

Sugar-Sweetened Soft Drink Consumption and Risk of Pancreatic Cancer in Two Prospective Cohorts

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Abstract

Background: A history of diabetes mellitus and a diet high in glycemic load are both potential risk factors for pancreatic cancer. Sugar-sweetened soft drinks are a prevalent source of readily absorbable sugars and have been associated with an increased risk of obesity and diabetes. We investigated whether higher consumption of sugar-sweetened soft drinks increases the risk of pancreatic cancer.

Methods: We examined the relation between consumption of sugar-sweetened soft drinks and the development of pancreatic cancer in the Nurses' Health Study and the Health Professionals Follow-up Study. Among 88,794 women and 49,364 men without cancer at baseline, we documented 379 cases of pancreatic cancer during up to 20 years of follow-up. Soft drink consumption was first assessed at baseline (1980 for the women, 1986 for the men) and updated periodically thereafter.

Results: Compared with participants who largely abstained from sugar-sweetened soft drinks, those who consumed more than three sugar-sweetened soft drinks weekly exper-

rienced overall a multivariate relative risk (RR) of pancreatic cancer of 1.13 [95% confidence interval (95% CI), 0.81-1.58; *P* for trend = 0.47]. Women in the highest category of sugar-sweetened soft drink intake did experience a significant increase in risk (RR, 1.57; 95% CI, 1.02-2.41; *P* for trend = 0.05), whereas there was no association between sweetened soft drink intake and pancreatic cancer among men. Among women, the risk associated with higher sugar-sweetened soft drink was limited to those with elevated body mass index (>25 kg/m²; RR, 1.89; 95% CI, 0.96-3.72) or with low physical activity (RR, 2.02; 95% CI, 1.06-3.85). In contrast, consumption of diet soft drinks was not associated with an elevated pancreatic cancer risk in either cohort.

Conclusion: Although soft drink consumption did not influence pancreatic cancer risk among men, consumption of sugar-sweetened soft drinks may be associated with a modest but significant increase in risk among women who have an underlying degree of insulin resistance. (Cancer Epidemiol Biomarkers Prev 2005;14(9):2098-105)

Introduction

Pancreatic cancer, the fourth leading cause of cancer-related mortality in the United States (1), is a rapidly fatal malignancy with little effective treatment. Patients with diabetes mellitus are at higher risk (2), and a positive association between postload plasma glucose concentration and pancreatic cancer risk was found in two studies, supporting the hypothesis that impaired glucose intolerance, insulin resistance, and hyperinsulinemia play a role in pancreatic cancer etiology (3, 4). Moreover, a diet high in glycemic load has been associated with an increase in the risk of both diabetes mellitus (5) and pancreatic cancer (6).

Sugar-sweetened soft drinks may increase the risk of diabetes due to their large amounts of high-fructose corn syrup, rapidly raising blood glucose (7). Soft drinks are the leading source of added sugar in the U.S. diet, thereby

contributing to a high glycemic index of the diet and promoting the development of obesity and diabetes (8). In a recent analysis of participants in the Nurses' Health Study (NHS), higher consumption of sugar-sweetened beverages was associated with both greater weight gain and an increased risk of type 2 diabetes, independent of known risk factors (9). Sugar-sweetened soft drinks might also increase risk of type 2 diabetes due to their readily absorbable carbohydrates (9). Due to the large amounts of high-fructose corn syrup, which has similar effects on blood glucose as sucrose (7), consumption of sugar-sweetened soft drinks might therefore contribute to a high glycemic load of the overall diet, a risk factor for pancreatic cancer (6). In addition, cola-type soft drinks contain caramel coloring, which is rich in advanced glycation end-products that might increase insulin resistance (10).

We hypothesized that a higher consumption of sugar-sweetened soft drinks may increase pancreatic cancer risk. We therefore prospectively examined the relation between soft drink consumption and pancreatic cancer in two large cohorts with up to 20 years of follow-up and detailed and repeated assessments of soft drink consumption and other dietary factors.

Materials and Methods

Study Cohorts. In 1976, the NHS enrolled 121,700 female registered nurses ages 30 to 55 years to gather, through mailed questionnaires, information on their health status, medical history, and known and suspected risk factors for cancer and coronary heart disease. The Health Professionals Follow-up Study (HPFS) began in 1986, when 51,529 American male

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dentists, optometrists, osteopaths, pharmacists, podiatrists, and veterinarians ages 40 to 75 years completed a mailed questionnaire on known or suspected risk factors for cancer and coronary heart disease, which also included an assessment of diet. Follow-up questionnaires were sent biennially to cohort participants thereafter. Further details of the cohorts are reported elsewhere (11-14).

Ascertainment of Soft Drink Consumption. In the NHS, a 61-item food frequency questionnaire (FFQ) was mailed to all participants in the study in 1980 that ascertained how often women consumed a commonly used unit or portion size of each food on average over the previous year, including three items on soft drink consumption: "Coca-Cola, Pepsi, other cola," "low-calorie carbonated drink," and "other carbonated beverage (root beer, ginger ale, 7-Up, etc.)." In 1984, a more comprehensive FFQ (116-item) was mailed to the NHS cohort that ascertained five items of soft drink consumption ("low-calorie cola," "low-calorie caffeine-free cola," "other low-calorie carbonated beverage," "Coke, Pepsi, or other cola with sugar," "caffeine-free Coke, Pepsi, or other cola," and "other carbonated beverage with sugar"). Similar questions were posed in 1990, 1994, and 1998 in the NHS. Of note, on the 1986 NHS FFQ, we also queried women about consumption of either "low-calorie soda" or "soda with sugar."

In 1986, the baseline questionnaire for the HPFS cohort included a 131-item semiquantitative FFQ. The same five items of soft drink consumption as in the NHS were assessed, with an update in 1990, 1994, and 1998.

Smoking History and Other Risk Factors. Smoking status and history of smoking were obtained at baseline and in all subsequent questionnaires in both cohorts. Current smokers also reported intensity of smoking (average number of cigarettes smoked daily) on each questionnaire. Past smokers reported when they last smoked, and time since quitting was calculated for those who quit during follow-up. Participants were asked about history of diabetes at baseline and in all subsequent questionnaires. We used baseline body mass index (BMI; 1976 in NHS and 1986 in HPFS, the start of the cohorts), which was most predictive for pancreatic cancer risk in the NHS cohort (15). We derived a score for physical activity as metabolic equivalent tasks (MET) per week (the caloric need per kilogram body weight per hour activity divided by the caloric need per kilogram per hour at rest) based on questions from the 1986 questionnaires for both cohorts. For NHS, we also used the responses on the 1980 questionnaire ("At least once a week, do you engage in any regular activity similar to brisk walking, jogging, bicycling, etc., long enough to break a sweat?" "If yes, how many times per week?" and "What activity is this?") to classify participants into five physical activity categories. The physical activity variable from the 1980 questionnaire has been shown to predict the risk of non-insulin-dependent diabetes mellitus in this cohort (16). The validity of the MET-hours per week has been reported previously for the HPFS (17).

Ascertainment of Pancreatic Cancer and Deaths. We ascertained pancreatic cancers reported on the biennial questionnaires between the return of the 1980 (women) or 1986 (men) questionnaire, respectively, and June 1, 2000 (women) or February 1, 2000 (men). With permission from study participants, pancreatic cancer was confirmed through physicians' review of medical records. If permission was denied, we attempted to confirm the self-reported cancer with an additional letter or telephone call. We also searched the National Death Index to identify deaths among the non-respondents to each 2-year questionnaire. The computerized National Death Index is a highly sensitive method for identifying deaths in these cohorts with a sensitivity of at least 98% (18, 19). If the primary cause of death on the death

certificate was a previously unreported pancreatic cancer case, we contacted a family member to obtain permission to retrieve medical records to confirm the diagnosis. In the HPFS cohort, we obtained pathology reports confirming the diagnosis of pancreatic cancer for 95% of cases (85% in the NHS). For the remaining 5% (15% in the NHS), we confirmed the self-reported cancer from a secondary source (e.g., death certificate, physician, or telephone interview of a family member). All medical records, in both cohorts, had complete information on histology (hospitals are recontacted if the original information sent is incomplete). In our analyses, associations were examined including and excluding cases with missing medical records. No differences were observed between these two types of analyses; thus, we included cases without medical records.

Statistical Analysis. We excluded participants who did not answer the baseline questionnaire or did not provide a complete dietary questionnaire in 1980 (women) or 1986 (men) if a significant number of items was left blank on the FFQ (>9 items of the 61-question FFQ in 1980 for the women and ≥ 70 items on the 131-item FFQ in 1986 for the men), if the reported dietary intake had an implausible total energy intake (<500 or >3,500 kcal/d for women and <800 or >4,200 kcal/d for men), or if they had a history of cancer (except non-melanoma skin cancer) at baseline. We computed person-years of follow-up from the date of return of the baseline questionnaire to the date of diagnosis of pancreatic cancer, death from any cause, or the end of the study period [June 1, 2000 (women) or February 1, 2000 (men)], whichever occurred first. After these exclusions, 88,794 women and 49,364 men were eligible for follow-up, and 2,240,548 person years were accrued. We conducted analyses for both cohorts separately and then combined analyses, pooling data from the NHS and HPFS with additional adjustment for gender. The primary analysis used incidence rates with person-years of follow-up in the denominator. We used relative risk (RR) as the measure of association; RR was defined as the incidence rate of pancreatic cancer among participants who reported consumption of sugar-sweetened soft drinks divided by the incidence rate among participants without such a report. In our main analyses, we examined RRs according to cumulatively updated consumption of sugar-sweetened soft drinks. Nutrient intakes were computed by multiplying the frequency response by the nutrient content of the specified portion size. Values for nutrients were derived from the U.S. Department of Agriculture sources (20) and supplemented with information from manufacturers. The nine possible responses for soda consumption, ranging from "almost never" to six or more times daily, were aggregated into three categories (less than once monthly, 1-12 times monthly, and >3 times weekly). We further aggregated cola-type soft drinks into "regular cola" ("Coke, Pepsi, or other cola with sugar" and "caffeine-free Coke, Pepsi, or other cola with sugar") and "diet cola" ("low-calorie cola with caffeine" and "low-calorie caffeine-free cola"). Because we had repeated measurements of cola and other soft drink consumption, we used cumulative averaging as a more powerful test of an association of cumulative exposure. Cumulative average measures are the average of all measures for an individual up to the start of each follow-up interval. For overall soft drink consumption, categories were based on a combination of the continuous variables for both cola and other sugar-sweetened soft drinks, which subsequently we cumulatively averaged. The validity and reliability of FFQs similar to those used in the NHS and HPFS have been described elsewhere (21, 22). Briefly, the corrected correlation coefficients between questionnaire and multiple dietary records were 0.84 for cola-type soft drinks (sugar-sweetened and diet combined) and 0.36 for other carbonated soft drinks in the NHS (21). Because the group of "non-cola carbonated beverages"

included diet beverages as well, a correlation coefficient for overall sugar-sweetened soft drink consumption was not derived. In the HPFS, they were 0.84 for sugar-sweetened cola, 0.55 for other sugar-sweetened soft drinks, 0.73 for diet cola, and 0.74 for other diet soft drinks (23).

RRs adjusted for potential confounders were estimated by using Cox proportional hazards models stratified on age in years. The assumptions of proportionality were satisfied. In these models, we controlled for smoking, BMI, total energy intake, physical activity, and history of diabetes and other soft drink consumption (all diet soft drinks in models for all sugar-sweetened soft drinks; all sugar-sweetened soft drinks in models for all diet soft drinks; sugar-sweetened cola, other sugar-sweetened soft drinks, diet cola, other diet soft drinks for single food items). Soft drink intake was cumulatively updated (i.e., the cumulative average of soft drink consumption from all available dietary questionnaires up to the start of each 2-year follow-up cycle) with successive dietary questionnaires in these cohorts. Smoking and history of diabetes were updated every other year with data from the follow-up questionnaires. BMI was not updated in the main analyses because pancreatic cancer is frequently associated with profound weight loss, and our previous findings in these cohorts showed the strongest associations between baseline BMI and pancreatic cancer risk. Previous studies have observed an increased risk of pancreatic cancer among diabetics (2). Participants in our study who developed diabetes during long-term follow-up may have substantially diminished sweetened soft drink consumption as a consequence of the diagnosis of diabetes; we therefore stopped updating soft drink consumption once a participant reported a history of diabetes mellitus. In addition, in secondary analyses, we repeated our analyses after excluding participants who reported diabetes at baseline and similarly stopped updating soft drink consumption when a participant reported the new onset of diabetes mellitus after study initiation. We also conducted stratified analyses to determine whether the influence of soda consumption was modified by baseline BMI or physical activity. Because physical activity was assessed relatively crudely in the NHS in 1980, we used 1986 physical activity for both cohorts in these stratified analyses. Tests for trends across categories of exposure, based on the midpoints of the original exposure categories, were calculated using Cox proportional hazards models. The presence of an interaction between soft drink consumption and gender was tested using the likelihood ratio test (LRT) and comparing the model with both the main effects and the interaction terms to that with the main effects only.

All *P*s are two-sided ($\alpha = 0.05$). The study was approved by the Human Research Committees at the Harvard School of Public Health and the Brigham and Women's Hospital.

Results

During up to 20 years and 2,240,547 person-years of follow-up, 205 women and 174 men were diagnosed with pancreatic cancer. Baseline characteristics of the 88,794 women and 49,364 men who completed the baseline dietary questionnaire in 1980 and 1986, respectively, are shown in Table 1. At baseline, 19% of the women and 18% of the men reported consumption of sugar-sweetened soft drinks more than three times weekly; 10% of women and 7.6% of men reported consuming sugar-sweetened soft drinks at least once daily. Participants who reported higher consumption of sugar-sweetened soft drinks were generally similar to participants who report no soft drink consumption. However, they tended to be younger and women who reported higher sweetened soft drink intake were less likely to have a history of diabetes mellitus at baseline. Consumption of carbohydrates and fats was highest among

participants who reported frequent sugar-sweetened soft drink consumption. In contrast, participants who reported higher consumption of diet soft drinks tended to be much heavier, had a higher prevalence of diabetes mellitus at baseline, and reported lower consumption of carbohydrates and fats when compared with participants who did not consume diet soft drinks.

Among women and men combined, higher sugar-sweetened soft drink consumption (>3 servings weekly) was not significantly associated with the risk of pancreatic cancer (Table 2). Compared with participants who consumed less than one sugar-sweetened soft drink monthly, those who consumed (cumulatively updated) sugar-sweetened soft drinks more than three times weekly experienced an age-adjusted RR of 1.18 [95% confidence interval (95% CI), 0.86-1.64]. This association remained essentially unchanged after adjustment for life-style variables, including smoking, a history of diabetes mellitus, physical activity, total calorie intake, diet soft drink intake, and BMI. The multivariate RR for each increase in one serving daily was 1.05 (95% CI, 0.89-1.24). Nonetheless, the influence of soft drink use did seem to differ according to gender (LRT; $P = 0.04$). Whereas sugar-sweetened soft drink use was not associated with risk among men, women in the highest category of sugar-sweetened soft drink intake experienced a significant elevation in risk (RR, 1.57; 95% CI, 1.02-2.41; P for trend = 0.05). Among men, the multivariate RR for each increase in one serving daily was 0.90 (95% CI, 0.69-1.16), whereas it was 1.19 (95% CI, 0.97-1.47) among the women.

In a prior analysis of the NHS, we observed a positive association between glycemic load and pancreatic cancer risk, although neither sucrose nor total carbohydrate intake was associated with risk. We considered the possibility that any relation between sugar-sweetened soft drink intake and pancreatic cancer could reflect confounding by dietary glycemic load. We therefore repeated our analysis after adding glycemic load to the multivariate model and observed modest increases in the RRs. Compared with participants who largely abstained from sugar-sweetened soft drink use, the RR for those who reported consumption more than three times weekly was 1.17 (95% CI, 0.84-1.64) among both cohorts, 0.75 (95% CI, 0.44-1.27) among the men, and 1.53 (95% CI, 0.99-2.38) among the women. We also repeated our analysis after adding glycemic index and free fructose to the multivariate model and observed no material alterations in RRs (data not shown).

Previous studies have reported an inverse relation between coffee and caffeine intake and the risk of diabetes mellitus, including an analysis of our two cohorts (24). Moreover, a previous analysis of these cohorts observed a nonsignificant inverse relation between coffee and caffeine and pancreatic cancer risk (25). We therefore repeated our analyses after adding caffeine consumption to our models, but the addition of this variable did not substantially change our estimates. Compared with participants who largely abstained from sugar-sweetened soft drink use, the RR for those who reported consumption more than three times weekly was 1.16 (95% CI, 0.83-1.61) among both cohorts, 0.75 (95% CI, 0.44-1.27) among the men, and 1.62 (95% CI, 1.05-2.49) among the women.

Previous studies have observed an increased risk of pancreatic cancer among diabetics. Participants in our study who developed diabetes during the long-term follow-up may have substantially diminished sweetened soft drink consumption. Although we have adjusted previously for a history of diabetes and stopped updating exposure for those who subsequently developed diabetes during follow-up, we repeated our analysis after excluding participants with a history of diabetes mellitus at baseline. Among the women, our findings became slightly stronger after the exclusion of diabetics from the analyses. Compared with participants who

Table 1. Age and age-standardized baseline (1980 for NHS, 1986 for HPFS) characteristics according to frequency of sugar-sweetened and diet soft drink consumption among 88,794 women from the NHS and 49,364 men from the HPFS

Population	Frequency of sugar-sweetened soft drink consumption			Frequency of diet soft drink consumption		
	<1/mo	1-12/mo	>3/wk	<1/mo	1-12/mo	>3/wk
Women						
<i>n</i>	40,458	31,701	16,635	44,745	23,691	20,358
Drinks/category (median)	0	5/mo	1.3/d	0	7/mo	1.6/d
Age [mean (SD)], y	47.8 (7.0)	46.3 (7.2)	44.8 (7.1)	46.9 (7.2)	46.9 (7.1)	46.0 (7.1)
Baseline BMI \geq 29 kg/m ² (%)	11.2	10.3	13.6	7.7	12.6	17.5
Vigorous physical activity [mean (SD)], h/wk	2.8 (3.1)	2.8 (3.3)	2.9 (3.2)	2.9 (3.3)	2.7 (3.2)	2.7 (3.0)
Height [mean (SD)],	64.4 (3.2)	64.4 (3.4)	64.4 (3.2)	64.4 (3.2)	64.4 (3.2)	64.5 (3.3)
Currently smoking (%)	29	26	33	33	24	27
Smoking [mean (SD)], pack-years	5.4 (8.3)	4.5 (7.6)	5.6 (8.4)	5.7 (8.5)	4.1 (7.2)	5.1 (8.0)
History of diabetes (%)	3.3	1.3	1.6	1.2	2.6	4.6
Regular aspirin use* (%)	59	57	53	59	56	53
Total carbohydrates (g)	137 (56)	153 (56)	187 (65)	159 (62)	147 (57)	144 (61)
Total sucrose (g)	30 (19)	36 (20)	42 (22)	36 (21)	33 (19)	31 (20)
Free fructose (g)	20 (13)	23 (12)	44 (23)	27 (18)	25 (15)	25 (18)
Glycemic index	50 (4.7)	52 (3.7)	55 (3.2)	52 (4.2)	51 (4.3)	50 (5.0)
Total fat (g)	64 (28)	70 (27)	76 (29)	70 (29)	66 (27)	67 (28)
Men						
<i>n</i>	22,102	18,556	8,706	22,094	13,075	14,195
Drinks/category (median)	0	5/mo	1.1/d	0	6/mo	1.5/d
Age [mean (SD)], y	50.1 (9.7)	48.0 (9.6)	45.1 (9.2)	49.3 (10.0)	49.2 (9.7)	46.4 (9.2)
Baseline BMI \geq 29 kg/m ² (%)	14.8	13.3	14.3	10.7	13.4	19.8
Total physical activity [†] [mean (SD)], MET/wk	22.6 (31)	20.0 (28)	18.9 (28)	19.5 (27)	21.2 (30)	23.0 (33)
Height [mean (SD)]	70.0 (3.4)	70.1 (3.4)	70.2 (3.5)	70.0 (3.5)	70.0 (3.3)	70.1 (3.3)
Currently smoking (%)	7.3	8.6	12.1	10.9	7.1	6.6
History of diabetes (%)	5.4	1.3	0.9	1.4	3.3	6.6
Total carbohydrates (g)	212 (80)	235 (80)	284 (88)	242 (87)	228 (84)	223 (83)
Total sucrose (g)	37 (20)	47 (22)	63 (27)	48 (25)	44 (23)	43 (23)
Free fructose (g)	22 (14)	25 (13)	38 (17)	28 (16)	26 (15)	24 (14)
Glycemic index	52 (3.9)	53 (3.3)	55 (2.9)	54 (3.7)	53 (3.6)	53 (3.6)
Total fat (g)	65 (26)	73 (27)	83 (29)	72 (29)	68 (27)	71 (28)

NOTE: Age standardized according to eight categories (<45, 45-49, 50-54, 55-59, 60-64, 65-69, 70-74, and \geq 75 years) as of the 2-year period when participants first entered follow-up.

*Regular aspirin use defined as two or more tablets weekly.

[†]Nonvigorous physical activity in MET/wk (i.e., the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram per hour at rest).

largely abstained from sugar-sweetened soft drinks, the RR for those who reported consumption more than three times weekly was 1.22 (95% CI, 0.86-1.73) among both cohorts, 0.74 (95% CI, 0.42-1.29) among men, and 1.78 (95% CI, 1.14-2.79) among women.

We similarly examined the risk of pancreatic cancer according to intake of diet soft drinks but failed to observe a significant relation between diet soft drink intake and pancreatic cancer risk (Table 3).

The effect of diet on insulin response may vary across strata of BMI or physical activity because both are strong determinants of insulin resistance, which could magnify an adverse effect of sweetened soft drink consumption. Generally, we would expect individuals who are overweight and sedentary to have a greater insulin response to their diet compared with lean or active individuals. We examined this possibility by stratifying our analyses separately into two BMI and physical activity strata (Table 4). Among women with high compared with low sugar-sweetened soft drink consumption, we observed a borderline significant increase in pancreatic cancer risk among those who were overweight (BMI = 25 kg/m²; RR, 1.89; 95% CI, 0.96-3.72) and a significant increase in risk among those who were relatively sedentary (RR, 2.02; 95% CI, 1.06-3.85). In contrast, sugar-sweetened soft drink intake did not significantly affect risk for lean women (BMI < 25 kg/m²) or those who were physically active. Although based on small case numbers, the apparent effect modification by BMI was also evident in subgroups of sugar-sweetened soft drinks (sugar-sweetened cola and other sugar-sweetened soft drinks). For men, our ability to examine effect modification of body habitus or physical activity on this relation was somewhat

limited due to the less frequent consumption of soft drinks among the male cohort. In the cohorts combined, higher intake of sugar-sweetened soft drinks was modestly associated with pancreatic cancer in the overweight stratum (RR, 1.23; 95% CI, 0.77-1.97; *P* for trend = 0.38), whereas there was no influence of sugar-sweetened soft drink consumption on risk among leaner participants. Among both cohorts, there was no material effect modification by either body habitus or physical activity on the association between diet soda consumption and pancreatic cancer.

Discussion

In these two prospective cohort studies combined, we did not observe a significant increase in the risk of pancreatic cancer among participants who reported higher consumption of sugar-sweetened soft drinks weekly when compared with those who largely abstained.

The prospective design of our studies precluded recall bias and the need for next-of-kin respondents. Moreover, to minimize misclassification of exposure, we updated reports of dietary intakes every 2 to 4 years. Imprecise dietary measurements and residual confounding are possible alternative explanations for some of the observed associations. Self-reported dietary intake is prone to error, but we would expect such measurement error to be random with respect to future events, such as occurrence or nonoccurrence of cancer; thus, random error in dietary assessment measures might have accounted for a lack of association but not the reverse (26). Finally, because identification of deaths is highly accurate in this cohort (18), differential follow-up is unlikely.

The repeated dietary measurements made in this study were an advantage because they allowed for less measurement error and for the opportunity to account for changes in eating patterns over time (26). We had, however, limited power to study associations with more extreme categories (i.e., beyond >3 drinks weekly) of soft drink consumption.

We are unaware of previous studies of the association between soft drinks and pancreatic cancer. Several studies of

carbohydrates and pancreatic cancer yielded mixed results (6, 27-31). Whereas one cohort study of male smokers reported an inverse association between carbohydrate intake and pancreatic cancer risk (31), data from our cohort of women (6) did not support such an association. However, within the NHS, we did find a modest increase in risk of pancreatic cancer (RR, 1.53; 95% CI, 0.96-2.45) among women with a high glycemic load intake and a similar association for fructose

Table 2. Risk of pancreatic cancer by frequencies of sugar-sweetened soft drink consumption among 88,794 women from the NHS and 49,364 men from the HPFS combined

Population	Categories of intake			P for trend
	<1/mo	1-12/mo	>3/wk	
All sugar-sweetened soft drinks combined				
Total				
Cases	205	128	46	
Person-years	1,132,893	787,724	319,930	
Age-adjusted RR	1.0	1.04 (0.83-1.30)	1.18 (0.86-1.64)	0.36
Multivariate-adjusted RR*	1.0	1.06 (0.84-1.32)	1.15 (0.83-1.61)	0.41
Multivariate-adjusted RR and BMI [†]	1.0	1.05 (0.84-1.31)	1.13 (0.81-1.58)	0.47
Women				
Cases	106	71	28	
Person-years	848,732	560,916	220,191	
Age-adjusted RR	1.0	1.19 (0.88-1.62)	1.56 (1.02-2.38)	0.03
Multivariate-adjusted RR*	1.0	1.29 (0.95-1.75)	1.59 (1.04-2.46)	0.04
Multivariate-adjusted RR and BMI [†]	1.0	1.29 (0.95-1.75)	1.57 (1.02-2.41)	0.05
Men				
Cases	99	57	18	
Person-years	284,161	226,809	99,739	
Age-adjusted RR	1.0	0.84 (0.61-1.16)	0.79 (0.48-1.29)	0.22
Multivariate-adjusted RR*	1.0	0.84 (0.60-1.18)	0.76 (0.45-1.28)	0.26
Multivariate-adjusted RR and BMI [†]	1.0	0.84 (0.60-1.17)	0.75 (0.44-1.26)	0.24
Sugar-sweetened cola				
Total				
Cases	243	107	29	
Person-years	1,363,927	663,831	212,790	
Age-adjusted RR	1.0	1.09 (0.87-1.37)	1.18 (0.80-1.73)	0.30
Multivariate-adjusted RR*	1.0	1.05 (0.81-1.35)	1.09 (0.72-1.65)	0.58
Multivariate-adjusted RR and BMI [†]	1.0	1.04 (0.81-1.34)	1.07 (0.71-1.62)	0.64
Women				
Cases	129	60	16	
Person-years	1,027,398	456,931	145,509	
Age-adjusted RR	1.0	1.29 (0.95-1.76)	1.33 (0.79-2.26)	0.09
Multivariate-adjusted RR*	1.0	1.27 (0.90-1.80)	1.25 (0.70-2.22)	0.33
Multivariate-adjusted RR and BMI [†]	1.0	1.27 (0.90-1.79)	1.22 (0.69-2.18)	0.36
Men				
Cases	114	47	13	
Person-years	336,529	206,900	67,280	
Age-adjusted RR	1.0	0.82 (0.58-1.15)	0.91 (0.52-1.61)	0.40
Multivariate-adjusted RR*	1.0	0.87 (0.60-1.25)	0.92 (0.50-1.69)	0.80
Multivariate-adjusted RR and BMI [†]	1.0	0.86 (0.60-1.24)	0.91 (0.50-1.67)	0.77
Other sugar-sweetened soft drinks				
Total				
Cases	284	88	7	
Person-years	1,605,035	572,643	62,870	
Age-adjusted RR	1.0	1.09 (0.86-1.38)	0.82 (0.39-1.75)	0.78
Multivariate-adjusted RR*	1.0	1.12 (0.86-1.47)	0.79 (0.36-1.71)	0.87
Multivariate-adjusted RR and BMI [†]	1.0	1.12 (0.85-1.46)	0.79 (0.36-1.70)	0.85
Women				
Cases	144	56	5	
Person-years	1,159,422	420,112	50,305	
Age-adjusted RR	1.0	1.29 (0.95-1.76)	1.00 (0.41-2.44)	0.19
Multivariate-adjusted RR*	1.0	1.25 (0.87-1.78)	0.89 (0.35-2.29)	0.86
Multivariate-adjusted RR and BMI [†]	1.0	1.24 (0.87-1.78)	0.89 (0.35-2.28)	0.87
Men				
Cases	140	32	2	
Person-years	445,613	152,531	12,565	
Age-adjusted RR	1.0	0.85 (0.58-1.24)	0.60 (0.15-2.45)	0.28
Multivariate-adjusted RR*	1.0	0.93 (0.61-1.42)	0.58 (0.14-2.38)	0.36
Multivariate-adjusted RR and BMI [†]	1.0	0.93 (0.61-1.42)	0.58 (0.14-2.38)	0.36

*RRs (95% CIs) adjusted for age in years, gender, follow-up cycle, history of diabetes (yes/no), smoking status in nine categories (never, currently not with no information on past smoking history, past smoker, currently smoking; 1-4, 5-14, 15-24, 25-34, 35-44, and 45+ cigarettes daily), quintiles of caloric intake, quintiles of nonvigorous physical activity in MET/wk (i.e., the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram per hour at rest), and other soft drink consumption (all diet soft drinks in model for all sugar-sweetened soft drinks; sugar-sweetened cola, other sugar-sweetened soft drinks, diet cola, other diet soft drinks for single food items depending on model).

[†]Further adjustment for 1976 BMI in five categories (<21, 21-22.9, 23-24.9, 25-28.9, and ≥29 kg/m²).

intake (RR, 1.57; 95% CI, 0.95-2.57). Similar to our findings with sugar-sweetened soft drinks in the NHS, the associations for both glycemic load and fructose were stronger among women who were overweight or sedentary.

The increase in consumption of sugar-added beverages over the past several decades may be partly responsible for the obesity epidemic in the United States, particularly among adolescents (32). Calories from beverages do not displace

calories from other foods throughout the day, often leading to energy imbalance, and numerous studies have documented that beverages are a leading contributor to energy intakes (32, 33). In the NHS, higher sugar-sweetened soft drink intake was associated with greater weight gain (9). Moreover, in previous analyses of both of our cohorts, increasing BMI was significantly associated with the risk of pancreatic cancer (15). In the current study, the positive association between sugar-sweetened soft

Table 3. Risk of pancreatic cancer by frequencies of diet soft drink consumption among 88,794 women from the NHS and 49,364 men from the HPFS combined

Population	Categories of intake			P for trend
	<1/mo	1-12/mo	>3/wk	
All diet soft drinks combined				
Total				
Cases	155	116	108	
Person-years	920,860	628,265	691,423	
Age-adjusted RR	1.0	1.01 (0.80-1.29)	0.95 (0.74-1.23)	0.77
Multivariate-adjusted RR*	1.0	1.12 (0.88-1.43)	1.09 (0.85-1.41)	0.61
Multivariate-adjusted RR and BMI [†]	1.0	1.08 (0.85-1.38)	1.02 (0.79-1.32)	0.98
Women				
Cases	77	62	66	
Person-years	662,249	460,414	507,176	
Age-adjusted RR	1.0	1.09 (0.78-1.52)	1.18 (0.85-1.64)	0.34
Multivariate-adjusted RR*	1.0	1.16 (0.83-1.63)	1.23 (0.87-1.73)	0.33
Multivariate-adjusted RR and BMI [†]	1.0	1.10 (0.78-1.55)	1.12 (0.79-1.59)	0.64
Men				
Cases	78	54	42	
Person-years	258,611	167,851	184,247	
Age-adjusted RR	1.0	1.05 (0.74-1.49)	0.94 (0.64-1.37)	0.81
Multivariate-adjusted RR*	1.0	1.10 (0.77-1.56)	0.94 (0.63-1.38)	0.67
Multivariate-adjusted RR and BMI [†]	1.0	1.08 (0.76-1.53)	0.89 (0.60-1.33)	0.52
Diet cola				
Total				
Cases	182	105	92	
Person-years	1,009,471	629,675	601,402	
Age-adjusted RR	1.0	0.94 (0.74-1.19)	1.05 (0.82-1.36)	0.84
Multivariate-adjusted RR*	1.0	0.92 (0.68-1.24)	0.89 (0.62-1.26)	0.55
Multivariate-adjusted RR and BMI [†]	1.0	0.90 (0.67-1.21)	0.85 (0.59-1.21)	0.39
Women				
Cases	83	63	59	
Person-years	705,185	467,922	455,732	
Age-adjusted RR	1.0	1.11 (0.80-1.54)	1.23 (0.88-1.72)	0.23
Multivariate-adjusted RR*	1.0	0.86 (0.50-1.46)	0.86 (0.45-1.65)	0.92
Multivariate-adjusted RR and BMI [†]	1.0	0.84 (0.49-1.42)	0.83 (0.43-1.59)	0.96
Men				
Cases	99	42	33	
Person-years	303,286	161,753	145,670	
Age-adjusted RR	1.0	0.82 (0.57-1.18)	0.93 (0.62-1.38)	0.51
Multivariate-adjusted RR*	1.0	0.87 (0.59-1.28)	0.88 (0.57-1.37)	0.46
Multivariate-adjusted RR and BMI [†]	1.0	0.86 (0.58-1.26)	0.85 (0.54-1.32)	0.38
Other diet soft drinks				
Total				
Cases	211	111	57	
Person-years	1,181,550	680,201	378,797	
Age-adjusted RR	1.0	0.97 (0.77-1.22)	1.19 (0.89-1.60)	0.46
Multivariate-adjusted RR*	1.0	1.16 (0.86-1.56)	1.46 (0.97-2.19)	0.08
Multivariate-adjusted RR and BMI [†]	1.0	1.14 (0.85-1.53)	1.40 (0.93-2.11)	0.13
Women				
Cases	87	74	44	
Person-years	769,487	513,700	346,652	
Age-adjusted RR	1.0	1.24 (0.91-1.69)	1.36 (0.95-1.95)	0.08
Multivariate-adjusted RR*	1.0	1.48 (0.88-2.51)	1.58 (0.80-3.12)	0.44
Multivariate-adjusted RR and BMI [†]	1.0	1.44 (0.85-2.44)	1.50 (0.76-2.97)	0.54
Men				
Cases	124	37	13	
Person-years	412,063	166,501	32,145	
Age-adjusted RR	1.0	0.81 (0.56-1.17)	1.59 (0.90-2.82)	0.75
Multivariate-adjusted RR*	1.0	0.91 (0.60-1.36)	1.66 (0.90-3.05)	0.13
Multivariate-adjusted RR and BMI [†]	1.0	0.89 (0.59-1.34)	1.62 (0.88-2.97)	0.15

*RRs (95% CIs) adjusted for age in years, gender, follow-up cycle, history of diabetes (yes/no), smoking status in nine categories (never, currently not with no information on past smoking history, past smoker, currently smoking; 1-4, 5-14, 15-24, 25-34, 35-44, and 45+ cigarettes daily), quintiles of caloric intake, quintiles of nonvigorous physical activity in MET/wk (i.e., the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram per hour at rest), and other soft drink consumption (all diet soft drinks in model for all sugar-sweetened soft drinks; sugar-sweetened cola, other sugar-sweetened soft drinks, diet cola, other diet soft drinks for single food items depending on model).

[†]Further adjustment for 1976 BMI in five categories (<21, 21-22.9, 23-24.9, 25-28.9, and ≥29 kg/m²).

Table 4. Multivariate RRs and 95% CIs for pancreatic cancer according to frequency of soft drink consumption, stratified by BMI and physical activity level in the NHS (1980-2000) and the HPFS (1986-2000) combined

Population*	BMI				Physical activity			
	Cases	BMI < 25	Cases	BMI ≥ 25	Cases	Low physical activity [†]	Cases	High physical activity [†]
All sugar-sweetened soft drinks combined								
Total								
<1/mo	108	1.0	91	1.0	83	1.0	122	1.0
1-12/mo	53	0.85 (0.61-1.19)	74	1.31 (0.96-1.80)	66	1.18 (0.85-1.64)	62	0.96 (0.70-1.31)
>3/wk	21	1.06 (0.65-1.73)	24	1.23 (0.77-1.97)	27	1.30 (0.83-2.05)	19	1.00 (0.61-1.64)
<i>P</i> for trend [‡]	0.89		0.38		0.28		0.96	
Women								
<1/mo	70	1.0	35	1.0	34	1.0	72	1.0
1-12/mo	34	0.94 (0.62-1.42)	36	1.94 (1.21-3.12)	32	1.57 (0.96-2.58)	39	1.16 (0.78-1.72)
>3/wk	15	1.33 (0.74-2.37)	12	1.89 (0.96-3.72)	14	2.02 (1.06-3.85)	14	1.37 (0.76-2.47)
<i>P</i> for trend [‡]	0.34		0.10		0.05		0.29	
Men								
<1/mo	38	1.0	56	1.0	49	1.0	50	1.0
1-12/mo	19	0.68 (0.39-1.20)	38	1.03 (0.67-1.57)	34	0.91 (0.58-1.42)	23	0.77 (0.47-1.28)
>3/wk	6	0.63 (0.26-1.55)	12	0.88 (0.46-1.68)	13	0.88 (0.46-1.66)	5	0.55 (0.21-1.42)
<i>P</i> for trend [‡]	0.23		0.74		0.68		0.17	
All diet soft drink consumption combined								
Total								
<1/mo	86	1.0	66	1.0	72	1.0	83	1.0
1-12/mo	59	1.24 (0.88-1.74)	56	0.96 (0.67-1.38)	53	1.07 (0.74-1.54)	63	1.07 (0.77-1.50)
>3/wk	37	0.95 (0.63-1.41)	67	1.03 (0.72-1.47)	51	0.99 (0.68-1.44)	57	1.03 (0.72-1.47)
<i>P</i> for trend [‡]	0.69		0.88		0.84		0.94	
Women								
<1/mo	55	1.0	21	1.0	24	1.0	53	1.0
1-12/mo	34	1.05 (0.68-1.62)	28	1.31 (0.74-2.32)	25	0.72 (0.41-1.28)	37	1.52 (0.98-2.36)
>3/wk	30	1.02 (0.64-1.62)	34	1.32 (0.75-2.33)	31	1.05 (0.63-1.76)	35	1.21 (0.75-1.94)
<i>P</i> for trend [‡]	0.93		0.62		0.38		0.72	
Men								
<1/mo	31	1.0	45	1.0	48	1.0	30	1.0
1-12/mo	25	1.65 (0.96-2.83)	28	0.77 (0.48-1.25)	28	0.94 (0.58-1.52)	26	1.26 (0.74-2.15)
>3/wk	7	0.68 (0.29-1.57)	33	0.81 (0.55-1.40)	20	0.71 (0.41-1.22)	22	1.19 (0.66-2.12)
<i>P</i> for trend [‡]	0.34		0.74		0.21		0.67	

NOTE: Multivariate RRs from Cox proportional hazards models that include age in years, gender, follow-up cycle, history of diabetes (yes/no), smoking status in nine categories (never, currently not with no information on past smoking history, past smoker, currently smoking: 1-4, 5-14, 15-24, 25-34, 35-44, and 45+ cigarettes daily), quintiles of caloric intake, quintiles of nonvigorous physical activity (1986) in MET/wk (i.e., the caloric need per kilogram of body weight per hour of activity divided by the caloric need per kilogram per hour at rest), and other soft drink consumption (all diet soft drinks in model for all sugar-sweetened soft drinks; sugar-sweetened cola, other sugar-sweetened soft drinks, diet cola, other diet soft drinks for single food items depending on model).

*Number of cases are fewer than total due to missing BMI.

[†]Stratified along the median: 11.5 MET/wk for the men and 7.7 MET/wk for the women both as assessed in 1986.

[‡]Test for trend across categories of exposure are based on the midpoints of the original exposure categories.

drink intake and pancreatic cancer risk among women may have reflected residual confounding by obesity. However, the influence of sugar-sweetened soft drink consumption on risk of pancreas cancer remained unchanged after adjustment for BMI.

Despite the effects on blood glucose and sucrose that any sugar-sweetened soft drinks have, and the potential of cola-type soft drinks to increase insulin resistance, we did not observe consistent differences between cola and other soft drinks for both sugar-sweetened and diet soft drinks, and diet cola was generally not associated with pancreatic cancer risk.

Reasons for the disparate influence of sugar-sweetened soft drinks between women and men in this analysis remain uncertain. Although the findings among women may be the result of chance, the stronger associations among those who were overweight or sedentary offer some consistency to this observation. Although we cannot exclude residual confounding by other factors associated with soft drink use, we observed no attenuation in the risk among women in our multivariate model. Alternatively, the less frequent consumption of soft drinks in our male cohort may have diminished our capacity to assess this relation in men.

In summary, although we failed to find a significant overall relation between sweetened soft drinks and pancreatic cancer risk in both cohorts combined, our data may suggest a modestly higher pancreatic cancer risk associated with higher consumption of sugar-sweetened soft drinks among women as well as those who are overweight. Although we cannot

exclude the possibility of residual confounding by other factors associated with sugar-sweetened soft drink consumption, this report lends support to the hypothesis that abnormal glucose metabolism and states of relative hyperinsulinemia enhance pancreatic carcinogenesis.

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BLOOD CANCER DISCOVERY

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