Coffee, Tea, and Sugar-Sweetened Carbonated Soft Drink Intake and Pancreatic Cancer Risk: A Pooled Analysis of 14 Cohort Studies

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Abstract

Background: Coffee has been hypothesized to have pro- and anticarcinogenic properties, whereas tea may contain anticarcinogenic compounds. Studies assessing coffee intake and pancreatic cancer risk have yielded mixed results, whereas findings for tea intake have mostly been null. Sugar-sweetened carbonated soft drink (SSB) intake has been associated with higher circulating levels of insulin, which may promote carcinogenesis. Few prospective studies have examined SSB intake and pancreatic cancer risk; results have been heterogeneous.

Methods: In this pooled analysis from 14 prospective cohort studies, 2,185 incident pancreatic cancer cases were identified among 833,894 individuals during follow-up. Multivariate (MV) study-specific relative risks (RR) and 95% confidence intervals (CI) were calculated using Cox proportional hazards models and then pooled using a random-effects model.

Results: No statistically significant associations were observed between pancreatic cancer risk and intake of coffee (MVRR = 1.10; 95% CI, 0.81–1.48 comparing ≥900 to <0 g/d; 237 g ≈ 8 oz), tea (MVRR = 0.96; 95% CI, 0.78–1.16 comparing ≥400 to 0 g/d; 237 g ≈ 8 oz), or SSB (MVRR = 1.19; 95% CI, 0.98–1.46 comparing ≥250 to 0 g/d; 355 ml ≈ 12 oz; P value, test for between-studies heterogeneity > 0.05). These associations were consistent across levels of sex, smoking status, and body mass index. When modeled as a continuous variable, a positive association was evident for SSB intake and pancreatic cancer risk; results have been heterogeneous.

Conclusion and Impact: Overall, no associations were observed for intakes of coffee or tea during adulthood and pancreatic cancer risk. Although we were only able to examine modest intake of SSB, there was a suggestive, modest positive association for risk of pancreatic cancer for intakes of SSB. Cancer Epidemiol Biomarkers Prev; 21(2): 305–18. ©2011 AACR.
Introduction

Worldwide, pancreatic tumors cause significant morbidity and mortality as the seventh and ninth most common cause of cancer death for males and females, respectively (1). Pancreatic cancer has few early symptoms, is usually diagnosed at late stages, and has a 5-year survival rate of 5% (1, 2). Thus, identifying modifiable factors for prevention may yield approaches to reduce the morbidity and mortality due to this disease.

More than 30 case–control (3–32) and 13 cohort studies (33–45) have examined the association between coffee intake and pancreatic cancer risk; results for both study designs have been conflicting. The differences may be due, in part, to the variable degree of confounding by smoking across studies (3–45). Initial studies that did not control for smoking observed positive associations between coffee intake and pancreatic cancer risk, whereas more recent publications, which have controlled for smoking, have generally reported null associations (3–45). A panel sponsored by the World Cancer Research Fund (WCRF) and the American Institute of Cancer Research (AICR) concluded from their review that there appears to be no relationship between coffee intake and pancreatic cancer risk (46). In comparison, tea consumption has been examined in relatively fewer studies of pancreatic cancer risk and generally results have been null (3, 5, 6, 8, 12, 16, 20, 24, 26, 36, 37, 44, 47). Overall, the WCRF/AICR review panel concluded that the evidence was too sparse and inconsistent to draw any conclusions on the association between tea intake and pancreatic cancer risk (46).

In recent years, studies have reported positive associations between diabetes, markers of diabetes, and obesity and risk of pancreatic cancer (46, 48–54). Factors that raise insulin and glucose levels, and promote obesity and diabetes, such as sugar-sweetened carbonated soft drinks (SSB; refs. 55–57), may be positively associated with pancreatic cancer risk. Eight prospective studies and 6 case–control studies have examined the association between SSB intake and pancreatic cancer risk but results have been inconclusive (6, 12, 58–67).

Caffeine, one of the biologically active compounds found in tea, coffee, and some SSBs (68) has been theorized to both increase and decrease the risk. Of the limited number of studies that have examined the association between caffeine intake and pancreatic cancer risk, results have generally been null or suggestive of a weak inverse association (37, 69). In addition, other components within tea and coffee, such as stimulants, catechins, and other bioactive constituents, may influence cancer risk (46).

In an effort to resolve inconsistencies in the literature, we investigated the association between intake of coffee, tea, and SSBs and pancreatic cancer risk in a pooled analysis of 14 cohort studies (37, 45, 70–80). Because the effect of each beverage may vary by potential pancreatic cancer risk factors, we also considered whether the association differed by environmental and nutritional factors. In addition, tumor subtypes of pancreatic cancer may be associated with different etiologies (80). Thus, we examined associations between intakes of beverages separately for adenocarcinomas of the pancreas, the predominant type of pancreatic cancer (80–84).

Materials and Methods

Population

A pooled analysis of the primary data from 14 cohort studies (37, 45, 70, 71, 73–80, 85) was conducted in The Pooling Project of Prospective Studies of Diet and Cancer (Pooling Project), a large international consortium. The following studies were included in our analysis: Alpha-Tocopherol Beta-Carotene Cancer Prevention Study (ATBC; ref. 45); Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP; ref. 71); Canadian National Breast Screening Study (CNBSS; ref. 73); Cancer Prevention Study II Nutrition Cohort (CPS II; ref. 74); California Teachers Study (CTS; ref. 85); Cohort of Swedish Men (COSM; ref. 79); Health Professionals Follow-up Study (HPFS; ref. 37); Iowa Women’s Health Study (IWHS; ref. 75); Melbourne Collaborative Cohort Study (MCCS; ref. 76); The Netherlands Cohort Study (NLCS; ref. 77); New York State Cohort (NYSC; ref. 70); Nurses’ Health Study (NHS; ref. 37); Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO; ref. 78); and Swedish Mammography Cohort Study (SMC; ref. 79). Each eligible study (Table 1) had to meet the following prespecified inclusion criteria: a minimum of 50 incident pancreatic cancer cases, an assessment of usual diet, validation of the dietary assessment tool or a closely related instrument, and prior publication of any diet and cancer association. Studies that met our inclusion criteria and agreed to participate sent us their primary data for analysis.

Because many cancers appear to have hormonal antecedents and because lifestyle factors may differ between women and men, studies including both women and men were split into 2 studies for our pooled analyses: a cohort of women and a cohort of men. This approach, in which all estimates were calculated separately for women and men for those studies including both genders, allowed for potential effect modification by sex for every determinant of the outcome. Two studies in the pooled analysis, the CNBSS and NLCS, were analyzed as case–cohort studies (73, 77). For the NHS, we divided the person-time of the NHS into 2 segments corresponding to the 1980–1986 follow-up period (Part A) and follow-up beginning in 1986 (Part B) to take advantage of the increased comprehensiveness of the food frequency questionnaire (FFQ) completed in 1986 compared with the FFQ completed in 1980. We excluded Part A because fewer than 50 pancreatic cancer cases were identified in the NHS between 1980 and 1986. For the SMC, we used 1997 as the baseline for the questionnaire data and the start of follow-up for the cohort members who had no history of cancer in 1997 because the 1997 questionnaire included information on...
Table 1. Beverage intake by cohort study in the pancreatic cancer analysis of the Pooling Project of Prospective Studies of Diet and Cancer

<table>
<thead>
<tr>
<th>Sex</th>
<th>Cohort</th>
<th>Follow-up years</th>
<th>Baseline cohort size</th>
<th>Number of cases</th>
<th>Age range, y</th>
<th>% coffee drinkers</th>
<th>Coffee</th>
<th>% tea drinkers</th>
<th>Tea</th>
<th>% SSB drinkers</th>
<th>SSB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Female</td>
<td>BCDDP</td>
<td>1987–1999</td>
<td>43,162</td>
<td>102</td>
<td>40–93</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>39</td>
<td>47.1 (16.5–141.1)</td>
</tr>
<tr>
<td></td>
<td>CNBSS</td>
<td>1980–2000</td>
<td>49,654</td>
<td>105</td>
<td>40–59</td>
<td>85</td>
<td>448.0 (224.0–896.0)</td>
<td>77</td>
<td>336.0 (128.0–672.0)</td>
<td>37</td>
<td>32.0 (14.7–64.0)</td>
</tr>
<tr>
<td></td>
<td>CPS II</td>
<td>1992–2001</td>
<td>74,138</td>
<td>164</td>
<td>50–74</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>36</td>
<td>28.9 (13.5–105.9)</td>
</tr>
<tr>
<td></td>
<td>CTS</td>
<td>1995–2003</td>
<td>97,945</td>
<td>114</td>
<td>22–104</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>34</td>
<td>49.7 (18.1–159.5)</td>
</tr>
<tr>
<td></td>
<td>IWHS</td>
<td>1986–2001</td>
<td>33,844</td>
<td>166</td>
<td>55–69</td>
<td>90</td>
<td>596.5 (292.7–1,065.6)</td>
<td>58</td>
<td>101.8 (18.9–236.8)</td>
<td>43</td>
<td>58.4 (29.8–159.1)</td>
</tr>
<tr>
<td></td>
<td>MCCS</td>
<td>1990–2003</td>
<td>22,830</td>
<td>35</td>
<td>40–69</td>
<td>85</td>
<td>475.0 (190.0–475.0)</td>
<td>86</td>
<td>500.0 (200.0–900.0)</td>
<td>41</td>
<td>22.4 (11.2–66.8)</td>
</tr>
<tr>
<td></td>
<td>NLCS</td>
<td>1986–1999</td>
<td>62,573</td>
<td>122</td>
<td>55–69</td>
<td>96</td>
<td>500.0 (375.0–625.0)</td>
<td>89</td>
<td>375.0 (250.0–500.0)</td>
<td>47</td>
<td>28.8 (14.8–66.8)</td>
</tr>
<tr>
<td></td>
<td>NYSC</td>
<td>1983–1987</td>
<td>22,550</td>
<td>48</td>
<td>15–107</td>
<td>85</td>
<td>473.6 (473.6–710.4)</td>
<td>51</td>
<td>473.6 (236.8–473.6)</td>
<td>↓</td>
<td>↓</td>
</tr>
<tr>
<td></td>
<td>NHSb</td>
<td>1986–2002</td>
<td>64,425</td>
<td>168</td>
<td>40–65</td>
<td>74</td>
<td>592.0 (236.8–592.0)</td>
<td>63</td>
<td>101.8 (33.2–236.8)</td>
<td>38</td>
<td>51.8 (29.6–159.1)</td>
</tr>
<tr>
<td></td>
<td>PLCO</td>
<td>1993–2004</td>
<td>28,315</td>
<td>60</td>
<td>55–74</td>
<td>85</td>
<td>842.0 (337.1–842.8)</td>
<td>85</td>
<td>140.8 (21.6–328.6)</td>
<td>65</td>
<td>22.2 (5.4–48.2)</td>
</tr>
<tr>
<td></td>
<td>SMC</td>
<td>1997–2004</td>
<td>36,630</td>
<td>54</td>
<td>49–83</td>
<td>94</td>
<td>492.0 (328.0–708.0)</td>
<td>52</td>
<td>222.0 (95.1–440.0)</td>
<td>42</td>
<td>112.0 (56.0–214.0)</td>
</tr>
<tr>
<td>Male</td>
<td>ATBC</td>
<td>1984–1999</td>
<td>26,987</td>
<td>204</td>
<td>50–69</td>
<td>98</td>
<td>600.0 (440.0–770.0)</td>
<td>36</td>
<td>157.1 (48.6–220.0)</td>
<td>42</td>
<td>47.1 (22.7–94.3)</td>
</tr>
<tr>
<td></td>
<td>CPS II</td>
<td>1992–2001</td>
<td>66,165</td>
<td>210</td>
<td>50–74</td>
<td>↑</td>
<td>↓</td>
<td>↑</td>
<td>↓</td>
<td>55</td>
<td>77.1 (20.0–141.4)</td>
</tr>
<tr>
<td></td>
<td>COSM</td>
<td>1998–2005</td>
<td>45,338</td>
<td>75</td>
<td>45–79</td>
<td>94</td>
<td>636.0 (420.0–908.0)</td>
<td>46</td>
<td>273.4 (119.2–507.6)</td>
<td>50</td>
<td>283.0 (110.3–514.7)</td>
</tr>
<tr>
<td></td>
<td>HPFS</td>
<td>1986–2002</td>
<td>45,874</td>
<td>205</td>
<td>40–75</td>
<td>83</td>
<td>592.0 (236.8–694.2)</td>
<td>58</td>
<td>101.8 (18.9–236.8)</td>
<td>56</td>
<td>88.2 (51.8–211.8)</td>
</tr>
<tr>
<td></td>
<td>MCCS</td>
<td>1990–2003</td>
<td>14,908</td>
<td>28</td>
<td>40–69</td>
<td>89</td>
<td>500.0 (200.0–500.0)</td>
<td>81</td>
<td>500.0 (156.0–514.0)</td>
<td>57</td>
<td>5.8 (10.0–86.0)</td>
</tr>
<tr>
<td></td>
<td>NLCS</td>
<td>1986–1999</td>
<td>58,279</td>
<td>145</td>
<td>55–69</td>
<td>97</td>
<td>500.0 (500.0–750.0)</td>
<td>84</td>
<td>375.0 (250.0–500.0)</td>
<td>53</td>
<td>49.9 (14.4–112.2)</td>
</tr>
<tr>
<td></td>
<td>NYSC</td>
<td>1980–1987</td>
<td>30,363</td>
<td>90</td>
<td>15–107</td>
<td>88</td>
<td>710.4 (473.6–942.7)</td>
<td>36</td>
<td>236.8 (236.8–473.6)</td>
<td>↓</td>
<td>↑</td>
</tr>
<tr>
<td></td>
<td>PLCO</td>
<td>1993–2004</td>
<td>29,914</td>
<td>90</td>
<td>55–74</td>
<td>90</td>
<td>874.5 (349.8–1,574.2)</td>
<td>81</td>
<td>43.5 (5.5–283.6)</td>
<td>82</td>
<td>49.2 (5.7–147.6)</td>
</tr>
</tbody>
</table>

Total 853,894 2,185

*ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study; BCDDP, Breast Cancer Detection Demonstration Project Follow-up Study; CNBSS, Canadian National Breast Screening Study; CPS II, Cancer Prevention Study II Nutrition Cohort; CTS, California Teachers Study; COSM, Cohort of Swedish Men; HPFS, Health Professionals Follow-up Study; IWHS, Iowa Women’s Health Study; MCCS, Melbourne Collaborative Cohort Study; NLCS, The Netherlands Cohort Study; NYSC, New York State Cohort; NHS, Nurses’ Health Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial; SMC, Swedish Mammography Cohort.

*bCohort size is determined after applying study-specific exclusion criteria and further excluding participants with energy intakes beyond 3 SDs of their log-transformed study-specific mean energy intake, history of cancer diagnosis at baseline (except for nonmelanoma skin cancer), and missing values for coffee, tea, and SSB intake (if the beverage was measured in the study); the CNBSS and the NLCS were analyzed as case–cohort studies and the above exclusions were not applied to their baseline cohort size; total cohort size = 853,894; total number of incident pancreatic cancer cases was 2,185.

c† Intake of the particular beverage was not assessed or was not assessed as a separate item (e.g., coffee and tea were included as a single line item in their dietary assessment tool).

dFor coffee and tea, 8 oz. weighs approximately 237 g; for sugar-sweetened carbonated soft drinks, 12 oz. weighs approximately 355 g.

*eSugar-sweetened carbonated soft drink is abbreviated as SSB.
smoking habits, an important pancreatic cancer risk factor (86). The methods for the Pooling Project have been described in detail elsewhere (87).

Exclusions
In addition to the exclusions that each study had predefined for their cohort, we excluded individuals if they had a prior cancer diagnosis other than non-melanoma skin cancer at baseline, had loge-transformed energy intakes beyond 3 SDs of the study- and sex-specific mean energy intake of their respective population, or were missing data on intake of coffee, tea, or SSBs (<2% of the total population). Thus, 853,894 individuals were included in the final analysis.

Exposure assessment
Usual dietary intake (e.g., intake of coffee, tea, soda) was estimated at baseline from study-specific FFQs or diet histories. The quantity of each beverage and food consumed was provided by each study as the amount (in grams) or frequency of a specific serving consumed per day. We converted the frequency data to grams consumed per day on the basis of the frequency and study-specific serving size for each food item. We calculated the consumption of coffee, tea, and SSBs by summing up the related individual beverages listed in each study. SSB intake included caffeine-free or decaffeinated colas and non-cola carbonated beverages. Diet or low-calorie sodas were not included in this definition. We were not able to separate caffeinated, decaffeinated, and herbal tea because most studies did not assess intakes of specific types of tea. Intake of caffeine was only calculated in 6 female cohorts (IWHS, NHSb, NLCS, NYSC, PLCO, SMC) and 5 male cohorts (HPFS, NLCS, NYSC, PLCO, COSM).

Although a validation study was conducted for the diet assessment method used in each study in this analysis, or a closely related instrument, the results for beverage consumption were reported in only a few of the validation studies. In these studies, the correlation coefficients comparing beverage intake from the FFQs with diet records ranged from 0.61 to 0.90 for coffee and tea and 0.35 to 0.85 for SSBs (88–91).

Information on nondietary factors was collected on the baseline self-administered questionnaires within each study. Smoking status (never, former, or current smoker) was ascertained in all studies. By design, the ATBC Study included only men who were current smokers (45). Smoking habits (e.g., duration of smoking and number of cigarettes smoked at baseline) were ascertained in all studies, except NYSC (70) which instead ascertained the usual number of cigarettes smoked daily and duration of smoking. All studies obtained information on height and weight. Thirteen studies ascertained physical activity and 11 studies ascertained diabetes status.

Outcome assessment
Invasive pancreatic cancer was ascertained by self-report with subsequent medical record review (37), through linkage with cancer registries (70, 72–77, 79), or both (45, 71, 74, 78). Some studies also identified pancreatic cancer cases through linkage with death registries (37, 70–75, 78). Of the 2,185 invasive pancreatic cancer cases identified, the majority was classified as adenocarcinoma (n = 1,594 cases) using ICD-O codes 8140–8149, 8160–8169, 8180–8229, 8250–8509, 8520–8560, and 8570–8579. The HPFS Cohort did not classify the subtypes of the pancreatic cancers; thus, they were excluded from the analysis of pancreatic adenocarcinomas (n = 205). Of the remaining 386 pancreatic cancer cases not known to be adenocarcinomas, 332 were of other histologies and 54 did not have histology information or were not otherwise specified (NOS).

Statistical analysis
Beverage intake was modeled continuously and categorically. For the categorical analysis, beverages were modeled using a priori cutoff points to capture approximate multiples of 8 oz (237g; 1 fl oz = 30 mL) servings of coffee and tea and 12 oz servings of SSBs (355g; ref. 92).

Relative risks (RR) and 95% confidence intervals (CI) were calculated by fitting Cox proportional hazards models to each study (93). If there were no cases in the highest intake category in the study, the RR for the highest category could not be estimated in that study and the noncases in the highest category were included in the second highest category. To test for a linear trend in pancreatic cancer risk with each beverage, a continuous variable with values corresponding to the median value for each exposure category was included in the model; the statistical significance of the coefficient for that variable was evaluated using the Wald test.

The models included stratification by age (years) at baseline and the calendar year at start of follow-up, and treated follow-up time (days) as the time scale, thereby creating a time metric which simultaneously accounted for age, calendar time, and time since entry into the study. Person-years of follow-up were calculated from the date of baseline questionnaire until the date of pancreatic cancer diagnosis, death, loss to follow-up, or end of follow-up, whichever came first. Multivariate RRs were adjusted for smoking habits (never smokers; past smokers, pack-years <15 years; past smokers, pack-years ≥15 years; current smokers, pack-years <40 years, current smokers, pack-years ≥40 years), personal history of diabetes (no, yes), alcohol intake (0, 0.1–14.9, 15–29.9, ≥30 g/d), body mass index (BMI; kg/m²; continuously), and energy intake (kcal/day; continuously). As excessive energy intake, personal history of diabetes and higher BMI may be in the causal pathway between SSBs and pancreatic cancer risk, we also conducted analyses removing energy, personal history of diabetes, and BMI as covariates. We conducted additional analyses in which we mutually adjusted for tea and coffee drinking. We also conducted separate analyses in which we adjusted for smoking history using different categorizations of status, duration, and dose to replace the
categorization we used for the main multivariate models. Because the proportion of participants with missing data for the covariates was generally low, an indicator variable was used for missing responses, when needed (87).

Study- and gender-specific RRs, weighted by the inverse of the sum of their variance and the estimated between-studies variance component, were pooled using a random-effects model (94). Between-studies heterogeneity was evaluated using the Q statistic (94, 95) and $I^2$ statistic (96). If heterogeneity was present between studies, mixed-effects meta-regression analyses (97) were conducted to evaluate whether the study-specific RRs varied according to follow-up time, percentage of current smokers, mean age at diagnosis, and by geographic location (North America vs. other).

To assess whether the association between intake of each beverage (e.g., coffee) and risk of pancreatic cancer was linear, we used a nonparametric regression analysis using restricted cubic spline regression (98–100). For these analyses, studies were combined into an aggregated data set. Age, year of questionnaire return and study were included as stratification variables; the risk estimates were adjusted for the same covariates as the main analyses. To test for nonlinearity, the model fit including the linear plus any cubic spline terms selected by a stepwise regression procedure was compared with the model fit with only the linear term using the likelihood ratio test. If linearity in the association between intake of the beverage and pancreatic cancer risk was suggested, we further analyzed the beverage as a continuous estimate. We also excluded participants with extremely high intakes of each beverage (approximately the highest 1%) to reduce the influence of outliers in the nonparametric regression analysis.

To examine variation in RRs by BMI, physical activity, and alcohol consumption, we assessed the statistical significance of the pooled cross-product term between the intake of that specific beverage and the stratification variable using a Wald test. We used a meta-regression model (101) to evaluate whether associations with beverage intake varied by gender, smoking status, age at diagnosis, and follow-up time as these are nominal variables or can only be assessed fully between-studies. We conducted sensitivity analyses excluding cases diagnosed during the first few years of follow-up to evaluate lag effects (5 years) and to address the concerns of reverse causation (2 years), as beverage intake of cases that occurred close in time to the completion of the baseline questionnaire might have changed because of prediagnostic disease symptoms. Separate analyses were also conducted for adenosarcomas, the most common pancreatic cancer subtype (80–84), for those studies that had information on histological subtypes, as well as for individuals who reported no personal history of diabetes at baseline. These analyses were conducted for those studies having more than 10 cases. SAS software, version 9.1, was used.

## Results

The study population consisted of 317,828 men and 536,066 women among whom 1,047 men and 1,138 women developed pancreatic cancer (Table 1). Among consumers, median coffee intake ranged from 448 to 875 g/d across the studies, whereas median tea and SSB consumption ranged from 44 to 500 g/d and 22 to 283 g/d, respectively.

Coffee consumption was not associated with pancreatic cancer risk overall (pooled multivariate RR $= 1.10$; 95% CI, 0.81–1.48; $P$ value, test for between-studies heterogeneity $= 0.08$; $P$ value, test for between-studies heterogeneity due to sex $= 0.69$; Table 2, Fig. 1A) in females (pooled multivariate RR $= 1.18$; 95% CI, 0.71–1.98; $P$ value, test for between-studies heterogeneity $= 0.01$) or in males (pooled multivariate RR $= 0.95$; 95% CI, 0.67–1.36; $P$ value, test for between-studies heterogeneity $= 0.83$) when comparing intake of $\geq 900$ to 0 g/d. Although not statistically significant, a suggestion of heterogeneity due to differences in the percentage of current smokers in the female cohorts was present ($P = 0.12$). For the same comparison, no statistically significant association between intake of coffee and pancreatic cancer risk was observed when we limited the study population to never smokers or nondiabetics or when we additionally adjusted for intake of total vegetables and red meat. Furthermore, when the case definition was limited to adenocarcinomas, no statistically significant association was observed for intake of coffee and risk of pancreatic adenocarcinomas (results not shown).

No statistically significant association was observed between tea intake and pancreatic cancer risk (pooled multivariate RR comparing $\geq 400$ with 0 g/d $= 0.96$; 95% CI, 0.78–1.16; $P$ value, test for between-studies heterogeneity $= 0.19$; Table 2, Fig. 1B). Similar results were observed for males and females ($P$ value, test for between-studies heterogeneity due to sex $= 0.17$). For the same contrast, no statistically significant association between intake of tea and pancreatic cancer risk was observed when we limited the analysis to nondiabetics or non-smokers or when we additionally adjusted for intake of total vegetables and red meat. When comparing $\geq 400$ with 0 g/d, no statistically significant association was observed for intake of tea and risk of pancreatic adenocarcinoma overall (pooled multivariate RR $= 1.03$; 95% CI, 0.82–1.30).

As suggested by the categorical analyses, the nonparametric regression analyses were most consistent with a linear association between intake of coffee and tea and pancreatic cancer risk ($P$ value, test for non-linearity $> 0.10$). The pooled multivariate RR for a 237 g/d increment in intake was $1.01$ (95% CI, 0.97–1.04) for coffee and $1.00$ (95% CI, 0.96–1.05) for tea. In analyses that mutually adjusted for tea intake and coffee intake, we found similar risk estimates for coffee intake (pooled multivariate RR $= 1.00$; 95% CI, 0.97–1.04 for a 237 g/d increment) and tea intake (pooled
### Table 2. Pooled age-adjusted and multivariate \(^a\) RRs and 95% CIs of pancreatic cancer for coffee, tea, and SSB intake

<table>
<thead>
<tr>
<th>Beverage</th>
<th>Intake category, g/d</th>
<th>No. of cases (females, males)</th>
<th>Age-adjusted RR (95% CI)</th>
<th>Multivariate RR (95% CI) (^a)</th>
<th>(P) value (^b), %</th>
<th>(P) value (^c)</th>
<th>(P) value due to sex (^d)</th>
<th>(P) for trend (^e)</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Coffee</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>95, 54</td>
<td>1.00 (Ref)</td>
<td>1.16 (0.84–1.60)</td>
<td>39</td>
<td>0.07</td>
<td>0.68</td>
<td>0.20</td>
</tr>
<tr>
<td></td>
<td>0.01–&lt;150</td>
<td>56, 79</td>
<td>1.03 (0.84–1.27)</td>
<td>1.15 (0.96–1.39)</td>
<td>65</td>
<td>0.01</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td></td>
<td>150–&lt;400</td>
<td>153, 163</td>
<td>1.01 (0.77–1.32)</td>
<td>1.10 (0.86–1.41)</td>
<td>65</td>
<td>0.01</td>
<td>0.11</td>
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<tr>
<td></td>
<td>400–&lt;900</td>
<td>327, 411</td>
<td>1.00 (0.76–1.47)</td>
<td>1.10 (0.86–1.41)</td>
<td>65</td>
<td>0.01</td>
<td>0.11</td>
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<tr>
<td></td>
<td>≥900</td>
<td>127, 130</td>
<td>0.88 (0.61–1.21)</td>
<td>0.92 (0.71–1.32)</td>
<td>65</td>
<td>0.01</td>
<td>0.11</td>
<td></td>
</tr>
<tr>
<td><strong>Tea</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>253, 380</td>
<td>1.00 (Ref)</td>
<td>1.16 (0.84–1.60)</td>
<td>38</td>
<td>0.08</td>
<td>0.69</td>
<td>0.71</td>
</tr>
<tr>
<td></td>
<td>0.01–&lt;150</td>
<td>190, 186</td>
<td>1.01 (0.82–1.25)</td>
<td>1.08 (0.89–1.31)</td>
<td>65</td>
<td>0.01</td>
<td>0.50</td>
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<tr>
<td></td>
<td>150–&lt;400</td>
<td>157, 146</td>
<td>1.00 (0.76–1.32)</td>
<td>1.10 (0.81–1.48)</td>
<td>65</td>
<td>0.01</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td></td>
<td>≥400</td>
<td>158, 125</td>
<td>1.02 (0.73–1.43)</td>
<td>1.18 (0.71–1.98)</td>
<td>65</td>
<td>0.01</td>
<td>0.50</td>
<td></td>
</tr>
<tr>
<td><strong>SSB</strong></td>
<td></td>
<td></td>
<td></td>
<td></td>
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<td></td>
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<td></td>
</tr>
<tr>
<td></td>
<td>0</td>
<td>656, 477</td>
<td>1.00 (Ref)</td>
<td>0.93 (0.81–1.08)</td>
<td>4</td>
<td>0.41</td>
<td>0.65</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>0.01–&lt;125</td>
<td>333, 322</td>
<td>0.97 (0.83–1.13)</td>
<td>0.96 (0.78–1.16)</td>
<td>4</td>
<td>0.41</td>
<td>0.65</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>125–&lt;250</td>
<td>61, 66</td>
<td>1.03 (0.83–1.28)</td>
<td>1.08 (0.71–1.98)</td>
<td>4</td>
<td>0.41</td>
<td>0.65</td>
<td>0.21</td>
</tr>
<tr>
<td></td>
<td>≥250</td>
<td>158, 125</td>
<td>0.91 (0.74–1.14)</td>
<td>0.84 (0.59–1.18)</td>
<td>4</td>
<td>0.41</td>
<td>0.65</td>
<td>0.21</td>
</tr>
</tbody>
</table>

\(^a\)Multivariate RRs were adjusted for smoking status (never smokers; past smokers, pack-years <15 years; past smokers, pack-years ≥15 years; current smokers, pack-years <40 years, current smokers, pack-years ≥40 years), alcohol intake (0, 0.1–14.9, 15–29.9, ≥30 g/d), history of diabetes (no, yes), BMI (continuous), and energy intake (continuous); age in years and year of questionnaire return were included as stratification variables.

\(^b\)\(^P\) statistic, which describes percentage of total variation that is due to heterogeneity rather than chance, is based on the highest category of beverage intake.

\(^c\)\(^P\) value, test for between-studies heterogeneity due to sex is based on the highest category of beverage intake.

\(^d\)\(^P\) value, test for between-studies heterogeneity due to sex is based on the highest category of beverage intake.

\(^e\)\(^P\) value, test for trend.

\(^f\)The BCDDP Follow-up Cohort, the CPS II Nutrition Cohort, and CTS were not included in these analyses because they did not measure consumption of this beverage or the particular beverage was not assessed as a separate item.

\(^g\)The NYSC (males and females) were not included in these analyses because consumption of this beverage was not assessed as a separate item.

\(^h\)The MCOCS (females) were not included in the analysis for the ≥250 category due to the small number of cases (\(n < 10\)).
multivariate RR = 1.01; 95% CI, 0.97–1.05 for a 237 g/d increment).

When comparing ≥250 with 0 g/d, no statistically significant association was observed between SSB consumption and pancreatic cancer risk overall (pooled multivariate RR = 1.19; 95% CI, 0.98–1.46; P value, test for between-studies heterogeneity = 0.54; Table 2, Fig. 1C) or among males (pooled multivariate RR = 1.19; 95% CI,
smoked, (iv) smoking status, smoking duration among different models that adjusted for smoking habits as: (i) smoking status and smoking duration among past smokers, and amount smoked by current smokers, or (v) smoking status and smoking pack-years (data not shown).

Overall, the null associations of intakes of coffee and tea with pancreatic cancer risk were not modified by lifestyle and cohort characteristics (P values, test for interaction > 0.05; Table 3). In addition, results for intakes of tea and coffee and pancreatic cancer risk were similar when we compared results from analyses limited to the first 5 years of follow-up with those of 5 or more years of follow-up, excluding cases diagnosed during the first 2 years of follow-up (data not shown), or stratified by the median age at diagnosis of the cases.

When modeled as a continuous estimate and for certain subgroups, the positive association with intake of SSB was more evident. For a 175 g/d increment of SSB consumption, positive associations with pancreatic cancer risk were observed for nondiabetics (pooled multivariate RR = 1.07; 95% CI, 1.02–1.13), in nondrinkers of alcohol (pooled multivariate RR = 1.14; 95% CI, 1.05–1.23), for those with a BMI < 25 kg/m² (pooled multivariate RR = 1.12; 95% CI, 1.03–1.22), for those ≥ 69 years of age (pooled multivariate RR = 1.10; 95% CI, 1.04–1.17), or when the outcome definition was limited to adenocarcinoma (pooled multivariate RR = 1.08; 95% CI, 1.03–1.14). Furthermore, positive results were observed when the follow-up was limited to ≥ 5 years (pooled multivariate RR = 1.08; 95% CI, 1.02–1.15) or when cases who were diagnosed during the first year (pooled multivariate RR = 1.06; 95% CI, 1.01–1.11) or the first 2 years (pooled multivariate RR = 1.06; 95% CI, 1.01–1.12) were excluded.

Discussion

In this pooled prospective analysis of 14 cohort studies, no association was observed between intake of coffee, tea, and caffeine during adulthood and pancreatic cancer risk. Our findings were consistent with the findings of the WCRF/AICR 2007 report (46) and a recent meta-analysis (102). In that report, the summary RR (95% CI) for a 1 cup of coffee/d (~237 grams) increment was 1.04 (1.01–1.07) for 26 case–control studies with moderate between-studies heterogeneity present and 1.00 (0.94–1.07) for 8 cohort studies, 3 of which are included in our analysis, with low between-studies heterogeneity (46). Similarly, in a recent meta-analysis by Turati and colleagues (102), which included 37 case–control and 17 cohort studies, no statistically significant risk of pancreatic cancer was observed for coffee intake, particularly when just including studies that adjusted for smoking. Similar null results were observed for tea intake. In the WCRF report, the summary estimate (95% CI) for a 1 cup of tea/d (~237 grams) increment was 0.99 (0.91–1.08) for 7 case–control studies with significant between-studies heterogeneity present and 0.95 (0.82–1.09) for 9 cohort studies with low between-studies heterogeneity present (46).

Although we were only able to examine a modest contrast in intake of SSBs in the categorical analyses due
Table 3. Pooled multivariate\textsuperscript{a} RRs (95% CI) for consumption of coffee, tea, and SSBs overall and by histologic subtype and risk factors for pancreatic cancer

<table>
<thead>
<tr>
<th></th>
<th>Coffee\textsuperscript{b,c} (increment 237 g/d)</th>
<th>Tea\textsuperscript{b,c} (increment 237 g/d)</th>
<th>SSB\textsuperscript{b,d} (increment 175 g/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>RR (95% CI)</td>
<td>$P_{\text{het}}$</td>
</tr>
<tr>
<td>Total pancreatic cancer</td>
<td>1,595</td>
<td>1.01 (0.97–1.04)</td>
<td>0.05</td>
</tr>
<tr>
<td>Females</td>
<td>758</td>
<td>1.04 (0.97–1.11)</td>
<td>0.01</td>
</tr>
<tr>
<td>Males</td>
<td>837</td>
<td>0.98 (0.95–1.01)</td>
<td>0.90</td>
</tr>
<tr>
<td>Adenocarcinoma\textsuperscript{g}</td>
<td>1,149</td>
<td>1.01 (0.98–1.05)</td>
<td>0.12</td>
</tr>
<tr>
<td>Nondiabetics\textsuperscript{h}</td>
<td>1,244</td>
<td>0.98 (0.95–1.02)</td>
<td>0.23</td>
</tr>
<tr>
<td>Smoking status\textsuperscript{i}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Never</td>
<td>525</td>
<td>1.04 (0.95–1.15)</td>
<td>&lt;0.01</td>
</tr>
<tr>
<td>Former</td>
<td>442</td>
<td>0.94 (0.89–1.01)</td>
<td>0.19</td>
</tr>
<tr>
<td>Current</td>
<td>591</td>
<td>1.00 (0.96–1.04)</td>
<td>0.62</td>
</tr>
<tr>
<td>Alcohol consumption, g/day</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>0</td>
<td>405</td>
<td>1.06 (0.99–1.13)</td>
<td>0.03</td>
</tr>
<tr>
<td>&gt;0–&lt;15</td>
<td>811</td>
<td>1.06 (0.99–1.04)</td>
<td>0.30</td>
</tr>
<tr>
<td>≥15</td>
<td>371</td>
<td>0.96 (0.89–1.04)</td>
<td>0.11</td>
</tr>
<tr>
<td>Physical activity\textsuperscript{j}</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Low</td>
<td>607</td>
<td>0.98 (0.94–1.02)</td>
<td>0.39</td>
</tr>
<tr>
<td>Medium</td>
<td>435</td>
<td>1.00 (0.94–1.06)</td>
<td>0.26</td>
</tr>
<tr>
<td>High</td>
<td>303</td>
<td>0.99 (0.94–1.04)</td>
<td>0.59</td>
</tr>
<tr>
<td>BMI, kg/m\textsuperscript{2}</td>
<td></td>
<td></td>
<td></td>
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<tr>
<td>&lt;25</td>
<td>671</td>
<td>1.03 (0.98–1.07)</td>
<td>0.19</td>
</tr>
<tr>
<td>≥25</td>
<td>892</td>
<td>0.98 (0.95–1.01)</td>
<td>0.43</td>
</tr>
</tbody>
</table>

(Continued on the following page)
Table 3. Pooled multivariate<sup>a</sup> RRs (95% CI) for consumption of coffee, tea, and SSBs overall and by histologic subtype and risk factors for pancreatic cancer (Cont’d)

<table>
<thead>
<tr>
<th></th>
<th>Coffee&lt;sup&gt;b,c&lt;/sup&gt; (increment 237 g/d)</th>
<th>Tea&lt;sup&gt;b,c&lt;/sup&gt; (increment 237 g/d)</th>
<th>SSB&lt;sup&gt;b,d&lt;/sup&gt; (increment 175 g/d)</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>No. of cases</td>
<td>RR (95% CI)</td>
<td>$P_{het}$</td>
</tr>
<tr>
<td>Age at diagnosis, y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;69</td>
<td>817</td>
<td>1.01 (0.98–1.04)</td>
<td>0.55</td>
</tr>
<tr>
<td>≥69</td>
<td>778</td>
<td>0.99 (0.94–1.05)</td>
<td>0.09</td>
</tr>
<tr>
<td>Follow-up&lt;sup&gt;k&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>≤5</td>
<td>487</td>
<td>0.99 (0.95–1.03)</td>
<td>0.71</td>
</tr>
<tr>
<td>&gt;5</td>
<td>1,093</td>
<td>1.02 (0.97–1.08)</td>
<td>0.01</td>
</tr>
</tbody>
</table>

<sup>a</sup>Multivariate RRs were adjusted for smoking status (never smokers; past smokers, pack-years < 15 years; past smokers, pack-years ≥ 15 years; current smokers, pack-years < 40 years, current smokers, pack-years ≥ 40 years), alcohol intake (0, 0.1–14.9, 15–29.9, ≥ 30 g/d), history of diabetes (no, yes), BMI (continuously), and energy intake (continuously); age in years and year of questionnaire return were included as stratification variable. In the smoking stratified analyses, past and current smoking analyses included pack-years (< 15, ≥ 15 years for past smokers; < 40, ≥ 40 years for current smokers) in the model; age in years and year of questionnaire return were included as stratification variables. For the other models, the stratification variable was excluded as a covariate.

<sup>b</sup>For coffee and tea, 8 oz. weighs approximately 237g; for sugar-sweetened carbonated soft drinks, 12 oz. weighs approximately 355g.

<sup>c</sup>The BCDDP Follow-up Cohort, the CPS II Nutrition Cohort, and CTS were not included in these analyses because they did not measure consumption of this particular beverage or the particular beverage was not assessed as a separate item.

<sup>d</sup>The NYSC (males and females) were not included in these analyses because the beverage was not assessed as a separate item.

<sup>e</sup>P value, test for between-studies heterogeneity.

<sup>f</sup>P value, test for interaction.

<sup>g</sup>The HPFS was not included in the analysis on pancreatic adenocarcinoma as they did not have the histology data available.

<sup>h</sup>BCDDP Follow-up Cohort, CNBSS, and NYSC were excluded from this analysis because they did not measure diabetes status at baseline.

<sup>i</sup>ATBC Cancer Prevention Study was excluded from the never and past smoking analyses because this study only included current smokers. Because of the small case numbers ($n < 10$), The NLCS male cohort was excluded from never smoking analysis, NYSC female cohort was excluded from past smoking analysis, and MCCS (males and females) were excluded from current smoking analysis.

<sup>j</sup>CNBSS was excluded from the physical activity analysis.

<sup>k</sup>The MCCS (males and females) were excluded from the follow-up less than 5 years analysis due to small case numbers (<10).
to the small number of cases who consumed at least 355 g (~12 oz) of SSBs, there was a suggestive and slightly positive association for intakes of SSBs which was more apparent when intake was modeled as a continuous variable. Our positive results were consistent with those observed by the Singapore Chinese Health Study (62), but not the null findings found in the NIH-AARP Diet and Health Study (61) and a Japanese cohort study (60), the only other cohort studies we are aware of that were not included in our analyses. Similarly, a recent meta-analysis by Gallus and colleagues (65), that included 4 case–control and 6 cohort studies, reported no association between soft drink consumers compared with nonconsumers (RR = 1.02; 95% CI, 0.93–1.12). Because of the sparse and inconsistent data, no summary statement on SSBs was given in the WCRF/AICR report. Our findings are consistent with the idea that factors that raise insulin and glucose levels, and promote obesity and diabetes, such as SSBs (55–57), may be positively associated with pancreatic cancer risk, particularly in certain “low risk” subgroups (e.g., normal weight, nondrinkers).

In addition, caffeine, a biologically active compound found in both tea and coffee (68), has been theorized to play a role in carcinogenesis. Caffeine may alter cell cycle checkpoint function and several mechanisms of DNA repair by overriding G1 and G2 checkpoints and by increasing the metabolic rate, thus theoretically increasing cancer risk (103). Alternatively, caffeine may lower pancreatic cancer risk. Caffeine has been shown to be inversely associated with the risk of diabetes (104), and diabetes has been suggested to increase pancreatic cancer risk (48). Of the limited number of studies that have examined caffeine intake and pancreatic cancer risk, results have generally been null or suggestive of a weak inverse association (37, 69). Our findings were similarly null.

Similar to many of the previous studies conducted, the majority of participants in each of the component studies in the Pooling Project were Caucasian (~94%). Thus, we did not have enough power to examine whether associations differed by race and ethnicity. However, the studies in our analyses comprise populations from different geographic regions with different age ranges and education levels which may be considered a strength, particularly given that the results generally were consistent across studies. One advantage of our study was that we were able to classify the main exposure and confounding variables uniformly, thereby lessening potential sources of heterogeneity across studies.

Our pancreatic cancer case definition may represent different subtypes of pancreatic cancer and histologic subtypes may be associated with different etiologies. When we limited the case definition for pancreatic cancer to adenocarcinoma, we observed similar estimates for intake of each beverage as those reported for all pancreatic cancers. Thus, our conclusions are applicable at least to the predominant group of pancreatic cancers.

In our study, we were unable to examine the association between types of tea (e.g., green vs. black) and coffee (e.g., caffeinated vs. decaffeinated), preparation methods and additions to the beverage (e.g., sugar, milk), and risk of pancreatic cancer as few studies had measured these exposures. In the few studies that have examined these associations, most studies reported no association with green tea (60, 105–107) and caffeinated coffee intake (46); teas and coffees contain a mixture of both anti- and procarcinogenic compounds (108–110). Two prospective cohort studies have assessed the association between sugar added to coffee and tea (59, 61) and cereal (59); one observed a weak modest, but not statistically significant association (1.12; 95% CI, 0.91–1.39 comparing 34.8 to 0 g/d; ref. 61), whereas the other observed a positive association (RR = 1.95; 95% CI, 1.10–3.46 comparing >5 to 0 g/d; ref. 59). Differences in varietals and preparation methods may have different effects on cancer risk, which should be explored in future studies.

Furthermore, we cannot rule out measurement error in consumption of beverages (e.g., coffee, tea, SSBs). In addition, using only baseline dietary information might result in greater misclassification of usual consumption versus diet information from multiple assessments throughout follow-up. However, inaccurate reporting of beverage intake (misclassification) should not vary by outcome status (i.e., pancreatic cancer risk) in this prospective study, and as such, may result in nondifferential misclassification. The effect of nondifferential misclassification would tend to attenuate the association between intakes of beverages with pancreatic cancer risk, and it is a possible explanation for the observed null associations.

In each component study, data on beverage intake were collected prior to cancer diagnosis; thus, a cancer diagnosis would not have influenced the reporting of beverage intake as may occur in a case–control study. However, individuals who were diagnosed close in time to baseline may have already experienced changes in beverage intake due to prediagnostic symptoms; results from analyses where we excluded cases diagnosed during the first 2 and 5 years of follow-up were similar to the overall results. Because of the inclusion of 14 cohort studies, we had greater statistical power than the individual studies to examine the associations between beverage intake and pancreatic cancer risk and to assess whether these associations were modified by other pancreatic cancer risk factors. Few prior studies have published on these potential effect modification associations.

In summary, we found no association between intakes of tea and coffee during adulthood and pancreatic cancer risk in this pooled analysis. Although we were only able to examine a modest intake of SSBs, there was a suggestive and slightly positive association for their intakes which reached statistical significance in certain subgroups of participants (e.g., nondiabetics, nondrinkers of alcohol).
Thus, these results are in accordance with the WCRF/AICR recommendation to limit consumption of SSBs (46).

**Disclosure of Potential Conflicts of Interest**

No potential conflicts of interests were disclosed.

**References**
