Consumption of sugar and sugar-sweetened foods and the risk of pancreatic cancer in a prospective study\textsuperscript{1–3}

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ABSTRACT

Background: Emerging evidence indicates that hyperglycemia and hyperinsulinemia may be implicated in the development of pancreatic cancer. Frequent consumption of sugar and high-sugar foods may increase the risk of pancreatic cancer by inducing frequent postprandial hyperglycemia, increasing insulin demand, and decreasing insulin sensitivity.

Objective: The objective of the study was to examine prospectively the association of the consumption of added sugar (ie, sugar added to coffee, tea, cereals, etc) and of high-sugar foods with the risk of pancreatic cancer in a population-based cohort study of Swedish women and men.

Design: A food-frequency questionnaire was completed in 1997 by 77,797 women and men aged 45–83 years who had no previous diagnosis of cancer or history of diabetes. The participants were followed through June 2005.

Results: During a mean follow-up of 7.2 years, we identified 131 incident cases of pancreatic cancer. The consumption of added sugar, soft drinks, and sweetened fruit soups or stewed fruit was positively associated with the risk of pancreatic cancer. The multivariate hazard ratios for the highest compared with the lowest consumption categories were 1.69 (95% CI: 0.99, 2.89; \( P \) for trend = 0.06) for sugar, 1.93 (1.18, 3.14; \( P \) for trend = 0.02) for soft drinks, and 1.51 (0.97, 2.36; \( P \) for trend = 0.05) for sweetened fruit soups or stewed fruit.

Conclusion: High consumption of sugar and high-sugar foods may be associated with a greater risk of pancreatic cancer. \textit{Am J Clin Nutr} 2006;84:1171–6.

KEY WORDS Cohort studies, diet, pancreatic cancer, soft drinks, sucrose, sugar

INTRODUCTION

Pancreatic cancer is among the most deadly cancers: the overall 5-year survival rate is only \( \approx 5\% \) (1). Because of this poor prognosis, identification of modifiable risk factors for pancreatic cancer is important. Evidence is mounting that abnormal glucose metabolism and hyperinsulinemia may be involved in the development of pancreatic cancer. Conditions such as diabetes mellitus, a high body mass index (BMI; in kg/m\(^2\)), and physical inactivity, all hallmarks of insulin resistance, have been directly related to the risk of this malignancy (2–5). Moreover, prospective studies have reported approximately twice the risk of pancreatic cancer in persons in the highest category of postload plasma glucose (6), fasting serum glucose (7, 8), or fasting insulin (7) concentrations compared with persons in the lowest category.

Given the possible role of hyperglycemia and hyperinsulinemia in the development of pancreatic cancer, frequent consumption of sugar and high-sugar foods may increase the risk of pancreatic cancer by inducing frequent postprandial hyperglycemia, increasing insulin demand, and decreasing insulin sensitivity. A recent prospective study provided support for this hypothesis when it reported a significantly greater risk of pancreatic cancer in association with high consumption of sugar-sweetened soft drinks in women, although no greater risk was found in men (9). High consumption of sugar-sweetened beverages has also been associated with a greater weight gain and with higher risk of type 2 diabetes (10).

Soft drinks are the leading source of added sugar in the US diet (11), and they could contribute to a high glycemic load of the diet. Dietary glycemic load, a quantitative measure of the glycemic effect of foods, has been positively associated with the risk of pancreatic cancer. In an international ecologic study (15), sugar consumption was the environmental factor most strongly and positively correlated with pancreatic cancer mortality in women.

On the basis of this background, we sought to evaluate the hypothesis that high consumption of added sugar (ie, sugar added to coffee, tea, cereals, etc), soft drinks, and other high-sugar foods is associated with a greater risk of pancreatic cancer by analyzing prospective data from the Swedish Mammography Cohort (SMC) and the Cohort of Swedish Men (COSM). Our group previously found that persons in these cohorts who were obese or had a history of diabetes mellitus had a risk of pancreatic cancer 1.8 to 1.9 times that in persons with normal weight or without diabetes (5).
SUBJECTS AND METHODS

Study population

This investigation is based on data from 2 population-based prospective cohorts, the SMC and the COSM. Detailed information on the SMC was published previously (16). In brief, the cohort was established between 1987 and 1990, when all women who were born between 1914 and 1948 and who lived in the counties of Västmanland and Örebro in central Sweden received a mailed questionnaire concerning diet, weight, height, and education. In the fall of 1997, a more comprehensive questionnaire (n = 350 items) was mailed to all 56,030 SMC participants who were still alive and residing in the study area. This questionnaire collected information on diet and other lifestyle factors (including smoking history) and medical history; 39,227 women (70%) returned a completed questionnaire. The COSM study was initiated in the fall of 1997, when all men who were born between 1918 and 1948 and who lived in the counties of Västmanland and Örebro in central Sweden received a questionnaire that was identical (except for some sex-specific questions) to the 1997 SMC questionnaire. Of the 100,303 eligible men, 48,850 (49%) completed the questionnaire.

For the current analyses, we used information from respondents to the 1997 questionnaire. We excluded participants with implausible values for energy intake [ie, 3 SDs from the log-transformed mean energy intake in women (n = 531) and men (n = 600)], those with an erroneous or missing National Registration Number (243 women and 260 men), and those who had a history of cancer (1837 women and 2684 men) or diabetes (1343 women and 2782 men). These exclusions left 77,979 participants (35,273 women and 42,524 men) aged 45–83 y for the analyses.

The subjects’ completion of the self-administered questionnaire was considered to convey informed consent. The study was approved by the Regional Ethics Review Board in Stockholm.

Dietary assessment

Dietary information was derived from a 96-item food-frequency questionnaire. Participants were asked how often, on average, they had consumed each food over the previous year. Eight previously defined-response categories were provided, ranging from never to ≥3 times/d. The questionnaire also included open questions about some commonly consumed foods, such as added sugar (ie, sugar added to coffee, tea, cereals, etc) and soft drinks (including carbonated soft drinks and noncarbonated sweetened drinks; the type of soft drink—ie, sugar-sweetened or artificially sweetened—was not specified). For these foods, a commonly used serving size [eg, 1 teaspoon or lump of sugar (ie, ≈5–7 g) and 1 glass (≈250–300 g) of a soft drink] was indicated. In a validity study of 129 women randomly chosen from the SMC, the correlation coefficients between the average intake assessed by four 1-wk diet records (completed 3–4 mo apart) and the food-frequency questionnaire were as follows: 0.7 for added sugar, 0.6 for soft drinks, 0.5 for sweetened fruit soups or stewed fruit, 0.5 for jam or marmalade, and 0.4 for sweet (A Wolk, unpublished observations, 1992).

Identification of pancreatic cancer cases and follow-up

Incident cases of pancreatic cancer [International Classification of Diseases, Ninth Revision (ICD-9) code 157] were identified through linkage to the national and regional Swedish cancer registries, both of which provide ≈100% case ascertainment in Sweden (17). Because their causes may be different from those of the exocrine tumors, islet cell carcinomas (ICD-9 code 157.4; n = 3 cases) were not included as cases in this study. We obtained information on dates of deaths and dates of migration (ie, moving from the study area) through linkage to the Swedish death and population registries at Statistics Sweden.

Statistical analysis

For each study participant, person-years of follow-up (ie, the number of persons studied times the number of years of follow-up) were counted from 1 January 1998 to the date of diagnosis of pancreatic cancer, the date of death, the date of migration, or 30 June 2005, whichever came first. Categories of frequency of consumption of added sugar and sweetened foods were created, and the lowest category was used as the reference category. Cox proportional hazards models (18) were used to estimate hazard ratios with 95% CIs. Separate analyses for women and men showed similar patterns of associations, and tests for interaction with sex were not significant (P > 0.4). We therefore present results for both sexes combined, after controlling for sex as a stratum variable in the Cox model to allow for different baseline hazard rates. Age adjustment was accomplished by stratifying on age (in mo) within each Cox model. In multivariate analyses, in addition to age and sex, we adjusted for education (less than high school, high school graduate, or more than high school), BMI (<25.0, 25.0–29.9, or ≥30), smoking status and pack-years of smoking (never smoker or past smoker and <20 pack-years, past smoker and ≥20 pack-years, current smoker and <20 pack-years, current smoker and 20–39 pack-years, or current smoker and ≥40 pack-years), and intakes of total energy (continuous) and alcohol (quartiles). We also adjusted for other potential confounders, including physical activity, aspirin use, and intakes of dietary folate, fruit, vegetables, red meat, coffee, and tea; however, because these adjustments did not change the risk estimates, the variables were not included in the final models. In additional analyses, to remove early cases in which the association between the consumption of sugar and sweetened food and the risk of pancreatic cancer may have been biased because of changes in diet due to preclinical symptoms, we excluded cases of pancreatic cancer diagnosed during the first 2 or 4 y of follow-up.

Tests for trends were conducted by assigning the median value to each intake category and modeling this value as a continuous variable. To examine whether the relations between sugar and soft drink consumption and the risk of pancreatic cancer were modified by BMI and physical inactivity, which can be important determinants of insulin resistance, we performed analyses stratified by BMI (<25 or ≥25) and exercise (≤1 or ≥2 h/wk). Statistical interaction was assessed by using the likelihood ratio test. All analyses were conducted by using SAS statistical software (version 9.1; SAS Institute Inc, Cary, NC). All P values are 2-sided.

RESULTS

Baseline characteristics of the study population by consumption of added sugar and soft drinks are shown in Table 1. At baseline, ≈4% of the women and ≈14% of the men reported consumption of ≥5 servings added sugar/d; 7% of the women and 13% of the men reported consumption of ≥2 servings soft drinks/d. Women and men in the highest category of sugar and soft drink consumption were less likely to have postsecondary
education and were more likely to smoke than were those who never consumed sugar and soft drinks. In addition, women and men who consumed more sugar and soft drinks generally drank less alcohol than did those who consumed less sugar and soft drinks. BMI decreased slightly across categories of sugar consumption but increased across categories of soft drink consumption. Intakes of each of the sweetened foods and sugar were weakly correlated with one another; Spearman’s correlation coefficients ranged from 0.06 for sugar and sweets to 0.26 for sweetened soft drinks/wk had a significantly greater (57%) risk than are added sugar and soft drinks (daily) and soft drinks and sweetened fruit soups or stewed fruit than low consumption of those items. No associations were found between the consumption of jam or marmalade or sweets and the risk of pancreatic cancer.

Among the 77,797 women and men followed for 563,430 person-years (mean: 7.2 y), 131 incident cases of pancreatic cancer (61 women and 70 men) were diagnosed. After adjustment for age, sex, education, smoking, BMI, and energy and alcohol intakes, we found that participants with high consumption of added sugar, soft drinks, and sweetened fruit soups or stewed fruit and jam or marmalade were more likely to smoke than were those who never consumed sugar and soft drinks. In the current study, the associations of added sugar and soft drink consumption with pancreatic cancer risk did not vary across strata of BMI or physical activity (P for interaction > 0.45 for all).

**DISCUSSION**

In this prospective analysis, we observed a significantly greater risk of pancreatic cancer associated with high consumption of added sugar, soft drinks, and sweetened fruit soups or stewed fruit than low consumption of those items. No associations were found between the consumption of jam or marmalade or sweets and pancreatic cancer risk. The lack of association with these foods may be due to the fact that these foods are consumed less frequently (weekly) and in smaller servings (≈30 g/serving) than are added sugar and soft drinks (daily) and soft drinks and fruit soups or stewed fruit (≈250 g/serving).

We are aware of only one previous study that investigated the association between soft drink consumption and the risk of pancreatic cancer. In that prospective analysis of US nurses and other health professionals (9), women who consumed >3 sugar-sweetened soft drinks/wk had a significantly greater (57%) risk of pancreatic cancer than did women who consumed <1 sugar-sweetened soft drink/mo; no increase in risk was observed in men. Results of this US prospective study may not be directly comparable with the results in the current study, however, because sucrose is the sugar added as a caloric sweetener to soft drinks in Sweden, whereas high-fructose corn syrup is the major source of caloric sweeteners in soft drinks in the United States. High-fructose corn syrup and sucrose do, however, have similar effects on blood glucose (19). In the current study, the risk of pancreatic cancer was greater only among those who consumed ≥2 soft drinks/d. Thus, the weaker association in women and the lack of association in men between soft drink consumption and pancreatic cancer in the US study (9) may be related to the lower consumption (highest category, >3 times/wk) in that more
TABLE 2
Hazard ratios (HRs) and 95% CIs for pancreatic cancer according to consumption of added sugar and sweetened foods.

<table>
<thead>
<tr>
<th>Food items (servings)</th>
<th>Cases</th>
<th>Person-years</th>
<th>Age- and sex-adjusted HR (95% CI)</th>
<th>Multivariate HR (95% CI)</th>
<th>Multivariate HR (95% CI)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Added sugar</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>66</td>
<td>307 399</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>0.1–1.9/d (1.0/d)</td>
<td>18</td>
<td>101 653</td>
<td>0.78 (0.46, 1.32)</td>
<td>0.82 (0.49, 1.40)</td>
<td>0.84 (0.47–1.50)</td>
</tr>
<tr>
<td>2.0–4.9/d (2.9/d)</td>
<td>26</td>
<td>99 229</td>
<td>1.03 (0.65, 1.64)</td>
<td>1.01 (0.63, 1.62)</td>
<td>0.98 (0.57, 1.66)</td>
</tr>
<tr>
<td>≥5.0/d (7.0/d)</td>
<td>21</td>
<td>55 149</td>
<td>1.92 (1.15, 3.20)</td>
<td>1.69 (0.99, 2.89)</td>
<td>1.95 (1.10, 3.46)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.02</td>
<td>0.06</td>
<td>0.03</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Soft drinks</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>66</td>
<td>298 098</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>0.1–0.4/d (0.3/d)</td>
<td>19</td>
<td>106 658</td>
<td>0.98 (0.59, 1.64)</td>
<td>1.06 (0.63, 1.78)</td>
<td>1.15 (0.65, 2.04)</td>
</tr>
<tr>
<td>0.5–1.9/d (1.0/d)</td>
<td>20</td>
<td>100 976</td>
<td>0.91 (0.55, 1.51)</td>
<td>0.93 (0.56, 1.56)</td>
<td>1.04 (0.59, 1.82)</td>
</tr>
<tr>
<td>≥2.0/d (2.1/d)</td>
<td>26</td>
<td>57 698</td>
<td>2.00 (1.26, 3.17)</td>
<td>1.93 (1.18, 3.14)</td>
<td>2.30 (1.35, 3.92)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.01</td>
<td>0.02</td>
<td>0.006</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Fruit soups or stewed fruit</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>41</td>
<td>216 718</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>1–3/mo (0.5/wk)</td>
<td>39</td>
<td>210 134</td>
<td>0.96 (0.62, 1.50)</td>
<td>1.04 (0.66, 1.63)</td>
<td>1.08 (0.66, 1.76)</td>
</tr>
<tr>
<td>≥1.0/wk (1.5/wk)</td>
<td>51</td>
<td>136 578</td>
<td>1.37 (0.90, 2.10)</td>
<td>1.51 (0.97, 2.36)</td>
<td>1.46 (0.89, 2.40)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.10</td>
<td>0.05</td>
<td>0.11</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Jam or marmalade</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>21</td>
<td>90 270</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>1–3/mo (0.5/wk)</td>
<td>30</td>
<td>161 975</td>
<td>1.01 (0.57, 1.78)</td>
<td>1.04 (0.59, 1.85)</td>
<td>1.08 (0.58, 1.98)</td>
</tr>
<tr>
<td>≥1.0/wk (3.5/wk)</td>
<td>80</td>
<td>311 185</td>
<td>1.06 (0.65, 1.73)</td>
<td>1.15 (0.70, 1.89)</td>
<td>0.98 (0.57, 1.70)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.75</td>
<td>0.54</td>
<td>0.79</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Sweets</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>58</td>
<td>192 523</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
<td>1.00 (reference)</td>
</tr>
<tr>
<td>1–3/mo (0.5/wk)</td>
<td>43</td>
<td>221 466</td>
<td>0.89 (0.59, 1.33)</td>
<td>0.90 (0.60, 1.36)</td>
<td>0.91 (0.58, 1.44)</td>
</tr>
<tr>
<td>≥1.0/wk (1.5/wk)</td>
<td>30</td>
<td>149 441</td>
<td>0.94 (0.60, 1.48)</td>
<td>0.90 (0.57, 1.43)</td>
<td>0.96 (0.58, 1.59)</td>
</tr>
<tr>
<td>P for trend</td>
<td>0.82</td>
<td>0.67</td>
<td>0.89</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

1 Cox proportional hazards models were used to calculate hazard ratios.
2 Range of intake; median in parentheses (all such values).
3 Adjusted for age (in mo), sex, education (less than high school, high school graduate, or more than high school), smoking status and pack-years (never smoked, past smoker <20 pack-years, past smoker ≥20 pack-years, current smoker <20 pack-years, current smoker 20–39 pack-years, or current smoker ≥40 pack-years), BMI [(in kg/m²) <25.0, 25.0–29.9, or ≥30], and intakes of total energy (continuous) and alcohol (quartiles).
4 Analysis excluded cases diagnosed during the first 2 y of follow-up. From lowest to highest category, n = 53, 15, 20, and 19 for added sugar; 51, 16, 17, and 23 for soft drinks; 33, 33, and 41 for sweetened fruit soups or stewed fruit; 18, 27, and 62 for jam or marmalade; and 46, 35, and 26 for sweets.
5 Added to coffee, tea, cereals, etc.

The observed positive relations between the consumption of sugar and soft drinks and the risk of pancreatic cancer may be explained within the context of hyperglycemia, insulin resistance, and resulting hyperinsulinemia. Consumption of sugar-sweetened soft drinks, which contain large amounts of rapidly absorbable sugars, induces a rapid and dramatic increase in both blood glucose and insulin concentrations (26). A state of relative postprandial hyperglycemia and primary hyperinsulinemia may cause insulin resistance, which in turn usually leads to compensatory hyperinsulinemia (27). Hyperinsulinemia has been shown to increase local blood flow and cell division within the pancreas (28, 29). During hyperinsulinemia, the exocrine cells of the pancreas are exposed to extremely high insulin concentrations because their blood supply passes through the insulin-producing pancreatic islet (30). Elevated insulin concentrations could activate the insulin-like growth factor I receptor, which may lead to growth-promoting effects (31). Moreover, by down-regulating insulin-like growth factor 1, excess insulin may result in greater exposure to free insulin-like growth factor I (32), which has been shown to stimulate growth in pancreatic cell lines (33–35).
Besides the mechanisms described above, the consumption of high-sugar foods may increase the risk of pancreatic cancer by the direct effects of elevated glucose concentrations. A chronic excess of glucose has toxic effects on the pancreatic islet and results in beta cell dysfunction and eventually cell death, a phenomenon that has been called glucose toxicity (36). One potential central mechanism for glucose toxicity is the increased formation of reactive oxygen species that in prolonged excess cause chronic oxidative stress (36). The pancreatic islet is especially sensitive to reactive oxygen species because of the islet’s low concentration of antioxidant enzymes (37). Thus, high-sugar diets may increase pancreatic cancer risk, at least in part, by hyperglycemia-induced oxidative stress and free radical damage to pancreatic cells.

The strengths of this study include its prospective and population-based design, high rates of follow-up, and the detailed information on diet and on potential risk factors for pancreatic cancer. The prospective design precluded recall and selection bias, and the completeness of follow-up reduces the possibility that our findings have been affected by differential follow-up. Because our results persisted after the exclusion of cases diagnosed during the first 2 and 4 y of follow-up, it is unlikely that the associations we observed arose because of dietary changes related to preclinical disease. One limitation of the current study is that we could not distinguish between sugar-sweetened and diet (ie, artificially sweetened) soft drinks. Other limitations are the relatively short follow-up and the small number of cases. Moreover, because diet was assessed with the use of a self-administered food-frequency questionnaire, some misclassification of sugar and sweetened food consumption is inevitable. However, because dietary information was collected before the diagnosis of pancreatic cancer, any misclassification would most likely have attenuated rather than exaggerated a true association.

In summary, results from this prospective study suggest that high consumption of sugar and sweetened foods may increase the risk of pancreatic cancer. Given the practical implications of these findings and the poor prognosis of pancreatic cancer, further research on sugar and high-sugar foods in relation to pancreatic cancer risk is warranted.

SCL and AW were responsible for the study concept and design; AW was responsible for data collection; SCL was responsible for statistical analyses; SCL, LB, and AW were responsible for interpretation of results; SCL was responsible for writing the draft of the manuscript; SCL, LB, and AW provided critical review of the manuscript; and all authors reviewed and approved the final manuscript. None of the authors had a financial or personal conflict of interest.

**REFERENCES**