Soft Drink and Juice Consumption and Risk of Pancreatic Cancer: The Singapore Chinese Health Study

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Abstract

Background: Sugar-sweetened carbonated beverages (called soft drinks) and juices, which have a high glycemic load relative to other foods and beverages, have been hypothesized as pancreatic cancer risk factors. However, data thus far are scarce, especially from non-European descent populations. We investigated whether higher consumption of soft drinks and juice increases the risk of pancreatic cancer in Chinese men and women.

Methods: A prospective cohort analysis was done to examine the association between soft drink and juice consumption and the risk of pancreatic cancer in 60,524 participants of the Singapore Chinese Health Study with up to 14 years of follow-up. Information on consumption of soft drinks, juice, and other dietary items, as well as lifestyle and environmental exposures, was collected through in-person interviews at recruitment. Pancreatic cancer cases and deaths were ascertained by record linkage of the cohort database with records of population-based Singapore Cancer Registry and the Singapore Registry of Births and Deaths.

Results: The first 14 years for the cohort resulted in cumulative 648,387 person-years and 140 incident pancreatic cancer cases. Individuals consuming ≥2 soft drinks/wk experienced a statistically significant increased risk of pancreatic cancer (hazard ratio, 1.87; 95% confidence interval, 1.10-3.15) compared with individuals who did not consume soft drinks after adjustment for potential confounders. There was no statistically significant association between juice consumption and risk of pancreatic cancer.

Conclusion: Regular consumption of soft drinks may play an independent role in the development of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev; 19(2); 447–55. ©2010 AACR.*

Introduction

Carcinoma of the pancreas is a serious medical and public health problem because of the late presentation of symptoms, high metastatic potential, inadequate therapeutic choices, and lack of primary prevention strategy. Pancreatic cancer is among the most rapidly fatal cancers in adults, with a 5-year survival rate of <5% (1). Although the age-standardized rate of pancreatic cancer has plateaued in the United States, it continues to increase in certain parts of Asia (2). For example, age-standardized rate among Chinese men in Singapore increased from 3.7/100,000 in 1968 to 1972 to 5.4/100,000 in 1998 to 2002. For women, the corresponding figures were 1.5 and 3.4, respectively

(3). This increase may reflect demographic and socioeconomic shifts as well as a transition towards a more westernized lifestyle and diet (3, 4).

Identifying modifiable risk factors is important due to the poor prognosis and minimal effect of conventional treatment methods for pancreatic cancer. Cigarette smoking is a modifiable risk factor consistently associated with pancreatic cancer (5). Recently, a large meta-analysis and an expert review report concluded that evidence for body fatness as a cause of pancreatic cancer is convincing (6, 7). A large body of evidence suggests that type 2 diabetes mellitus may be a cause and is a consequence of the carcinogenesis of the pancreas (8). A recent prospective analysis found positive associations between these risk factors and pancreatic cancer risk in Asians as well (4).

Cigarette smokers, obese individuals, and patients with type 2 diabetes mellitus, who are all at increased risk of pancreatic cancer, have elevated glucose, C-protein, and insulin levels (9). Elevated post-load and fasting plasma glucose (10-12), nonfasting C-protein (13), and fasting serum insulin (14) have been linked with pancreatic cancer risk. Experimental studies have shown that insulin promotes pancreatic cancer cell growth *in vitro* in a dose-dependent manner, which could occur through the mitogenic effects of insulin and insulin growth factors on the exocrine cells of the pancreas (15). Accordingly, it is thought that dietary items that induce hyperglycemia

and hyperinsulinemia could result in exposure of exocrine pancreatic cells to high concentrations of insulin, which might contribute to malignant transformation of pancreatic cells.

Soft drinks are the leading sources of added sugar in the U.S. diet (16) and greatly contribute to hyperglycemia and hyperinsulinemia (17). Some studies found that individuals who consume large quantities of soft drinks were at increased risk for obesity (17-20) and type 2 diabetes mellitus (20-22), conditions that may be on the causal pathway to pancreatic cancer (6-8). Fruit juice also contributes to added sugar in a U.S. diet (16). However, its effect on raising glucose and insulin levels is much less than soft drinks (23). Four prospective studies have investigated the association between soft drink consumption and the risk of pancreatic cancer. Findings were inconsistent. Two of the four studies found a positive association (24, 25), whereas the other two did not find any association between soft drinks and pancreatic cancer risk (26, 27). Only one of these four studies also examined the association between juice intake and pancreatic cancer risk and found a positive but nonsignificant association (26).

To date, all prospective studies examining the role of soft drinks and juice on the development of pancreatic cancer have been conducted in American (24, 26, 27) and European (25) populations, of which the majority of participants were Caucasians. By comparison, there are no studies in Asian populations. This is of importance given the distinct lifestyle and risk factors for obesity and diabetes in Asians compared with Caucasians (28). We conducted the present analysis to examine the association between consumption of soft drinks and juice and risk of pancreatic cancer in a cohort of >60,000 middle-aged or older Chinese men and women in Singapore.

Materials and Methods

Study Cohort

The Singapore Chinese Health Study is a population-based, prospective investigation of diet and cancer risk (29). The study was approved by the institutional review boards of the National University of Singapore and the University of Minnesota. The cohort was drawn from permanent residents of government-built housing estates, where 86% of the Singapore population resided during the enrollment period. Study subjects were restricted to the two major dialect groups of Chinese in Singapore (Hokkien and Cantonese), who originated from the contiguous provinces of Fujian and Guangdong, respectively, in the southern part of China. Recruitment was initiated with a letter informing potential participants of the study and inviting them to take part. Five to 7 days later, study staff went door-to-door to invite subjects to participate. Approximately 85% of eligible subjects who were invited responded positively (29). At recruitment, each subject was interviewed face-to-face in their home by a trained interviewer using a structured,

scanner-readable questionnaire, which requested information on demographics, height, weight, use of tobacco, usual physical activity, menstrual and reproductive history (women only), medical history, familial history of cancer, and a 165-item food frequency section assessing usual intake during the previous year. Between April 1993 and December 1998, 63,257 Chinese women and men ages 45 to 74 years (mean age, 56.5 years) were enrolled in the study (29). All subjects gave informed consent as deemed by the completion of the questionnaire.

Dietary Assessment

A semiquantitative food frequency questionnaire, specifically developed for this population and assessing 165 commonly consumed food items, was administered during the baseline interview. During the interview, the respondent referred to accompanying photographs to select from eight food frequency categories (ranging from "never or hardly ever" to "two or more times a day") and three portion sizes. The food frequency questionnaire has been validated against a series of 24-h dietary recall interviews in a random sample of ≥1,000 participants that occurred on one weekday and one weekend day ~2 months apart (29) and against selected biomarkers (30). Correlation coefficients for energy/nutrients ranged from 0.24 to 0.79, and the majority of macronutrients and food groups had correlation coefficients in the high end of this range (30).

Assessment of Soft Drink and Juice Intake

Three different questions from the food frequency questionnaire specifically asked subjects to report the intake frequency and portion size: (*a*) soft drinks such as Coca-Cola and 7-Up with one-glass portion; (*b*) orange juice with one glass, packet, or hawker (vendor) portion; and (*c*) other fruit and vegetable juices with one glass, packet, or hawker portion. The intake frequency was selected from nine predefined categories: never or hardly ever, 1 to 3 times a month, once a week, 2 to 3 times a week, 4 to 6 times a week, once a day, 2 to 3 times a day, 4 to 5 times a day, and ≥6 times a day. Hawker centers, ubiquitous in Singapore and other parts of Asia, serve a variety of foods all day long and resemble fast-food courts in U.S. shopping malls. Based on 24-h diet recalls conducted on ≥1,000 cohort subjects as part of the food frequency questionnaire validation study (29), participants reported consuming the following juices, estimated as a percentage of total juice consumption: sugarcane juice (20.3%), honeydew melon juice (14.1%), apple juice (12.8%), watermelon juice (9%), carrot juice (9%), pineapple juice (6.4%), star fruit juice (5.1%), and lemon juice drink (5.1%). The remaining canned grape, tomato, prune and juice, along with papaya, plum, and fresh celery juice, each comprised 1.3% to 2.6% of the total juice consumption reported. One glass was assigned a value of 237 mL or equivalent to ~1 cup.

In conjunction with the Singapore Chinese Health Study, the Singapore Food Composition Table was developed. This food nutrient database lists the levels of

96 nutritive/nonnutritive dietary components per 100 g of cooked food and beverages in the diet of the Singaporean Chinese. By combining the information obtained from the food frequency response with the Food Composition Table, we were able to compute the mean daily intake of nutrients for each subject (29).

Ascertainment of Other Risk Factors

Other known or suspected risk factors for pancreatic cancer assessed with the baseline questionnaire included age (years), medical history, familial history of cancer, tobacco use (age started/quit, amount, frequency, type), highest level of education attained, body mass index (BMI; kg/m^2) calculated using self-reported height and weight, and hours of moderate (e.g., brisk walking and bicycling on ground level) and vigorous (e.g., jogging, bicycling on hills, and tennis) physical activity on a weekly basis.

Ascertainment of Pancreatic Cancer and Deaths

Pancreatic cancer cases and deaths among cohort members were identified by record linkage of the cohort database with the population-based Singapore Cancer Registry and the Singapore Registry of Births and Deaths. The nationwide registry has been in place since 1968 and has been shown to be comprehensive in its recording of cancer cases (3). The linkage analysis identified 142 incident cases of pancreatic cancer diagnosed on or before December 31, 2006. Eighty-three (56.4%) pancreatic cancer cases were diagnosed histologically and their diagnoses were confirmed via manual review of pathology reports by medically trained research staff. Fifty-seven (38.8%) cases were diagnosed based on positive clinical signs and symptoms with consistent radiologic history, and 7 (4.8%) cases were identified through death certificates. We excluded one case with endocrine-type pancreatic cancer. Based on our follow-up telephone/in-person interviews conducted between 1999 and 2004, in which 61,685 (97.5%) of the original cohort were contacted, only 17 (0.03%) of the participants emigrated from Singapore. Therefore, the follow-up for identification of pancreatic cancer was virtually complete for the cohort.

Statistical Analysis

Among 63,257 original cohort participants, 1,936 had reported a history of invasive cancer other than nonmelanoma skin cancer. After excluding these prevalent cancer cases, and 796 participants who reported an implausible total energy intake (<500 or >3,500 kcal/d for women and <800 or >4,200 kcal/d for men), we included 60,524 subjects in the present analysis. Person-years of follow-up were counted on a continuous scale from the date of baseline interview to the date of diagnosis of pancreatic cancer, death, or December 31, 2006, whichever occurred first. Cox proportional hazards regression models were used to examine the association between beverage consumption and pancreatic cancer with adjustment for potential confounders. The frequency instead of amount of beverages consumed was used as primary exposure variable given

the heterogeneity in serving size of different soft drinks or juices in the study population. The strength of association was measured by hazard ratios (HR) and their corresponding 95% confidence intervals (95% CI) and two-sided P values. The HRs per category of soft drink and juice consumption were estimated with simultaneous adjustment for demographic, lifestyle, and dietary variables. Testing indicated that the assumptions of proportionality were not violated.

Soft drink and juice categories were based on intakes that allowed for logical cut points and provided sufficient participants and cases per category. We combined all participants with ≥2 servings/wk to obtain a robust estimate of HR. We grouped orange juice and fruit juices together because they were similarly associated with baseline characteristics and risk of pancreatic cancer in this population.

Three primary models were constructed including risk factors known to be associated with pancreatic cancer, with the final model including baseline BMI, total energy, and history of diabetes, which may be on the causal pathway between beverage intakes and pancreatic cancer risk. In model 1, we calculated HRs after adjusting for sex, age at baseline interview in quintiles, year of interview (1993-1995, 1996-1998), and dialect group (Cantonese, Hokkien). Model 2 further adjusted for highest educational level reached (none, primary, secondary, secondary-plus), smoking status (never, light, heavy), alcohol intake (no, monthly, weekly, daily), moderate physical activity (h/wk), consumption of added sugar and candy combined (g/d), caloric intake (kcal/d), and consumption of either juices (to calculate HR for soft drinks) or soft drinks (to calculate HR for juices). Heavy smokers were defined as those who started to smoke before age 15 years or smoked ≥13 cigarettes/d, whereas the remaining smokers were characterized as light smokers. Model 3 included additional variables for BMI (<18.5, 18.5 to <25, ≤25) at baseline and prevalent or incident diabetes (yes/no). We also adjusted for other potential confounders, including vigorous physical activity, red meat intake, fiber intake, total and saturated fat, and tea, coffee, and dairy intake. Because the adjustment for these additional variables did not materially change the risk estimates, we presented results without adjustment for these variables.

In a sensitivity analysis, we excluded pancreatic cancer cases and the observed person-years occurring in the first 1 year, first 3 years, and first 5 years of follow-up to rule out the potential effect of subclinical symptoms of the disease on the soft drink intake-pancreatic cancer association. Participants in our study who developed diabetes mellitus before baseline may have changed their diet as a consequence of the diagnosis; therefore, we repeated our analysis after excluding participants who reported diabetes mellitus at baseline. We also repeated our analyses in exclusive consumers of soft drink to avoid the potential confounding effect of juice after excluding subjects who consumed ≥1 drink of juice/mo. Similarly, we examined the juice-pancreatic cancer risk association after excluding subjects with at least 1 soft drink/mo. Linear trends

Table 1. Baseline characteristics according to frequency of soft drink and juice consumption in the Singapore Chinese Health Study

	Soft drink consumption		
	None	**<2 servings/wk**	**≥2 servings/wk**
n	45,846	8,789	5,889
Soft drinks (servings/wk), mean	0	0.59	5.11
Age at baseline (y)	57.1 (8.0)	54.4 (7.5)	53.2 (7.0)
Sex, female (%)	57.7	55.3	42.7
BMI (kg/m^2)	23.1 (3.2)	23.2 (3.3)	23.4 (3.4)
Smoking, ever (%)	30.0	27.7	36.6
Smoking, pack-years	8.82 (18.3)	7.9 (17.3)	10.7 (19.7)
Type 2 diabetes* (%)	10.4	4.4	3.9
Moderate activity (h/wk)	0.9 (2.6)	0.8 (2.6)	0.7 (2.6)
Education (% secondary-plus)	26.4	34.5	35.7
Alcohol (drinks/wk)	0.9 (4.1)	1.0 (4.1)	1.5 (5.2)
Total carbohydrates (g/d)	221.3 (75.2)	234.2 (76.9)	272.9 (87.7)
Sugar and candy (g/d)	11.4 (8.5)	13.4 (8.7)	15.5 (10.0)
Total fat (g/d)	42.1 (19.0)	47.1 (20.3)	54.0 (23.7)
Red meat intake (g/d)	28.3 (22.2)	34.0 (23.2)	41.9 (28.1)
Total intake (kcal/d)	1,505.5 (512.6)	1,617.6 (533.9)	1,872.0 (614.9)
	Juice consumption		
	None	**<2 servings/wk**	**≥2 servings/wk**
n	40,921	13,416	6,187
Juice (servings/wk), mean	0	0.65	4.01
Age at baseline (y)	57.3 (8.0)	54.4 (7.5)	54.1 (7.4)
Sex, female (%)	58.1	52.5	48.9
BMI (kg/m^2)	23.1 (3.2)	23.2 (3.3)	23.3 (3.4)
Smoking, ever (%)	30.3	30.4	30.4
Smoking, pack-years	9.1 (18.7)	8.4 (17.4)	8.3 (17.5)
Type 2 diabetes* (%)	9.8	6.8	7.2
Moderate activity (h/wk)	0.8 (2.6)	0.9 (2.8)	1.0 (2.6)
Education (% secondary-plus)	23.6	35.5	45.8
Alcohol (drinks/wk)	0.9 (4.1)	1.0 (4.0)	1.4 (5.1)
Total carbohydrates (g/d)	220.1 (75.1)	235.6 (77.9)	265.5 (86.4)
Sugar and candy (g/d)	11.5 (8.6)	12.9 (8.7)	14.6 (9.9)
Total fat (g/d)	41.3 (18.5)	47.1 (20.3)	55.4 (23.7)
Red meat intake (g/d)	28.7 (22.2)	33.3 (24.4)	36.3 (27.2)
Total intake (kcal/d)	1,490.8 (506.3)	1,624.7 (539.7)	1,852.9 (614.0)

NOTE: Data are mean (SD) unless noted as percentages.

*Includes prevalent diabetes at baseline.

were tested by using the Wald test of a score variable that contained median values for intake categories. The presence of an interaction between soft drink consumption and sex, age (quintiles), smoking status (never, light, heavy), BMI (<18.5, 18.5 to <25, ≤25), and history of diabetes mellitus was tested using the likelihood ratio test.

Statistical computing was conducted using SAS statistical software version 9.1 (SAS Institute). All statistical tests were two-sided. *P* values < 0.05 were considered statistically significant.

Results

Characteristics of the 60,524 people who completed the baseline questionnaire between April 1993 and December 1998 are shown in Table 1. At baseline, 9.7% of the participants consumed at least 2 soft drinks/wk and 10.2% of the participants consumed at least 2 servings of juice/wk. The Spearman correlation between soft drinks and juice was 0.13 (*P* < 0.01). Compared with nondrinkers of soft drinks, participants who consumed ≥2 soft drinks/wk

were younger, more likely to be men, and smoke cigarettes. They also had higher levels of educational attainment, alcohol consumption, total energy intake, and lower levels of physical activity. Patients with a history of type 2 diabetes mellitus at baseline consumed a lower amount of soft drinks (on average, 0.29 drinks/wk) compared with subjects without type 2 diabetes mellitus (0.62 drinks/wk). BMI values were comparable across different categories of soft drink consumption. Subjects who consumed ≥2 soft drinks/wk also had higher consumption of total carbohydrate, fat, added sugar, and red meat. Similarly, participants who reported ≥2 drinks of juice were younger, more likely to be men, and had higher levels of physical activity, education, alcohol consumption, and total energy intake. The consumptions of fat, carbohydrate, added sugar, and red meat intake were higher in more frequent drinkers of juice than nondrinkers. There was no association between juice intake and cigarette smoking or BMI.

After 14 years and 648,387 person-years of follow-up (an average of 10.7 years per person), 140 cohort participants who were cancer free at baseline had developed invasive exocrine pancreatic cancer. In age-adjusted analyses, after exclusion of former smokers, current smokers had a 49% increased risk of pancreatic cancer compared with never smokers (HR, 1.49; 95% CI, 0.98-2.27), which was unaffected by adjustment for diabetes and BMI. There was no statistical evidence for a dose-response association between pack-years of smoking and HR of pancreatic cancer. Neither BMI nor history of type 2 diabetes mellitus was associated with increased risk of pancreatic cancer (HR for BMI ≥25 versus 18.5 to <25, 1.16; 95% CI, 0.77-1.74; HR for type 2 diabetes mellitus versus no type 2 diabetes mellitus, 1.06; 95% CI, 0.65-1.71).

HRs for pancreatic cancer by categories of soft drink and juice consumption are given in Table 2 for the different regression models. We present results of both sexes combined, with the adjustment for gender, given that there was no evidence of interaction by sex. In all models, the risk for pancreatic cancer for individuals with ≥2 drinks of soft drink/wk was statistically significantly ~85% higher than nondrinkers. Adjustment for multiple confounders including BMI, type 2 diabetes mellitus, and

Table 2. HR (95% CI) for pancreatic cancer according to category of consumption of soft drinks and juices

	None	<2 servings/wk	≥2 servings/wk	P_{trend}*
Soft drinks				
Mean (servings/d)	0	0.59	5.11	
Cases (n)	110	12	18	
Person-years	492,508	93,836	62,043	
Age and sex HRs[†]	1.0	0.72 (0.39-1.30)	1.83 (1.10-3.04)	0.02
Multivariate HRs[‡]	1.0	0.73 (0.40-1.33)	1.86 (1.11-3.13)	0.02
Multivariate HRs, BMI and diabetes[§]	1.0	0.73 (0.40-1.33)	1.87 (1.10-3.15)	0.02
Multivariate HRs after excluding first 5 y of follow-up[‖]	1.0	0.83 (0.41-1.69)	1.94 (1.04-3.63)	0.03
Multivariate HRs after excluding diabetics at baseline[¶]	1.0	0.71 (0.38-1.33)	1.87 (1.09-3.21)	0.02
Juice				
Mean (servings/d)	0	0.65	4.01	
Cases (n)	98	27	15	
Person-years	439,002	143,066	66,319	
Age and sex HRs[†]	1.0	1.07 (0.70-1.64)	1.33 (0.77-2.29)	0.31
Multivariate HRs[‡]	1.0	1.05 (0.68-1.63)	1.32 (0.75-2.30)	0.34
Multivariate HRs, BMI and diabetes[§]	1.0	1.06 (0.68-1.63)	1.31 (0.74-2.30)	0.35
Multivariate HRs after excluding first 5 y of follow-up[‖]	1.0	1.07 (0.63-1.83)	1.42 (0.73-2.77)	0.31
Multivariate HRs after excluding diabetics at baseline[¶]	1.0	1.03 (0.65-1.63)	1.35 (0.75-2.42)	0.32

*Test for trend across categories of exposure based on the medians of the original exposure categories.
[†]Adjusted for age (quintiles), sex, ethnicity (Cantonese, Hokkien), and year of interview (1993-1995, 1996-1998).
[‡]Further adjusted for education (none, primary, secondary), smoking index (never, light, heavy), moderate physical activity (h/wk), alcohol (none, monthly, weekly, daily), added sugar and candy (g/d), and total calories (continuous). Regular soft drinks and juice were mutually adjusted.
[§]Further adjusted for type 2 diabetes mellitus (yes/no) and BMI (<18.5, 18.5 to <25, ≥25).
[‖]Analysis excluded cases diagnosed during the first 5 years of follow-up. From lowest to highest category, n = 71, 9, and 13 for soft drinks and n = 64, 18, and 11 for juice.
[¶]Analysis excluded baseline diabetes. From the lowest to highest category, n = 100, 11, and 17 for soft drinks and n = 90, 24, and 14 for juice.

consumption of juice did not materially change the results (HR, 1.87; 95% CI, 1.10-3.15).

We also examined the association between juice intake and the risk of developing pancreatic cancer. Compared with nondrinkers, individuals who consumed ≥2 drinks of juice/wk had ~30% increased risk of pancreatic cancer (Table 2). However, in all models with various adjustment variables, including consumption of soft drink, the elevated HRs were not statistically significant.

To avoid potential effect of subclinical symptoms of pancreatic cancer on subjects' consumption patterns of soft drink and juice, we re-examined the soft drink/juice-pancreatic cancer risk association after excluding incident pancreatic cancer cases and person-year observations within the first year ($n = 20$), the first 3 years ($n = 30$), and the first 5 years ($n = 49$) of follow-up post-enrollment. The associations between consumption of soft drink or juice and risk of pancreatic cancer risk in the subset were comparable with those based on the entire cohort follow-up. After excluding incident pancreatic cancer cases and person-years of the first 5 years of follow-up post-enrollment, the inverse association between consumption of soft drink or juice and risk of pancreatic cancer remained statistically significant (P_{trend} = 0.03; Table 2). We also conducted subcohort analyses after excluding subjects who reported a history of type 2 diabetes mellitus at enrollment ($n = 5,380$) to avoid the potential confounding effect of diabetes, which could result in reduced consumption of sugar-containing soft drink and juice, on the association between intake of soft drink or juice and pancreatic cancer risk. The relation between soft drink or juice and pancreatic cancer risk remained unchanged (Table 2).

Further analyses on exclusive consumers of soft drink after excluding subjects consuming ≥1 drink of juice/mo ($n = 19,603$) were carried out as well. Compared with nondrinkers of soft drinks, individuals who consumed ≥2 drinks/wk experienced two times the risk of pancreatic cancer (HR, 2.12; 95% CI, 1.07-4.19). Conversely, after excluding 14,678 subjects who consumed at least 1 soft drink/mo, the association between juice intake and pancreatic cancer risk remained statistically nonsignificant (HR, 1.60; 95% CI, 0.86-2.99). Because cigarette smoking was associated with soft drink intake and causally related to pancreatic cancer, we conducted subcohort analyses after excluding current, and then ever, smokers. The relative risks were not materially changed. We also examined but did not observe any interaction effect for either soft drink or juice intake with age, BMI, cigarette smoking, or history of diabetes mellitus on risk of pancreatic cancer (data not shown).

Discussion

In this large prospective cohort of Chinese men and women in Singapore, those who reported regular soft drink consumption were at increased risk of pancreatic cancer when compared with those who largely abstained. There was no association between consumption of juice and risk of pancreatic cancer.

To date, four prospective studies have investigated soft drink consumption and pancreatic cancer (26-29), one of which included fruit juice (ref. 28; Table 3). Our findings are largely consistent with three of the four studies. In a prospective analysis of U.S. nurses and other health professionals, women (205 cases/20 years follow-up) who consumed >3 sugar-sweetened drinks/wk had a 57% greater risk of pancreatic cancer than did women who consumed ≤1 sugar-sweetened soft drinks/mo; however, there was no association in men (174 cases/20 years follow-up; ref. 24). A prospective analysis of Swedish adults (131 cases/7.2 years follow-up) reported that those who consumed ≥2 soft drinks/d had a 93% significantly greater risk of pancreatic cancer than did those who consumed no soft drinks (25). A large prospective study (434 cases/8 years follow-up) of the Multiethnic Cohort reported a positive but statistically nonsignificant association between the two highest categories of soda intake and pancreatic cancer risk (26). This same cohort also reported a null effect of juice intake on pancreatic cancer risk, again consistent with our findings. In contrast to these studies, a prospective study, including 1,258 pancreatic cancer cases (7.2 years follow-up), reported no association between soft drink intake and pancreatic cancer (27).

Our results are also in agreement with most case-control studies (5); however, a recent case-control study found no association between soft drink consumption and pancreatic cancer (31).

Soft drink consumption coincides with many other unhealthy lifestyle characteristics, making it difficult to separate smoking, caloric intake, body weight, and type 2 diabetes mellitus from soft drink consumption. In agreement with a previous Asian cohort study (4), current smokers in our study had an increased risk for pancreatic cancer. Unlike our study, the other study observed a significant association between pack-years and pancreatic cancer risk. Also consistent with their study, overweight and obesity (BMI ≥25 versus 18 to <25) in our study were not significantly associated with pancreatic cancer risk. However, in their study, waist circumference was associated with a significantly greater risk of pancreatic cancer; suggesting that central obesity is an independent risk factor for the disease. Our study did not ascertain waist circumference. Contrary to our findings, the other Asian study found that individuals with diabetes mellitus had a 75% significantly greater risk of pancreatic cancer compared with individuals without diabetes mellitus. Finally, in our analyses, the influence of soft drink intake on the risk of pancreatic cancer remained virtually unchanged after adjustment for smoking status, energy intake, BMI, and type 2 diabetes mellitus.

The hypothesized mechanism linking type 2 diabetes mellitus or abnormal glucose metabolism to pancreatic cancer involves insulin. Chronically elevated glucose

Table 3. Prospective studies of sugar-sweetened beverages and pancreatic cancer

Author (reference)	Study design	Study population	Incident cases; length follow-up	Findings
Schernhammer et al. (24)	Prospective cohort analysis	2 U.S. cohorts: 138,158 U.S. nurses and other health professionals; females ages 30-55 y and males ages 40-75 y	Total cohort: 379 cases; 20 y follow-up Females: 205 cases; 20 y follow-up Males: 174 cases; 20 y follow-up	Women who consumed >3 servings sugar-sweetened soft drink/wk had elevated risk of pancreatic cancer (HR, 1.57; 95% CI, 1.02-2.41), but no association observed in males
Larsson et al. (25)	Prospective cohort analysis	77,797 Swedish nurses and other health professionals ages 45-83 y	Total cohort: 131 cases; 7.2 y follow-up	Elevated risk of pancreatic cancer for ≥2 glasses total soft drink/d (HR, 1.93; 95% CI, 1.18-3.14)
Nothlings et al. (26)	Prospective cohort analysis	Multiethnic Cohort Study: 162,150 healthy women and men in Hawaii-Los Angeles ages 45-75 y	Total cohort: 434 cases; 8 y follow-up	No association between soft drink or juice intake and pancreatic cancer but elevated risk for highest category of juice and fruit combined intake (HR, 1.37; 95% CI, 1.02-1.84)
Bao et al. (27)	Prospective cohort analysis	AARP Diet and Health Study: 487,922 U.S. healthy men and women ages 50-71 y	Total cohort: 1258 cases; 7.2 y follow-up	No association between soft drink or juice intake and pancreatic cancer

concentrations are directly associated with a reduction in insulin sensitivity (10). Hyperinsulinemia, a result of insulin insensitivity, has been shown to increase local circulation and cell division within the pancreas (32, 33). Because their blood supply first passes through the insulin-producing islets of Langerhans, pancreatic exocrine cells are estimated to be exposed to insulin concentrations that are 20-fold higher than the systemic circulation, which some have hypothesized may have implications for pancreatic cancer promotion (34).

High insulin concentrations may increase free insulin-like growth factor (IGF) levels by reducing levels of IGF-binding proteins (35). Exposure to IGF has been shown to cause proliferation in pancreatic cancer cell lines (36). Elevated insulin concentrations have also been shown to activate IGF receptors, which may lead to cancer cell proliferation (37). Overexpression of IGF-I, IGF-I receptor, and IGF-II receptor has been found in human pancreatic cancer cells in comparison with normal pancreatic cancer cells, further suggesting that the signaling pathways of IGF and IGF receptors may be involved in pancreatic carcinogenesis (36, 38). A recent nested case-control study, within four large prospective studies, observed no evidence that the risk of pancreatic cancer was influenced by prediagnostic plasma levels of IGF-I, IGF-II, or IGF-binding protein-3 (39). However, in the same cohort, the researchers observed a significant inverse association between IGF-binding protein-1 and the risk of pancreatic cancer (40).

Elevated post-load and fasting plasma glucose (10-12), nonfasting plasma C-peptide (13), and fasting serum insulin (14) have been associated with an increased risk of pancreatic cancer in prospective studies, suggesting that dietary items that lead to hyperglycemia can similarly influence pancreatic carcinogenesis. In a recent large epidemiologic study, researchers observed a statistically significant positive trend between C-peptide levels and pancreatic cancer risk among those participants who provided nonfasting blood specimens (13). No association was observed between fasting plasma insulin levels and pancreatic cancer risk. This suggests that postprandial insulin may be a better measure for the association with cancer risk than fasting insulin levels and is consistent with the independent role of soft drink consumption in the development of pancreatic cancer observed in our study.

The mechanism presented here supports the notion that sugar-sweetened beverages with a high glycemic load may increase risk for pancreatic cancer. Most studies have shown no association between glycemic load and pancreatic cancer, except in subgroup analyses (41-46). The contradictory findings from these studies may be due to the measurement errors inherent in food frequency questionnaire for the calculation of a summary score for the overall exposure to glycemic load (47). Given that glycemic loads for food items in our study questionnaire were unavailable, we were unable to examine the total glycemic load in relation to risk of pancreatic cancer risk in this study population.

The lack of association between juice intake and pancreatic cancer risk may result from difference in the composition of juices and soft drinks. This notion is supported by our findings that showed an elevated risk of pancreatic cancer among soft drink consumers after excluding juice consumers. Finally, another explanation is that juice consumption is related with healthier lifestyle and dietary patterns than soft drink consumption, as seen in Table 1.

Our study has several strengths. To our knowledge, this is the first prospective cohort of an Asian population to examine the association between sugar-sweetened beverages and pancreatic cancer. The prospective design of our study precluded recall bias and the need for next-of-kin respondents. Also in this study, differential follow-up is unlikely because identification of deaths and cases is highly accurate in this cohort. Other strengths include the high response rate, a detailed face-to-face interview at baseline, and a virtually complete ascertainment of cancer cases and deaths (3).

There are limitations to consider as well. Pancreatic cancer is rare; therefore, the number of cases in this study is relatively small. The combination of lower relative soft drink consumption compared with other populations and the lower case rates limits the ability to examine a wider distribution of drink consumption. Due to the rarity of pancreatic cancer, we had a slim distribution of cases, limiting the power and giving potential to a chance association. Also, because we were unable to collect repeated dietary measurements in this study, we were unable to account for changes in consumption of soft drinks and juices, especially when the diagnosis of diabetes occurred after the baseline interview. Finally, we could not rule out the possibility of residual confounding by factors associated with the habit of drinking soft drinks or other unascertained factors such as waist circumference.

In conclusion, the present study adds to the evidence that soft drink consumption may play a role in the development of pancreatic cancer. Our findings underscore the need for further large prospective epidemiologic studies in Asian populations. As well, clinical studies examining biomarkers for glycemia and insulinemia and taking a mechanistic approach to the question of soft drink consumption and pancreatic cancer are warranted as there is still much to understand on the link between sugar-sweetened beverages and pancreatic cancer.

Disclosure of Potential Conflicts of Interest

Acknowledgments

Grant Support

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