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Nfn Kiran Date

ASSOCIATION OF SUCROSE INTAKE WITH INCIDENT COLORECTAL CANCER

By

Nfn Kiran, MD

Master of Public Health

Epidemiology

Dr. Roberd M. Bostick, MD, MPH

Faculty Thesis Advisor

A thesis submitted to the Faculty of the
Rollins School of Public Health of Emory University in partial
fulfillment of the requirements for the degree of
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ABSTRACT

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High sucrose diets are hypothesized to increase colorectal cancer (CRC) risk by several mechanisms; however, sucrose intakes have been inconsistently associated with CRC in human studies. To investigate associations of sucrose intake with incident CRC, we analyzed data from the prospective Iowa Women's Health Study of 35,221 cancer-free Iowa women, aged 55 – 69 years old at baseline in 1986. During follow up through 2012, 1,731 women were diagnosed with CRC. Baseline dietary intakes were assessed with a Willett semiquantitative food frequency questionnaire. Multivariable Cox proportional hazards regression models were used to estimate adjusted hazards ratios (HRs) and their 95% confidence intervals (CI). 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 intake, 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. Our findings do not support that intakes of sucrose or sucrose-containing foods are associated with risk of colorectal cancer among older women.

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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 is associated with CRC due to its high content of meats, fat, and refined carbohydrates, and low content of fruit, vegetables, whole grains, and legumes (3).

Sucrose ("table sugar"), induces various potential mechanisms by which it may increase risk for colorectal neoplasms. Diets high in sucrose have been associated with higher fasting triglyceride concentrations, and diets high in simple carbohydrates (mono- and disaccharides) and low in fiber increase serum triglycerides and plasma glucose. It is hypothesized that serum triglycerides, plasma glucose, and insulin resistance might be risk factors for colorectal cancer (4). Diets high in sugars activate synthesis of insulin and insulin-like growth factor-I (IGF-I) (5). Insulin and IGF-I induce cell division and inhibit apoptosis in normal and malignant colonic epithelial cells (3), and it was reported that higher circulating IGF-1 concentrations were associated with higher colorectal, prostate, and breast cancer risk (6). Additionally, uncooked sucrose increases colonic epithelial cell proliferation and aberrant crypt foci formation in rodents (7). Cooked sucrose contains the thermolysis product, 5-hydroxymethyl-2-furaldehyde, a compound that increased microadenoma formation in rodents (8), 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 the fecal concentration of total and secondary bile acids (9).

Fourteen epidemiologic studies reported on an association of sucrose intakes with incident CRC. Some studies found direct (10) and others inverse associations (3) of dietary carbohydrates with colon/colorectal cancer, but most studies found no association (11). One study that previously reported a direct 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 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 associations of sucrose with CRC, 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 study design and protocols of the prospective Iowa Women's Health Study (IWHS) were previously described (12). Briefly, women aged 55 – 69 years who had a valid Iowa driver's license in 1985 were mailed a questionnaire in 1986. A total of 41,836 (42.7% of eligible women) completed baseline mailed questionnaires on demographics, medical history, family history of colorectal cancer, self-reported diet, and lifestyle. Participants were followed for mortality and cancer incidence, with follow-up surveys mailed in 1987, 1989, 1992, 1997, and 2004.

Exposure Assessment

All exposure data were self-reported on the mailed questionnaires. Diet was assessed with a 127-item semiquantitative food Willett food frequency questionnaire at baseline. Questionnaires covered usual food intake and vitamin and mineral supplement use. The reproducibility and validity of this questionnaire in the study population was previously reported (13). Sucrose-containing foods was calculated as 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). Non-dairy sucrose-containing foods was calculated as sucrose-containing foods minus ice cream and ice milk. Only baseline exposure information was used in present analyses, since diet was only comprehensively reassessed in 2004, at which time only 68.3% of the participants remained alive.

Participants were asked about their level of 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.

For body measurements, 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 were asked to get someone to help measure the circumference of their waist (one inch above the umbilicus) and hips (maximal protrusion). From these measures, a waist:hip ratio was computed for each participant. This self-report measurement methodology was validated in this cohort (14). Body mass index (BMI) was calculated as weight divided by the square of the height (kg/m_2).

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 (15).

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 food items blank on their food frequency questionnaire (n = 2,499), or who reported implausible total daily energy intakes (< 600 or > 5,000kcal/ day; n = 286). After exclusions, 35,221 participants were included in the final analyses.

Sucrose and sucrose-containing foods were categorized into quintiles based on their distributions in the entire analytic population at baseline. Follow-up time was calculated as the time from the date of completion of the baseline questionnaire to the date of 1) a diagnosis of CRC; 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.

The baseline characteristics of the participants were summarized and compared 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 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 model 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 (grams/day); physical activity level (low/moderate/high); post-menopausal hormone use (ever/never); body mass index (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). Proportional hazards assumptions were tested 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 and sensitivity analyses, to assess potential effect modification, we conducted analyses stratified by age (</≥ 65 yrs.), family history of CRC in smoking status (current/past/never), current alcohol consumption (any/none), physical activity level (low/moderate/high), current postmenopausal hormone use (yes/no), BMI (</≥ 30 kg/m2). 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, ICD-O-3 codes 19.9 and 20.9). As a sensitivity analysis, we excluded participants who were diagnosed with CRC or died within 2 years after baseline.

A two-sided P value < 0.05 or a 95% CI that did not include 1.0 was considered statistically significant. All statistical analyses were performed 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 are presented in Table 1. At baseline, the mean age was 62 years, 98% were white, and 3% of the population had a first degree relative with colorectal cancer. The participants consumed a weekly average of 11.7 servings of sucrose-containing foods, and 10.1 servings of non-dairy sucrose containing foods. Those in the higher relative to those in 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 quintile of sucrose intake were more likely to currently smoke and to consume more than 7 drinks/week.

Associations of intakes of sucrose and sucrose-containing foods intakes with incident colorectal cancer are presented in Table 2. All estimated associations were very close to null and not statistically significant. The estimated risk for CRC for those in the highest relative to the lowest quintiles of sucrose and for non-dairy sucrose-containing foods were close to null (4% and 1% higher, respectively, and not statistically significant.

As shown in Table 3, all estimated associations of sucrose intakes with incident proximal and distal colorectal cancers were very close to null and not statistically significant. Similarly, in analyses stratified by selected participant characteristics (Table 4), none of the estimated associations were statistically significant. However, the estimated direct sucrose-CRC associations tended to be slightly stronger among those who were obese

(18% higher), current/previous HRT users (22% higher), or had medium or high physical activity (11% higher); although none of the estimates was statistically significant, and the 95% CIs for the corresponding HRs across strata overlapped substantially.

When we assessed the sensitivity of our findings to excluding participants who died or were diagnosed with CRC within 2 years of follow up (Table 5), we found no substantial change in the estimated associations shown in Table 2.

DISCUSSION

Our findings do not support that intakes of sucrose or sucrose-containing foods are 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 direct sucrose-CRC association, other prospective cohort studies found no evidence for a sucrose-CRC association, consistent with our findings.

Sucrose intakes have been hypothesized to reduce risk for colorectal cancer by various mechanisms. Sucrose can lead to changes in carbohydrate metabolic pathways that release hormones from the gastrointestinal tract and activate epithelial proliferation (4). Uncooked sucrose increased colonic epithelial cell proliferation and aberrant crypt foci formation in rodents (7). Cooked sucrose contains the thermolysis product, 5-hydroxymethyl-2-furaldehyde, a compound that increased microadenoma formation in rodents (8), 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 the fecal concentration of total and secondary bile acids (9). Additionally, diets high in sugars activate synthesis of insulin and insulin-like growth factor-I (IGF-I) (5). Insulin and IGF-I induce cell division and inhibit apoptosis in normal and malignant colonic epithelial cells (3).

The present study builds on a previous analysis of IWHS data after the study participants had been followed for the first 5 years (1986 to 1990). The present analysis includes

follow-up data through 2012 (26 years of follow up). From the previous analysis, it was reported that there was a higher relative risk (RR) of CRC with higher sucrose intake: 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) (9), which are not consistent with the null findings from our present analysis. The discrepancy in these 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.

Fourteen previous studies (including the aforementioned previous analysis of early IWHS data), reported associations of sucrose-related exposures with colorectal neoplasms with mixed results. Of eight case-control studies conducted in various populations across the world from 1990 to 2019, all eight found direct associations of sucrose or sucrose-containing foods with colorectal neoplasms. However, of six prospective cohort studies, mostly conducted in the United States, except for the previous analysis of early IWHS data, all found null associations, consistent with the present analysis of IWHS data after 26 years of follow up. Our study adds to the literature prospective investigation of associations of sucrose with different colorectal cancer sites and according to various population subgroups; these various associations, like our overall associations, were close to null. Null associations by colon site were also reported from the Women's Health Study cohort. However, in a population-based case-control study in Canada, sucrose intake was similarly directly associated with proximal and distal colon cancers.

In summary, although case-control studies have found direct sucrose-CRC associations, prospective cohort studies have yielded null associations. Case-control studies are more susceptible to biases and do not address temporality (i.e., which came first, the exposure or the outcome). 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 homogenous diets within populations.

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. Study limitations include that > 99% 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. Our exposure measurements were assessed at baseline only, and the diets and habits of some participants may have changed during follow up. However, these types of measurement error in prospective cohort studies are considered non-differential, because participants at baseline do not know what their eventual outcomes will be, which tend to result in attenuated estimates of the true associations. Another limitation was lack of data on CRC screening, as removal of adenomas via screening will minimize the risk of CRC. In effect, such patients are misclassified, thus attenuating what the associations may have been, had there been no screening.

In conclusion, our results, combined with the balance of results from previous studies, suggest that sucrose intakes may not be independently associated with risk for colorectal cancer. 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.

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Table 1. Selected baseline characteristics of Iowa Women's Health Study participants 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)	P^b
Demographics						
Age, years	61.0 (4.1)	61.3 (4.2)	61.6 (4.2)	61.7 (4.3)	62.0 (4.2)	<0.0001
White, %	98.3	98.4	98.5	98.0	97.6	0.002
First degree relative with CRC, %	3.1	3.0	3.2	3.3	2.6	0.02
% College graduate or higher, %	12.9	14.2	14.3	12.2	10.8	<0.0001
Lifestyle 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)	<0.0001
Waist:hip ratio	0.848 (0.091)	0.834 (0.083)	0.833 (0.082)	0.833 (0.081)	0.835 (0.083)	<0.0001
Physical activity, %						
Moderate	25.2	28.4	27.8	28.0	26.2	<0.0001
High	22.8	25.6	26.1	25.2	23.5	<0.0001
Current smokers, %	23.9	13.8	11.8	11.5	12.7	<0.0001
Alcohol beverages						
0 - 7 drrinks/wk	34.7	39.1	41.0	37.9	34.2	<0.0001
> 7 drinks/wk	19.0	8.4	4.9	3.5	3.0	<0.0001
Current or previous PHT, %	39.7	39.1	38.5	37.8	38.2	0.14
Dietary intakes						
Total energy, kcal/day	1,718 (586)	1,766 (552)	1,797 (588)	1,828 (604)	1,884 (683)	<0.0001
Total fat, g/day	69.4 (29.1)	68.6 (25.9)	68.3 (26.6)	68.2 (26.9)	67.7 (29.7)	<0.000
Saturtaed fat, g/day	24.8 (11.4)	24.2 (9.9)	24.0 (10.1)	23.7 (10.0)	23.4 (11.1)	<0.0001
Total calcium, mg/day	1,123 (589)	1,140 (559)	1,120 (555)	1,087 (535)	1,009 (524)	<0.0001
Fructose, mg/day	17.6 (9.6)	21.9 (10.2)	24.1 (11.3)	26.0 (12.4)	28.8 (16.6)	<0.0001
Total Carbohydrate, g/day	179 (65.7)	205 (66.0)	219 (72.6)	233 (77.5)	257 (94.1)	<0.0001
Toatl Protien, g/day	87.1(35.3)	84.7 (29.2)	81.8 (28.7)	78.6 (27.4)	72.2 (27.3)	<0.0001
Total meats, servings/wk	7.8 (5.7)	7.0 (4.3)	6.6 (4.2)	6.3 (3.8)	5.5 (3.6)	<0.0001
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)	<0.0001
Dietary fiber, g/day	16.9 (7.3)	19.4 (7.2)	20.2 (7.7)	20.9 (8.0)	21.2 (8.9)	<0.0001
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)	<0.0001
Non-dairy[d]	4.4 (4.3)	7.3 (5.9)	9.6 (7.0)	12.2 (8.9)	17.2 (14.1)	<0.0001

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

[a] Continuous variables are presented as means (standard deviations); categorical variables are presented as percentages.

[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

	Quantiles					
	1	2	3	4	5	*P for trend*[a]
Sucrose	N = 7,044	N = 7,044	N = 7,045	N = 7,044	N = 7,044	
Range (g/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*
Sucrose-containing foods						
Total[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*
Sucrose-containing foods						
Non-Dairy[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: HR: hazard ratio; Minimally-adj.: minimally-adjusted; 95% CI: 95% confidence interval; Ref.: reference.

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

[b] Adjusted for age, family history of cancer, total energy intake.

[c] Adjusted for age, family history of colorectal cancer, 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[e] minus ice milk and ice cream).

Table 3. Multivariable-adjusted associations of sucrose intakes with incident proximal and distal colorectal cancers among Iowa Women's Health Study participants (n = 35,221), 1986 – 2012.

	Proximal colon[a]			Distal colon[b]		
Sucrose quintiles	No. of cases	HR[c]	95% CI	No. of cases	HR[c]	95% CI
1	175	1.00	Ref.	129	1.00	Ref.
2	186	1.01	(0.81, 1.25)	152	1.17	(0.92, 1.49)
3	182	1.00	(0.80, 1.24)	151	1.15	(0.90, 1.47)
4	194	1.07	(0.86, 1.33)	182	1.30	(1.02, 1.66)
5	187	1.02	(0.81,1.28)	14	1.02	(0.79, 1.33)
P for trend[e]		*0.74*			*0.79*	

Abbreviations: HR, hazards ratio; 95% CI, 95% confidence interval; Ref.: reference.

[a] Proximal includes cecum, appendix, ascending colon, hepatic flexure, transverse colon, overlapping lesion of colon.

[b] Distal includes splenic flexure, descending colon, sigmoid colon, recto-sigmoid junction, and rectum.

[c] Adjusted for age, family history of colorectal cancer, body mass index, waist:hip ratio, smoking, alcohol, physical activity, postmenopausal hormone use, total energy intake, fruit and vegetable intake, red and processed meat intake and total calcium intake.

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

Table 4. Multivariable-adjusted associations of sucrose intakes with incident colorectal cancer according to categories of other risk factors; the Iowa Women's Health Study (n = 35,221), 1986 – 2012.

Stratification variable, sucrose intake quintiles		**Adjusted HR[a]**	**95% CI**
Age, years			
<65			
	1	1.00	(Ref.)
	2	1.09	(0.90, 1.32)
	3	1.04	(0.85, 1.26)
	4	1.29	(1.06, 1.57)
	5	1.06	(0.86, 1.31)
P for trend[b]		*0.29*	
≥65			
	1	1.00	(Ref.)
	2	1.09	(0.81, 1.47)
	3	1.15	(0.86, 1.55)
	4	0.97	(0.72, 1.32)
	5	0.97	(0.71, 1.33)
P for trend[b]		*0.53*	
Smoking Status			
Current/Former			
	1	1.00	(Ref.)
	2	1.07	(0.82, 1.39)
	3	1.27	(0.98, 1.65)
	4	1.21	(0.92, 1.60)
	5	0.98	(0.73, 1.32)

P for trend[b]		*0.73*	
Never			
	1	1.00	(Ref.)
	2	1.08	(0.88, 1.33)
	3	0.97	(0.79, 1.19)
	4	1.13	(0.92, 1.38)
	5	1.02	(0.82, 1.27)
P for trend[b]		0.71	
Body mass index			
Non-obese [<30kg/m2]			
	1	1.00	(Ref.)
	2	1.08	(0.90, 1.30)
	3	0.99	(0.82, 1.20)
	4	1.08	(0.90, 1.31)
	5	0.99	(0.81, 1.21)
P for trend[b]		*0.86*	
Obese [≥30 kg/m2]			
	1	1.00	(Ref.)
	2	1.11	(0.81, 1.52)
	3	1.37	(1.00, 1.87)
	4	1.47	(1.08, 2.01)
	5	1.18	(0.84, 1.66)
P for trend[b]		*0.16*	
Use of HRT			
Current or past			
	1	1.00	(Ref.)
	2	1.45	(1.10, 1.91)
	3	1.46	(1.10, 1.94)

	4	1.36	(1.02, 1.82)
	5	1.22	(0.90, 1.67)
P for trend[b]		*0.49*	
Never			
	1	1.00	(Ref.)
	2	0.95	(0.78, 1.15)
	3	0.91	(0.74, 1.11)
	4	1.10	(0.90, 1.34)
	5	0.96	(0.78, 1.19)
P for trend[b]		*0.79*	
Alcohol			
Currently drink			
	1	1.00	(Ref.)
	2	1.06	(0.84, 1.33)
	3	1.02	(0.80, 1.29)
	4	1.39	(1.10, 1.75)
	5	0.92	(0.70, 1.21)
P for trend[b]		*0.80*	
Do not drink			
	1	1.00	(Ref.)
	2	1.11	(0.89, 1.39)
	3	1.10	(0.88, 1.37)
	4	1.01	(0.80, 1.26)
	5	1.06	(0.85, 1.34)
P for trend[b]		*0.95*	
Physical activity			
Low			

	1	1.00	(Ref.)
	2	1.14	(0.91, 1.43)
	3	1.17	(0.93, 1.47)
	4	1.22	(0.97, 1.53)
	5	0.92	(0.72, 1.18)
P for trend[b]		*0.64*	
Medium/High			
	1	1.00	(Ref.)
	2	1.03	(0.82, 1.29)
	3	0.96	(0.76, 1.21)
	4	1.10	(0.87, 1.39)
	5	1.11	(0.87, 1.42)
P for trend[b]		*0.31*	

Abbreviations: HR, hazards ratio; 95% CI, 95% confidence interval; HRT, hormone replacement therapy; Ref., reference.

[a]Adjusted for age, family history of colorectal cancer, 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 except for HRT, and physical activity (model for HRT does not include HRT, and model for physical activity does not include physical activity).

Table 5. Associations of sucrose intakes with incident colorectal cancer after excluding study participants who died or were diagnosed with colorectal cancer within 2 years of follow up; the Iowa Women's Health Study (n = 35,221), 1986 – 2012.

Sucrose intake quintiles	**Unadjusted HR**	**95% CI**	**Adjusted HR[a]**	**95% CI**
1	1.00	Ref.	1.00	Ref.
2	1.05	(0.90, 1.22)	1.08	(0.91, 1.27)
3	0.97	(0.83, 1.14)	1.02	(0.86, 1.21)
4	1.14	(0.98, 1.32)	1.18	(1.00, 1.39)
5	1.03	(0.88, 1.20)	1.03	(0.86, 1.24)
P for trend[b]	*0.49*		*0.55*	

Abbreviations: HR, hazard ratio; 95% CI, 95% confidence interval, Ref., reference.

[a] Adjusted for age, family history of colorectal cancer, 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.

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

Appendix 1: Summary of results of previous observational epidemiologic studies of associations of sucrose and/or sucrose-containing foods with colorectal neoplasms

Study	Study design/location	Endpoint	No of cases	N (cohort) or # controls (case-control)	Exposure (Characterization)	OR/RR (95% CI) (highest vs lowest quantile)	P for trend	Comments
Cancer								
Case-Control								
Benito et al, 19	Population-based/Majroca,Spain	Colorectal	286	295 Population 203 Hospital	Quartiles	1.64	Nearly significant at P< 0.05	Exposure = Sugar
Bidoli.et al, 1990	Hospital-based/ Italy	Colon Rectal	123 125	699	Tertiles	Colon and Rectum 1.6. High , 1.6 High	Nearly significant at P≤0.05	Exposure =Sugar
Franceschi et al. 1997	Hospitalbased/ Italy	Colorectal Colon rectum and recto-sigmoid junction	1,225 (688 M 537 F), 728 (437 M and 291 F)	4,154	Quintiles	Colorectal 1.43 (1.19–1.73)	10.1	Exposure =Refind sugar
LA Vecchia et al, 1998	Hospital-based/ Italy	Colorectal Colon Rectal	575 339 236	778 controls	Tertiles	Colon 1.01 (Intermediate level) 1.22. (High level) Rectal 1.01 (Intermediate) 0.51 (High level)	Not reported	Exposure =Sugar
Stefani et al, 1999	Hospital-based/Uruguay	Colorectal Colon Rectal	289 157. 132	564	Quartiles	Sucrose Colorectal 2.18 (1.35–3.51) Colon 2.49 (1.39–4.47) Rectum 1.86 (0.98–3.54) Sucrose rich foods Colorectal 1.94 (1.20–3.13) Colon 2.02 (0.73–2.21) Rectum 1.96 (1.04–3.69)	Sucrose Colorectal >0.001 Colon >0.001 Rectum 0.08 Sucrose rich foods Colorectal 0.006 Colon 0.02 Rectum 0.04	Exposure =Sucrose,sucrose rich foods
Hu et al.2010	Population-based /Canadian	Colon PCC DCC	1731 (964 M, 767 F) 737 994	3097 (1635 M, 1462 F)	Quartiles	1.61 (1.27–2.04) CC 1.67 (1.22–2.29) PCC 1.58 (1.18–2.10) DCC	<0.0001 CC 0.0001. PCC 0.002. DCC	Exposure =Sucrose
Zhi Chen et al. 2015	Population-based/Canadian	Colorectal PCC DCC Rectal	506 (306 M, 200 F)	673 (400 M, 273 F)	Quintiles	2.26 (1.39-3.66) Colorectal 2.90 (1.54-5.45) PCC 2.40 (1.20-4.81) DCC 2.01 (1.01-4.00) Rectal	0.40 0.11 0.08 0.65	Exposure =Sugary-diet pattern (pies, tarts, desserts,
Bahrami et al. 2019	Hospital-based/Iran	Colorectal cancer Colorectal adenoma	129 130	240	Westernized pattern low/high	Colorectal 3.5 (2.13-5.19) Adenoma 2.47(1.49-4.08)	<0.0001	Exposure =high intake of Sweets and desert

Cohort Study								
Bostick et al, 1994	Iowa Women's Health Study (IWHS)	Colon	212	35,216 (women)	Categories	Sucrose 1.45 (0.88-2.39). Sucrose-contaning foods 1.74 (1.06-2.87) 2.00 (1.21-3.30)	Sucrose 0.14. Sucrose-contaning food 0.12 0.03	Exposure =Sucrose and sucrose contaning foods.
Terry et al. 2003	Population-based / Canadian National Breast Screening Study	Colorectal Colon Rectal	616 436 180	49 124(women)	Quintile	Colorectum 1.03 (0.73-1.44) Total sugar 1.05 (0.73 to 1.53) Glycemic Load 1.01 (0.68 to 1.51) Total	Colorectum 0.71 Total sugar 0.94 Glycemic Load 0.66 Total Carbohydate Colon	Exposure =Total sugar per day including sucrose, glucose, fructose, and
Michaud et al. 2005	Health Professionals Follow-up Study (HPFS) and the NHS I.	Colorectal Colon Rectal	**NHS I,** 1,113 870 243 **HPFS,** 696 561 135	83,927 women 47,422 Men	Quintile	Colorectum 1.30(0.99-1.69) (M) 0.89(0.72-1.11). (F) Colon 1.25 (0.93-1.68) (M) 0.99 (0.78-1.26) (F) Rectum 1.47 (0.81-2.66) (M) 0.62 (0.39-0.99) (F)	0.03 M. 0.10 F 0.13 M. 0.49 F 0.11 M. 0.17 F	Exposure =Sucrose
McCarl et al. 2006	Iowa Women's Health Study	Colorectal Colon Rectal	954 757 209	35,197	Quintile	Colorectal Glycemic Index 1.08 (0.88-1.32) Glycemic load	0.15 Glycemic Index 0.33 Glycemic load	Exposure= Glycemic Index Glycemic load
Higginbotham et al. 2014	Women's Health Study	Colorectal Colon Rectal	174 148 26	38 451(women)	Quintile	Colorectal 1.51 (0.90 to 2.54) only	0.06	Exposure =Sucrose
Howarth et al 2015	The Multiethnic Cohort (MEC) study /Hawaii or Southern California	Colorectal Colon Rectal	2379	191 004 (85 898 men) and (105 106 women)	Quintile	Colorectal carbohydrate intake 1.09 (0.84, 1.40) M 0.71 (0.53, 0.95) F Glycemic load 1.15 (0.89, 1.48) M	Carbohydrate intake 0.603. M 0.025 F. Glycemic load 0.193 M 0.017 F	Exposure =Carbohydate Glycemic load