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Association between dietary sugar intake and colorectal adenoma among cancer screening examinees in Japan

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Abstract

Although intake of highly sugary foods is considered to be a potential risk factor for colorectal cancer through hyperinsulinemia, the association of sugar intake and colorectal adenoma, a precursor lesion to most colorectal cancer, is poorly understood, particularly in Asian populations. We undertook a cross-sectional study in a Japanese population to investigate the association between dietary sugar intake and the prevalence of colorectal adenoma. Study subjects were selected from participants who underwent magnifying colonoscopy with dye spraying as part of a cancer screening program and who responded to a self-administered questionnaire before the colonoscopy. A total of 738 cases with colorectal adenoma and 697 controls were enrolled. Dietary intakes of glucose, fructose, galactose, sucrose, maltose, lactose, and total sugars (sum of these six mono- or disaccharides) were calculated from a food frequency questionnaire, and divided into quartiles based on the distribution among controls. Odds ratios and 95% confidence intervals of colorectal adenoma were estimated using unconditional logistic regression models, with adjustment for potential confounding factors. Total sugar intake was not significantly associated with the prevalence of colorectal adenoma (odds ratio for the highest intake group compared to reference group = 1.18; 95% confidence interval, 0.81-1.73; *P* for trend = .34). Furthermore, no statistically significant positive associations were observed for any of the six mono- or disaccharides. Findings were similar on additional analyses by site, size, and number of adenomas. Our findings do not support an association between high sugar intake and increased odds ratios of colorectal adenoma.

KEYWORDS
carbohydrate, colorectal adenoma, cross-sectional study, epidemiology, sugar

1 | INTRODUCTION

Colorectal cancer is the third most common cancer worldwide, accounting for approximately 1 850 000 new cases and more than 880 000 deaths in 2018.[1] In Japan, CRC has recently become the most common cancer diagnosis and the third leading cause of cancer-related death.[2]

Lifestyle factors play an important role in the carcinogenesis of CRC.[3] A high sugar diet, such as high consumption of sugar-sweetened beverages, has been linked to obesity and DM,[4,5] which are related to hyperinsulinemia. Rapidly digested sugar induces a postprandial elevation in blood glucose, which also leads to hyperinsulinemia.[6] It is hypothesized that chronically elevated levels of insulin and insulin-like growth factor 1 result in an increase in cancer risk by stimulating cellular growth and the suppression of cell apoptosis through the Akt and MAPK intracellular signaling pathways.[7-9] Previous studies have indicated an association between CRC risk and high insulin resistance,[10,11] obesity,[12] and diabetes.[13] In addition, the role of specific sugars, such as sucrose, in colorectal tumorigenesis has also been investigated.[14,15] Several groups have reported a positive association between CRC and sucrose intake[16-18] or excessive intake of sugary beverages, which contain sucrose as a predominant sweetener.[19]

Although several studies have investigated the association between high sugar intake and CRC risk, results have been inconsistent.[18-25] Some case-control and cohort studies showed an increased risk of CRC with high sugar intake,[18,20,21,23] whereas other studies revealed no association.[22,24,25] In addition, few reports from Asian countries have appeared[18]; most were carried out in non-Asian countries, which have substantially different dietary habits. In particular, the major food sources of sugars in North America and Europe are sweet products, sugar-sweetened beverages, and breads.[26,27] In contrast, sugars in Japan are mainly provided by fruits and vegetables, and the contribution of sweetened beverages is lower than in North America and Europe.[28] A previous cohort study investigating the association of GL and carbohydrate intake with CRC risk in multiethnic groups indicated that results differed between Caucasian and Japanese-American participants,[29] although a previous meta-analysis found no clear association between intake of carbohydrates, GL, or GI.[30] Moreover, few studies have examined the association between high sugar intake and CRA, which is a precursor of CRC.[31-35] To our knowledge, no study has been reported from Asian countries.

To investigate the contribution of sugar to the early stage of colorectal tumorigenesis, we analyzed the association between dietary sugar intake and the prevalence of CRA in a cross-sectional study in a middle-aged and elderly Japanese population.

2 | MATERIALS AND METHODS

2.1 | Study population

Study subjects were selected from examinees of magnifying colonoscopy with dye spraying as a part of a cancer screening program, CAST, undertaken by the National Cancer Center, Tokyo, Japan. Details of the study have been described previously.[36] Briefly, eligible examinees were men aged 50-79 years and women aged 40-79 years who received total colonoscopy from the anus to the cecum and who did not have a history of CRA, hyperplastic polyp, any malignant neoplasm, ulcerative colitis, Crohn's disease, familial adenomatous polyposis, neuroendocrine tumor, or colectomy. Among a consecutive series of 3212 examinees who underwent colonoscopy between February 2004 and February 2005, 2234 met the above conditions. Based on the pit-pattern classification of colorectal lesions,[37] 526 men and 256 women were determined to have at least 1 adenoma and were thus included as adenoma cases. Of the remaining 1452 examinees, 482 men and 721 women were also free from other benign lesions (eg, hyperplastic polyps, inflammatory polyps, and diverticulum) and were identified as potential controls. Because there were fewer potential male controls than male cases, all men of the potential controls were included in the study. The potential control of 256 women was frequency matched to the female cases in 5 age categories (40-49, 50-54, 55-59, 60-64, and 65 years or older) and screening periods (first and second half). Finally, CAST enrolled 526 cases and 482 controls in men and 256 cases and 256 controls in women. All subjects gave written informed consent, and the study protocol was approved by the institutional review board of the National Cancer Center, Tokyo, Japan.

2.2 | Assessment of sugar intake

All participants answered a self-administered questionnaire survey before their colonoscopic examination. The questionnaire included information on lifestyle, such as smoking, alcohol consumption, and usual physical activity, as well as medical history, medication, and family CRC history. Weight and height were measured at the time of examination. Subjects were also encouraged to complete an FFQ, which consisted of 145 food and beverage items with 9 frequency categories and standard portions/units, and asked about the usual consumption of listed foods during the previous year. Frequency response choices for food items were less than once per month, 1-3 times per month, 1-2 times per week, 3-4 times per week, 5-6 times per week, once per day, 2-3 times per day, 4-6 times per day, and more than 7 times per day. For consumption of rice, the FFQ asked about bowl size and the number of bowls per day, and also about the number of cups per day or week for beverages.[38] The standard portion sizes of respective food items were specified in the FFQ and the amounts were determined into 3 categories of less than half, the same as, and more than 1.5 times the reference portion size. Daily food intake was calculated by multiplying frequency by the standard portion and relative size for each food item.

Intakes of energy and carbohydrate were calculated using the 2015 Japan Standard Tables of Food Composition,[39] while intakes of glucose, fructose, galactose, sucrose, maltose, lactose, total sugars (sum of these six mono- or disaccharides), and starch were calculated using the 2015 Standard Tables of Food Composition in Japan for

the available carbohydrates.[40] For food items that were not covered by the food composition table, we updated values using substitution methods. Sugar intakes from table sugar, miso, soy sauce, cooking sake, and sweet cooking rice wine (mirin) were considered by calculating sugars added to foods during cooking. Daily nutrient intakes for each individual were calculated by summing the product of intake of each food multiplied by the nutrient content of that food. Details of sugar intake calculation have been described previously.[41]

This FFQ was modified from an FFQ used in a previous population-based prospective study that had additional food items. The modified FFQ was validated in middle-aged urban participants undergoing cancer screening.[42] Validity for sugar intake was assessed among subsamples of a prospective cohort study—the Japan Public Health Center-based Prospective (JPHC) study—using 14- or 28-day DRs. Subjects were divided into 2 cohorts, Cohort I (1990-1995) and Cohort II (1993-1998). Spearman's correlation coefficients of the energy-adjusted total sugars intake between the FFQ and DR for men and women were 0.52 and 0.36 (Cohort I) and 0.56 and 0.38 (Cohort II), respectively. Similarly, Spearman's correlation coefficients of starch intake between the FFQ and DR for men and women were 0.42 and 0.44 (Cohort I) and 0.55 and 0.39 (Cohort II), respectively.[41]

2.3 | Statistical analysis

For the present analysis, participants above or below 2.5% in the sex-specific distribution of total energy intake (n = 74), and those with missing values for covariates (smoking, drinking, BMI, physical activity, family cancer history, NSAID use) (n = 11) were excluded, leaving a total of 738 cases and 697 controls for final analysis.

Sugar intake was adjusted for total energy intake using the residual regression model by sex. All subjects were divided into sex-specific quartiles of total sugar consumption by cut-off points calculated from the distributions among controls. Case-control comparisons of mean, median, and proportions were tested with the t test, Wilcoxon rank-sum test, and χ^2 test, respectively. Characteristics by quartiles of total sugar intake were assessed by the Cochran-Mantel-Haenszel statistics. An unconditional logistic regression model was used to calculate ORs and 95% CIs of CRA according to quartile of total sugars and each mono- or disaccharide sugar, with the lowest category as reference. The regression models were adjusted for age (continuous), sex, screening period (first or second half), physical activity (MET-hours/day, all variables adjusted in continuous scale), cigarette smoking (never, past, and current: 1-20 pack-years, 21-40 pack-years, and over 40 pack-years), alcohol drinking (never, past, and current: 1-149 g/wk, 150-299 g/wk, and over 300 g/wk), family CRC history, NSAID use, total calorie intake, energy-adjusted intakes of fiber and calcium, BMI (kg/m^2; all variables adjusted in continuous scale), and medical history of DM. Linear trends in the ORs of CRA were assessed by assigning ordinal values to the quartile categories of total sugar intake. A multinomial logistic regression model was applied to evaluate the association of total sugar intake with adenoma site, size, and number. Stratified analyses were carried out

with regard to smoking status (never or past/current), alcohol drinking habit (never or past/current), BMI (≤25 and >25 kg/m^2), physical activity (MET-hours/d, >34.3 or ≤34.3), gender (male and female), and DM history (never or ever). Two-sided P values of <.05 were considered statistically significant. An interaction term was created by multiplying ordinal values for quartiles of total sugar intake by those for dichotomous categories of each stratified variable, and its significance was statistically evaluated by the likelihood ratio test with 1 df. All statistical analyses were carried out using SAS version 9.3 (SAS Institute).

3 | RESULTS

Selected characteristics of adenoma cases and controls are summarized in Table 1. In brief, the number of men was 498 (67.5%) in the case group and 453 (65.0%) in the control group. Mean age was 60.8 and 59.9 years in cases and controls, respectively (P = .004). Compared with the controls, cases were more likely to smoke, have a higher BMI, family CRC history, and DM history, and have lower NSAID use. Cases consumed lower amounts of fiber, isoflavone, maltose, starch, and total carbohydrate than controls but had higher total energy intake. Selected features of controls according to quartile of total sugars intake are summarized in Table 2. Subjects with higher intake of total sugars tended to have lower cigarette smoking and alcohol consumption. Among subjects in the highest quartile category of total sugars, intakes of fiber, folate, calcium, and isoflavone were high.

Associations of intake of total sugars and the six mono- and disaccharides with the prevalence of CRA are shown in Table 3. Total sugars intake was not significantly associated with the prevalence of CRA in the fully adjusted model (OR for the highest intake group compared to reference group = 1.18; 95% CI, 0.81-1.73; P for trend = .34). As a whole, we did not observe statistically significant positive associations for the six mono- or disaccharides. When adjusted for age, sex, and screening period, statistically significant inverse associations were found for the intake of lactose and maltose. However, statistical significance was lost on further adjustment (models 2, 3, and 4). We further categorized the subjects into deciles to clarify the impact of extreme low and high intake on the associations. Similar to the results by quartile, no association was found for intake of total sugars or the six mono- and disaccharides, even in subjects in the highest decile category (data not shown).

Table 4 presents the association between total sugars intake and the prevalence of CRA by site, size, and number of adenomas. The site-specific analysis was undertaken in 382 proximal, 263 distal, and 81 rectal adenoma cases, following the exclusion of 12 cases that lacked information on adenoma site. No significant associations with CRA were shown. We further analyzed the association of total sugars intake and the prevalence of CRA stratified by smoking, alcohol drinking, BMI, physical activity, gender, and DM history (Table 5). Because of the small number of subjects with a history of DM, the results are limited to subjects without

TABLE 1 Characteristics of colorectal adenoma cases and controls

Variable	Colorectal adenoma (n = 738)	Control (n = 697)	*P* value
Men, n (%)	498 (67.5)	453 (65.0)	.32
Age (y), mean (SD)	60.8 (6.2)	59.9 (6.0)	.004
BMI (kg/m^2), mean (SD)	23.5 (2.9)	23.0 (2.8)	.001
Physical activity (MET-hours/d), mean (SD)	36.7 (9.2)	36.5 (7.7)	.57
Ever smoker, n (%)	407 (55.2)	336 (48.2)	.009
Alcohol consumer, n (%)	576 (78.1)	522 (74.9)	.16
Familial CRC history, (%)	120 (16.3)	86 (12.3)	.03
DM history, (%)	75 (10.2)	47 (6.7)	.02
NSAID use, (%)	32 (4.3)	53 (7.6)	.009
Dietary intake, median (IQR)			
Total energy (kcal/d)	1960.0 (1637.0-2375.0)	1901.0 (1602.0-2252.0)	.01
Total carbohydrate (g/d)	244.6 (217.8-275.2)	252.3 (225.6-277.7)	.01
Total sugars (g/d)	56.7 (41.1-72.2)	57.4 (43.9-74.7)	.11
Glucose (g/d)	12.4 (9.3-15.7)	12.7 (9.7-16.1)	.21
Fructose (g/d)	10.4 (7.0-14.8)	11.1 (7.6-15.1)	.07
Galactose (g/d)	0.45 (0.11-0.96)	0.52 (0.13-0.98)	.14
Sucrose (g/d)	21.0 (13.8-29.1)	21.9 (15.0-30.1)	.18
Maltose (g/d)	1.20 (0.77-1.58)	1.24 (0.84-1.64)	.02
Lactose (g/d)	7.7 (3.4-12.1)	8.1 (4.1-12.7)	.09
Starch (g/d)	165.6 (138.1-193.5)	169.8 (145.5-194.7)	.05
Fiber (g/d)	13.1 (9.8-16.6)	13.5 (10.5-17.2)	.02
Folate (µg/d)	357.0 (274.9-438.1)	365.4 (282.2-462.1)	.05
Calcium (mg/d)	542.5 (384.2-690.1)	550.4 (416.4-725.7)	.07
Isoflavone (mg/d)	35.6 (21.1-56.2)	38.8 (23.7-61.2)	.01
Red meat (g/d)	28.2 (15.0-43.5)	26.2 (15.3-42.5)	.22
Processed meat (g/d)	3.7 (1.0-8.8)	3.6 (0.79-8.5)	.45

Abbreviations: BMI, body mass index; CRC, colorectal cancer; DM, diabetes mellitus; IQR, interquartile range; MET, metabolic equivalent; NSAID, nonsteroidal antiinflammatory drug.

a history of DM. No statistically significant association was observed regardless of strata for smoking, BMI, physical activity, or gender. Moreover, tests for interaction were also not statistically significant. However, *P* for interaction was statistically significant for drinking status, despite the lack of a statistically significant association for each stratum.

4 | DISCUSSION

In this cross-sectional study, dietary sugar intake was not statistically significantly associated with CRA. In addition to total sugar intake, we examined whether the intake of any of six mono- and disaccharides was associated with the prevalence of CRA, and investigated whether associations differed by adenoma site, size, or number and major risk factors of CRC. However, none of these analyses showed a statistically significant association, and

stratified analyses by major risk factors showed no substantial difference between strata.

Given that high insulin resistance has been proven to increase CRC risk,[10,43-45] we hypothesized the presence of a positive association between dietary sugar intake and CRA, but the results did not support this expectation. Although several studies have examined the association between diets high in sugars, carbohydrates, GI, or GL and CRC risk, results to date have been inconsistent.[13,18,20-25,29,46-50] Two cohort studies reported a positive association between fructose intake and CRC risk.[20,23] Three cohort studies found a positive association between sucrose intake and CRC and only one case-control study from Japan showed a positive association between sucrose intake and CRC risk among smokers and nonalcohol drinkers in men.[16-18] In contrast, a recent metaanalysis of cohort studies found no significant association between sucrose or fructose intake and the risk of CRC,[30] which is in general agreement with our findings.

TABLE 2 Selected characteristics according to total sugar intake among controls[a]

Variable	Q1 (n = 174)	Q2 (n = 174)	Q3 (n = 174)	Q4 (n = 175)	*P* trend
Men, n (%)	113 (64.9)	113 (64.9)	113 (64.9)	114 (65.1)	.97
Age (y), mean (SD)	58.1 (6.3)	60.4 (5.8)	60.6 (5.6)	60.4 (5.9)	.0005
BMI (kg/m²), mean (SD)	23.2 (2.8)	22.8 (3.1)	23.2 (2.7)	22.9 (2.7)	.59
Physical activity (MET-hours/d), mean (SD)	36.6 (8.2)	36.4 (7.2)	36.1 (7.4)	36.7 (8.0)	.98
Ever smoker, n%	97 (55.8)	81 (46.6)	84 (48.3)	74 (42.3)	.022
Alcohol consumer, n%	141 (81.0)	133 (76.4)	126 (72.4)	122 (69.7)	.0098
Familial CRC history, (%)	21 (12.1)	20 (11.5)	21 (12.1)	24 (13.7)	.62
DM history, (%)	15 (8.6)	11 (6.3)	9 (5.2)	12 (6.9)	.45
NSAID use, (%)	6 (3.5)	16 (9.2)	11 (6.3)	20 (11.4)	.019
Dietary intake, median (IQR)					
Total energy (kcal/d)	1869 (1582-2252)	1914 (1625-2170)	1847 (1595-2201)	1971 (1597-2392)	.33
Total carbohydrate (g/d)	238.9 (212.0-272.9)	252.7 (224.4-277.8)	249.4 (227.4-270.8)	262.7 (234.6-286.1)	<.0001
Total sugars (g/d)[b]	35.4 (28.3-46.2)	47.7 (43.6-61.9)	61.0 (55.0-73.5)	88.1 (75.8-99.3)	<.0001
Glucose (g/d)	8.8 (6.8-11.3)	11.7 (9.3-13.9)	13.8 (11.5-16.8)	18.6 (14.4-21.9)	<.0001
Fructose (g/d)	6.4 (4.6-9.0)	9.8 (7.3-12.0)	12.5 (10.6-14.8)	18.3 (14.4-24.0)	<.0001
Galactose (g/d)	0.19 (0.03-0.59)	0.48 (0.12-9.94)	0.80 (0.22-1.03)	0.86 (0.22-1.10)	<.0001
Sucrose (g/d)	12.7 (9.5-17.5)	19.3 (15.1-23.7)	23.7 (18.8-28.8)	35.7 (28.6-42.5)	<.0001
Maltose (g/d)	1.0 (0.6-1.4)	1.2 (0.8-1.7)	1.4 (0.9-1.7)	1.4 (1.1-1.7)	<.0001
Lactose (g/d)	4.9 (1.9-8.0)	7.5 (3.3-12.0)	9.2 (5.9-14.2)	11.7 (7.7-16.7)	<.0001
Starch (g/d)	179.1 (156.2-211.0)	179.7 (155.3-205.3)	166.0 (145.1-185.9)	153.2 (131.5-175.1)	<.0001
Fiber (g/d)	10.6 (8.5-13.0)	12.9 (10.1-16.0)	14.4 (11.6-17.4)	17.5 (14.1-20.6)	<.0001
Folate (µg/d)	301.3 (242.6-377.0)	332.0 (266.1-449.5)	384.8 (316.7-457.1)	443.3 (347.4-541.9)	<.0001
Calcium (mg/d)	409 (283-511)	517 (388-657)	607 (475-778)	701 (576-877)	<.0001
Isoflavone (mg/d)	34.7 (23.2-53.1)	37.3 (23.3-63.0)	40.0 (26.0-62.2)	46.2 (23.9-62.7)	.20
Red meat (g/d)	27.6 (16.3-52.7)	27.7 (16.0-46.4)	27.3 (16.6-43.2)	22.6 (12.5-33.7)	<.0001
Processed meat (g/d)	3.8 (0.8-7.8)	3.5 (0.9-8.8)	3.5 (1.0-7.3)	3.6 (0.5-9.1)	.84

Abbreviations: BMI, body mass index; CRC, colorectal cancer; DM, diabetes mellitus; IQR, interquartile range; MET, metabolic equivalent; NSAID, nonsteroidal antiinflammatory drug.

[a]Quartile of total sugar intake is calculated for men and women separately. Each category in the table above includes both men and women classified according to sugar intake.

[b]Total sugars represent the sum of glucose, galactose, fructose, sucrose, lactose, and maltose.

Colorectal adenoma has been proven to be a major precursor of CRC through the adenoma-carcinoma sequence. Whereas some previous studies have indicated that insulin resistance is a risk factor for CRA,[51-54] few studies have investigated the association between sugar intake and the risk of CRA. A case-control study by Flood et al implied an inverse association of carbohydrate intake and the risk of distal adenoma in men,[31] whereas a cohort study in the United States observed no association between carbohydrate intake and distal CRA.[35] Both studies focused on distal adenoma only because all participants had undergone sigmoidoscopy. In addition, although a few other case-control studies have investigated the association between carbohydrate or sugar intake and the risk of CRA, results

were inconsistent and most took insufficient account of potential confounding factors.[32-34] The present study is, to our knowledge, the first to investigate the association between dietary sugar intake and the prevalence of CRA in an Asian population.

Several possible explanations for the lack of association between sugar intake and CRA should be considered. First, sugar intake might be related to a late stage of tumor growth, and have no association with earlier development. We did not undertake stratified analyses by the severity of adenoma dysplasia due to a lack of information, which might be a limitation of this study. Further studies are required to reveal the influence of high sugar intake on developing colorectal neoplasms with comparison of risk

TABLE 3 Odds ratios (ORs) and 95% confidence intervals (CI) of colorectal adenoma according to sugar intake

	Quartile category				
	Q1	Q2	Q3	Q4	P trend
Total sugars[a]					
Case (N)	203	174	182	179	
OR (95% CI) 1	1.00 (Ref.)	0.82 (0.61-1.10)	0.83 (0.62-1.12)	0.83 (0.61-1.11)	.24
OR (95% CI) 2	1.00 (Ref.)	0.93 (0.68-1.26)	0.98 (0.72-1.34)	1.03 (0.75-1.42)	.75
OR (95% CI) 3	1.00 (Ref.)	0.97 (0.71-1.33)	1.08 (0.77-1.51)	1.18 (0.81-1.72)	.33
OR (95% CI) 4	1.00 (Ref.)	1.01 (0.74-1.39)	1.10 (0.78-1.55)	1.18 (0.81-1.73)	.34
Glucose					
Case (N)	199	190	171	178	
OR (95% CI) 1	1.00 (Ref.)	0.92 (0.69-1.23)	0.82 (0.61-1.10)	0.84 (0.62-1.13)	.17
OR (95% CI) 2	1.00 (Ref.)	0.97 (0.72-1.31)	0.87 (0.64-1.18)	0.91 (0.68-1.24)	.44
OR (95% CI) 3	1.00 (Ref.)	1.02 (0.75-1.38)	0.94 (0.68-1.30)	1.05 (0.74-1.50)	.91
OR (95% CI) 4	1.00 (Ref.)	1.05 (0.77-1.42)	0.96 (0.70-1.33)	1.06 (0.74-1.51)	.89
Fructose					
Case (N)	197	209	153	179	
OR (95% CI) 1	1.00 (Ref.)	1.01 (0.76-1.35)	0.73 (0.54-0.99)	0.86 (0.64-1.16)	.11
OR (95% CI) 2	1.00 (Ref.)	1.13 (0.84-1.52)	0.85 (0.62-1.15)	1.04 (0.76-1.42)	.74
OR (95% CI) 3	1.00 (Ref.)	1.16 (0.86-1.57)	0.91 (0.65-1.27)	1.16 (0.82-1.65)	.70
OR (95% CI) 4	1.00 (Ref.)	1.16 (0.85-1.57)	0.91 (0.65-1.28)	1.14 (0.80-1.63)	.76
Galactose					
Case (N)	200	198	176	164	
OR (95% CI) 1	1.00 (Ref.)	0.99 (0.74-1.33)	0.86 (0.64-1.15)	0.78 (0.58-1.05)	.069
OR (95% CI) 2	1.00 (Ref.)	1.11 (0.82-1.49)	0.96 (0.71-1.30)	0.93 (0.68-1.27)	.46
OR (95% CI) 3	1.00 (Ref.)	1.15 (0.85-1.55)	0.96 (0.70-1.31)	0.98 (0.70-1.38)	.67
OR (95% CI) 4	1.00 (Ref.)	1.17 (0.87-1.59)	0.97 (0.71-1.32)	1.00 (0.71-1.41)	.74
Sucrose					
Case (N)	204	168	193	173	
OR (95% CI) 1	1.00 (Ref.)	0.79 (0.59-1.07)	0.91 (0.68-1.22)	0.82 (0.61-1.09)	.30
OR (95% CI) 2	1.00 (Ref.)	0.89 (0.66-1.21)	1.04 (0.77-1.42)	0.98 (0.71-1.34)	.86
OR (95% CI) 3	1.00 (Ref.)	0.91 (0.67-1.24)	1.09 (0.79-1.49)	1.02 (0.73-1.43)	.64
OR (95% CI) 4	1.00 (Ref.)	0.91 (0.67-1.25)	1.11 (0.81-1.52)	1.03 (0.73-1.44)	.61
Maltose					
Case (N)	232	172	181	153	
OR (95% CI) 1	1.00 (Ref.)	0.73 (0.54-0.97)	0.75 (0.56-1.00)	0.62 (0.46-0.84)	.0033
OR (95% CI) 2	1.00 (Ref.)	0.77 (0.57-1.03)	0.85 (0.63-1.14)	0.72 (0.53-0.99)	.079
OR (95% CI) 3	1.00 (Ref.)	0.77 (0.57-1.04)	0.85 (0.63-1.16)	0.72 (0.52-0.99)	.081
OR (95% CI) 4	1.00 (Ref.)	0.77 (0.57-1.05)	0.89 (0.66-1.21)	0.75 (0.54-1.03)	.15
Lactose					
Case (N)	204	201	162	171	
OR (95% CI) 1	1.00 (Ref.)	0.97 (0.73-1.30)	0.76 (0.57-1.03)	0.79 (0.59-1.06)	.046
OR (95% CI) 2	1.00 (Ref.)	1.07 (0.80-1.44)	0.90 (0.66-1.23)	0.96 (0.70-1.31)	.55
OR (95% CI) 3	1.00 (Ref.)	1.05 (0.77-1.43)	0.87 (0.61-1.24)	0.89 (0.55-1.43)	.45
OR (95% CI) 4	1.00 (Ref.)	1.06 (0.78-1.45)	0.88 (0.62-1.26)	0.90 (0.56-1.45)	.49

Note: Model 1: Adjusted for age, sex, and screening period. Model 2: Further adjusted for physical activity, smoking status, alcohol use, family history of colorectal cancer, and nonsteroidal antiinflammatory drug use. Model 3: Further adjusted for intake of total calorie, fiber, and calcium. Model 4: Further adjusted for body mass index and diabetes history.

Abbreviation: Ref., reference.

[a]Total sugars represent the sum of glucose, fructose, galactose, sucrose, maltose, and lactose.

TABLE 4 Odds ratios (ORs) and 95% confidence intervals (CI) of colorectal adenoma according to total sugar intake by site, size, and number of adenomas

	Quartile category				
	Q1	Q2	Q3	Q4	P trend
Adenoma site					
Proximal					
Case (n)	94	81	99	108	
OR (95% CI) 1	1.00 (Ref.)	0.88 (0.60-1.30)	1.12 (0.75-1.69)	1.29 (0.82-2.03)	.16
OR (95% CI) 2	1.00 (Ref.)	0.93 (0.63-1.38)	1.17 (0.78-1.77)	1.32 (0.84-2.09)	.14
Distal					
Case (n)	85	63	64	51	
OR (95% CI)1	1.00 (Ref.)	0.96 (0.63-1.46)	1.03 (0.65-1.62)	0.97 (0.57-1.67)	1.00
OR (95% CI) 2	1.00 (Ref.)	0.99 (0.65-1.52)	1.06 (0.67-1.68)	1.01 (0.59-1.74)	.89
Rectal					
Case (n)	22	25	17	17	
OR (95% CI)1	1.00 (Ref.)	1.68 (0.86-3.29)	1.33 (0.61-2.90)	1.64 (0.68-3.95)	.38
OR (95% CI) 2	1.00 (Ref.)	1.77 (0.89-3.50)	1.32 (0.60-2.93)	1.75 (0.72-4.30)	.35
Adenoma size (mm)					
≥5					
Case (n)	96	89	72	68	
OR (95% CI)1	1.00 (Ref.)	1.10 (0.75-1.62)	0.95 (0.61-1.47)	1.09 (0.66-1.80)	.92
OR (95% CI) 2	1.00 (Ref.)	1.14 (0.77-1.69)	0.95 (0.62-1.47)	1.11 (0.67-1.84)	.90
<5					
Case (n)	107	85	110	111	
OR (95% CI)1	1.00 (Ref.)	0.90 (0.62-1.31)	1.20 (0.81-1.78)	1.31 (0.84-2.02)	.12
OR (95% CI) 2	1.00 (Ref.)	0.96 (0.65-1.40)	1.29 (0.86-1.92)	1.37 (0.87-2.14)	.087
Adenoma number					
≥2					
Case (n)	92	68	75	78	
OR (95% CI)1	1.00 (Ref.)	0.91 (0.60-1.38)	1.15 (0.73-1.79)	1.53 (0.92-2.54)	.075
OR (95% CI) 2	1.00 (Ref.)	0.94 (0.62-1.44)	1.14 (0.73-1.79)	1.53 (0.92-2.54)	.086
1					
Case (n)	111	106	107	101	
OR (95% CI)1	1.00 (Ref.)	1.02 (0.71-1.46)	1.04 (0.71-1.53)	1.01 (0.65-1.56)	.96
OR (95% CI) 2	1.00 (Ref.)	1.08 (0.75-1.56)	1.10 (0.74-1.63)	1.06 (0.68-1.65)	.80

Note: Model 1: Adjusted for age, sex, screening period, physical activity, smoking status, alcohol use, family history of colorectal cancer, nonsteroidal antiinflammatory drug use, intake of total calories, fiber, and calcium. Model 2: Further adjusted for body mass index and diabetes history.

Abbreviation: Ref., reference.

by histological tumor grade. Second, the range of sugar consumption in our Japanese population might be relatively narrow, and shifted to a comparatively lower level than those in the previous non-Asian studies.[20,22,23,25] For example, Michaud et al reported a positive association between sucrose intake and CRC risk in men, wherein median sucrose intake among male participants in the lowest and highest quintile categories was 26 and 67 g/d, respectively.[23] The absence of subjects with higher sugar intake in our study might be another reason why we did not observe a significant association between sugar intake and CRA.

Among the strengths of this study, all participants underwent total colonoscopy, which likely reduced the possibility of misclassification of case and control status. Dietary habits and other lifestyle information were ascertained prior to colonoscopy procedures, namely before the determination of case and control status, which likely minimized concerns regarding recall bias.

Several limitations of our study also warrant mention. First, as it was carried out under a cross-sectional design, the observed associations might be due to reverse causality. However, it is unlikely that participants changed their dietary habits because of

TABLE 5 Odds ratios (ORs) and 95% confidence intervals (CI) of colorectal adenoma according to total sugar intake stratified by smoking, drinking, body mass index (BMI), physical activity, and gender

	Quartile category					
	Q1	Q2	Q3	Q4	P trend	P int.
Smoking status						
Never						
Case/controls (n)	68/77	85/93	80/90	98/101		
OR (95% CI) 1	1.00 (Ref.)	1.01 (0.64-1.60)	1.04 (0.63-1.72)	1.18 (0.69-2.00)	.52	
OR (95% CI) 2	1.00 (Ref.)	1.04 (0.66-1.66)	1.07 (0.65-1.78)	1.20 (0.70-2.05)	.49	
Past/current						
Case/controls (n)	135/97	89/81	102/84	81/74		
OR (95% CI) 1	1.00 (Ref.)	0.91 (0.60-1.40)	1.11 (0.70-1.76)	1.27 (0.73-2.18)	.38	.66
OR (95% CI) 2	1.00 (Ref.)	0.96 (0.62-1.49)	1.14 (0.72-1.82)	1.26 (0.73-2.18)	.35	.64
Drinking status						
Never						
Case/controls (n)	23/33	29/41	50/48	60/53		
OR (95% CI) 1	1.00 (Ref.)	1.04 (0.49-2.20)	1.67 (0.81-3.42)	1.64 (0.76-3.52)	.11	
OR (95% CI) 2	1.00 (Ref.)	1.08 (0.51-2.30)	1.70 (0.83-3.52)	1.62 (0.75-3.50)	.13	
Past/current						
Case/controls (n)	180/141	145/133	132/126	119/122		
OR (95% CI) 1	1.00 (Ref.)	0.98 (0.69-1.39)	0.94 (0.64-1.38)	1.01 (0.65-1.56)	.97	.03
OR (95% CI) 2	1.00 (Ref.)	1.03 (0.72-1.46)	0.96 (0.65-1.42)	1.02 (0.66-1.58)	.99	.04
BMI (kg/m^2)						
≤25						
Case/controls (n)	147/136	126/142	136/129	113/143		
OR (95% CI) 1	1.00 (Ref.)	0.92 (0.64-1.35)	1.14 (0.77-1.68)	0.92 (0.59-1.43)	.97	
OR (95% CI) 2	1.00 (Ref.)	0.96 (0.67-1.37)	1.20 (0.81-1.79)	0.97 (0.62-1.51)	.84	
>25						
Case/controls (n)	56/38	48/32	46/45	66/32		
OR (95% CI) 1	1.00 (Ref.)	1.25 (0.64-2.42)	0.93 (0.46-1.85)	2.16 (0.99-4.69)	.11	.13
OR (95% CI) 2	1.00 (Ref.)	1.26 (0.65-2.44)	0.92 (0.46-1.85)	2.16 (0.99-4.71)	.11	.15
Physical activity (MET-hours/d)						
≤Median						
Case/controls (n)	110/84	94/83	92/86	83/83		
OR (95% CI) 1	1.00 (Ref.)	1.03 (0.66-1.60)	1.04 (0.65-1.66)	1.09 (0.65-1.85)	.75	
OR (95% CI) 2	1.00 (Ref.)	1.04 (0.67-1.61)	1.03 (0.64-1.65)	1.06 (0.62-1.80)	.86	
>Median						
Case/controls (n)	93/90	80/91	90/88	96/92		
OR (95% CI) 1	1.00 (Ref.)	0.93 (0.59-1.47)	1.16 (0.71-1.91)	1.30 (0.75-2.27)	.25	.18
OR (95% CI) 2	1.00 (Ref.)	0.98 (0.62-1.56)	1.20 (0.73-1.97)	1.35 (0.77-2.37)	.23	.20
Gender						
Male						
Case/controls (n)	143/113	117/113	129/113	109/114		
OR (95% CI) 1	1.00 (Ref.)	0.92 (0.63-1.35)	1.06 (0.70-1.60)	1.00 (0.62-1.62)	.85	
OR (95% CI) 2	1.00 (Ref.)	0.96 (0.65-1.42)	1.08 (0.71-1.64)	1.00 (0.62-1.63)	.87	

TABLE 5 (Continued)

	Quartile category				P trend	P int.
	Q1	Q2	Q3	Q4		
Female						
Case/controls (n)	60/61	57/61	53/61	70/61		
OR (95% CI) 1	1.00 (Ref.)	1.05 (0.60-1.84)	1.04 (0.57-1.90)	1.45 (0.77-2.75)	.26	.55
OR (95% CI) 2	1.00 (Ref.)	1.10 (0.63-1.94)	1.10 (0.60-2.03)	1.54 (0.80-2.94)	.20	.52
DM history						
Absence						
Case/controls (n)	175/159	162/163	166/165	160/163		
OR (95% CI) 1	1.00 (Ref.)	1.00 (0.72-1.39)	1.05 (0.74-1.50)	1.14 (0.77-1.69)	.49	
OR (95% CI) 2	1.00 (Ref.)	1.02 (0.73-1.41)	1.05 (0.74-1.50)	1.12 (0.75-1.66)	.57	

Note: Model 1: Adjusted for age, sex, screening period, physical activity, smoking status, alcohol use, family history of colorectal cancer, nonsteroidal antiinflammatory drug use, intake of total calories, fiber, and calcium. Model 2: Further adjusted for BMI and diabetes history.

Abbreviations: DM, diabetes mellitus; MET, metabolic equivalent; *P* int, *P* values for interaction; Ref., reference.

the presence of adenoma, as these lesions are usually asymptomatic, and such reverse association is therefore unlikely. Second, adenoma cases were not histologically confirmed and necessarily included patients with early cancer and nonneoplastic lesions. However, our preliminary survey reported that the accuracy of diagnosis by magnifying chromoendoscopy was high (90%), and the influence of any misclassification due to this technique is likely to be minimal.[55] Third, sugar intake and other dietary factors were self-reported by FFQ and might therefore have suffered from a degree of nondifferential misclassification. Against this, however, our earlier study showed moderate validity and reproducibility for sugar intake.[41] Fourth, high-risk groups such as obese individuals might reduce their sugar intake intentionally or underreport their intake.[56] This type of misclassification could also lead to the attenuation of observed associations. Fifth, subjects with a higher intake of total sugar tended to consume larger amounts of fiber, folate, calcium, and isoflavone in this study. This might reflect the major food sources of sugars in Japan, such as fruits and vegetables.[28] We therefore adjusted for known and potential confounders, including dietary factors, but the possibility of residual confounding cannot be ruled out. Finally, although our study included a total of 738 cases and 697 controls, it might not have had sufficient statistical power to detect a relatively weak association. In fact, this study had approximately 80% statistical power, with a two-sided alpha error level of 5% to detect a true OR of 1.52 for colorectal adenoma among the highest vs lowest quartile group for total sugar intake. Although our findings therefore suggest that total sugar intake is not associated with an approximately 50% or greater increase in the OR of colorectal adenoma, we cannot deny the possibility of a relatively weak association.

In conclusion, our study did not support a positive association between dietary sugar intake and the prevalence of CRA in a Japanese population. However, given the limited evidence of this association and the inherent limitations of our study design, further investigations are required.

CONFLICT OF INTEREST

All other authors declare that they have no conflict of interest.

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