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Sweets, sweetened beverages, and risk of pancreatic cancer in a large population-based case–control study

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Abstract

Objective   We examined the associations between sweets, sweetened and unsweetened beverages, and sugars and pancreatic cancer risk.

Methods   We conducted a population-based case–control study (532 cases, 1,701 controls) and used multivariate logistic regression models to calculate odds ratios (OR) and 95% confidence intervals (CI). Because associations were often different by sex, we present results for men and women combined and separately.

Results   Among men, greater intakes of total and specific sweets were associated with pancreatic cancer risk (total sweets: OR = 1.9, 95% CI: 1.0, 3.6; sweet condiments: OR = 1.9, 95% CI: 1.2, 3.1; chocolate candy: OR = 2.4, 95% CI: 1.1, 5.0; other mixed candy bars: OR = 3.3, 95% CI: 1.5, 7.3 for 1 + servings/day versus none/rarely). Sweets were not consistently associated with risk among women. Sweetened beverages were not associated with increased pancreatic cancer risk. In contrast, low-calorie soft drinks were associated with increased risk among men only; while other low-/non-caloric beverages (e.g., coffee, tea, and water) were unassociated with risk. Of the three sugars assessed (lactose, fructose, and sucrose), only the milk sugar lactose was associated with pancreatic cancer risk (OR = 2.0, 95% CI: 1.5, 2.7 comparing extreme quartiles).

Conclusion   These results provide limited support for the hypothesis that sweets or sugars increase pancreatic cancer risk.

Introduction

Pancreatic cancer is the fourth leading cause of cancer death among men and women in the United States and the most fatal cancer. A number of 37,680 individuals were estimated to have been diagnosed with pancreatic cancer and 34,290 people were expected to die of the disease in 2008 [1]. Greater age, cigarette smoking, and male sex are fairly well-established risk factors for this deadly cancer. Diabetes also has been linked to greater risk of pancreatic cancer, and meta-analyses suggest that this link may be causal, or at least that metabolic conditions predisposing to diabetes precede pancreatic cancer [2, 3]. Four prospective studies that examined banked serum have linked higher fasting glucose levels with subsequent risk of pancreatic cancer several years later [4–7], and pre-diagnostic plasma C-peptide levels have been linked to greater risk of pancreatic cancer [8]. In vitro, insulin increases pancreatic cancer cell proliferation in a dose-dependent manner [9]. Hyperglycemia, insulin insensitivity, and hyperinsulinemia can lead to very high insulin exposure of the exocrine pancreatic cells, and this may play a role in pancreatic cancer development [4, 9].

Accordingly, it has been of interest to investigate dietary practices that may predispose to diabetes, hyperglycemia, or hyperinsulinemia. We examined sweets, sweetened beverages, and sugars as risk factors for pancreatic cancer

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in a large population-based case–control study. For comparison, we examined artificially sweetened, low-calorie, or non-caloric beverages (e.g., diet soft drinks, water, tea, and coffee) and pancreatic cancer risk. We hypothesized that intake of sweets, sugar, and beverages with sugar would be associated with an elevated risk of pancreatic cancer, based on their possible positive correlation with hyperglycemia and hyperinsulinemia; while artificially sweetened or low-calorie beverages would be unassociated with risk given their lesser effect on insulin response.
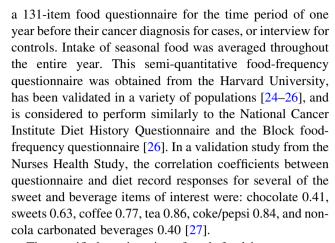
Materials and methods

Study population

Details of this study have been published previously [10–23]. Briefly, between 1995 and 1999, men and women with incident adenocarcinoma of the exocrine pancreas were identified in six counties of the San Francisco Bay Area (in-area cases) using rapid case ascertainment operated by the Northern California Cancer Center. Pancreatic cancer diagnoses were confirmed by contacting the participants' physicians and using Surveillance, Epidemiology, and End Results (SEER) abstracts. Eligible in-area cases were 21–85 years of age, residents of one of the six counties, alive upon first contact, and could complete an in-person interview in English. Sixty-five eligible out-of-area cases also were interviewed. They were seen in the University of California San Francisco clinics and met the same criteria as in-area cases except that most were residents of counties adjacent to the six Bay Area counties. Of 798 eligible cases, 532 (67%) completed an interview for this study and 8% refused to participate. The main reason the remaining eligible cases did not participate was because they died prior to contact. Control participants were frequency-matched to cases by sex and age within five-year categories and were selected from the target population using random digit dial. Controls older than 65 years were supplemented by random selection from Health Care Finance Administration lists (now the Centers for Medicare & Medicaid Services). Of 2,525 eligible controls, 1,701 (67%) completed an interview for this study. No proxy interviews were conducted. This study was reviewed and approved by the University of California San Francisco Institutional Review Board and written informed consent was obtained from all the participants prior to interview.

Assessment of intake of sweets and non-alcoholic beverages

Participants reported, via in-person interviews, their frequency of intake of individual food items that were listed on a 131-item food questionnaire for the time period of one year before their cancer diagnosis for cases, or interview for controls. Intake of seasonal food was averaged throughout the entire year. This semi-quantitative food-frequency questionnaire was obtained from the Harvard University, has been validated in a variety of populations [24–26], and is considered to perform similarly to the National Cancer Institute Diet History Questionnaire and the Block food-frequency questionnaire [26]. In a validation study from the Nurses Health Study, the correlation coefficients between questionnaire and diet record responses for several of the sweet and beverage items of interest were: chocolate 0.41, sweets 0.63, coffee 0.77, tea 0.86, coke/pepsi 0.84, and non-cola carbonated beverages 0.40 [27].

The specified portion size of each food item was considered as one serving, and the food frequency responses were transformed into servings per day. The options for frequency of food intake were: never, <1/month (rarely), 1–3/month, 1/week, 2–4/week, 5–6/week, 1/day, 2–3/day, 4–5/day, and 6+/day. Consumption of total and individual sweets and beverage items was examined. Sweets included pure chocolate candy bars or packets of candy (e.g., M&Ms), other mixed candy bars (e.g., Snickers/Milky Way/Reeses), candy without chocolate (e.g., mints, lifesavers), and sweet condiments (i.e., jams/jellies/preserves/syrup/honey). Total carbonated beverages included those with sugar (i.e., Coke/Pepsi/other colas, caffeine-free Coke/Pepsi/other colas, and other) and sugar-free types (i.e., low-calorie colas, low-calorie caffeine-free colas, and other low-calorie carbonated beverages such as diet 7-up, Fresca, diet ginger ale, etc.). Other sweetened beverages assessed included punch/lemonade/non-carbonated fruit drinks (not juice). Other non-caloric or low-calorie beverages assessed for comparison included plain water, herbal tea, non-herbal tea, decaffeinated coffee, and caffeinated coffee. While we did not have specific information regarding sugar added to tea or coffee, we were able to examine overall teaspoons of sugar added to food or beverages. The range of the correlation coefficients among all of the sweets was 0.09–0.41. The strongest correlation was observed between pure chocolate candy bars or packets of candy and other mixed candy bars, and the weakest association was found between sweet condiments and candy without chocolate. The range of the correlation coefficients among all of the beverages was 0.00–0.32. The strongest correlations were observed for items such as Coke/Pepsi/other colas with sugar and other carbonated beverages (correlation coefficient = 0.32) and low-calorie colas with other low-calorie carbonated beverages (correlation coefficient = 0.24).

The completed food frequency questionnaires were sent to the Harvard School of Public Health, Department of Nutrition for assessment of nutrient intake using their previously published methods [28]. Of interest to this

report, nutrients assessed included total calories, and three sugars—fructose, sucrose, and lactose. These were examined in quartiles based on control group cut-points.

Statistical methods

Odds ratios (OR) and 95% confidence intervals (CI) were computed using unconditional logistic regression to estimate the relative risk (hereafter called risk) of pancreatic cancer. No substantial difference in ORs was observed when we included or excluded study participants with extremely low (<500 kcal/day) or extremely high (>3,500 kcal/day) caloric intake, and these participants were retained in the final analyses. The linear trend test was performed using the Wald procedure. Potential confounding effects were investigated for total calories, sex, body-mass index (BMI), cigarette smoking, race, education, history of diabetes, physical activity, and other food groups. Total caloric intake was divided into quartiles based on the consumption among control participants by sex (cutpoints: men: ≤1,545; 1,546–1,925; 1,926–2,364; ≥2,365 kcal/day; women: ≤1,333; 1,334–1,695; 1,696–2,113; ≥2,114 kcal/day). BMI was categorized as <25 (normal), 25.0–29.9 (overweight), and ≥30 (obese) kg/m^2, based on the World Health Organization criteria. Smokers were defined as participants who had smoked >100 cigarettes in their lifetime, or a pipe or cigar for at least once a month for ≥6 months. Participants were classified as: never smokers; former cigarette smokers who quit smoking >15 years ago; former cigarette smokers who quit smoking 1–15 years ago; former smokers who quit within one year prior to diagnosis or to interview, and current cigarette smokers; and pipe and/or cigar smokers. Participants provided self-reported data on race (white, black or African American, Asian or Pacific Islander, or "other"); education (<high-school graduate, high-school graduate, 1–4 years college, and graduate work); history of diabetes (yes/no); and frequency of non-occupational physical activity (i.e., 30 min intervals performed ≤1/month, 2–4/month, 2–6/week, or 1+/day). We also considered intake of other food groups in quartiles based on previous publications from this population (i.e., red meat, white meat, dairy, vegetable and fruit, eggs, fish, whole grain, and refined grain) [11, 19, 20].

Stepwise logistic regression modeling (using p = 0.05) was used to determine the variables that provided the best-fit among the potentially confounding factors. By these criteria, only total energy appeared to confound the relationships between sweets and beverages and pancreatic cancer risk. For comparability with other studies and our previous publications, we first present a parsimonious model in the tables that was adjusted for the matching factors of age and sex, and for total energy intake. We then present a full multivariable model additionally adjusted for

the following putative confounding factors: BMI, smoking status, race, education, history of diabetes, physical activity, and other food groups. Adjustment for other food groups included mutual adjustment for all sweet and beverage risk factors of interest plus previously examined food groups [11, 19, 20] (e.g., total sweets were adjusted for all sweetened and unsweetened beverage intake, as well as consumption of red meat, white meat, vegetables and fruits, eggs, fish, dairy, whole grains, and refined grains). The results for men and women are presented combined and separately. Because there was little difference between the parsimonious model and the fully adjusted model, we present only the full model for the results stratified by sex. To further consider the effects of confounding or effect modification on these results, we examined total sweets and carbonated beverages (with or without sugar) in multivariable models within strata of BMI (normal, overweight, and obese), exercise (monthly vs. daily exercisers), diabetes (yes/no), and smoking history (current, former, never). We considered stratifying BMI further, however, limited numbers made this infeasible (e.g., BMI ≥ 35: n = 13 cases/31 controls; BMI ≥ 40: n = 3 cases/6 controls).

All statistical tests were two-sided and considered statistically significant when p < 0.05. Statistical analyses were conducted using SAS software 9.1 (SAS Institute, Inc., Cary, NC).

Results

Demographic and other factors in this large population-based case–control study are presented in Table 1. Cases and controls were similar with regards to race, BMI, and history of diabetes; and the majority of participants were non-Hispanic whites. Cases were more likely to have a recent smoking history than controls, whereas controls were slightly more educated than cases.

There was some evidence for positive associations between consumption of total and individual sweets and risk of pancreatic cancer among men (for comparisons of 1+ servings/day versus rarely or never, total sweets OR = 1.9, 95% CI: 1.0, 3.6; sweet condiments OR = 1.9, 95% CI: 1.2, 3.1; chocolate candy OR = 2.4, 95% CI: 1.1, 5.0; other mixed candy bars OR = 3.3, 95% CI: 1.5, 7.3) (Table 2). Among women, there was overall less support for any association with total or individual sweets, although there was a positive trend for sweet condiments (Table 2). Candy without chocolate was unassociated with risk of pancreatic cancer.

To further examine the impact of foods high in sugar, we examined sweetened beverages and the risk of pancreatic cancer (Table 3). Overall, total sweetened beverages, including sugar-based sodas, colas, and non-carbonated fruit
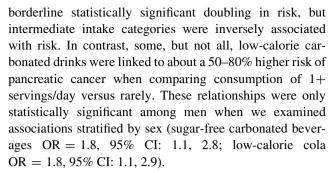
Table 1 Demographic characteristics of pancreatic cancer patients and control participants in a population-based case–control study in the San Francisco Bay Area, California

Characteristic	Cases (N = 532)		Controls (N = 1,701)	
	n	%	n	%
Age[a], years				
<50	46	9	164	10
50–59	120	22	438	25
60–69	172	33	473	28
70–79	158	39	498	30
80–85	36	7	128	8
Sex				
Men	291	55	883	52
Women	241	45	818	48
Race				
White	442	83	1,471	86
Black or African American	46	9	78	5
Asian or Pacific Islander	35	7	119	7
American Indian or Alaskan Native or other	9	2	33	2
Hispanic ethnicity				
Yes	25	5	114	7
No	507	95	1,585	93
Body mass index (WHO), kg/m^2				
Normal, <25.0	280	53	993	58
Overweight, 25.0–29.9	197	37	552	33
Obese, ≥30	52	10	147	9
Smoking				
Never	163	31	652	38
Cigarette				
Former, quit >15 years ago	133	25	508	30
Former, quit 1–15 years ago	89	17	260	15
Current or quit <1 year ago	131	25	208	12
Pipe/cigar	16	3	73	4
Education				
<High-school graduate	71	13	162	10
High-school graduate	164	31	372	22
1–4 years college	200	38	754	44
Graduate school	97	18	413	24
History of diabetes mellitus				
No	455	86	1,538	90
Yes	76	11	161	10

Numbers may not add to total number of participants due to missing values

[a] Age at pancreatic cancer diagnosis for cases or age at interview for controls

drinks were unassociated with risk of pancreatic cancer. Among women, the highest versus lowest intake of punch/lemonade/non-carbonated fruit drinks was associated with a borderline statistically significant doubling in risk, but intermediate intake categories were inversely associated with risk. In contrast, some, but not all, low-calorie carbonated drinks were linked to about a 50–80% higher risk of pancreatic cancer when comparing consumption of 1+ servings/day versus rarely. These relationships were only statistically significant among men when we examined associations stratified by sex (sugar-free carbonated beverages OR = 1.8, 95% CI: 1.1, 2.8; low-calorie cola OR = 1.8, 95% CI: 1.1, 2.9).

For further comparison, we examined other low- or non-caloric beverages and risk of pancreatic cancer. Coffee (with or without caffeine), herbal tea, and water were not associated with risk of pancreatic cancer among men, women, or both sexes combined. Non-herbal tea was not associated with risk among women, but there was a positive trend among men only (OR = 1.6, 95% CI 1.1, 2.2 for 1+ servings/day versus <1/month; p-value trend = 0.02). Teaspoons of sugar or artificial sweeteners added to foods or beverages was also unassociated with risk of pancreatic cancer (multivariate OR = 0.7, 95% CI: 0.5, 1.1 for ≥3 vs. 0 teaspoons of sugar per day; multivariate OR = 1.3, 95% CI 0.8-1.9 for ≥1 packet sweetener vs. none per day; adjusted for age sex, calories, BMI, race, education, smoking, diabetes, and exercise).

In order to further consider the effects of confounding or effect modification on these results, we examined total sweets and carbonated beverages in multivariable models within strata of BMI, exercise, diabetes, and smoking history (data not shown in tables). There was some suggestion that the positive association for total sweets was stronger or limited to those who were obese, infrequent exercisers, or current smokers; although, with the smaller numbers in the finer categories, results were not statistically significant. When comparing consumption of 1+ servings/day of total sweets versus none, the risks of pancreatic cancer across strata of BMI were: obese, OR = 3.2, 95% CI: 0.7, 15; overweight, OR = 1.1, 95% CI: 0.5, 2.4; and normal, OR = 1.2, 95% CI: 0.7, 2.1. Similarly, across categories of smoking, the odds ratios of pancreatic cancer for 1+ servings/day of total sweets versus none were: current smoker, OR = 1.8, 95% CI: 0.6, 5.4; former smoker, OR = 1.2, 95% CI: 0.5, 2.9; and never smoker, OR = 1.1, 95% CI: 0.6, 2.4. Lastly, for the same comparison by exercise the odds ratios were: infrequent exercise, OR = 2.0, 95% CI: 1.0, 4.0 for and daily exercisers, OR = 1.0, 95% CI: 0.3, 2.7. The previously observed elevated risk for sugar-free carbonated beverages also appeared to be limited to those who were obese (obese, OR = 2.6, 95% CI: 0.9, 7.7; overweight, OR = 1.5, 95% CI: 0.9, 2.6; and normal BMI, OR = 1.3, 95% CI: 0.8, 2.1), did not have diabetes (no diabetes, OR = 1.6, 95% CI: 1.1, 2.3; yes diabetes, OR = 0.9, 95%

Table 2 Odds ratios (OR) and 95% confidence intervals (CI) for pancreatic cancer and consumption of sweets in a population-based case–control study, San Francisco Bay Area, California

Sweets (1 serving)	Men + Women								Men		Women	
	Case n	%	Control n	%	OR[a]	95% CI[a]	OR[b]	95% CI[b]	OR[b]	95% CI[b]	OR[b]	95% CI[b]
Total sweets, servings/day												
0	54	10	183	11	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref
<1	316	60	1,156	68	0.8	0.6, 1.2	0.9	0.6, 1.3	1.2	0.7, 2.2	0.6	0.4, 1.1
≥1	156	30	362	21	1.2	0.8, 1.8	1.3	0.8, 1.9	1.9	1.0, 3.6	0.8	0.4, 1.4
Trend-p					0.3		0.1		0.01		0.5	
Sweet condiments (1 tablespoon)												
<1/month	106	20	428	25	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref
1–3/month	82	16	364	21	0.9	0.6, 1.2	0.9	0.6, 1.2	1.1	0.7, 1.7	0.8	0.5, 1.3
1–6/week	254	48	696	41	1.3	1.0, 1.7	1.5	1.1, 1.9	1.6	1.1, 2.4	1.5	1.0, 2.2
≥1/day	84	16	212	13	1.4	1.0, 2.0	1.6	1.1, 2.3	1.9	1.2, 3.1	1.5	0.9, 2.6
Trend-p					0.007		0.0004		0.002		0.02	
Pure chocolate candy bar or packet (1)												
<1/month	245	47	863	51	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref
1–3/month	131	25	439	26	1.0	0.8, 1.3	1.1	0.8, 1.4	1.3	0.9, 1.9	0.9	0.6, 1.2
1–6/week	122	23	355	21	1.1	0.8,1.4	1.1	0.9, 1.5	1.2	0.8, 1.7	1.0	0.7, 1.5
≥1/day	28	5	44	3	2.0	1.2, 3.2	2.0	1.2, 3.4	2.4	1.1, 5.0	1.7	0.8, 3.7
Trend-p					0.08		0.06		0.07		0.5	
Candy without chocolate (1 pack)												
<1/month	316	60	1,080	63	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref
1–3/month	93	18	298	18	1.0	0.8, 1.4	1.1	0.8, 1.4	1.1	0.8, 1.6	1.0	0.7, 1.6
1–6/week	90	17	250	15	1.2	0.9, 1.6	1.1	0.8, 1.5	1.3	0.9, 1.9	0.9	0.6, 1.5
≥1/day	27	5	73	4	1.1	0.7, 1.8	1.0	0.6, 1.6	1.5	0.8, 2.9	0.6	0.3, 1.3
Trend-p					0.2		0.5		0.09		0.3	
Other mixed candy bar (1)												
<1/month	276	52	1,041	61	1.0	Ref	1.0	Ref	1.0	Ref	1.0	Ref
1–3/month	119	23	382	22	1.1	0.9, 1.4	1.1	0.9, 1.4	1.4	1.0, 2.0	0.8	0.5, 1.2
1–6/week	109	21	253	15	1.4	1.1, 1.9	1.4	1.0, 1.8	1.5	1.1, 2.2	1.2	0.8, 1.9
≥1/day	22	4	25	1	2.7	1.5, 4.9	2.2	1.2, 4.1	3.3	1.5, 7.3	1.0	0.3, 3.4
Trend-p					0.0004		0.005		0.001		0.7	

[a] Adjusted for age, sex, and energy intake (kcal/day, men: quartiles, women: quartiles); ORs were not computed if cells had <5 observations

[b] Additionally adjusted for body mass index (<25.0, 25.0–29.9, ≥30 kg/m^2), race (white, black/African American, Asian/Pacific Islander, others), education (< high-school graduate, high-school graduate, college, graduate work), smoking (never smoker, former cigarette smoker who quit smoking >15 years ago, former cigarette smoker who quit smoking 1–15 years, current cigarette smoker or quit <1 year ago, pipe, and/or cigar smoker), history of diabetes (yes, no) and physical activity (30-min moderate exercise each time: <1 month, 1–4/month, 2–6/week, and daily); total sweets was additionally adjusted for quartiles of total red meat, white meat, vegetable and fruit, eggs, fish, dairy, whole grain, and refined grain, and sweetened beverages (0, <1, and ≥1 serving per day)

CI: 0.3, 2.6), or were current smokers (current, OR = 2.6, 95% CI: 1.1, 5.9; former, OR = 0.5, 95% CI: 0.2, 1.3; never, OR = 0.8, 95% CI: 0.4, 1.5).

We examined the risk of pancreatic cancer associated with intake of the sugars fructose, sucrose, and lactose (Table 4). Of these, only lactose was associated with an elevated risk of pancreatic cancer when comparing extreme quartiles. To address the possibility that this result for lactose (found in milk products) may have been confounded by fat intake, we further adjusted for total fat intake and results were similar (combined: OR = 2.0, 95%

CI: 1.5, 2.7, $p < 0.0001$; men: OR = 2.1, 95% CI: 1.3, 3.0, $p = 0.003$; women: OR = 1.7, 95% CI: 1.1, 2.7, $p = 0.03$, when comparing extreme quartiles, Table 4).

Discussion

These results provide limited evidence for our original hypothesis that sweets and sweetened beverages would be positively associated with risk of pancreatic cancer, although results varied by sex. Total sweets and specific

Table 3 Odds ratios (OR) and 95% confidence intervals (CI) for pancreatic cancer and daily servings of sweetened beverages in a population-based case–control study, San Francisco Bay Area, California

Sweetened beverages (1 serving = 1 can, glass, bottle, or cup)	Men + Women								Men		Women	
	Case n	%	Control n	%	OR[a]	95% CI[a]	OR[b]	95% CI[b]	OR[b]	95% CI[b]	OR[b]	95% CI[b]
All sweetened beverages/day												
0	111	21	348	21	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
<1	249	47	942	55	0.8	0.6, 1.0	0.7	0.6, 1.0	1.0	0.6, 1.5	0.6	0.4, 0.9
≥1	166	32	411	24	1.1	0.8, 1.5	1.0	0.7, 1.3	1.0	0.6, 1.7	1.0	0.6, 1.6
Trend-p					0.03		0.7		0.6		0.1	
Total carbonated beverages/day												
0	140	27	468	28	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
<1	242	46	894	53	0.9	0.7, 1.1	0.8	0.6, 1.0	1.0	0.7, 1.6	0.7	0.5, 1.0
≥1	144	27	339	20	1.3	1.0, 1.7	1.1	0.8, 1.5	1.2	0.8, 2.0	1.1	0.7, 1.7
Trend-p					0.02		0.6		0.9		0.2	
Total sugar-type carbonated beverages/day												
0	284	54	961	57	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
<1	190	36	610	36	1.0	0.8, 1.2	1.0	0.8, 1.2	1.1	0.8, 1.5	0.8	0.6, 1.2
≥1	52	10	130	8	1.1	0.8, 1.6	0.9	0.6, 1.3	0.9	0.5, 1.5	0.9	0.4, 1.8
Trend-p					0.3		0.4		0.3		0.9	
Total sugar-free carbonated beverages/day												
0	310	59	1,016	60	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
<1	124	24	487	29	0.8	0.7, 1.1	0.8	0.7, 1.1	1.2	0.8, 1.7	0.6	0.4, 1.0
≥1	92	17	198	12	1.5	1.2, 2.1	1.5	1.1, 2.1	1.8	1.1, 2.8	1.4	0.9, 2.3
Trend-p					0.04		0.2		0.4		0.3	
Coke, Pepsi, or other cola with sugar												
<1/month	347	66	1,175	69	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
1–3/month	55	11	179	11	1.0	0.7, 1.4	1.0	0.7, 1.4	1.2	0.8, 1.8	0.8	0.5, 1.4
1–6/week	86	16	247	15	1.1	0.8, 1.4	1.1	0.8, 1.5	1.1	0.8, 1.7	1.0	0.6, 1.7
≥1/day	38	7	100	6	1.1	0.7, 1.7	0.9	0.6, 1.4	0.9	0.5, 1.5	1.0	0.5, 2.1
Trend-p					0.6		0.99		0.9		0.9	
Caffeine-free coke, Pepsi, or other cola with sugar												
<1/month	497	94	1,598	94	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
1–3/month	13	2	55	3	0.8	0.4, 1.4	0.9	0.5, 1.6	0.9	0.4, 2.0	0.8	0.3, 2.4
1–6/week	15	3	37	2	1.1	0.6, 2.1	1.0	0.6, 2.0	1.4	0.7, 3.0	0.5	0.1, 1.9
≥1/day	1	0.2	10	0.6	0.3	0.04, 2.3	0.3	0.04, 2.7	0.4	0.05, 2.3	NA	NA
Trend-p					0.5		0.5		0.96		0.2	
Other carbonated beverage with sugar												
<1/month	364	69	1,229	72	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
1–3/month	67	13	200	12	1.1	0.8, 1.5	1.1	0.8, 1.5	1.2	0.8 1.8	0.8	0.5, 1.4
1–6/week	78	15	241	14	1.0	0.7, 1.3	1.0	0.7, 1.3	1.0	0.6, 1.4	1.1	0.7, 1.8
≥1/day	17	3	31	2	1.6	0.8, 2.9	1.2	0.6, 2.2	1.4	0.6, 3.1	0.7	0.2, 2.3
Trend-p					0.5		0.8		0.7		0.8	
Low calorie cola												
<1/month	381	72	1,272	75	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
1–3/month	34	6	122	7	1.0	0.6, 1.4	1.0	0.7, 1.5	1.0	0.6, 1.8	1.0	0.5, 1.9
1–6/week	54	10	197	12	0.9	0.7, 1.3	0.9	0.7, 1.3	1.1	0.7, 1.7	0.8	0.4, 1.4
≥1/day	57	11	110	6	1.8	1.2, 2.5	1.7	1.2, 2.4	1.8	1.1, 2.9	1.6	0.9, 2.8
Trend-p					0.04		0.06		0.06		0.4	

Table 3 continued

Sweetened beverages (1 serving = 1 can, glass, bottle, or cup)	Men + Women								Men		Women	
	Case n	%	Control n	%	OR[a]	95% CI[a]	OR[b]	95% CI[b]	OR[b]	95% CI[b]	OR[b]	95% CI[b]
Low calorie caffeine-free cola												
<1/month	437	83	1,394	82	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
1–3/month	24	5	83	5	1.0	0.6, 1.6	1.0	0.6, 1.6	1.1	0.5, 2.2	0.9	0.5, 1.8
1–6/week	43	8	171	10	0.8	0.6, 1.1	0.8	0.5, 1.1	0.9	0.5, 1.4	0.7	0.4, 1.3
≥1/day	22	4	51	3	1.4	0.8, 2.4	1.1	0.7, 2.0	1.1	0.5, 2.5	1.3	0.6, 2.7
Trend-p					0.96		0.6		0.9		0.7	
Other low calorie carbonated beverage												
<1/month	418	79	1,366	80	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
1–3/month	40	8	128	8	1.0	0.7, 1.5	1.0	0.7, 1.5	1.5	0.9, 2.5	0.7	0.4, 1.3
1–6/week	47	9	167	10	0.9	0.6, 1.2	0.9	0.6, 1.2	1.0	0.6, 1.6	0.6	0.4, 1.2
≥1/day	21	4	39	2	1.6	0.9, 2.8	1.4	0.8, 2.5	1.8	0.8, 3.8	1.2	0.4, 3.2
Trend-p					0.6		0.97		0.2		0.2	
Hawaii punch, lemonade, or other non-carbonated fruit drinks												
<1/month	359	68	1,075	63	1.0	Ref.	1.0	Ref.	1.0	Ref.	1.0	Ref.
1–3/month	71	14	286	17	0.7	0.5, 1.0	0.7	0.5, 1.0	0.7	0.5, 1.1	0.7	0.5, 1.2
1–6/week	75	14	292	17	0.7	0.5, 0.9	0.7	0.5, 0.9	0.8	0.5, 1.2	0.5	0.3, 0.9
≥1/day	21	4	48	3	1.1	0.6, 1.9	1.0	0.6, 1.8	0.4	0.2, 1.1	2.0	1.0, 4.2
Trend-p					0.03		0.03		0.06		0.4	

[a] Adjusted for age, sex, and energy intake (kcal/day, men: quartiles, women: quartiles)

[b] Additionally adjusted for body mass index (<25.0, 25.0–29.9, ≥30 kg/m^2), race (white, black/African American, Asian/Pacific Islander, others), education (<high-school graduate, high-school graduate, 1–4 years college, graduate school), smoking (never smoker, former cigarette smoker who had quit smoking >15 years previously, former cigarette smoker who had quit smoking 1–15 years previously, current cigarette smoker or former cigarette smoker who had quit smoking <1 year previously, pipe and/or cigar smoker), history of diabetes (yes, no), and physical activity (30-min moderate exercise each time: <1 month, 1–4/month, 2–6/week, and daily); Additionally, all sweetened beverages, sugar-type carbonated beverages, and sugar-free carbonated beverages were adjusted for quartiles of red meat, white meat, vegetable and fruit, eggs, fish, dairy, whole grain, and refined grain, and sweets (0, <1, and ≥1 serving per day), and were mutually adjusted for each other

forms of candy were linked to greater risk of pancreatic cancer among men, but inconsistently, or not related, among women. The individual sweets that were positively associated with pancreatic cancer risk included sweet condiments, pure chocolate, and other mixed candy bars, but not candy without chocolate. It is possible that saturated fat intake may underlie several of these associations, as we previously reported an increased risk of pancreatic cancer for greater intake of total and saturated fat in this population [20], and pure or mixed chocolate bars are high in fat content. Furthermore, sweet condiments may often be eaten on bread with butter, the latter of which was also strongly positively associated with risk in our prior report [20]. Furthermore, beverages with added sugar and teaspoons of sugar added to food were not linked to greater risk, whereas some sugar-free sodas and low-calorie colas were moderately positively related to risk among men. Consistent with our hypotheses, other non- or low-calorie beverages such as water, tea, or coffee were unassociated with risk.

The positive association for sweets and pancreatic cancer risk among men but not women and the positive association for low-calorie, but not sugar-sweetened, soft drinks are somewhat inconsistent with prior reports, although the literature is limited on this topic. Previous cohort studies have reported associations for sweets and pancreatic cancer risk among men and women combined, or just among women. In the Swedish Mammography Cohort, intake of sugar, soft drinks, and sweetened fruit soups/stew were positively associated with 50–90% increased risk among women [29]. In the Nurses Health Study and Health Professionals Follow-up Study, soft drinks were modestly positively associated with pancreatic cancer risk among women, but not men [30]. In this two-cohort analysis, non-cola diet soft drinks were also associated with a 50% increase in risk of pancreatic cancer; although confidence estimates included the null [30]. In a distinct large cohort of men and women, fruit and fruit juice intake, but not soda, was positively associated with risk [31]. However, the authors commented that this likely

Table 4 Odds ratios (OR) and 95% confidence intervals (CI) for pancreatic cancer and intake of fructose, sucrose, lactose in a population-based case–control study, San Francisco Bay Area, California

Quartiles	Men + Women								Men		Women	
	Case n	%	Control n	%	OR[a]	95% CI[a]	OR[b]	95% CI[b]	OR[b]	95% CI[b]	OR[b]	95% CI[b]
Fructose, gm/day												
Quartile 1	160	30	426	25	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Quartile 2	129	25	424	25	0.8	0.6–1.1	0.9	0.7–1.2	1.0	0.7–1.4	0.8	0.5–1.2
Quartile 3	124	24	425	25	0.8	0.6–1.0	0.9	0.7–1.2	0.8	0.6–1.2	0.9	0.6–1.4
Quartile 4	112	21	426	25	0.7	0.5–0.9	0.8	0.6–1.1	0.8	0.5–1.1	0.9	0.6–1.3
Trend-p					0.01		0.2		0.05		0.9	
Sucrose, gm/day												
Quartile 1	141	27	425	25	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Quartile 2	125	24	425	25	0.9	0.7–1.2	1.0	0.8–1.4	1.1	0.8–1.7	0.9	0.6–1.5
Quartile 3	121	23	425	25	0.9	0.7–1.2	1.0	0.7–1.3	1.0	0.7–1.5	1.2	0.8–1.8
Quartile 4	138	26	426	25	1.0	0.8–1.3	1.0	0.8–1.4	1.0	0.7–1.5	1.1	0.7–1.7
Trend-p					1.0		0.9		1.0		0.6	
Lactose[c], gm/day												
Quartile 1	94	18	425	25	1.0	Referent	1.0	Referent	1.0	Referent	1.0	Referent
Quartile 2	136	26	425	25	1.5	1.1–2.0	1.5	1.1–2.0	1.6	1.1–2.7	1.2	0.7–1.9
Quartile 3	131	25	425	25	1.4	1.1–1.9	1.6	1.2–2.1	1.8	1.2–2.8	2.0	1.3–3.1
Quartile 4	164	31	425	25	1.8	1.3–2.4	2.0	1.5–2.7	2.1	1.3–3.0	1.7	1.1–2.7
Trend-p					0.0003		<0.0001		0.003		0.03	

[a] Used energy residual model; adjusted for age, sex, and energy intake (kcal/day, men: quartiles, women: quartiles)

[b] Additionally adjusted for body mass index (<25.0, 25.0–29.9, ≥30 kg/m^2), race (white, black/African American, Asian/Pacific Islander, others), education (<high-school graduate, high-school graduate, 1–4 years college, graduate school), smoking (never smoker, former cigarette smoker who had quit smoking >15 years previously, former cigarette smoker who had quit smoking 1–15 years previously, current cigarette smoker or former cigarette smoker who had quit smoking <1 year previously, pipe and/or cigar smoker), history of diabetes (yes, no), and physical activity (30-min moderate exercise each time: <1 month, 1–4/month, 2–6/week, and daily)

[c] Additionally adjusted for total fat consumption by quartiles

reflected an overall positive association for fructose/sugars that were strongly correlated with fruits and juices, and that there may have been measurement error in the assessment of sodas. In contrast, the large prospective National Institutes of Health (NIH)–AARP Diet and Health Study reported no association for high intake of total added sugar, sugar-sweetened foods and beverages, or diet soft drinks and pancreatic cancer [32].

The trend toward stronger associations for sweets being more common among those who were obese or exercised infrequently is consistent with results from the Nurses Health Study, where positive associations for sweetened soft-drink intake [30] and fructose [33] and pancreatic cancer risk were stronger among women with a high BMI or who exercised less. Similarly, in the NIH–AARP cohort, there were suggestive (but not always statistically significant) positive trends for total added sugar and pancreatic cancer risk only among those who were obese or less frequent exercisers [32].

Data from case–control studies are also limited, but one previous case–control study reported a non-statistically

significant 50% increased risk for sweet foods [34], while another observed a statistically significant 80% elevation in risk associated with dessert intake among women and no association among men [35]. In contrast to our results, an early case–control study that examined a wide range of individual dietary factors reported an inverse association for consumption of diet soda and risk of pancreatic cancer [36]. It is possible that comparison of these early results with our study is inappropriate given the dramatic changes in diet soda consumption patterns over the last several decades.

Another way to examine the impact of sweets on pancreatic cancer risk has been to examine intake of different sugars. Similar to our study, four case–control studies and one cohort have reported no association for simple sugars [35, 37] or sucrose consumption [37–40]; although two of these reported statistically significant doubling to tripling of risk for added or refined sugar intake [38, 40]. Polysaccharides but not mono- or disaccharides were related to a 2.6-fold increase in risk in a case–control study [34]. In contrast to our findings, in the large Hawaii-Los Angeles

Multiethnic Cohort, risk increased with greater intake of total sugars, fructose, and sucrose, and was statistically significant for fructose (relative risk = 1.4; 95% CI: 1.0, 1.8; for highest vs. lowest quartiles) [31]. In the Nurses Health Study, fructose was positively associated with pancreatic cancer risk among overweight women with low physical activity levels (fructose relative risk = 3.2, 95% CI: 1.1, 8.9 when comparing extreme quartiles).

Lactose is a sugar naturally occurring in milk and milk products, and there are very limited prior reports on lactose and pancreatic cancer. Baghurst et al. observed no association for lactose and risk of pancreatic cancer in an earlier case–control study [38]. Milk and dairy intake have not been consistently associated with pancreatic cancer [41], with most studies reporting null associations [34, 35, 40–47], and only a few observing positive [20, 48] or inverse associations [49]. In a study of cases only, Morales et al. reported that daily versus non-daily intake of dairy products, but not other food groups, was associated with a five-fold greater occurrence of K-Ras mutated pancreatic tumors, and K-ras mutations are considered to be an early event in pancreatic carcinogenesis [50]. We observed a positive association for lactose and pancreatic cancer risk, independent of total energy and fat; consistent with and expanding on the previously reported positive association for dairy products and pancreatic cancer risk in this population [20],

The observed null results for coffee and pancreatic cancer risk were consistent with several previous studies [36, 42, 48, 49, 51–54]. The slightly elevated risk for non-herbal tea among men in our study may be due to chance, and was contrary to several other null reports [36, 42, 53]. We did not directly examine sweetened tea or coffee; however, teaspoons of added sugar to foods or beverages and artificial sweeteners were unassociated with risk.

Simple carbohydrates (e.g., sugars) raise blood glucose levels more than starches and other macronutrients [55, 56]. Chronic high intake of sweets may increase pancreatic cancer risk by affecting glucose metabolism and predisposing to hyperglycemia, insulin insensitivity, and hyperinsulinemia. Glycemic load and index are measures of the body's glucose-response (or insulin demand) to carbohydrate intake. Six cohort studies examining estimated glycemic load or index from self-reported questionnaires and pancreatic cancer risk observed no associations [31, 37, 57–59], while the Nurses Health Study reported that glycemic load was strongly related to risk among overweight or sedentary women [33].

In contrast, prospective studies have linked higher circulating fasting glucose [4–7] and insulin levels [4] to future risk of pancreatic cancer many years later. The Chicago Heart Association Detection Project, with an average of 25 years of follow-up examined fasting glucose and pancreatic cancer mortality. Their results for fasting glucose and risk of pancreatic cancer were similar even when they excluded cases that occurred within the first five years of follow-up [5]. In the Alpha Tocopherol Beta-Carotene Cancer Prevention trial, associations for fasting glucose and pancreatic cancer were stronger when limited only to those participants with more than 10 years of follow-up [4]. Taken together, these studies support a positive dose-dependent relationship between hyperglycemia and pancreatic cancer incidence or mortality. The lack of consistent association between sweet foods or sweetened beverages and pancreatic cancer risk in this study may in part be due to the variable effects of sugar intake on glucose metabolism, depending on sugar type, fiber, protein, fat and starch composition, temperature, cooking, and processing of the food [55].

We cannot exclude the possibility of chance to explain some of our results. The elevated risk observed in the current study for total and specific sweets, in particular among those who exercised less, had a high BMI, or smoked, provides some support for the hypothesis that sweets intake plus lifestyle factors combined may predispose to impaired glucose tolerance that can subsequently influence pancreatic cancer risk. Impaired glucose tolerance is positively correlated with high glucose intake, obesity, sedentary habits, and smoking [33, 60–62]. The elevated risks associated with diet soda intake, in particular among men, those who were obese, did not have diabetes, or who were smokers, could possibly be due to residual confounding by other unmeasured diet and lifestyle factors.

This study had several possible limitations that must be considered. Recall bias may have affected the results, although, when this study was conducted little was known about dietary risk factors for pancreatic cancer. Non-differential measurement error in assessment of the dietary exposures could have led to a bias toward the null, although prior publications from this population reported positive associations for specific meats and fats, and inverse associations for fruit and vegetable intake, consistent with other cohort and case–control studies [11, 20, 41]. We were unable to examine the effects of glycemic load or index or pre-diagnostic circulating glucose on risk of pancreatic cancer in this study. There was a 67% response rate among eligible cases and controls. It is possible that eligible control subjects who chose to participate were those who tended to be more health conscious and thus different than the population that gave rise to the cases. There is also the possibility of survivor bias, whereby those cases who did not survive long enough to be interviewed may have differed meaningfully in their diets compared to those who were included.

Strengths of this study include the population-based design, large sample size, detailed validated dietary questionnaire completed using only direct in-person interviews, and no proxy interviews. We interviewed participants about dietary practices one year before their cancer diagnosis or interview for controls to avoid recent assessment of dietary

changes due to pancreatic cancer. The refusal rate was low at 8%, and the primary reason we lost patients was the rapid mortality rate. In conclusion, these data provide limited evidence for our original hypotheses that sweets, sugars, and sweetened beverages increase the risk of pancreatic cancer. The stronger associations stratified by sex, BMI, exercise, diabetes status, and smoking were intriguing and warrant further research.

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