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ORIGINAL ARTICLE

Sugars, sucrose and colorectal cancer risk: the Fukuoka colorectal cancer study

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Abstract

Objective. A diet high in sugars may promote colorectal carcinogenesis, but it remains uncertain whether high intake of sugars or sucrose confers increased risk of colorectal cancer. The authors investigated the associations of sugars and sucrose intake with colorectal cancer risk in a community-based case–control study in Japan. ***Methods.*** The study subjects comprised 816 incident cases of colorectal cancer and 815 community controls. Consumption frequencies and portion sizes of 148 food and beverage items were ascertained by a computer-assisted interview. The authors used the consumption of 29 food items to estimate sugars and sucrose intake. The odds ratios of colorectal cancer risk according to intake categories were obtained using a logistic regression model with adjustment for potential confounding variables. ***Results.*** Overall, intakes of sugars and sucrose were not related to colorectal cancer risk either in men or women. The association between sugars intake and colorectal cancer risk differed by smoking status and alcohol use in men, but not in women. In men, sugars intake tended to be associated with colorectal cancer risk inversely among never-smokers and positively among male ever-smokers (interaction $p = 0.01$). Sugars intake was associated with an increased risk among men with no alcohol consumption, but was unrelated to the risk among male alcohol drinkers (interaction $p = 0.02$). Body mass index did not modify the association with sugars intake in either men or women. ***Conclusion.*** Sugars intake was associated with increased risk of colorectal cancer among smokers and non-alcohol drinkers in men selectively.

Key Words: *colorectal cancer, fructose, sucrose, sugars*

Introduction

Colorectal cancer is the third most common cancer worldwide, and the incidence rates vary across different countries showing a more than 25-fold variation [1]. In Japan, the incidence of colorectal cancer, especially of colon cancer, has markedly increased since the 1990s [2]. The descriptive features indicate that environmental

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and lifestyle factors play an important role in the development of colorectal cancer [3].

Worldwide, the consumption of caloric sweeteners has increased, resulting in an average increase of 74 kcal/day in energy intake during the period from 1962 to 2000 [4]. The consumption of sugar-sweetened beverages has been linked to weight gain, obesity, insulin resistance and type 2 diabetes [4], all of which are potential risk factors for colorectal cancer [5–7]. A diet high in sugars may promote colorectal carcinogenesis by stimulating synthesis of insulin and insulin-like growth factor-I [8]. High intake of sugars (i.e. sucrose) may also increase the risk of colorectal cancer by increasing the mouth-to-anus transit time and fecal concentration of secondary bile acids [9,10]. Several epidemiological studies directly showed a positive association between high intake of sugars or sucrose and colorectal cancer risk, but the findings are not consistent. According to a review of human studies [11], 7 of the 21 studies reported risk estimates consistent with a positive association between sugars consumption and the risk of colorectal cancer. In the 1997 report of the World Cancer Research Fund [12], it was described that 8 of the 12 case–control studies found an increased risk of colorectal cancer associated with intake of refined sucrose or sucrose-rich foods. However, it remains uncertain whether high intake of sugars or sucrose confers increased risk of colorectal cancer, as summarized in the 2007 report of the World Cancer Research Fund [13].

As per the authors' knowledge, none has addressed the relation between sugars intake and colorectal cancer risk in Japan. The authors investigated the association of intake of soft drinks, sweetened foods, sugars and sucrose with colorectal cancer risk using data from a community-based case–control study in Japan [14].

Materials and method

The present data were derived from the Fukuoka Colorectal Cancer Study, a community-based case–control study to investigate factors associated with colorectal cancer in Fukuoka and three adjacent areas of Japan. The research protocol was approved by the ethics committee of Kyushu University and collaborating hospitals. Details of the design and conduct of the study have been described elsewhere [14].

Study subjects

Cases comprised a consecutive series of histologically confirmed incident cases of colorectal adenocarcinomas admitted for surgical treatment to one of the collaborating hospitals during the period from September 2000 to December 2003. Of 1053 eligible cases, a total of 840 cases (80%) participated in the interview. The eligible cases were aged between 20 and 74 years at the time of diagnosis, lived in the study area, had no prior history of partial or total removal of the colon, familial adenomatous polyposis or inflammatory bowel disease and were mentally competent to give informed consent and to complete the interview. Research staff visited each hospital regularly, determined the eligibility of cases by referring to admission logs and medical records, and interviewed the patients after obtaining written informed consent.

Eligibility criteria for controls were the same as described for the cases except that they had no history of colorectal cancer. A total of 1500 control candidates living in 15 geographical areas were randomly selected by two-stage random sampling of a resident registry matched by sex and 10-year age class to the sex- and age-specific frequencies of the cases. Recruitment was initiated by a letter of invitation, which was followed by phone calls if available. After exclusion of 113 who were found to be ineligible and 5 who were diagnosed with colorectal cancer after the interview, 833 (60%) of 1382 eligible candidates participated in the interview.

In the analysis, the authors excluded 42 subjects (24 cases and 18 controls) who were in the top 1% or bottom 1% of total energy intake within each stratum of sex and age class (<55, 55–64 and ≥65 years of age). A total of 816 cases and 815 controls were included in the study.

Lifestyle questionnaire

Cases and controls were interviewed in person by research nurses to determine smoking habit, alcohol use, physical activity and other factors using a uniform questionnaire. The index date was taken as the date of onset of symptoms or the screening leading to the diagnosis of colorectal cancer for cases, and the date of interview for controls. Anthropometric questions determined body height (cm) and body weight (kg) at the time of interview and 10 years earlier. Body mass index (kg/m^2) 10 years earlier was used in the analysis because the current body mass index was unrelated to the risk [15]. Current body weight was used for 4 cases and 11 controls because their body weight 10 years before was not ascertained. Habitual alcohol consumption 5 years prior to the index date was ascertained. The amount of alcohol was expressed using the conventional Japanese unit: one go (180 ml) of sake, one large bottle (633 ml) of beer and half a go

(90 ml) of shochu were each expressed as one unit; and one drink (30 ml) of whisky or brandy and one glass (100 ml) of wine were each converted to half a unit. Regarding smoking, ever smokers reported years of smoking and the numbers of cigarettes per day for each decade of life, and the authors calculated the cumulative exposure to cigarette smoking until the beginning of the previous decade of age. Questions on work-related physical activities and non-work physical activities 5 years earlier were ascertained. As described in detail previously [15], the amount of non-occupational physical activity was expressed as a sum of metabolic equivalents (MET) multiplied by the hours of weekly participation in each activity, that is, MET-hours per week. A history of parental colorectal cancer was also obtained.

Dietary assessment

The methods of dietary assessment and dietary interview have been described elsewhere [16]. In brief, consumption frequencies and portion sizes of 148 food and beverage items were ascertained by a computer-assisted interview, typical dishes and portion sizes being shown on the display. Participants were asked to report their usual consumption over the 1 year prior to the index date. Intakes of nutrients were calculated based on Japanese food composition tables [17]. To estimate dietary intakes of sugars, sucrose and fructose, the authors used 24 items of sweetened foods and 5 items of soft drinks (see Appendix). Sugars, sucrose and fructose contents of the 23 food items were derived from a Japanese study [18]. As for the remaining six foods which were not listed in the Japanese study [18], the US Department of Agriculture Database [19] was used for two foods (Japanese pears canned in syrup and mandarin juice), and information on the Japanese websites [20,21] was used for four foods (sweetened yogurt, ice creams, sweetened canned coffee and carbonated drink other than cola). Fructose intake was assessed by combining intakes of free fructose and fructose from sucrose (half of sucrose). Sugars used for cooking was not considered because it was difficult to estimate.

Statistical analysis

Dietary intakes of nutrients, soft drinks, sweetened foods, sugars, sucrose and fructose were transformed to a natural log scale and were adjusted to an energy intake of 2000 kcal/day by the regression residual method [22]. Subjects were divided into quintile categories of the intakes among controls. Logistic regression analysis was used to estimate odds ratios (OR) and 95% confidence intervals (CI) of colorectal cancer for each category with the lowest quintile category as the reference group. Confounding variables under consideration were age, residential area (Fukuoka City or others), parental history of colorectal cancer, smoking (0, 1−399, 400−799 or >800 cigarette-years), alcohol consumption (0, 0.1−0.9, 1.0−1.9 or ≥2 units per day), body mass index 10 years before (<22.5, 22.5−24.9, 25.0−27.4 or ≥27.5 kg/m^2), type of job (sedentary or non-sedentary), leisure-time physical activity (0, 1−15.9 or ≥16 MET-hours/week) and dietary intakes of calcium and *n*-3 polyunsaturated fatty acids (PUFA). Calcium and *n*-3 PUFA intakes were related to a decreased risk of colorectal cancer in the study population [23,24]. Trend of the association was assessed with ordinal scores assigned to quintile categories of the intakes.

Stratified analysis was done with respect to smoking (never-smokers and ever-smokers), alcohol consumption (non-drinkers and drinkers) and body mass index (<25 and ≥25 kg/m^2). Tertile categories of the dietary intake were used in the stratified analysis, because the number of the subjects was smaller within strata. Interaction was evaluated by the Wald statistic for the interaction term, that is, a product of an ordinal variable for the dietary intake and a dichotomous variable for stratification. Statistical significance was declared with a two-sided p-value < 0.05. Statistical analyses were performed using SAS version 9.2 (SAS Institute Inc., Cary, NC, USA).

Results

Selected characteristics of colorectal cancer cases and controls are summarized for men and women separately in Table I. Compared with controls, the cases were slightly older and had a greater body mass index. Smoking and alcohol drinking did not differ in cases and controls among men, while smoking was less prevalent in cases than in controls among women. There was no material difference in the intake of soft drinks, sweetened foods, sugars, sucrose or fructose between cases and controls in either sex.

In the whole sample (cases and controls combined), intake of sugars derived from soft drinks and sweetened foods were 24% and 76%, respectively. Soft drinks accounted for 23% of sucrose intake and 25% of fructose intake while sweetened foods contributed to 77% of sucrose intake and 75% of fructose intake. Intake of sweetened foods was highly correlated with sugars intake (r = 0.88), sucrose intake (r = 0.87) and fructose intake (r = 0.87). The

Table I. Characteristics of colorectal cancer cases and controls.

Variables	Men		Women	
	Cases (n = 488)	Controls (n = 504)	Cases (n = 328)	Controls (n = 311)
Age (years), mean (SD)	60.9 (8.8)	59.0 (10.2)	60.0 (9.4)	58.6 (11.4)
Body mass index 10 years before, mean (SD)	23.8 (3.1)	23.2 (3.0)	22.7 (3.3)	22.4 (3.2)
Ever-smoking, %	81.4	80.6	12.8	18.0
Alcohol use, %	77.9	77.4	28.1	29.6
Dietary intake, median (IQR)*				
Soft drinks (g/day)	0.34 (0.07–27.25)	0.26 (0.06–24.87)	0.26 (0.09–5.49)	0.25 (0.10–9.65)
Sweetened foods (g/day)	25.75 (10.96–48.42)	25.90 (12.84–47.06)	52.17 (30.39–74.93)	52.47 (30.29–76.95)
Sugars (g/day)	12.63 (5.46–23.36)	12.53 (5.89–21.80)	18.60 (11.75–29.81)	19.78 (12.49–27.46)
Sucrose (g/day)	10.75 (4.61–21.21)	10.14 (4.88–19.61)	16.42 (10.46–26.25)	16.96 (11.05–27.46)
Fructose (g/day)	6.17 (2.70–11.65)	6.11 (2.82–10.77)	8.98 (5.67–14.58)	9.63 (5.98–14.87)

*Dietary intakes were energy-adjusted to 2000 kcal/day.
Abbreviations: IQR = interquartile range; SD = standard deviation.

correlation between sugars intake and sucrose (r = 0.98) or fructose (r = 0.99) intake was almost unity.

The associations of intakes of soft drinks, sweetened foods, sugars, sucrose and fructose with colorectal cancer are presented in Table II. None of the five factors under study was measurably associated with colorectal cancer risk.

The association between sugars intake and colorectal cancer risk differed by smoking status and alcohol use in men, but not in women (Table III). In men, sugars intake tended to be associated with colorectal cancer risk inversely among never-smokers and positively among male ever-smokers, and the interaction was highly significant. In other words, the risk seemed to be decreased in association with smoking in men at the lowest and intermediate categories of sugars intake. Sugars intake was associated with an increased risk among men with no alcohol consumption, but was unrelated to the risk among male alcohol drinkers. Body mass index did not modify the association with sugars intake in either men or women. Similar effects modifications were also observed for sucrose and fructose intake (data not shown).

Discussion

Overall, sugars intake and sweetened foods were unrelated to the risk of colorectal cancer in men and women. Smoking and alcohol use modified the association between sugars intake and colorectal cancer risk in men, but not in women.

Epidemiological evidence has been inconclusive regarding sugars or sucrose intake and colorectal cancer risk although several epidemiological studies have suggested an increased risk of colorectal cancer associated with high intake of sugar-containing foods and sugar as nutrient [13]. Sucrose and fructose are main components of sugars. Some recent studies examined the association with sucrose and fructose intake separately [10,25,26]. One study reported a positive association with fructose and a weaker positive association with sucrose in men but not in women [25], while other studies failed to find such an association with either fructose or sucrose [10,26]. The present findings are in agreement with the observation in the latter studies [10,26].

The present study examined the effect of modifications of smoking, alcohol use and body mass index on the association between sugars and sucrose intake and colorectal cancer risk. These factors are generally associated with an increased risk of colorectal cancer [2,25], although the association with smoking is less consistent [27]. In the present study, alcohol use and body mass index were positively associated with colorectal cancer [15,28], and light smoking was associated with a decreased risk [29]. Only one previous study addressed the effect modifications of lifestyle factors and reported that a positive association with sucrose intake was more evident among individuals with high alcohol consumption (≥20 g/day) and among those with high body mass index (≥25.0 kg/m^2) especially in men [25]. Contrary to the previous observation, the present study showed a positive association with sugars or sucrose intake only among male non-alcohol drinkers and failed to find an effect modification of body mass index.

It is a unique finding that sugars intake was positively associated with colorectal cancer risk in male ever-smokers. The risk of colorectal cancer was rather decreased among male smokers with low sugars intake. The risk associated with smoking are highly variable between studies [27], and the

Table II. Associations of soft drinks, sweetened foods, sugar, sucrose and fructose intakes with colorectal cancer risk*.

	Quintiles of intake					
	Q1 (lowest)	Q2	Q3	Q4	Q5 (highest)	P_{trend}
Men						
Soft drinks						
Median (g/day)	0.03	0.08	0.26	14.25	87.96	
Cases/controls	95/101	88/101	94/101	110/101	101/100	
OR (95% CI)	1.00 (reference)	0.92 (0.61–1.40)	0.91 (0.60–1.39)	1.17 (0.77–1.76)	1.16 (0.76–1.77)	0.27
Sweetened foods						
Median (g/day)	4.17	15.18	25.95	39.69	72.64	
Cases/controls	120/101	76/101	93/101	100/101	99/100	
OR (95% CI)	1.00 (reference)	0.62 (0.41–0.93)	0.77 (0.51–1.15)	0.92 (0.61–1.39)	0.89 (0.58–1.35)	0.87
Sugars						
Median (g/day)	2.50	7.16	12.56	19.94	31.00	
Cases/controls	107/101	82/101	92/101	97/101	110/100	
OR (95% CI)	1.00 (reference)	0.74 (0.49–1.13)	0.91 (0.60–1.38)	0.97 (0.64–1.46)	1.15 (0.75–1.75)	0.31
Sucrose						
Median (g/day)	1.93	5.95	10.15	17.51	29.19	
Cases/controls	110/101	75/101	106/101	87/101	110/100	
OR (95% CI)	1.00 (reference)	0.67 (0.44–1.02)	1.00 (0.66–1.49)	0.81 (0.53–1.23)	1.09 (0.71–1.67)	0.50
Fructose						
Median (g/day)	1.18	3.57	6.11	9.84	17.55	
Cases/controls	105/101	84/101	92/101	91/101	116/100	
OR (95% CI)	1.00 (reference)	0.77 (0.51–1.17)	0.93 (0.61–1.40)	0.91 (0.60–1.39)	1.26 (0.82–1.92)	0.22
Women						
Soft drinks						
Median (g/day)	0.05	0.12	0.25	3.91	69.37	
Cases/controls	68/63	64/62	59/62	78/62	59/62	
OR (95% CI)	1.00 (reference)	0.84 (0.50–1.41)	0.75 (0.44–1.28)	1.14 (0.69–1.89)	0.87 (0.51–1.48)	0.90
Sweetened foods						
Median (g/day)	17.59	35.57	52.47	70.87	113.51	
Cases/controls	63/63	83/62	62/62	50/62	70/62	
OR (95% CI)	1.00 (reference)	1.45 (0.87–2.39)	1.11 (0.66–1.88)	0.86 (0.50–1.48)	1.32 (0.78–2.23)	0.94
Sugars						
Median (g/day)	6.93	14.54	19.78	28.25	40.80	
Cases/controls	71/63	69/62	68/62	52/62	68/62	
OR (95% CI)	1.00 (reference)	1.03 (0.63–1.71)	1.01 (0.61–1.68)	0.80 (0.47–1.36)	1.07 (0.64–1.78)	0.87
Sucrose						
Median (g/day)	5.96	12.15	17.02	24.79	36.62	
Cases/controls	64/63	74/62	72/62	50/62	68/62	
OR (95% CI)	1.00 (reference)	1.22 (0.74–2.03)	1.21 (0.72–2.02)	0.86 (0.50–1.47)	1.16 (0.69–1.96)	0.95
Fructose						
Median (g/day)	3.35	6.98	9.66	13.76	19.60	
Cases/controls	72/63	68/62	70/62	49/62	69/62	
OR (95% CI)	1.00 (reference)	1.02 (0.61–1.69)	1.06 (0.64–1.76)	0.74 (0.44–1.26)	1.10 (0.66–1.83)	0.88

*Adjusted for age, residence area, job, parental history of colorectal cancer, smoking, alcohol drinking, body mass index 10 years before, leisure-time physical activity, calcium and *n*-3 polyunsaturated fatty acids.
Abbreviations: CI = confidence interval; OR = odds ratio.

present findings suggest that the variability may depend on sugars intake. Sugars or sucrose intake is probably much lower in Japan as compared with Western countries [30]. Interestingly, an inverse association between smoking and colorectal cancer was observed in earlier studies while recent studies suggested a modest increase in the risk among smokers in Japan [31]. The temporal change in the association between smoking and colorectal cancer in Japan may be explained by increasing intake of sugars.

There was no effect modification of smoking or alcohol use in women. In Japan, as observed in the present study, smoking and alcohol use was much less prevalent in women [32]. Gender difference in the effect modification of smoking and alcohol use deserve further investigation, because the effect modifications observed in men may have been due to chance.

In addition to the large sample size and the use of community controls, the detailed dietary assessment was a notable strength in the present study. The

Table III. Odds ratio (95% confidence interval) of colorectal cancer according to sugar intake stratified by selected covariates in men and women*.

	Tertiles of sugar intake				
	T1 (lowest)	T2	T3 (highest)	P_{trend}	$P_{interaction}$
Men					
Smoking[a]					
Never-smokers					
Cases/controls	33/25	28/27	30/46		
OR (95% CI)	1.00 (reference)	0.90 (0.42–1.96)	0.52 (0.25–1.08)	0.06	0.01
Ever-smokers					
Cases/controls	130/143	127/142	140/121		
OR (95% CI)	0.65 (0.36–1.16)	0.64 (0.35–1.16)	0.90 (0.49–1.63)	0.08	
Alcohol drinking[b]					
Non-drinkers					
Cases/controls	16/29	27/30	65/55		
OR (95% CI)	1.00 (reference)	2.01 (0.87–4.63)	2.45 (1.18–5.12)	0.08	0.02
Drinkers					
Cases/controls	147/139	128/139	105/112		
OR (95% CI)	2.25 (1.15–4.41)	1.90 (0.97–3.74)	2.00 (1.00–4.00)	0.56	
Body mass index [c]					
<25 kg/m^2					
Cases/controls	108/129	101/124	118/125		
OR (95% CI)	1.00 (reference)	1.09 (0.74–1.61)	1.25 (0.85–1.85)	0.23	0.36
≥25 kg/m^2					
Cases/controls	55/39	54/45	52/42		
OR (95% CI)	1.83 (1.11–3.01)	1.45 (0.89–2.37)	1.64 (0.99–2.73)	0.56	
Women					
Smoking[a]					
Never-smokers					
Cases/controls	107/86	97/88	82/81		
OR (95% CI)	1.00 (reference)	0.89 (0.59–1.36)	0.83 (0.53–1.28)	0.49	0.59
Ever-smokers					
Cases/controls	20/18	8/16	14/22		
OR (95% CI)	0.83 (0.40–1.72)	0.41 (0.16–1.02)	0.52 (0.24–1.09)	0.49	
Alcohol drinking[b]					
Non-drinkers					
Cases/controls	78/ 68	80/ 74	78/ 77		
OR (95% CI)	1.00 (reference)	0.94 (0.59–1.50)	0.93 (0.58–1.48)	0.82	0.15
Drinkers					
Cases/controls	49/36	25/30	18/26		
OR (95% CI)	1.34 (0.76–2.37)	0.81 (0.42–1.54)	0.67 (0.33–1.37)	0.06	
Body mass index [c]					
<25 kg/m^2					
Cases/controls	99/84	80/84	78/83		
OR (95% CI)	1.00 (reference)	0.82 (0.53–1.27)	0.81 (0.52–1.27)	0.33	0.89
≥25 kg/m^2					
Cases/controls	28/20	25/20	18/20		
OR (95% CI)	1.09 (0.55–2.13)	0.97 (0.49–1.93)	0.82 (0.39–1.69)	0.51	

*Adjusted for age, residence area, job, parental history of colorectal cancer, smoking, alcohol drinking, body mass index 10 years before, leisure-time physical activity, calcium and *n*-3 polyunsaturated fatty acids.
[a]Models did not include smoking.
[b]Models did not include alcohol drinking.
[c]Models did not include body mass index.
Abbreviations: CI = confidence interval; OR = odds ratio.

present study had some weaknesses. The retrospective assessment of diet is a problem inherent to case–control studies. The dietary interview did not include all types of sweetened foods and soft drinks, and sugars added in cooking were not considered. Thus, sugars or sucrose intake may have been underestimated. Additionally, the participation rate was lower in the controls (60%) than in the cases (80%), and this may have caused a selection bias.

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Supplementary materials available on online

Appendix Table