# Sugary Drink Consumption and Subsequent Colorectal Cancer Risk: The Japan Public Health Center–Based Prospective Cohort Study

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## ABSTRACT

**Background:** Most studies examining the associations of sugary drink consumption on colorectal cancer risk have been conducted in Western populations.

**Methods:** This study consisted of 74,070 participants in the Japan Public Health Center–based Prospective Study who completed a food frequency questionnaire (1995–1999). The participants were followed until December 2013 to investigate the associations between sugary drink consumption and colorectal cancer risk using Cox proportional hazards regression models.

**Results:** Among the 74,070 participants, mean age was 56.5 years at baseline, with a mean body mass index (BMI) of 23.5 and a mean daily consumption of 286 mL/day for men and 145 mL/day for women. During a follow-up of 15 years, 1,648 colorectal cancer cases were identified. No overall greater risk of colorectal cancer was observed among men [multivariable HR = 0.84; 95% confidence of interval (CI), 0.70–1.02; ≥254 mL/day vs. nonconsumers] and women (HR = 1.20; 95% CI, 0.96–1.50, ≥134 mL/day vs. nonconsumers). Sugary drink consumption was associated with colon cancer among women (HR = 1.36; 95% CI, 1.03–1.78, ≥134 mL/day vs. nonconsumers). HRs for proximal colon cancer among women who consumed sugary drinks, as compared with nonconsumers, were 1.47 (95% CI, 1.03–2.10) for sugary drink consumption less than 134 mL/day, and 1.45 (95% CI, 1.01–2.09) for at least 134 mL/day.

**Conclusions:** In this large prospective cohort of Japanese with a moderate sugary drink consumption level and low prevalence of obesity, we observed a 36% increased risk of colon cancer in women.

**Impact:** Our findings highlight the importance of subsite- and sex-specific investigation.

## Introduction

Colorectal cancer is the third-most commonly diagnosed cancer worldwide, leading to an estimated 881,000 cancer-related deaths in 2018 (1). Despite the expansion of screening programs globally, there were an estimated 1.8 million new colorectal cancer cases in 2017, with an increase in age-standardized incidence rate by 9.5% from 1990 to 2017 (2). Substantial regional disparities in incidence highlight the potential role of modifiable dietary and lifestyle factors in cancer prevention efforts and their implications for policy making (2).

Sugary drink consumption has been linked to weight gain, obesity, and diabetes mellitus (3–5), all of which are potential risk factors in the development of colorectal cancer. A number of studies hypothesized that the insulin-like growth factor axis was a potential pathway for colorectal cancer (6–8). Moreover, the International Agency for Research on Cancer (IARC) suggested that exposure to 4-methylimidazole in sugary drinks is possibly carcinogenic to humans (Group 2B; ref. 9). To date, only a few studies have prospectively evaluated the association between sugary drinks and colorectal cancer risk, and the evidence is inconclusive (10–17). Although individual studies suggested a significant positive association of sugary drinks with the risk of colorectal cancer (15, 16), a pooled analysis of 10 prospective cohorts reported a null association with colon cancer (10). Most studies examining the association with colorectal cancer risk have been done in Western populations (10–17), and their findings might not be generalizable to Asian populations due to different dietary factors and levels of sugary drink consumption (18). Moreover, evidence of the association of sugary drinks with the risk of subsites of colorectal cancer is sparse. Although anatomic subsites of colorectal cancer have been suggested to be heterogeneous in etiology as well as tumor characteristics (19), less is known regarding the magnitude of cancer risk in subsites.

The aim of this study was to evaluate the association of consumption of sugary drinks with colorectal cancer risk using data from the Japan Public Health Center-based Prospective Study (JPHC Study). In addition, we assessed the risk estimates by individual anatomic subsite and lifestyle factors, including alcohol consumption, body mass index (BMI), past history of diabetes, physical activity, and smoking status.

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**Note:** Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

Research group members are listed at the following site (as of August 2020): https://epi.ncc.go.jp/en/jphc/781/8390.html.

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## Materials and Methods

### Study population

The JPHC Study includes 140,420 participants from two cohorts, with 61,595 individuals ages 40 to 59 years enrolled in Cohort I and 78,825 individuals ages 40 to 69 years enrolled in Cohort II. Participants were recruited between 1990 and 1994 from the general populations of 11 prefectural public health center (PHC) areas across Japan (Cohort I: Iwate, Akita, Nagano, Okinawa, and Tokyo; and Cohort II: Ibaraki, Niigata, Kochi, Nagasaki, Okinawa, and Osaka). All enrolled participants were informed of the study objectives, and the completion of self-administered questionnaires were considered to indicate consent to participate in the study. Five-year follow-up survey questionnaires that expanded to include the intake of 138 food and beverage items were re-administered between 1995 and 1999. For this study, we used the data collected from the 5-year follow-up questionnaires as baseline because information on dietary behavior in that survey was more comprehensive (**Fig. 1**). For this study, individuals who lived in the Tokyo area were excluded due to a lack of cancer incidence data ($n = 7{,}097$). We excluded ineligible participants, namely those who were non-Japanese nationals ($n = 51$), and those who emigrated before commencement ($n = 188$), had an incorrect date of birth ($n = 7$) or duplicate registration ($n = 10$), or had died or moved out of the study area prior to the 5-year follow-up survey ($n = 12{,}166$). We further excluded participants who had a prior cancer diagnosis ($n = 4{,}103$), did not complete the questionnaires during follow-up ($n = 22{,}704$), were in the highest or lowest 2.5 percentile of total energy intake (<837 or >3 683 kcal/day for women and <993 or >4,204 kcal/day for men; $n = 5{,}675$), with carcinoma *in situ* ($n = 499$), or had missing covariate information ($n = 13{,}850$) in the baseline of this analysis. The key characteristics of included and excluded participants were presented in Supplementary Table S1. The study received approval from the Institutional Review Board, National Cancer Center Japan (approval number: 2001–021).

### Dietary assessment

Consumption of sugary drinks and other food items was assessed using a 138-item self-administered semiquantitative food frequency questionnaire, which was validated using 14- or 28-day dietary records. The validation studies were described elsewhere (20, 21). In this study, sugary drinks were defined as beverages containing caloric sweeteners, which included β-carotene fortified beverages, calcium fortified beverages, canned coffee, carbonated beverages, 100% fruit juices (apple juice and orange juice), lactic acid bacteria beverages, and vitamin-fortified beverages. Sugar-sweetened tea was not included in the questionnaire. On each self-administrated questionnaire, participants were asked how often they consumed sugary drinks using nine possible responses ranging from "Never," "1–2 times/week," "3–4 times/week," "5–6 times/week," "1 cup/day," "2–3 cups/day," "4–6 cups/day," "7–9 cups/day," to "10 or more cups/day." We defined each serving as 200 mL for β-carotene fortified beverages, calcium fortified

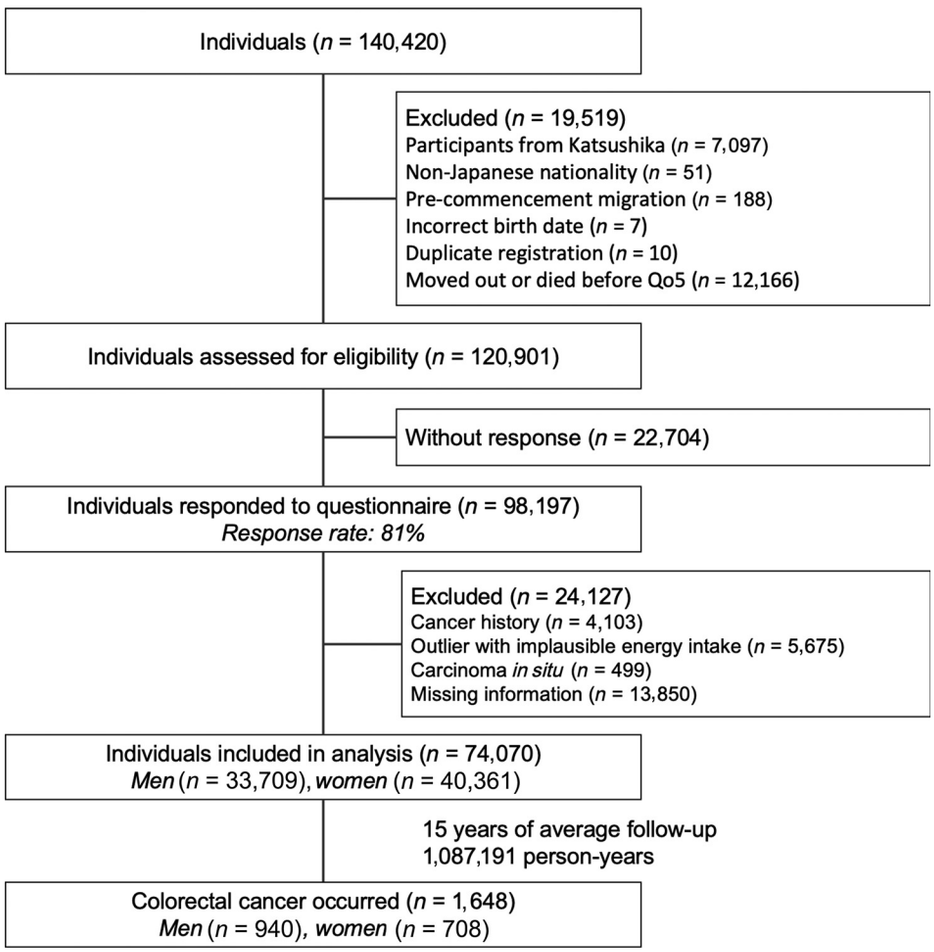


**Figure 1.**
Participant flow chart. The flow chart summarizes the inclusion and exclusion criteria for participant selection. *n*, number; Qo5, 5-year follow-up questionnaire.

beverages, 100% fruit juices (apple juice and orange juice), and vitamin-fortified beverages; 250 mL for canned coffee and carbonated beverages; and 65 mL for lactic acid bacteria beverages. Spearman's coefficient for validity for sugary drinks was 0.32 for men and 0.21 for women in the cohort. Reproducibility was evaluated by conducting two questionnaires 1 year apart. Spearman's coefficient for reproducibility for sugary drinks was 0.63 for men and 0.56 for women in the cohort.

### Outcome assessment

Colorectal cancer incident cases were ascertained by record linkage with population cancer registries as well as by active patient notification from hospitals located in the study areas. Death certificate files were also used as a supplemental data. Population cancer registries contain data on cancer diagnosis date, location, and histologic type. Among colorectal cancer cases, 3.5% were initially notified by death certificate and 2.5% were derived from death certificate only. Colorectal cancers cases were classified with the use of codes in the third edition of the International Classification of Diseases for Oncology (22). Colorectal cancers (C18–C20) were divided into colon cancer (C18), proximal colon cancers (C18.0–C18.5), distal colon cancer (C18.6 and C18.7), and rectal cancers (C19 and C20).

### Statistical analysis

Person-years of follow-up were calculated from the response date to the 5-year survey questionnaire until the date of colorectal cancer diagnosis, moving out of a study area, death, or December 31, 2013, whichever was earliest, except for participants in Osaka, for which follow-up ended on December 31, 2012. In the categorical analysis, nonconsumers (reference group) were compared with two sex-specific consumption categories according to the consumption distributions (<254 and ≥254 mL/day for men, and <134 and ≥134 mL/day for women). In addition, sugary drink intake was analyzed as a continuous variable using an increment of 100 mL/day.

HRs with 95% confidence intervals (CI) of colorectal cancers were calculated with Cox proportional hazards regression models. Multivariable Cox models were adjusted for age (years, continuous) and study area (10 PHC areas) and further adjusted for potential risk factors for colorectal cancer, including BMI (<18.5, 18.5 to <25, 25 to <30, or 30 to <45; refs. 23, 24), colorectal cancer screening (yes or no; ref. 25), history of diabetes (yes or no; refs. 24, 26), physical activity (metabolic equivalent of task, hours per day; ref. 27), smoking status and intensity (never; former; current: <20 cigarettes per day; current: ≥20 cigarettes per day; ref. 28), alcohol consumption (grams ethanol per day, continuous; ref. 28), and intakes of total energy (kcal/day, continuous), vegetables (g/day, continuous; ref. 29), red and processed meat (g/day, continuous; ref. 30), and fish (g/day, continuous; ref. 31). Proportionality of hazards for covariates included in the Cox model were examined using Schoenfeld residuals and no violation was found (32). Tests for trends across categories of sugary drink consumption were performed using the medians of each category modelled continuously. All covariates of dietary intake were energy-adjusted using the residual method (33).

We performed stratified analyses to evaluate if the association between sugary drink consumption and colorectal cancer risk was modified by other potential risk factors: alcohol consumption level (nondrinker and current drinker), BMI status (<25 and ≥25), history of diabetes (presence and absence), level of physical activity (metabolic equivalent of task, hours per day <31.85 and ≥31.85), and smoking status (never and ever). Interactions were tested with likelihood ratio tests which compared models with and without the interaction term. Data were analyzed using STATA 14 (Stata Corp.). *P* values of less than 0.05 were considered statistically significant.

## Results

A total of 74,070 participants (33,709 men and 40,361 women ages 45 to 74 years at response for questionnaire) were included. The participant flow chart is presented in **Fig. 1**.

Over the mean follow-up period of 14.7 years (1,087,191 person-years), 1,648 colorectal cancer case patients (940 in men and 708 in women), including 1,121 with colon cancer and 527 with rectal cancer, were documented. Compared with nonconsumers, sugary drinks consumers had higher physical activity and were less likely to have diabetes and colorectal cancer screening. They also had a higher likelihood of being smokers, were less likely to be drinkers, had a greater intake of red as well as processed meat, and a lower vegetables and fish consumption than nonconsumers (**Table 1**). Mean consumption of sugary drinks was 209 mL/day (286 mL/day for men and 145 mL/day for women).

Consumption of sugary drinks was not associated with a greater risk of colorectal cancer (**Table 2**). After adjustment for major colorectal cancer risk factors, the multivariable HRs for colorectal cancer were 0.84 (95% CI, 0.70–1.02) for men consuming ≥254 mL of sugary drinks per day and 1.20 (95% CI, 0.96–1.50) for women consuming ≥134 mL/day, comparing with nonconsumers. We further examined associations of sugary drink consumption with risk of cancer in different anatomic subsites by sex (**Table 2**). In women, a higher colon cancer risk 1.36 (95% CI, 1.03–1.78) was found for those who consumed ≥134 mL of sugary drinks per day compared with nonconsumers. The multivariable HRs for proximal colon cancer among women who consumed sugary drinks, as compared with nonconsumers, were 1.47 (95% CI, 1.03–2.10) for the sugary drink consumption <134 mL/day and 1.45 (95% CI, 1.01–2.09) for ≥134 mL/day. There is no association of sugary drink consumption with distal colon cancer and rectal cancer. In contrast, sugary drink consumption showed no association with the risk of colon cancer (HR = 0.80; 95% CI, 0.63–1.02; comparing ≥254 mL/day consumption vs. nonconsumers) and rectal cancer (HR = 0.91; 95% CI, 0.66–1.26; comparing ≥254 mL/day vs. nonconsumers) in men.

In stratified analyses, no significant interaction was detected for smoking status, alcohol consumption, or physical activity (Supplementary Tables S2–S4). In subgroups defined by history of diabetes, null association with proximal colon cancer was observed among women with history of diabetes and a positive association was observed among women with no history of diabetes (*P* value for interaction = 0.02). There was a 72% greater risk of proximal colon cancer among women (HR = 1.72; 95% CI, 1.16–2.56; *P* = 0.09 for trend; comparing ≥134 mL/day vs. nonconsumers; Supplementary Table S5). When stratified by BMI, we found a positive association between consumption of sugary drinks and risk of distal colon cancer among women who had a BMI <25 but not among those with a BMI ≥25 (*P* value for interaction = 0.04; Supplementary Table S6).

## Discussion

In this large prospective cohort of 74,070 Japanese men and women, with a mean 15-year follow-up period, we found no overall association between sugary drink consumption and risk of colorectal cancer. However, compared with nonconsumers, women who consumed at least 134 mL of sugary drinks per day showed an associated 36% increased risk of colon cancer. Similarly, our results suggested that

**Table 1.** Baseline characteristics of participating Japanese men and women according to sugary drink consumption.

| Characteristic | Categories of sugary drink consumption | | | *P* value[a] |
|---|---|---|---|---|
| **Men** | | | | |
| Intake category, mL/day | Nonconsumers | >0–254 | ≥254 | |
| No. of participants | 4,690 | 14,510 | 14,509 | |
| Age, mean (SD), year | 58.3 (7.9) | 57.0 (7.6) | 55.2 (7.6) | <0.001 |
| BMI, mean (SD), kg/m$^2$ | 23.5 (2.9) | 23.6 (2.9) | 23.6 (2.9) | 0.08 |
| Physical activity, mean (SD), METS-hour/day | 31.7 (6.4) | 32.7 (6.8) | 33.3 (6.9) | <0.001 |
| Past history of diabetes, % | 14.8 | 9.7 | 6.4 | <0.001 |
| Colorectal screening, % | 32.0 | 33.2 | 27.8 | <0.001 |
| Current smoker, % | 42.7 | 43.6 | 52.9 | <0.001 |
| Current alcohol consumption, % | 75.0 | 75.5 | 68.6 | <0.001 |
| Dietary intake[b] | | | | |
| Total energy, mean (SD), kcal/day | 1,951.3 (573.5) | 2,204.2 (629.1) | 2,220.8 (644.6) | <0.001 |
| Vegetables, mean (SD), g/day | 136.9 (90.9) | 133.4 (85.9) | 125.0 (76.4) | <0.001 |
| Meat, mean (SD), g/day | 52.8 (37.3) | 55.6 (36.0) | 58.1 (35.1) | <0.001 |
| Fish, mean (SD), g/day | 76.4 (47.0) | 74.3 (42.9) | 71.9 (40.9) | <0.001 |
| **Women** | | | | |
| Intake category, mL/day | Nonconsumers | >0–134 | ≥134 | |
| No. of participants | 6,701 | 16,830 | 16,830 | |
| Age, mean (SD), year | 57.1 (8.0) | 56.9 (7.7) | 56.3 (7.7) | <0.001 |
| BMI, mean (SD), kg/m$^2$ | 23.3 (3.2) | 23.5 (3.1) | 23.6 (3.2) | <0.001 |
| Physical activity, mean (SD), METS-hour/day | 31.5 (5.6) | 32.0 (5.7) | 32.3 (5.9) | <0.001 |
| Past history of diabetes, % | 7.2 | 4.1 | 2.9 | <0.001 |
| Colorectal screening, % | 30.4 | 33.0 | 27.2 | <0.001 |
| Current smoker, % | 5.5 | 4.7 | 6.5 | <0.001 |
| Current alcohol consumption, % | 19.1 | 18.1 | 17.9 | <0.001 |
| Dietary intake[b] | | | | |
| Total energy, mean (SD), kcal/day | 1,654.7 (483.9) | 1,914.8 (548.9) | 1,930.3 (567.8) | <0.001 |
| Vegetables, mean (SD), g/day | 235.2 (138.2) | 226.2 (125.5) | 214.0 (116.2) | <0.001 |
| Meat, mean (SD), g/day | 52.3 (36.3) | 52.6 (33.4) | 56.6 (34.5) | <0.001 |
| Fish, mean (SD), g/day | 82.6 (47.6) | 83.7 (44.8) | 81.7 (43.7) | <0.001 |

Abbreviations: MET, metabolic equivalent of task; *n*, number.

[a]Determined using the chi-squared test for categorical variables or the ANOVA test for continuous variables.

[b]All dietary intakes were energy-adjusted by the residual method. Sugary drinks included β-carotene fortified beverages, calcium fortified beverages, canned coffee, carbonated beverages, 100% fruit juices (apple juice and orange juice), lactic acid bacteria beverages, and vitamin-fortified beverages.

consumption of sugary drinks was associated with a greater risk of proximal colon cancer among women.

Albeit accumulating evidence suggests that the clinical features and etiologies of colorectal cancer vary by anatomic subsite (18, 34), only the California Teachers Study has investigated the association of sugary drink consumption with cancer risk in specific subsites within the colorectum (12). In that cohort study of 99,798 women with 1,318 incident colorectal cancer cases, null associations with cancer risks of colorectum and subsites were reported. In the current analyses, we observed that sugary drink consumption was positively associated with colon cancer risk in women. The discrepancy of the observed associations could be due to higher insulin resistance susceptibility among Asian populations as compared with Western populations (35). The biological mechanisms through which sugary drinks potentially increase colon cancer risk but not risk of rectal cancer are uncertain. However, increasing evidence has demonstrated that dietary sugars play critical roles in the composition and function of the gut microbiome (36), which modifies local and systemic immune homeostasis, the balance of intestinal cell apoptosis and proliferation, and genetic and epigenetic aberrations, thereby contributing to carcinogenesis (37). The diversity and composition of the gut microbiota vary substantially across subsites of colorectum (38), suggesting that the interplay between sugar, gut microbiota, and colorectal cancer may be intricate, and dependent on anatomic subsite.

In agreement with previous studies (10, 12), we found no statistically significant association of sugary drinks with risk of colorectal cancer in both men and women. However, a positive association between sugary drink consumption and proximal colon cancer risk was observed in women only. The reasons for this gender discrepancy are unclear, but our findings suggest differences in tumor susceptibility between colon and rectum for men and women. Microsatellite instability (MSI) is the clonal change in the repeated sequence of DNA nucleotides, which has been recognized as a potential pathway of colorectal cancer development (39). The frequency of MSI is higher among women and in proximal colon (40, 41). Albeit the association between sugary drinks and MSI has not been investigated to date; this provides a potential mechanism for the gender difference observed in our analyses. Also, previous studies have suggested that dietary factors are associated differently with colorectal cancer risk in men and women and this gender difference could be further complicated by anatomic subsites (42, 43). For example, high carbohydrate intake was associated with proximal colon cancer risk in women but with rectal cancer in men (43). Overall, our analyses increase understanding of colorectal cancer risk in specific bowel subsites and highlight the importance of subsite-specific and sex-specific investigation for future studies.

To our knowledge, this study is the first population-based prospective study to examine the effect of sugary drink consumption on

**Table 2.** Hazards for colorectal cancer incidence according to intake of sugary drinks in participants.

| | Categories of sugary drink consumption, HR (95% CI) | | | *P* value for trend | Per 100 mL/day increment, HR (95% CI) |
|---|---|---|---|---|---|
| **Men** | | | | | |
| Intake category, mL/day | Nonconsumers | >0–254 | ≥254 | | |
| **Colorectal cancer** | | | | | |
| Person-years | 63,194 | 202,514 | 209,012 | | |
| No. of cases | 166 | 406 | 368 | | |
| Multivariable model[a] | 1 [Reference] | 0.86 (0.71–1.03) | 0.84 (0.70–1.02) | 0.22 | 0.99 (0.97–1.01) |
| **Colon cancer** | | | | | |
| No. of cases | 109 | 270 | 227 | | |
| Multivariable model[a] | 1 [Reference] | 0.87 (0.69–1.09) | 0.80 (0.63–1.02) | 0.11 | 0.99 (0.96–1.02) |
| **Proximal colon cancer** | | | | | |
| No. of cases | 43 | 122 | 93 | | |
| Multivariable model[a] | 1 [Reference] | 0.98 (0.69–1.40) | 0.82 (0.57–1.19) | 0.17 | 0.99 (0.95–1.04) |
| **Distal colon cancer** | | | | | |
| No. of cases | 56 | 135 | 120 | | |
| Multivariable model[a] | 1 [Reference] | 0.84 (0.62–1.16) | 0.83 (0.60–1.15) | 0.42 | 1.00 (0.95–1.04) |
| **Rectal cancer** | | | | | |
| No. of cases | 57 | 136 | 141 | | |
| Multivariable model[a] | 1 [Reference] | 0.83 (0.61–1.14) | 0.91 (0.66–1.26) | 0.94 | 0.98 (0.94–1.02) |
| **Women** | | | | | |
| Intake category, mL/day | Nonconsumers | >0–134 | ≥134 | | |
| **Colorectal cancer** | | | | | |
| Person-years | 99,515 | 255,833 | 257,123 | | |
| No. of cases | 108 | 281 | 319 | | |
| Multivariable model[a] | 1 [Reference] | 1.05 (0.83–1.31) | 1.20 (0.96–1.50) | 0.04 | 1.00 (0.96–1.05) |
| **Colon cancer** | | | | | |
| No. of cases | 70 | 212 | 233 | | |
| Multivariable model[a] | 1 [Reference] | 1.21 (0.92–1.60) | 1.36 (1.03–1.78) | 0.04 | 0.99 (0.93–1.04) |
| **Proximal colon cancer** | | | | | |
| No. of cases | 39 | 144 | 139 | | |
| Multivariable model[a] | 1 [Reference] | 1.47 (1.03–2.10) | 1.45 (1.01–2.09) | 0.22 | 0.98 (0.92–1.06) |
| **Distal colon cancer** | | | | | |
| No. of cases | 23 | 58 | 79 | | |
| Multivariable model[a] | 1 [Reference] | 1.01 (0.62–1.65) | 1.38 (0.86–2.22) | 0.05 | 1.00 (0.91–1.10) |
| **Rectal cancer** | | | | | |
| No. of cases | 38 | 69 | 86 | | |
| Multivariable model[a] | 1 [Reference] | 0.73 (0.49–1.10) | 0.91 (0.62–1.35) | 0.66 | 1.04 (0.96–1.11) |

Note: CI, confidence interval; HR, hazard ratio; No., number.

[a]Multivariable Cox regression model adjusted for age (years), public health center (10 areas), history of diabetes (yes or no), body mass index (BMI; <18.5, 18.5 to <25, 25 to <30, or 30 to <45), physical activity (metabolic equivalent of task, hours per day), smoking status and intensity (never; former; current: <20 cigarettes per day; current: ≥20 cigarettes per day), alcohol consumption (ethanol grams per week), colorectal cancer screening (yes or no), intakes of total energy (kcal/day), vegetables (g/day), red and processed meat (g/day), and fish (g/day; all continuous). All dietary intakes were energy-adjusted by the residual method. Sugary drinks included beta-carotene fortified beverages, calcium fortified beverages, canned coffee, carbonated beverages, 100% fruit juices (apple juice and orange juice), lactic acid bacteria beverages, and vitamin-fortified beverages.

colorectal cancer risk in an Asian population. Despite the relatively low consumption level compared with Western countries, the consumption level in Japan remained the highest in Asia (44). Of note, the annual sugary drink consumption in Japan rose from 135 to 143 liters per capita from 2005 to 2015 (44). Previous cohort studies investigated the association of sugary drinks and colorectal cancer risk in populations characterized by high sugary drink consumption and high BMI. The findings in our study population with a low sugary drink consumption level and a low prevalence of obesity provided a unique perspective of this study. Another strength of this study is that its prospective design together with a high follow-up rate precludes the potential for selection bias and recall bias. The large sample size also allowed subgroup analyses by colorectal subsite.

Our study has several limitations that merit further discussion. Measurement errors in self-reported data are inevitable in this study, but misclassification of sugary drink consumption may be of minor importance, given the high correlation for sugary drinks observed. In addition, patients with obesity or diabetes may limit or under-report their sugary drink consumption (45), which would bias downward the estimates. To address this issue, we restricted the analysis to those who reported no obesity or history of diabetes, and found that the association was unchanged. Another limitation is that, in our study, nonconsumers had a higher rate of colorectal cancer screening, which may increase the likelihood of colorectal cancer diagnosis and the true strength of the associations may therefore be underestimated. Although potential screening bias was minimized by the inclusion of colorectal cancer screening in multivariable models,

residual confounding could not be totally ruled out. Finally, given the relatively low consumption of sugary drinks in our study population, our findings may not be generalizable to other populations because levels of sugary drink consumption across populations may be different.

In conclusion, this large prospective cohort study suggests that sugary drink consumption is not associated with colorectal cancer risk. However, we observed a positive association with colon cancer risk in women. Future studies on the association between sugary drink consumption and cancer risk across the colorectum should account for specific anatomic subsites.

## Authors' Disclosures

N. Sawada reports grants from National Cancer Center Research and Development Fund outside the submitted work. R. Takachi reports grants from Kagome Co., Ltd. outside the submitted work. T. Yamaji reports grants from Ministry of Health, Labour and Welfare of Japan during the conduct of the study. No disclosures were reported by the other authors.

## Data Availability

For information on how to submit an application for gaining access to JPHC data and/or biospecimens, please follow the instructions at http://epi.ncc.go.jp/en/jphc/805/8155.html.

## Ethics Approval and Consent to Participate

The study was conducted in compliance with the provisions of the Declaration of Helsinki. The study protocol was approved by the Institutional Review Board of the National Cancer Center, Japan. The participants were informed of the study objectives, and those who completed the survey questionnaire were regarded as consenting to participation.

## Authors' Contributions

**C.Y. Leung:** Conceptualization, formal analysis, investigation, methodology, writing–original draft, writing–review and editing. **S.K. Abe:** Methodology, writing–review and editing. **N. Sawada:** Funding acquisition, writing–review and editing. **J. Ishihara:** Writing–review and editing. **R. Takachi:** Writing–review and editing. **T. Yamaji:** Writing–review and editing. **M. Iwasaki:** Writing–review and editing. **M. Hashizume:** Writing–review and editing. **M. Inoue:** Conceptualization, methodology, writing–review and editing. **S. Tsugane:** Funding acquisition, writing–review and editing.

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