

Given the inconsistent sucrose-CRC associations and the previous suggestion that sucrose/sucrose-containing food intakes were associated with CRC during early follow up in the IWHS, we conducted an updated and expanded investigation of associations of sucrose/sucrose-containing food intakes with incident CRC in the IWHS.

Methods

Study Population and Design

The design of the prospective Iowa Women’s Health Study (IWHS) was previously described (20). Briefly, women aged 55 – 69 years with a valid Iowa driver’s license in 1985 were mailed a questionnaire in 1986. A total of 41,836 (42.7% of eligible women)

self-reported answers to questions on demographics, medical history, family history of CRC, diet, and lifestyle. Participants were followed for mortality and cancer incidence, with follow-up surveys mailed in 1987, 1989, 1992, 1997, and 2004. Diet was comprehensively reassessed after baseline only in 2004, at which time only 68.3% of participants remained alive. So, for our primary analyses we used only baseline exposure information, but included 2004 exposure information in one of two sensitivity analyses (described further below) that supported the validity of this choice. Information on aspirin and other nonsteroidal anti-inflammatory drug (NSAID) use was not collected until 1992, and was used in sensitivity analyses described further below.

Exposure Assessment

Diet was assessed with a 127-item semiquantitative food Willett food frequency questionnaire (FFQ). Questions covered usual food intake and vitamin and mineral supplement use over the previous year. The reproducibility and validity of this questionnaire in the study population was previously reported (21). We defined ‘sucrose-containing foods’ as ice milk, ice cream, sucrose-containing beverages, chocolate candy, candy bars, candy without chocolate, cookies, brownies, doughnuts, cake, pastries, pie, and jelly (includes jam, preserves, syrup, honey). We defined ‘non-dairy sucrose-containing foods’ as sucrose-containing foods minus ice cream and ice milk, which contain calcium, which is consistently inversely associated with CRC (7).

Participants were asked about their physical activity using two questions concerning the participant’s usual frequency of moderate and vigorous free-time physical activity. Moderate activity was defined as activities such as bowling, golf, light sports or physical exercise, gardening, or taking long walks; vigorous activity was defined as activities such as jogging, racket sports, swimming, aerobics, or strenuous sports. Physical activity was categorized as heavy (defined as vigorous activity twice a week or moderate activity > 4 times/week), moderate (vigorous activity once a week and moderate activity once a week, or moderate activity 2 – 4 times/week), or low.

Participants self-reported their height, weight, and waist and hip circumferences. To assist with this, they were provided with written instructions and a paper tape measure, and asked to get someone to help measure the circumference of their waist (one inch above the umbilicus) and hips (maximal protrusion). This self-report measurement methodology was validated in this cohort (22). From these measures, a waist:hip ratio and body mass index (BMI; weight divided by the square of the height [kg/m^2]) were calculated for each participant.

Outcome Assessment

Cancer diagnoses were ascertained via linkage with the State Health Registry of Iowa, which is part of the Surveillance, Epidemiology, and End Results Program of the National Cancer Institute. Through 2012, 1,731 incident CRC cases (International Classification of Diseases for Oncology codes (ICD-O-3) 18.0, 18.2 – 18.9, 19.9, 20.9) were documented. Deaths were identified through the State Health Registry of Iowa and the National Death Index.

Statistical Analyses

Prior to analysis, we excluded study participants who reported a history of cancer (excluding non-melanoma skin cancer) at baseline (n = 3,830), and those who left ≥ 30 FFQ items blank (n = 2,499), or who reported implausible total daily energy intakes (< 600 or > 5,000 kcal/ day; n = 286). After exclusions, 35,221 participants were included in the final analyses. As noted above, we used only baseline exposure information for our primary analyses, since diet was only comprehensively reassessed in 2004, at which time only 68.3% of the participants remained alive. However, we used 2004 exposure data in one of two sensitivity analyses, described further below, that supported the validity of this choice. Since analyzing daily sucrose intakes in grams, percentage of total energy intake (%kcal), or sucrose residuals (from linear regression of sucrose on total energy intake (23), made no difference in our findings (Supplemental Table 1), herein we report all results using the sucrose %kcal variable.

We categorized sucrose and sucrose-containing foods into quintiles based on their distributions in the entire analytic population at baseline. We calculated follow-up time as the time from the date of completion of the baseline questionnaire to the date of 1) a CRC diagnosis; 2) death, for those who died in Iowa; 3) when the participant moved out of Iowa, if known; 4) the midpoint between the date of the last contact in Iowa and the first known date outside of Iowa or the end of the follow-up period if the participant moved from Iowa at an unknown date; 5) the midpoint between the date of the last contact in Iowa and the date of death for those who did not die in Iowa; or 6) the end of follow up (December 31, 2012), whichever was earliest.

We summarized and compared the participants' baseline characteristics using general linear models for continuous variables (transformed by the natural logarithm to improve normality, when indicated) and chi-square tests for categorical variables. We calculated multivariable-adjusted hazard ratios (HRs) and their 95% confidence intervals (CIs) using Cox proportional hazards models to estimate associations of sucrose and sucrose-containing foods with incident CRC. Potential covariates included in the final models were selected based on biological plausibility and previous literature. The covariates selected for the final models were age (continuous); family history of CRC in a first-degree relative (yes/ no); smoking status (current/past/never); alcohol consumption (g/day); physical activity level (low/moderate/high); post-menopausal hormone use (ever/never); BMI (continuous); and intakes of total energy (kcal/day), total (dietary plus supplemental) calcium (mg/day), total red and processed meats (servings/week), and total fruits and vegetables (servings/ week). Other covariates considered but not included because they negligibly affected the estimated associations of interest included diabetes mellitus or taking an oral hypoglycemic agent at baseline or during follow up. We tested proportional hazards assumptions using Schoenfeld residuals and Log-Log survival curves for each exposure and potential covariate. We conducted trend tests across quantiles of intake using the quantiles' median values as a continuous variable.

In secondary analyses, to assess potential differences in associations across selected participant characteristics, we conducted analyses stratified by age (</≥ 65 yrs.), family history of CRC in a first degree relative, smoking status (current/past/never), current

alcohol consumption (any/none), physical activity level (low/moderate/high), current postmenopausal hormone use (yes/no), and BMI (</≥ 25 kg/m^2). We also estimated associations of the primary exposure variables with cancers of different colorectal sites, including the proximal (cecum through the transverse colon; ICD-O-3 codes 18.0 – 18.9) and distal colon (splenic flexure through sigmoid colon and rectum; ICD-O-3 codes 18.5 – 18.7, 19.9, and 20.9).

We conducted several sensitivity analyses. Since diet was not comprehensively reassessed after baseline until 2004, and some participants may have changed their diets during follow up, we assessed potential differences in associations considering study end dates of 5, 10, 15, 20, and 25 years after baseline. Also, among those not censored before 2004, we assessed using the average of their baseline (1986) and 2004 follow-up sucrose intakes, as well as only their 2004 follow-up sucrose intakes. Since aspirin and other NSAID use is associated with lower CRC risk, but data on their use were not collected until 1992 (six years after baseline), we estimated sucrose-CRC associations using 1992 as the baseline date (i.e., excluded those who were diagnosed with CRC or censored before 1992 or did not complete the 1992 questionnaires) in models with and without aspirin and other NSAID use as covariates as well as stratified by aspirin and other NSAID use. Finally, to rule out potential attenuation of associations from reverse causality, we assessed excluding participants diagnosed with CRC or who died within 2 years after baseline.

We considered two-sided *P*-values < 0.05 or 95% CIs that excluded 1.0 statistically significant. We conducted all statistical analyses using SAS version 9.4 software (SAS Institute Inc., Cary, North Carolina).

Results

Selected baseline characteristics of the study population by quintiles of sucrose intake (as a percentage of total energy intake) are presented in Table 1. At baseline, the mean age was 62 years, 98% were white, and 3% had a first degree relative with CRC. On average, participants consumed 11.7 servings/wk. of sucrose-containing foods and 10.1 serving/wk. of non-dairy sucrose-containing foods. Those in the higher relative to the lower quintiles of sucrose intake, on average, had higher intakes of total energy, fructose, total carbohydrates, and dietary fiber; and lower intakes of total calcium, protein, and red meat. Those in the lowest sucrose intake quintile were more likely to currently smoke, consume > 7 drinks/week, and to have diabetes mellitus.

All associations of sucrose and sucrose-containing foods intakes with incident CRC overall (Table 2) and with incident proximal and distal CRCs (Supplemental Table 2) were very close to null and not statistically significant (we do note that the HR for the sucrose-overall CRC association in the fourth sucrose intake quintile was 1.18 and borderline statistically significant; however, there was no consistent pattern for increasing risk with increasing intake, the P_{trend} was 0.59, and the HR for the fifth quintile was 1.04 and not statistically significant). Similarly, in analyses stratified by selected participant characteristics (Supplemental Table 3), no P_{trend} nor estimated association for those in the fifth relative to the first sucrose intake quintile was statistically significant. However, the

estimated positive sucrose-CRC associations tended to be slightly stronger among those who were overweight/obese (18% higher among those in the fifth relative to the lowest sucrose quintile), current/previous HRT users (22% higher), or had medium or high physical activity levels (11% higher), although these point estimates were not statistically significant and the 95% CIs for the corresponding HRs across strata overlapped substantially.

In the sensitivity analyses, the estimated risks for CRC among participants in the highest relative to the lowest sucrose intake quintile were 60%, 33%, 7%, 10%, and 4% higher, when stopping follow-up at 5, 10, 15, 20, and 25 years, respectively (Supplemental Table 4). Also, when we incorporated 2004 exposure data two ways, the estimated CRC risk for those in the highest relative to the lowest sucrose intake quintile remained close to null (Supplemental Table 5). Similarly, when we used 1992 as baseline, the estimated sucrose-CRC association was close to null regardless of whether or not aspirin or other NSAID use was included in the model, and the null association did not differ according to aspirin or other NSAID use (Supplemental Table 6). Finally, excluding participants who died or were diagnosed with CRC within 2 years of follow up (Supplemental Table 7) yielded no substantial change from the estimated associations shown in Table 2.

Discussion

Our findings do not support that intakes of sucrose or sucrose-containing foods alone are substantially associated with risk for CRC, overall or for proximal or distal colon cancers, among older women overall or in selected population subgroups. As discussed below, although there is ample biological plausibility for sucrose increasing CRC risk, and previous case-control studies supported a positive sucrose-CRC association, other prospective cohort studies did not support a sucrose-CRC association, consistent with our findings.

Sucrose intakes are hypothesized to increase CRC risk by various mechanisms. Sucrose can lead to changes in carbohydrate metabolic pathways that release hormones from the gastrointestinal tract and activate epithelial proliferation (24). Uncooked sucrose increased colonic epithelial cell proliferation and aberrant crypt foci formation in rodents (8). Cooked sucrose contains the thermolysis product, 5-hydroxymethyl-2-furaldehyde, a compound that increased microadenoma formation in rodents (4), and cooked sucrose contains other compounds that are genotoxic *in vitro*. In humans, high sucrose diets increase mouth-to-anus transit time despite decreasing the mouth-to-cecum time, and increase total and secondary fecal bile acid concentrations (5). Additionally, diets high in sugars activate synthesis of insulin and insulin-like growth factor-I (IGF-I) (6), insulin and IGF-I induce cell division and inhibit apoptosis in normal and malignant colonic epithelial cells (3), and higher circulating IGF-I concentrations were positively associated with CRC risk (7).

The present study builds on a previous analysis of IWHS data after the study participants had been followed for the first four years (1986 to 1990). The present analysis includes follow-up data through 2012 (26 years of follow up). From the previous analysis, higher CRC risk was reported with higher intakes of total sucrose (RR = 1.45; 95% CI, 0.88–2.39), sucrose-containing foods (RR = 1.74; 95% CI, 1.06–2.87), and non-dairy sucrose containing foods (RR = 2.00; 95% CI, 1.21–3.30) (5), findings that substantially differ

from the null findings from our present analysis. The discrepant findings may be related to chance (primarily in the analyses of early follow-up data) or changes in sucrose intakes or in potential confounding or effect modifying exposures during follow up. In our sensitivity analyses, we observed that the estimated positive sucrose-CRC association after five years of follow up dropped precipitously with continued follow up, becoming null and no longer statistically significant thereafter. Also, among participants not censored as of 2004, 63.6% of participants remained in the same or adjacent sucrose intake quintiles, and including 2004 exposure data two different ways negligibly affected our estimated sucrose-CRC associations. These observations tend to support that the discrepant early and later follow-up findings may most likely have been due to the early findings being due to chance, especially considering findings from other prospective cohort studies.

Thirteen previous studies (3, 6, 9–19) (including the aforementioned previous analysis of early IWHS data (5)), reported associations of sucrose-related exposures with colorectal neoplasms with mixed results. Of eight case-control studies (9–16) conducted in various populations across the world from 1990 to 2019, all eight found positive associations of sucrose or sucrose-containing foods with colorectal neoplasms. However, of five prospective cohort studies (3, 5, 17–19), all of which were based in the United States and Canada, except for the previous analysis of early IWHS data (5), all found null associations (although in two (17, 19), the estimated associations were positive, but not statistically significant), consistent with the present analysis of IWHS data after 26 years of follow up. Our study adds to the literature prospective investigation of sucrose-CRC associations according to different CRC sites and various population subgroups; these various associations, like our overall associations, were close to null. The only other study that reported associations of sucrose with proximal vs. distal colon cancers, a population-based case-control study in Canada, found positive associations of sucrose intake with proximal and distal colon cancers that were almost identical to each other (14).

In summary, although case-control studies reported positive sucrose-CRC associations, prospective cohort studies yielded null associations. Case-control studies are more susceptible to biases and can have limitations for addressing the temporality of associations of modifiable exposures with chronic diseases (i.e., which came first, the reported exposure or the disease). Other possible explanations for differences by study design may involve differences in study populations, variation in food preparation and consumption across populations/countries, diet assessment methods, and analysis procedures. Null associations in the cohort studies may be due to homogeneous diets within populations or that sucrose intakes do not substantially increase CRC risk. Another possibility is that sucrose intakes, as an individual exposure, may increase risk so modestly that it cannot be reliably detected, especially using current dietary assessment methods. Supporting this is that when included in dietary pattern scores, such as the Dietary Inflammation Index (25), the Dietary Inflammation Score (26), and the Evolutionary Concordance Diet Score (27), sucrose or sucrose-containing foods intakes contributed to the scores' associations with incident CRC.

Our study had several strengths and limitations. Strengths include the large sample size and number of cases, long follow up, and extensive data on potential confounding and effect modifying variables. As discussed above, study limitations include that diet was

not comprehensively reassessed until after 18 years of follow up, and the diets of some participants may have changed somewhat during follow up. We did not collect data on aspirin and other NSAID use until six years after baseline; however, when we used 1992 rather than 1986 as baseline, adjustment for aspirin/NSAID use did not meaningfully affect our findings, and our findings did not differ according to aspirin/NSAID use. FFQs have known limitations, such as recall error and limited detail on food preparation (28); however, these types of measurement error in prospective cohort studies are considered non-differential, likely attenuating true associations. Another limitation was lack of data on CRC screening, as removal of adenomas via screening minimizes CRC risk. In effect, such patients are misclassified, thus attenuating what the associations may have been, had there been no screening. Finally, > 98% of participants were white, thus limiting the generalizability of our results; on the other hand, our results were consistent with those from other prospective cohort studies.

In conclusion, our results, combined with the balance of results from previous studies, suggest that sucrose intakes may not be independently, substantially associated with CRC risk, but do not rule out that they may modestly contribute to higher risk. Further investigations to understand the differences in findings between case-control and prospective studies of sucrose intakes and CRC may reveal important insights into investigations of diet and CRC etiology.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Data Availability Statement:

The data that support the findings of this study are available upon reasonable request from co-author DL. The data are not publicly available due to their containing information that could compromise the privacy of research participants.

Abbreviations:

BMI	body mass index
CI	confidence interval
CRC	colorectal cancer
FFQ	food frequency questionnaire
HR	hazards ratio
HRT	hormone replacement therapy

IRB	Institutional Review Board
IWHS	Iowa Women's Health Study

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Table 1.

Selected baseline characteristics of Iowa Women's Health Study participants (n = 35,221) by quintiles of sucrose intakes[a]

	Sucrose intake quintiles				
	1 (n = 7,044)	**2 (n = 7,044)**	**3 (n = 7,045)**	**4 (n = 7,044)**	**5 (n =7,044)**
Demographics					
Age, years	61.0 (4.1)	61.3 (4.2)	61.6 (4.2)	61.7 (4.3)	62.0 (4.2)
White, %	98.3	98.4	98.5	98.0	97.6
First degree relative with CRC, %	3.1	3.0	3.2	3.3	2.6
% College graduate or higher, %	12.9	14.2	14.3	12.2	10.8
Lifestyle and medical factors					
Body mass index, kg/m^2	27.4 (5.5)	27.1 (5.0)	26.9 (5.0)	26.7 (4.8)	26.6 (5.0)
Waist:hip ratio	0.848 (0.091)	0.834 (0.083)	0.833 (0.082)	0.833 (0.081)	0.835 (0.083)
Physical activity, %					
Moderate	25.2	28.4	27.8	28.0	26.2
High	22.8	25.6	26.1	25.2	23.5
Current smokers, %	23.9	13.8	11.8	11.5	12.7
Alcohol intake, %					
> 0 – 7 drinks/wk	34.7	39.1	41.0	37.9	34.2
> 7 drinks/wk	19.0	8.4	4.9	3.5	3.0
Current or previous PHT, %	39.7	39.1	38.5	37.8	38.2
Diabetes mellitus, %	13.6	6.6	4.2	3.2	2.6
Dietary intakes					
Total energy, kcal/day	1,718 (586)	1,766 (552)	1,797 (588)	1,828 (604)	1,884 (683)
Total fat, g/day	69.4 (29.1)	68.6 (25.9)	68.3 (26.6)	68.2 (26.9)	67.7 (29.7)
Saturated fat, g/day	24.8 (11.4)	24.2 (9.9)	24.0 (10.1)	23.7 (10.0)	23.4 (11.1)
Total calcium, mg/day	1,123 (589)	1,140 (559)	1,120 (555)	1,087 (535)	1,009 (524)
Fructose, mg/day	17.6 (9.6)	21.9 (10.2)	24.1 (11.3)	26.0 (12.4)	28.8 (16.6)
Total carbohydrates, g/day	179 (65.7)	205 (66.0)	219 (72.6)	233 (77.5)	257 (94.1)
Total protein, g/day	87.1 (35.3)	84.7 (29.2)	81.8 (28.7)	78.6 (27.4)	72.2 (27.3)
Total meats, servings/wk	7.8 (5.7)	7.0 (4.3)	6.6 (4.2)	6.3 (3.8)	5.5 (3.6)
Total fruits and vegetables, servings/wk	39.0 (20.2)	43.8 (19.5)	45.4 (21.1)	46.2 (21.4)	46.2 (25.2)

	Sucrose intake quintiles				
	1 (*n* = 7,044)	**2 (*n* = 7,044)**	**3 (*n* = 7,045)**	**4 (*n* = 7,044)**	**5 (*n* =7,044)**
Dietary fiber, g/day	16.9 (7.3)	19.4 (7.2)	20.2 (7.7)	20.9 (8.0)	21.2 (8.9)
Sucrose-containing foods, servings/wk					
Total[c]	5.3 (4.7)	8.7 (6.4)	11.2 (7.6)	14.1 (9.5)	19.2 (14.9)
Non-dairy[d]	4.4 (4.3)	7.3 (5.9)	9.6 (7.0)	12.2 (8.9)	17.2 (14.1)

Abbreviations: CRC, colorectal cancer; PHT, postmenopausal hormone therapy.

[a]Continuous variables are presented as means (standard deviations); categorical variables are presented as percentages; sucrose is sucrose as a percentage of total energy intake (%kcal).

[b]*P* values from chi-square test for categorical variables and general linear models for continuous variables (transformed by the natural logarithm to meet normality assumption when indicated).

[c]Total = sucrose-containing foods (ice milk, ice cream, sucrose-containing beverages, chocolate, candy, candy bars, candy without chocolate, cookies, brownies, doughnuts, cake, pastries, pie, jelly (includes jam, preserves, syrup, honey).

[d]Non-dairy = sucrose-containing foods (same as total[c] minus ice milk and ice cream).

Table 2.

Associations of sucrose intakes with incident colorectal cancer among Iowa Women's Health Study participants (n = 35,221), 1986 – 2012

Sucrose-related exposure	Quintiles					P_{trend} [a]
	1	2	3	4	5	
Sucrose	n = 7,044	n = 7,044	n = 7,045	n = 7,044	n = 7,044	
Range (%kcal/day)	0 – 6.6	>6.6 – 8.2	>8.2 – 9.6	>9.6 – 11.4	>11.4 – 37.7	
Person-years	142,504	147,987	149,267	150,095	146,897	
No. of cases	315	350	343	383	340	
Unadjusted HR (95% CI)	1.00 (Ref.)	1.06 (0.91, 1.24)	1.03 (0.89, 1.20)	1.15 (0.99, 1.33)	1.04 (0.89, 1.22)	*0.43*
Minimally-adj. HR (95% CI) [b]	1.00 (Ref.)	1.06 (0.91, 1.24)	1.00 (0.86, 1.17)	1.10 (0.95, 1.28)	0.98 (0.84, 1.15)	*0.90*
Adjusted HR (95% CI) [c]	1.00 (Ref.)	1.09 (0.93, 1.28)	1.08 (0.91, 1.27)	1.18 (1.00, 1.39)	1.04 (0.87, 1.23)	*0.59*
Total sucrose-containing foods [d]	n = 6,826	n = 6,354	n = 6,837	n = 7,077	n = 7,415	
Range (servings/week)	0 – 3.5	>3.5 – 6.5	>6.5 – 10.5	>10.5 – 17.0	17.5 – 158.0	
Person-years	136,310	132,237	152,909	161,692	153,604	
No. of cases	322	339	359	352	359	
Unadjusted HR (95% CI)	1.00 (Ref.)	1.08 (0.93, 1.26)	0.99 (0.85, 1.15)	0.91 (0.78, 1.06)	0.98 (0.84, 1.14)	*0.33*
Minimally-adj. HR (95% CI) [b]	1.00 (Ref.)	1.08 (0.93, 1.26)	0.97 (0.83, 1.13)	0.90 (0.77, 1.06)	0.99 (0.83, 1.17)	*0.46*
Adjusted HR (95% CI) [c]	1.00 (Ref.)	1.05 (0.90, 1.23)	0.97 (0.83, 1.14)	0.90 (0.76, 1.07)	1.00 (0.82, 1.21)	*0.67*
Non-dairy sucrose-containing foods [e]	n = 6,561	n = 7,331	n = 6,837	n = 7,077	n = 7,415	
Range (servings/week)	0 – 2.5	>2.5 – 5.5	>5.5 – 9.0	9.5 – 14.5	>14.5 – 157.0	
Person-years	130,679	152,943	144,065	151,703	157,360	
No. of cases	307	400	331	320	373	
Unadjusted HR (95% CI)	1.00 (Ref.)	1.11 (0.95, 1.28)	0.97 (0.83, 1.13)	0.89 (0.76, 1.04)	1.00 (0.86, 1.16)	*0.35*
Minimally-adj. HR (95% CI) [b]	1.00 (Ref.)	1.10 (0.95, 1.28)	0.96 (0.82, 1.12)	0.89 (0.75, 1.05)	1.00 (0.84, 1.18)	*0.41*
Adjusted HR (95% CI) [c]	1.00 (Ref.)	1.09 (0.94, 1.27)	0.97 (0.82, 1.14)	0.89 (0.75, 1.06)	1.01 (0.83, 1.22)	*0.56*

Abbreviations: CI, confidence interval; HR, hazards ratio; Minimally-adj., minimally-adjusted; Ref., reference.

[a] P for trend calculated using medians of each quantile.

[b] Adjusted for age, family history of colorectal cancer in a first degree relative, total energy intake.

[c] Adjusted for age, family history of colorectal cancer in a first degree relative, body mass index, waist:hip ratio, smoking, alcohol, physical activity, postmenopausal hormone use, total energy intake, total fruits and vegetables intake, red and processed meat intake, and total calcium intake.

[d] Total = sucrose-containing foods (ice milk, ice cream, sucrose-containing beverages, chocolate, candy, candy bars, candy without chocolate, cookies, brownies, doughnuts, cake, pastries, pie, jelly (includes jam, preserves, syrup, honey).

[e] Non-dairy = sucrose-containing foods (same as total[d] minus ice milk and ice cream).

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