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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 anti-carcinogenic properties, while tea may contain anti-carcinogenic compounds. Studies assessing coffee intake and pancreatic cancer risk have yielded mixed results, while findings for tea intake have mostly been null. Sugar-sweetened carbonated soft drink (abbreviated as 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 853,894 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 <0g/day; 237g≈8oz), tea (MVRR=0.96, 95% CI=0.78-1.16 comparing 400 to 0g/day; 237g≈8oz) or SSB (MVRR=1.19, 95% CI=0.98-1.46 comparing 250 to 0g/day; 355g≈12oz) (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 (MVRR=1.06, 95% CI=1.02-1.12).

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.

Keywords

Pancreatic Cancer; Beverages; Pooled Analysis

INTRODUCTION

Worldwide, pancreatic tumors cause significant morbidity and mortality as the 7th and 9th 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.

Over 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(3-32). Initial studies that did not control for smoking observed positive associations between coffee intake and pancreatic cancer risk, while more recent publications, which have controlled for smoking, have generally reported null associations(3-32). 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 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(55-57), may be positively associated with pancreatic cancer risk. Eight prospective studies and six case-control studies have examined the association between sugar-sweetened soft drink 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 sugar-sweetened carbonated soft drinks (68) has been theorized to both increase and decrease 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 sugar-sweetened carbonated soft drinks and pancreatic cancer risk in a pooled analysis of 14 cohort studies(70-81). 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 (82). Thus, we examined associations between intakes of beverages separately for adenocarcinomas of the pancreas, the predominant type of pancreatic cancer (82-86).

MATERIALS AND METHODS

Population

A pooled analysis of the primary data from fourteen cohort studies(73-81, 87-89) 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)(81); Breast Cancer Detection Demonstration Project Follow-up Study (BCDDP) (71); Canadian National Breast Screening Study (CNBSS) (73); Cancer Prevention Study II Nutrition Cohort (CPS II) (74); California Teachers Study (CTS) (72); Cohort of Swedish Men (COSM)(80); Health Professionals Follow-up Study (HPFS)(77); Iowa Women's Health Study (IWHS)(75); Melbourne Collaborative Cohort Study (MCCS)(76); The Netherlands Cohort Study (NLCS) (78); New York State Cohort (NYSC) (70); Nurses' Health Study (NHS)(77); Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial (PLCO) (79); Swedish Mammography Cohort(SMC)(80). Each eligible study (Table 1) had to meet the following pre-specified 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 two 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 Canadian National Breast Screening Study and Netherlands Cohort Study, were analyzed as case-cohort studies(73, 78). For the Nurses' Health Study, we divided the person-time of the Nurses' Health Study into two 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 Nurses' Health Study between 1980 and 1986. For the Swedish Mammography Cohort, we utilized 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 smoking habits, an important pancreatic cancer risk factor(90). The methods for the Pooling Project have been described in detail elsewhere(91).

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 \log_e -transformed energy intakes beyond three standard deviations of the study- and sex-specific \log_e -transformed mean energy intake of their respective population, or were missing data on intake of coffee, tea or sugar-sweetened carbonated soft drinks (< 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 based on the frequency and study-specific serving size for each food item. We calculated the consumption of coffee, tea, and sugar-sweetened carbonated soft drinks by summing up the related individual beverages listed in each study. Sugar-sweetened carbonated soft drink intake included caffeine-free or caffeinated colas and non-colas 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 six female cohorts (IWHS, NHSb, NLCS, NYSC, PLCO, SMC) and five 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 to diet records ranged from 0.61 to 0.90 for coffee and tea and 0.35 to 0.85 for sugar-sweetened carbonated soft drinks (92-95).

Information on non-dietary 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 Alpha-Tocopherol Beta-Carotene Cancer Prevention Study included only men who were current smokers(81). Smoking habits (e.g., duration of smoking and number of cigarettes smoked at baseline) were ascertained in all studies, except The New York State Cohort(87) 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; eleven studies ascertained diabetes status.

Outcome Assessment

Invasive pancreatic cancer(96) was ascertained by self-report with subsequent medical record review(77), through linkage with cancer registries(72, 73, 75, 76, 78, 80, 87), or both(74, 79, 81, 88). Some studies also identified pancreatic cancer cases through linkage with death registries(72-75, 77, 79, 87, 88). 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, 8570-8579. The Health Professionals Follow-up Cohort did not classify the subtypes of the pancreatic cancers; thus, they were excluded from the analysis of pancreatic adenocarcinomas ($n_{\text{cases}}=205$). 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 cutpoints to capture approximate multiples of 8 oz (237g; 1 fl oz = 30 ml) servings of coffee and tea and 12 oz servings of sugar-sweetened carbonated soft drinks (355g)(97) .

Relative risks (RRs) and 95% confidence intervals (CI) were calculated by fitting Cox proportional hazards models to each study (98). 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 relative risks (RR) were adjusted for smoking habits (never smokers; past smokers, pack-years <15yrs; past smokers, pack-years 15-40yrs; current smokers, pack-years >40yrs), personal history of diabetes (no, yes), alcohol intake (0, 0.1-14.9, 15-29.9, 30g/day), 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 sugar-sweetened carbonated soft drinks 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 (91).

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 (99). Between-studies heterogeneity was evaluated using the Q statistic (99, 100) and I² statistic(101). If heterogeneity was present between studies, mixed-effects meta-regression analyses (102) 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 versus other).

To assess whether the association between intake of each beverage (e.g., coffee) and risk of pancreatic cancer was linear, we used a non-parametric regression analysis using restricted cubic spline regression (103-105). 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 non-linearity, the model fit including the linear plus any cubic spline terms selected by a stepwise regression procedure was compared to 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 that beverage as a continuous estimate. We also excluded participants with extremely high intakes of each

beverage (approximately the highest one percent) to reduce the influence of outliers in the non-parametric regression analysis.

To examine variation in RRs by body mass index (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 (106) 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 due to prediagnostic disease symptoms. Separate analyses were also conducted for adenocarcinomas, the most common pancreatic cancer subtype (82-86), 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 875g/day across the studies, while median tea and sugar-sweetened carbonated soft drink consumption ranged from 44 to 500g/day and 22 to 283g/day, 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, Figure 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 900g/day to 0g/day. Although not statistically significant, a suggestion of heterogeneity due to differences in the percentage of current smokers in the female cohorts was present (p-value = 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 non-diabetics or when we additionally adjusted for intake of total vegetables and red meat. Further, 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 400g/day to 0g/day = 0.96, 95% CI=0.78-1.16; p-value, test for between-studies heterogeneity = 0.19) (Table 2, Figure 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 non-diabetics or non-smokers or when we additionally adjusted for intake of total vegetables and red meat. When comparing 400g/day compared to 0g/day, 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 non-parametric 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 237g/day 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 237g/day increment) and tea intake (pooled multivariate RR= 1.01, 95% CI: 0.97-1.05 for a 237g/day increment).

When comparing 250g/day to 0g/day, no statistically significant association was observed between sugar-sweetened carbonated soft drink 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, Figure 1c) or among males (pooled multivariate RR = 1.19, 95% CI = 0.89-1.59; p-value, test for between-studies heterogeneity=0.28) or females (pooled multivariate RR = 1.22, 95% CI = 0.87-1.70; p-value, test for between-studies heterogeneity=0.60). *The results were similar when we additionally adjusted for intake of total vegetables and red meat.* When we examined a larger contrast in intake of sugar-sweetened carbonated soft drinks in men, no statistically significant association was observed for intakes of 250g/day-<375g/day compared to 0g/day. However, a 56% (95% CI=1.09-2.23) higher risk of pancreatic cancer was observed among those who consumed 375g/day of sugar-sweetened carbonated soft drinks compared to 0g/day (n_{malecases}=45). We were unable to examine the same contrast in women due to the small number of women consuming 375g/day of sugar-sweetened carbonated soft drinks (n_{femalecases}=14).

Due to the small number of cases drinking 250g/day of sugar-sweetened carbonated soft drinks in each study, for sub-analyses we examined the contrast 125g/day compared to 0g/day (pooled multivariate RR=1.06, 95% CI=0.91-1.23). Results were similar when we limited the study population to never smokers or non-diabetics for the same comparison (125g/day compared to 0g/day). Further, when the case definition was limited to adenocarcinomas, no statistically significant association was observed for the same contrast in sugar-sweetened carbonated soft drink intake. If the association between sugar-sweetened carbonated soft drink intake and pancreatic cancer risk is mediated by excessive energy and weight gain, adjustment for total energy might represent over control. When energy, personal history of diabetes and BMI were not included as covariates, the estimates were similar to the main results.

The non-parametric regression analysis was most consistent with a linear association between intake of sugar-sweetened carbonated soft drink and pancreatic cancer risk (p-value, test for non-linearity > 0.10). A positive association was observed for a 177.5g/day increment in sugar-sweetened carbonated soft drink intake and pancreatic cancer risk (pooled multivariate RR=1.06, 95% CI=1.02-1.12). Although there was no statistically significant difference in risk between men and women (p-value, test for between studies heterogeneity by sex = 0.38), a statistically significant positive association was observed in men (pooled multivariate RR=1.08, 95% CI =1.02-1.14), but not in women (pooled multivariate RR=1.03, 95% CI=0.93-1.13).

Further, we examined the relation between caffeine intake and pancreatic cancer risk, as coffee, tea and sugar-sweetened beverages are major contributors to caffeine intake. Comparing the highest to lowest quintile for five male (COSM, HPFS, NLCS, NYSC, PLCO) and six female cohorts (IWHs, NLCS, NYSC, NHS, PLCO, SMC), no statistically significant association was observed between caffeine intake and pancreatic cancer risk (pooled multivariate RR = 0.87, 95% CI = 0.71-1.07; p-value, test for between studies heterogeneity = 0.34; p-value, test for trend = 0.12; n_{cases}=1223; data not shown).

The association for each beverage was similar for the different models that adjusted for smoking habits as: 1) smoking status (never, past, current), 2) smoking status and smoking duration, 3) smoking status and amount smoked, 4) smoking status, smoking duration among past smokers, and amount smoked by current smokers, or 5) 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 five years of follow-up with those of five or more years of follow-up, excluding cases diagnosed during the first two 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 sugar-sweetened carbonated soft drink was more evident. For a 175 g/day increment of sugar-sweetened carbonated soft drink consumption, positive associations with pancreatic cancer risk were observed for non-diabetics (pooled multivariate RR = 1.07, 95% CI = 1.02-1.13), in nondrinkers of alcohol (pooled multivariate RR = 1.14, 1.05-1.23), for those with a BMI <25kg/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). Further, 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-.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(107). In that report, the summary RR (95% CI) for a 1 cup of coffee/day (approximately 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 eight cohort studies, three of which are included in our analysis, with low between-studies heterogeneity (46). Similarly, in a recent meta-analysis by Turati et al (107), 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/day (approximately 237 grams) increment was 0.99 (0.91-1.08) for seven case-control studies with significant between-studies heterogeneity present and 0.95 (0.82-1.09) for nine cohort studies with low between-studies heterogeneity present(46).

Although we were only able to examine a modest contrast in intake of sugar-sweetened carbonated soft drinks in the categorical analyses due to the small number of cases who consumed at least 355g (~12oz) of sugar-sweetened carbonated soft drinks, there was a suggestive and slightly positive association for intakes of sugar-sweetened carbonated soft drinks 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 National Institutes of Health-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 et al (65), that included four case-control and six cohort studies, reported no association between soft drink consumers compared to non-consumers (RR=1.02, 95% CI=0.93-1.12). Due to the sparse and inconsistent data, no summary statement on sugar-sweetened carbonated soft drinks 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 sugar-sweetened carbonated soft drinks(55-57), may be positively associated with pancreatic cancer risk, particularly in certain “low risk” subgroups (e.g., normal weight, nondrinkers).

Additionally, 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 (108). Alternatively, caffeine may lower pancreatic cancer risk. Caffeine has been shown to be inversely associated with the risk of diabetes (109), 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 (approximately 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 histological 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 versus black) and coffee (e.g., caffeinated versus 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, 110-112) and caffeinated coffee intake(46); teas and coffees contain a mixture of both anti- and pro-carcinogenic compounds(113-115). 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 0grams/day) (61), while the other observed a positive association (RR=1.95, 95% CI = 1.10-3.46 comparing > 5 to 0 grams/day(59). Differences in varieties 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, sugar-sweetened carbonated soft drinks). 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 non-differential 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 two and five years of follow-up were similar to the overall results. Due to 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 sugar-sweetened carbonated soft drinks, there was a suggestive and slightly positive association for their intakes which reached statistical significance in certain subgroups of participants (e.g., nondiabetics, non-drinkers of alcohol). Thus, these results are in accordance with the WCRF/AICR recommendation to limit consumption of sugar-sweetened carbonated soft drinks (46).

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References

1. GLOBOCAN 2002: Cancer Incidence, Mortality and Prevalence Worldwide. IARC Press; Lyon: 2004.
2. Cancer Facts & Figures 2009. American Cancer Society; Atlanta, GA: 2009.
3. Gullo L, Pezzilli R, Morselli-Labate AM. Coffee and cancer of the pancreas: an Italian multicenter study. The Italian Pancreatic Cancer Study Group. *Pancreas*. 1995; 11:223–9.
4. Lin RS, Kessler II. A multifactorial model for pancreatic cancer in man. Epidemiologic evidence. *JAMA*. 1981; 245:147–52. [PubMed: 7452829]
5. MacMahon B, Yen S, Trichopoulos D, Warren K, Nardi G. Coffee and cancer of the pancreas. *N Engl J Med*. 1981; 304:630–3. [PubMed: 7453739]
6. Gold EB, Gordis L, Diener MD, Seltser R, Boitnott JK, Bynum TE, et al. Diet and other risk factors for cancer of the pancreas. *Cancer*. 1985; 55:460–7. [PubMed: 3965101]
7. Hsieh CC, MacMahon B, Yen S, Trichopoulos D, Warren K, Nardi G. Coffee and pancreatic cancer (Chapter 2). *N Engl J Med*. 1986; 315:587–9. [PubMed: 3736647]
8. La Vecchia C, Liati P, Decarli A, Negri E, Franceschi S. Coffee consumption and risk of pancreatic cancer. *Int J Cancer*. 1987; 40:309–13. [PubMed: 3623714]
9. Jick H, Dinan BJ. Coffee and pancreatic cancer. *Lancet*. 1981; 2:92. [PubMed: 6113465]
10. Goldstein HR. No association found between coffee and cancer of the pancreas. *N Engl J Med*. 1982; 306:997. [PubMed: 7062988]
11. Norell SE, Ahlbom A, Erwald R, Jacobson G, Lindberg-Navier I, Olin R, et al. Diet and pancreatic cancer: A case-control study. *Am J Epidemiol*. 1986; 124:894–902. [PubMed: 3776972]
12. Mack TM, Yu MC, Hanisch R, Henderson BE. Pancreas Cancer and Smoking, Beverage Consumption, and Past Medical History. *J Natl Cancer Inst*. 1986; 76:49–60. [PubMed: 3455742]

13. Falk RT, Williams Pickle L, Fontham ET, Correa P, Fraumeni JF. Life-style risk factors for pancreatic cancer in Louisiana: A case-control study. *Am J Epidemiol.* 1988; 128:324–36. [PubMed: 3394699]
14. Gorham ED, Garland CF, Garland FC, Benenson AS, Cottrell L. Coffee and pancreatic cancer in a rural California county. *West J Med.* 1988; 148:48–53. [PubMed: 3277336]
15. Wynder EL, Hall NE, Polansky M. Epidemiology of coffee and pancreatic cancer. *Cancer Res.* 1983; 43:3900–6. [PubMed: 6861152]
16. Kinlen LJ, McPherson K. Pancreas cancer and coffee and tea consumption: a case-control study. *Br J Cancer.* 1984; 49:93–6. [PubMed: 6691902]
17. Elinder C, Millqvist K, Floderus-Myrhed B, Pershagen G. Swedish studies do not support the hypothesis about a connection between coffee and cancer of the pancreas. *Lakartidningen.* 1981; 78:3676–7.
18. Clavel F, Benhamou E, Auquier A, Tarayre M, Flamant R. Coffee, alcohol, smoking and cancer of the pancreas: a case-control study. *Int J Cancer.* 1989; 43:17–21. [PubMed: 2910828]
19. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. A case-control study of pancreatic cancer and cigarettes, alcohol, coffee and diet. *Am J Public Health.* 1989; 79:1016–9. [PubMed: 2751016]
20. Cuzick J, Babiker AG. Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. *Int J Cancer.* 1989; 43:415–21. [PubMed: 2925272]
21. Farrow DC, Davis S. Risk of pancreatic cancer in relation to medical history and the use of tobacco, alcohol and coffee. *Int J Cancer.* 1990; 45:816–20. [PubMed: 2335385]
22. Jain M, Howe GR, Louis P, Miller AB. Coffee and alcohol as determinants of risk of pancreas cancer: a case-control study from Toronto. *Int J Cancer.* 1991; 47:384–9. [PubMed: 1993545]
23. Ghadirian P, Simard A, Baillargeon J. Tobacco, alcohol, and coffee and cancer of the pancreas. A population-based, case-control study in Quebec, Canada. *Cancer.* 1991; 67:2664–70. [PubMed: 2015568]
24. Bueno de Mesquita HB, Maisonneuve P, Moerman CJ, Runia S, Boyle P. Lifetime consumption of alcoholic beverages, tea and coffee and exocrine carcinoma of the pancreas: a population-based case-control study in The Netherlands. *Int J Cancer.* 1992; 50:514–22. [PubMed: 1537615]
25. Stefanati A, Saletti C, Califano A, Piva E, De Rosa E, Rausa G. Coffee, alcohol, smoking and risk of cancer of the pancreas: A case-control study. *J Prev Med Hyg.* 1992; 33:65–70.
26. Zatonski WA, Boyle P, Przewozniak K, Maisonneuve P, Drosik K, Walker AM. Cigarette smoking, alcohol, tea and coffee consumption and pancreas cancer risk: a case-control study from Opole, Poland. *Int J Cancer.* 1993; 53:601–7. [PubMed: 8436433]
27. Kalapothaki V, Tzonou A, Hsieh C-C, Toupadaki N, Karakatsani A, Trichopoulos D. Tobacco, ethanol, coffee, pancreatitis, diabetes mellitus, and cholelithiasis as risk factors for pancreatic carcinoma. *Cancer Causes Control.* 1993; 4:375–82. [PubMed: 8347787]
28. Sciallero S, Bonelli L, Saccomanno S, Conio M, Bruzzi P, Pugliese V. Socioeconomic characteristics, life style, diabetes, family history of cancer and risk of pancreatic cancer. *Eur J Gastroenterol Hepatol.* 1993; 5:367–71.
29. Silverman DT, Swanson CA, Gridley G, Wacholder S, Greenberg RS, Brown LM, et al. Dietary and nutritional factors and pancreatic cancer: a case-control study based on direct interviews. *J Natl Cancer Inst.* 1998; 90:1710–9. [PubMed: 9827525]
30. Partanen T, Hemminki K, Vainio H, Kauppinen T. Coffee consumption not associated with risk of pancreas cancer in Finland. *Prev Med.* 1995; 24:213–6. [PubMed: 7597024]
31. Villeneuve PJ, Johnson KC, Hanley AJ, Mao Y, Canadian Cancer Registries Epidemiology Research Group. Alcohol, tobacco and coffee consumption and the risk of pancreatic cancer: results from the Canadian Enhanced Surveillance System case-control project. *Eur J Cancer Prev.* 2000; 9:49–58. [PubMed: 10777010]
32. Kreiger N, Lacroix J, Sloan M. Hormonal factors and pancreatic cancer in women. *Ann Epidemiol.* 2001; 11:563–7. [PubMed: 11709276]
33. Nomura AM, Lee J, Kolonel LN, Hirohata T. Breast cancer in two populations with different levels of risk for the disease. *Am J Epidemiol.* 1984; 119:496–502. [PubMed: 6711538]

34. Lin Y, Tamakoshi A, Kawamura T, Inaba Y, Kikuchi S, Motohashi Y, et al. Risk of pancreatic cancer in relation to alcohol drinking, coffee consumption and medical history: findings from the Japan collaborative cohort study for evaluation of cancer risk. *Int J Cancer*. 2002; 99:742–6. [PubMed: 12115510]
35. Mills PK, Beeson L, Abbey DE, Fraser GE, Phillips RL. Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. *Cancer*. 1988; 61:2578–85. [PubMed: 3365678]
36. Harnack LJ, Anderson KE, Zheng W, Folsom AR, Sellers TA, Kushi LH. Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's Health Study. *Cancer Epidemiol Biomarkers Prev*. 1997; 6:1081–6. [PubMed: 9419407]
37. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. *Cancer Epidemiol Biomarkers Prev*. 2001; 10:429–37. [PubMed: 11352851]
38. Isaksson B, Jonsson F, Pedersen NL, Larsson J, Feychting M, Permert J. Lifestyle factors and pancreatic cancer risk: a cohort study from the Swedish Twin Registry. *Int J Cancer*. 2002; 98:480–2. [PubMed: 11920604]
39. Heuch I, Kvale G, Jacobsen BK, Bjelke E. Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. *Br J Cancer*. 1983; 48:637–43. [PubMed: 6685527]
40. Hiatt RA, Klatsky AL, Armstrong MA. Pancreatic cancer, blood glucose and beverage consumption. *Int J Cancer*. 1988; 41:794–7. [PubMed: 3372055]
41. Stensvold I, Jacobsen BK. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. *Cancer Causes Control*. 1994; 5:401–8. [PubMed: 7999961]
42. Whittemore AS, Paffenbarger RS Jr, Anderson K, Halpern J. Early precursors of pancreatic cancer in college men. *J Chronic Dis*. 1983; 36:251–6. [PubMed: 6826689]
43. Snowdon DA, Phillips RL. Coffee consumption and risk of fatal cancers. *Am J Public Health*. 1984; 74:820–3. [PubMed: 6742274]
44. Shibata A, Mack TM, Paganini-Hill A, Ross RK, Henderson BE. A prospective study of pancreatic cancer in the elderly. *Int J Cancer*. 1994; 58:46–9. [PubMed: 8014014]
45. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. Prospective study of diet and pancreatic cancer in male smokers. *Am J Epidemiol*. 2002; 155:783–92. [PubMed: 11978580]
46. Food, Nutrition, Physical Activity and the Prevention of Cancer: A Global Perspective. World Cancer Research Fund and the American Institute for Cancer Research; Washington, DC: 2007.
47. Lyon JL, Egger MJ, Robison LM, French TK, Gao R. Misclassification of exposure in a case-control study: the effects of different types of exposure and different proxy respondents in a study of pancreatic cancer. *Epidemiology*. 1992; 3:223–31. [PubMed: 1591321]
48. Huxley R, Ansary-Moghaddam A, Berrington de Gonzalez A, Barzi F, Woodward M. Type-II diabetes and pancreatic cancer: a meta-analysis of 36 studies. *Br J Cancer*. 2005; 92:2076–83. [PubMed: 15886696]
49. Solaymani-Mohammadi S, Genkinger JM, Loffredo CA, Singer SM. A Meta- analysis of the Effectiveness of Albendazole Compared with Metronidazole as Treatments for Infections with *Giardia duodenalis*. *PLoS Negl Trop Dis*. 4:e682. [PubMed: 20485492]
50. Li D, Morris JS, Liu J, Hassan MM, Day RS, Bondy ML, et al. Body mass index and risk, age of onset, and survival in patients with pancreatic cancer. *JAMA*. 2009; 301:2553–62. [PubMed: 19549972]
51. McWilliams RR, Petersen GM. Overweight, obesity, and pancreatic cancer: beyond risk alone. *JAMA*. 2009; 301:2592–3. [PubMed: 19549978]
52. Yun JE, Jo I, Park J, Kim MT, Gun Ryu H, Odongua N, et al. Cigarette smoking, elevated fasting serum glucose, and risk of pancreatic cancer in Korean men. *Int J Cancer*. 2006
53. Stolzenberg-Solomon RZ, Graubard BI, Chari S, Limburg P, Taylor PR, Virtamo J, et al. Insulin, glucose, insulin resistance, and pancreatic cancer in male smokers. *JAMA*. 2005; 294:2872–8. [PubMed: 16352795]
54. Johansen D, Stocks T, Jonsson H, Lindkvist B, Bjorge T, Concin H, et al. Metabolic factors and the risk of pancreatic cancer: a prospective analysis of almost 580,000 men and women in the

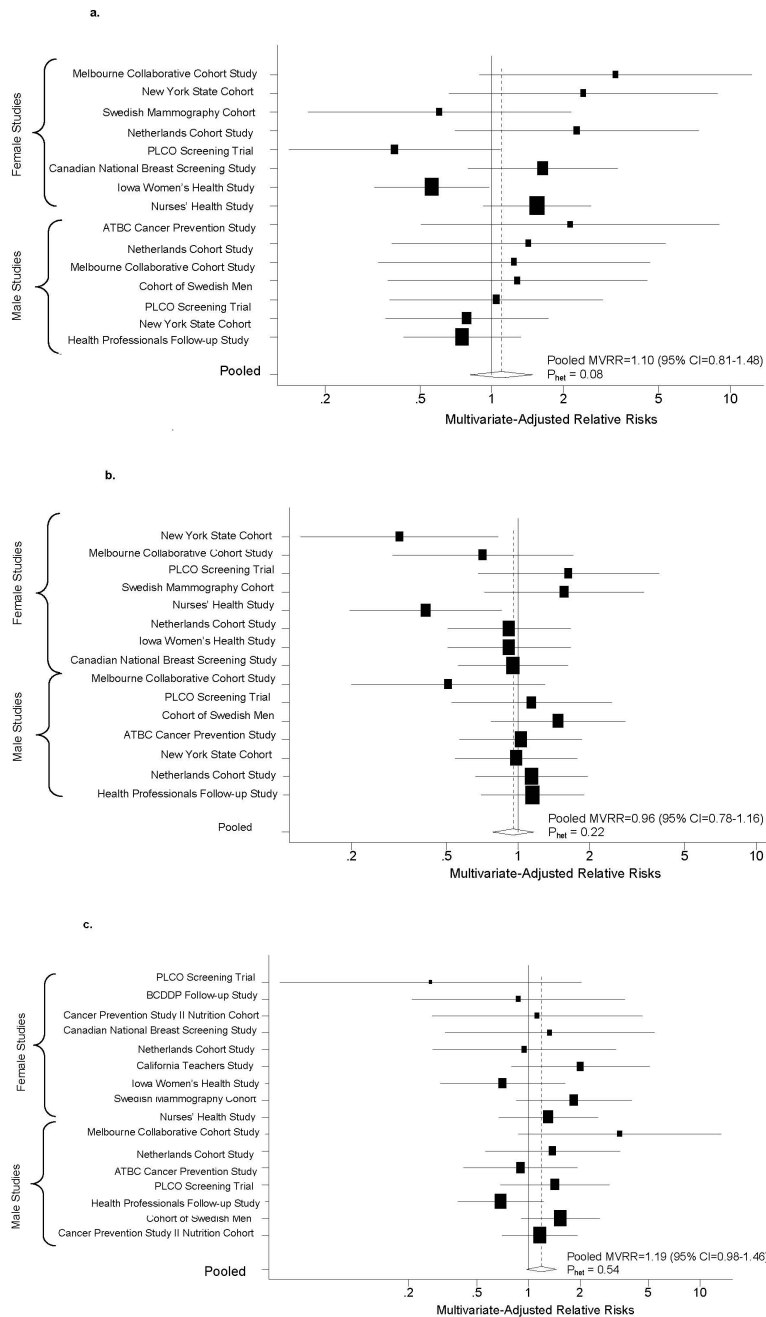
Metabolic Syndrome and Cancer Project. *Cancer Epidemiol Biomarkers Prev.* 19:2307–17. [PubMed: 20826833]

55. Akgun S, Ertel NH. The effects of sucrose, fructose, and high-fructose corn syrup meals on plasma glucose and insulin in non-insulin-dependent diabetic subjects. *Diabetes Care.* 1985; 8:279–83. [PubMed: 3891268]
56. Willett W, Manson J, Liu S. Glycemic index, glycemic load, and risk of type 2 diabetes. *Am J Clin Nutr.* 2002; 76:274S–80S. [PubMed: 12081851]
57. Schulze MB, Manson JE, Ludwig DS, Colditz GA, Stampfer MJ, Willett WC, et al. Sugar-sweetened beverages, weight gain, and incidence of type 2 diabetes in young and middle-aged women. *JAMA.* 2004; 292:927–34. [PubMed: 15328324]
58. Schernhammer ES, Hu FB, Giovannucci E, Michaud DS, Colditz GA, Stampfer MJ, et al. Sugar-sweetened soft drink consumption and risk of pancreatic cancer in two prospective cohorts. *Cancer Epidemiol Biomarkers Prev.* 2005; 14:2098–105. [PubMed: 16172216]
59. Larsson SC, Bergkvist L, Wolk A. Consumption of sugar and sugar-sweetened foods and the risk of pancreatic cancer in a prospective study. *Am J Clin Nutr.* 2006; 84:1171–6. [PubMed: 17093171]
60. Khan MM, Goto R, Kobayashi K, Suzumura S, Nagata Y, Sonoda T, et al. Dietary habits and cancer mortality among middle aged and older Japanese living in hokkaido, Japan by cancer site and sex. *Asian Pac J Cancer Prev.* 2004; 5:58–65. [PubMed: 15075007]
61. Bao Y, Stolzenberg-Solomon R, Jiao L, Silverman DT, Subar AF, Park Y, et al. Added sugar and sugar-sweetened foods and beverages and the risk of pancreatic cancer in the National Institutes of Health-AARP Diet and Health Study. *Am J Clin Nutr.* 2008; 88:431–40. [PubMed: 18689380]
62. Mueller NT, Odegaard A, Anderson K, Yuan JM, Gross M, Koh WP, et al. Soft drink and juice consumption and risk of pancreatic cancer: the Singapore Chinese Health Study. *Cancer Epidemiol Biomarkers Prev.* 19:447–55. [PubMed: 20142243]
63. Lyon JL, Mahoney AW, French TK, Moser R Jr. Coffee consumption and the risk of cancer of the exocrine pancreas: a case-control study in a low-risk population. *Epidemiology.* 1992; 3:164–70. [PubMed: 1576222]
64. Baghurst PA, McMichael AJ, Slavotinek AH, Baghurst KI, Boyle P, Walker AM. A case-control study of diet and cancer of the pancreas. *Am J Epidemiol.* 1991; 134:167–79. [PubMed: 1862800]
65. Gallus S, Turati F, Tavani A, Polesel J, Talamini R, Franceschi S, et al. Soft drinks, sweetened beverages and risk of pancreatic cancer. *Cancer Causes Control.* 22:33–9. [PubMed: 20981481]
66. Chan JM, Wang F, Holly EA. Sweets, sweetened beverages, and risk of pancreatic cancer in a large population-based case-control study. *Cancer Causes Control.* 2009; 20:835–46. [PubMed: 19277880]
67. Nothlings U, Murphy SP, Wilkens LR, Henderson BE, Kolonel LN. Dietary glycemic load, added sugars, and carbohydrates as risk factors for pancreatic cancer: the Multiethnic Cohort Study. *Am J Clin Nutr.* 2007; 86:1495–501. [PubMed: 17991664]
68. Knight CA, Knight I, Mitchell DC, Zepp JE. Beverage caffeine intake in US consumers and subpopulations of interest: estimates from the Share of Intake Panel survey. *Food Chem Toxicol.* 2004; 42:1923–30. [PubMed: 15500929]
69. Olsen GW, Mandel JS, Gibson RW, Wattenberg LW, Schuman LM. Nutrients and pancreatic cancer: a population-based case-control study. *Cancer Causes Control.* 1991; 2:291–7. [PubMed: 1932541]
70. Bandera EV, Freudenheim JL, Marshall JR, Zielezny M, Priore RL, Brasure J, et al. Diet and alcohol consumption and lung cancer risk in the New York State Cohort (United States). *Cancer Causes Control.* 1997; 8:828–40. [PubMed: 9427425]
71. Calton BA, Stolzenberg-Solomon RZ, Moore SC, Schatzkin A, Schairer C, Albanes D, et al. A prospective study of physical activity and the risk of pancreatic cancer among women (United States). *BMC Cancer.* 2008; 8:63. [PubMed: 18307811]
72. Chang ET, Canchola AJ, Lee VS, Clarke CA, Purdie DM, Reynolds P, et al. Wine and other alcohol consumption and risk of ovarian cancer in the California Teachers Study cohort. *Cancer Causes Control.* 2007; 18:91–103. [PubMed: 17186425]

73. Silvera SA, Rohan TE, Jain M, Terry PD, Howe GR, Miller AB. Glycemic index, glycemic load, and pancreatic cancer risk (Canada). *Cancer Causes Control*. 2005; 16:431–6. [PubMed: 15953985]
74. Patel AV, McCullough ML, Pavluck AL, Jacobs EJ, Thun MJ, Calle EE. Glycemic load, glycemic index, and carbohydrate intake in relation to pancreatic cancer risk in a large US cohort. *Cancer Causes Control*. 2007; 18:287–94. [PubMed: 17219014]
75. Sinner PJ, Schmitz KH, Anderson KE, Folsom AR. Lack of association of physical activity and obesity with incident pancreatic cancer in elderly women. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:1571–3. [PubMed: 15941975]
76. Giles GG, English DR. The Melbourne Collaborative Cohort Study. *IARC Sci Publ*. 2002; 156:69–70. [PubMed: 12484128]
77. Michaud DS, Giovannucci E, Willett WC, Colditz GA, Fuchs CS. Coffee and alcohol consumption and the risk of pancreatic cancer in two prospective United States cohorts. *Cancer Epidemiol Biomarkers Prev*. 2001; 10:429–37. [PubMed: 11352851]
78. Verhage BA, Schouten LJ, Goldbohm RA, van den Brandt PA. Anthropometry and pancreatic cancer risk: an illustration of the importance of microscopic verification. *Cancer Epidemiol Biomarkers Prev*. 2007; 16:1449–54. [PubMed: 17585056]
79. Prorok PC, Andriole GL, Bresalier RS, Buys SS, Chia D, Crawford ED, et al. Design of the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial. *Control Clin Trials*. 2000; 21:273S–309S. [PubMed: 11189684]
80. Larsson SC, Hakansson N, Giovannucci E, Wolk A. Folate intake and pancreatic cancer incidence: a prospective study of Swedish women and men. *J Natl Cancer Inst*. 2006; 98:407–13. [PubMed: 16537833]
81. Stolzenberg-Solomon RZ, Pietinen P, Taylor PR, Virtamo J, Albanes D. Prospective study of diet and pancreatic cancer in male smokers. *Am J Epidemiol*. 2002; 155:783–92. [PubMed: 11978580]
82. Fesinmeyer MD, Austin MA, Li CI, De Roos AJ, Bowen DJ. Differences in survival by histologic type of pancreatic cancer. *Cancer Epidemiol Biomarkers Prev*. 2005; 14:1766–73. [PubMed: 16030115]
83. Cowgill SM, Muscarella P. The genetics of pancreatic cancer. *Am J Surg*. 2003; 186:279–86. [PubMed: 12946833]
84. Li D, Jiao L. Molecular epidemiology of pancreatic cancer. *International journal of gastrointestinal cancer*. 2003; 33:3–14. [PubMed: 12909734]
85. Lichtenstein DR, Carr-Locke DL. Mucin-secreting tumors of the pancreas. *Gastrointestinal endoscopy clinics of North America*. 1995; 5:237–58. [PubMed: 7728346]
86. Mullan MH, Gauger PG, Thompson NW. Endocrine tumours of the pancreas: review and recent advances. *ANZ J Surg*. 2001; 71:475–82. [PubMed: 11504292]
87. Bandera EV, Freudenheim JL, Marshall JR, Zielezny M, Priore RL, Brasure J, et al. Diet and alcohol consumption and lung cancer risk in the New York State Cohort (United States). *Cancer Causes Control*. 1997; 8:828–40. [PubMed: 9427425]
88. Calton BA, Stolzenberg-Solomon RZ, Moore SC, Schatzkin A, Schairer C, Albanes D, et al. A prospective study of physical activity and the risk of pancreatic cancer among women (United States). *BMC Cancer*. 2008; 8:63. [PubMed: 18307811]
89. Bernstein L, Allen M, Anton-Culver H, Deapen D, Horn-Ross PL, Peel D, et al. High breast cancer incidence rates among California teachers: results from the California Teachers Study (United States). *Cancer Causes Control*. 2002; 13:625–35. [PubMed: 12296510]
90. Hart AR, Kennedy H, Harvey I. Pancreatic cancer: a review of the evidence on causation. *Clin Gastroenterol Hepatol*. 2008; 6:275–82. [PubMed: 18328435]
91. Smith-Warner SA, Spiegelman D, Ritz J, Albanes D, Beeson WL, Bernstein L, et al. Methods for pooling results of epidemiologic studies: the Pooling Project of Prospective Studies of Diet and Cancer. *Am J Epidemiol*. 2006; 163:1053–64. [PubMed: 16624970]
92. Giovannucci E, Colditz G, Stampfer MJ, Rimm EB, Litin L, Sampson L, et al. The assessment of alcohol consumption by a simple self-administered questionnaire. 1991; 133:810–7.

93. Pietinen P, Hartman AM, Haapa E, Rasanen L, Haapakoski J, Palmgren J, et al. Reproducibility and validity of dietary assessment instruments II. A qualitative food frequency questionnaire. *Am J Epidemiol.* 1988; 128:667–76. [PubMed: 2843041]
94. Subar AF, Thompson FE, Kipnis V, Midthune D, Hurwitz P, McNutt S, et al. Comparative validation of the Block, Willett, and National Cancer Institute food frequency questionnaires: the Eating at America's Table Study. *Am J Epidemiol.* 2001; 154:1089–99. [PubMed: 11744511]
95. Messerer M, Johansson SE, Wolk A. The validity of questionnaire-based micronutrient intake estimates is increased by including dietary supplement use in Swedish men. *J Nutr.* 2004; 134:1800–5. [PubMed: 15226472]
96. Liu S, Serdula MK, Byers T, Williamson DF, Mokdad AH, Flanders WD. Reliability of alcohol intake as recalled from 10 years in the past. *Am J Epidemiol.* 1996; 143:177–86. [PubMed: 8546119]
97. Pennington, JAT. *Bowes and Church's Food Values of Portions Commonly Used.* 17ed.. Lippincott-Raven; New York: 1998.
98. Cox DR. Regression models and life-tables. *Journal of the Royal Statistical Society, Series (B).* 1972; 34:187–220.
99. DerSimonian R, Laird N. Meta-analysis in clinical trials. *Control Clin Trials.* 1986; 7:177–88. [PubMed: 3802833]
100. Cochran WG. The combination of estimates from different experiments. *Biometrics.* 1954; 10:101–29.
101. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ.* 2003; 327:557–60. [PubMed: 12958120]
102. Stram DO. Meta-analysis of published data using a linear mixed-effects model. *Biometrics.* 1996; 52:536–44. [PubMed: 8672702]
103. Durrleman S, Simon R. Flexible regression models with cubic splines. *Stat Med.* 1989; 8:551–61. [PubMed: 2657958]
104. Govindarajulu US, Malloy EJ, Ganguli B, Spiegelman D, Eisen EA. The Comparison of Alternative Smoothing Methods for Fitting Non-Linear Exposure- Response Relationships with Cox Models in a Simulation Study. *Int J Biostat.* 2009; 5 Article 2.
105. Govindarajulu US, Spiegelman D, Thurston SW, Ganguli B, Eisen EA. Comparing smoothing techniques in Cox models for exposure-response relationships. *Stat Med.* 2007; 26:3735–52. [PubMed: 17538974]
106. Kuha J. Corrections for exposure measurement error in logistic regression models with an application to nutritional data. *Stat Med.* 1994; 13:1135–48. [PubMed: 8091040]
107. Turati F, Galeone C, Edefonti V, Ferraroni M, Lagiou P, La Vecchia C, et al. A meta-analysis of coffee consumption and pancreatic cancer. *Ann Oncol.*
108. Porta M, Vioque J, Ayude D, Alguacil J, Jariod M, Ruiz L, et al. Coffee drinking: the rationale for treating it as a potential effect modifier of carcinogenic exposures. *Eur J Epidemiol.* 2003; 18:289–98. [PubMed: 12803368]
109. van Dam RM, Hu FB. Coffee consumption and risk of type 2 diabetes: a systematic review. *JAMA.* 2005; 294:97–104. [PubMed: 15998896]
110. Lin Y, Kikuchi S, Tamakoshi A, Yagyu K, Obata Y, Kurosawa M, et al. Green tea consumption and the risk of pancreatic cancer in Japanese adults. *Pancreas.* 2008; 37:25–30. [PubMed: 18580440]
111. Luo J, Inoue M, Iwasaki M, Sasazuki S, Otani T, Ye W, et al. Green tea and coffee intake and risk of pancreatic cancer in a large-scale, population-based cohort study in Japan (JPHC study). *Eur J Cancer Prev.* 2007; 16:542–8. [PubMed: 18090127]
112. Ji BT, Chow WH, Hsing AW, McLaughlin JK, Dai Q, Gao YT, et al. Green tea consumption and the risk of pancreatic and colorectal cancers. *Int J Cancer.* 1997; 70:255–8. [PubMed: 9033623]
113. Trevisanato SI, Kim YI. Tea and health. *Nutr Rev.* 2000; 58:1–10. [PubMed: 10697388]
114. Wiseman SA, Balentine DA, Frei B. Antioxidants in tea. *Crit Rev Food Sci Nutr.* 1997; 37:705–18. [PubMed: 9447271]

115. Yang CS, Maliakal P, Meng X. Inhibition of carcinogenesis by tea. *Annu Rev Pharmacol Toxicol.* 2002; 42:25–54. [PubMed: 11807163]



1. . Multivariate Adjusted Relative Risks and 95% Confidence Intervals for Pancreatic Cancer According to Intake of Coffee (Figure a; 900g/day compared to <0g/day), Tea (Figure b; 400g/day compared to 0g/day) and Sugar-Sweetened Carbonated Soft Drinks (Figure c; 50g/day compared to 0g/day) by Study

The black squares and horizontal lines correspond to the study-specific relative risks and 95% confidence intervals. The area of the black squares is proportional to the inverse of the sum of the between-studies variance and the study-specific variance. The studies are ordered within each sex strata according to their weight in calculating the pooled estimate. The diamond represents the pooled multivariate relative risk and the 95% confidence interval. The vertical dashed line represents the pooled multivariate relative risk. Abbreviations: ATBC, Alpha-Tocopherol Beta-Carotene Cancer Prevention Study, BCDDP, Breast Cancer

Detection Demonstration Project Follow-up Study; PLCO, Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial.

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Table 1
Beverage Intake by Cohort Study in the Pancreatic Analysis of the Pooling Project of Prospective Studies of Diet and Cancer

Sex	Cohort ¹	Follow-up Years	Baseline Cohort Size ²	Number of Cases	Age Range (yrs)	Median (Interquartile Range, unit: gram/day) among drinkers ^{3,4}					
						% Coffee drinkers	Coffee	% Tea drinkers	Tea	% SSB ⁵ drinkers	SSB
Female											
	BCDDP	1987-1999	43162	102	40-93	‡	‡	‡	‡	39	47.1 (16.5-141.1)
	CNBSS	1980-2000	49654	105	40-59	85	448.0 (224.0-896.0)	77	336.0 (128.0-672.0)	37	32.0 (14.7-64.0)
	CPS II	1992-2001	74138	164	50-74	‡	‡	‡	‡	36	28.9 (13.5-105.9)
	CTS	1995-2003	97945	114	22-104	‡	‡	‡	‡	34	49.7 (18.1-159.5)
	IWHS	1986-2001	33844	166	55-69	90	596.5 (292.7-1065.6)	58	101.8 (18.9-236.8)	43	58.4 (29.8-159.1)
	MCCS	1990-2003	22830	35	40-69	85	475.0 (190.0-475.0)	86	500.0 (200.0-900.0)	41	22.4 (11.2-68.8)
	NLCS	1986-1999	62573	122	55-69	96	500.0 (375.0-625.0)	89	375.0 (250.0-500.0)	47	28.8 (14.4-68.8)
	NYSC	1980-1987	22550	48	15-107	85	473.6 (473.6-710.4)	51	473.6 (236.8-473.6)	‡	‡
	NHSb	1986-2002	64425	168	40-65	74	592.0 (236.8-592.0)	63	101.8 (33.2-236.8)	38	51.8 (29.6-159.1)
	PLCO	1993-2004	28315	60	55-74	85	842.0 (337.1-842.8)	85	140.8 (21.6-328.6)	65	22.2 (5.54-48.2)
	SMC	1997-2004	36630	54	49-83	94	492.0 (328.0-708.0)	52	222.0 (95.1-444.0)	42	112.0 (56.0-214.0)
Male											
	ATBC	1984-1999	26987	204	50-69	98	600.0 (440.0-770.0)	36	157.1 (48.6-220.0)	42	47.1 (22.7-94.3)
	CPS II	1992-2001	66165	210	50-74	‡	‡	‡	‡	55	77.1 (20.0-141.4)
	COSM	1998-2005	45338	75	45-79	94	636.0 (424.0-908.6)	46	273.4 (119.2-507.6)	50	283.0 (110.3-514.7)
	HPFS	1986-2002	45874	205	40-75	83	592 (236.8-694.2)	58	101.8 (18.9-236.8)	56	88.2 (51.8-211.8)

Sex	Cohort ¹	Follow-up Years	Baseline Cohort Size ²	Number of Cases	Age Range (yrs)	Median (Interquartile Range, unit: gram/day) among drinkers ^{3,4}					
						% Coffee drinkers	Coffee	% Tea drinkers	Tea	% SSB ⁵ drinkers	SSB
	MCCS	1990-2003	14908	28	40-69	89	500.0 (200.0-500.0)	81	500.0 (156.0-514.0)	‡ 57	28 (14-86)
	NLCS	1986-1999	58279	145	55-69	97	500.0 (500.0-750.0)	84	375.0 (250.0-500.0)	53	49.9 (14.4-112.2)
	NYSC	1980-1987	30363	90	15-107	88	710.4 (473.6-947.2)	36	236.8 (236.8-473.6)	‡	‡
Total	PLCO	1993-2004	29914 853894	90 2185	55-74	90	874.5 (349.8-1574.2)	81	43.5 (5.51-283.6)	82	49.2 (5.7-147.6)

¹ATBC, 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.

²Cohort size is determined after applying study-specific exclusion criteria and further excluding participants with energy intakes beyond 3 SD of their loge-transformed study-specific mean energy intake, history of cancer diagnosis at baseline (except for non-melanoma skin cancer) and missing values for coffee, tea and sugar-sweetened carbonated soft drink intake (if the beverage was measured in the study); the Canadian National Breast Screening Study and the Netherlands Cohort Study were analyzed as a case-cohort studies and the above exclusions were not applied to their baseline cohort size; total cohort size = 853,894; total number of incidence pancreatic cancer cases was 2,185.

³(‡) 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).

⁴For coffee and tea, 8 oz. weighs approximately 237 g; for carbonated soft drinks, 12 oz. weighs approximately 355g.

⁵Sugar-sweetened carbonated soft drink is abbreviated as SSB

Table 2

Pooled Age-Adjusted and Multivariate⁷ Relative Risks (RRs) and 95% Confidence Intervals (CIs) of Pancreatic Cancer for Coffee, Tea and Sugar-Sweetened Carbonated Soft Drink Intake

Beverage	Categories of Beverage Intake					I ²²	P _{het} ³	P _{het} ⁴	P _{trend} ⁵
	0	0-<150	150-<400	400-<900	900				
Coffee⁶									
Intake category (g/day)	0	0-<150	150-<400	400-<900	900				
No. of cases (females, males)	95,54	56, 79	153, 163	327, 411	127, 130				
Age-adjusted RR (95% CI)									
Total	1.00 (Ref)	1.16(0.84-1.60)	1.03(0.84-1.27)	1.15(0.96-1.39)	1.33(0.99-1.78)	39%	0.07	0.68	0.20
Females	1.00 (Ref)	0.87(0.54-1.40)	1.01(0.77-1.32)	1.10(0.86-1.41)	1.44(0.88-2.37)	65%	0.01		0.11
Males	1.00 (Ref)	1.56(1.06-2.29)	1.06(0.76-1.47)	1.24(0.91-1.67)	1.15(0.82-1.63)	0%	0.83		0.68
Multivariate RR (95% CI) ⁷									
Total	1.00 (Ref)	1.16(0.84-1.60)	1.01(0.82-1.25)	1.08(0.89-1.31)	1.10(0.81-1.48)	38%	0.08	0.69	0.71
Females	1.00 (Ref)	0.87(0.53-1.43)	1.00(0.76-1.32)	1.04(0.80-1.34)	1.18(0.71-1.98)	65%	0.01		0.50
Males	1.00 (Ref)	1.53(1.03-2.26)	1.02(0.73-1.43)	1.15(0.84-1.58)	0.95(0.67-1.36)	0%	0.83		0.06
Tea⁶									
Intake category (g/day)	0	0-<150	150-<400	400					
No. of cases (females, males)	253, 380	190, 186	157, 146	158, 125					
Age-adjusted RR (95% CI)									
Total	1.00 (Ref)	0.88 (0.76-1.01)	0.90(0.77-1.04)	0.89(0.73-1.07)		21%	0.22	0.13	0.42
Females	1.00 (Ref)	0.88 (0.72-1.08)	0.96(0.77-1.18)	0.77(0.55-1.07)		45%	0.09		0.37
Males	1.00 (Ref)	0.87 (0.71-1.07)	0.84(0.68-1.04)	1.01(0.80-1.27)		0%	0.82		0.94
Multivariate RR (95% CI) ⁷									
Total	1.00 (Ref)	0.93 (0.81-1.08)	0.97(0.83-1.13)	0.96(0.78-1.16)		24%	0.19	0.17	0.96
Females	1.00 (Ref)	0.95 (0.77-1.16)	1.03(0.83-1.28)	0.84(0.59-1.18)		46%	0.08		0.65
Males	1.00 (Ref)	0.92 (0.74-1.14)	0.91(0.74-1.13)	1.08(0.86-1.37)		0%	0.73		0.59
Sugar-sweetened carbonated soft drinks⁷									

Beverage	Categories of Beverage Intake				I^2	P_{het}^3	P_{het}^4	P_{trend}^5
	0	0-<125	125-<250	250				
Intake category (g/day)	0	0-<125	125-<250	250				
No. of cases (females, males)	656, 477	333, 322	61, 66	40, 92				
Age-adjusted RR (95% CI)								
Total	1.00 (Ref)	0.95 (0.86-1.05)	0.95(0.78-1.16)	1.19(0.97-1.45)	4%	0.41	0.65	0.21
Females	1.00 (Ref)	1.02 (0.89-1.17)	1.05(0.81-1.38)	1.26(0.91-1.76)	0%	0.60		0.23
Males	1.00 (Ref)	0.87 (0.75-1.01)	0.82(0.54-1.23)	1.17(0.86-1.59)	34%	0.18		0.54
Multivariate RR (95% CI) ¹								
Total	1.00 (Ref)	1.01 (0.91-1.11)	1.00(0.82-1.21)	1.19(0.98-1.46)	0%	0.54	0.89	0.15
Females	1.00 (Ref)	1.07 (0.93-1.23)	1.09(0.83-1.43)	1.22(0.87-1.70)	0%	0.60		0.32
Males	1.00 (Ref)	0.93 (0.80-1.08)	0.86(0.59-1.24)	1.19(0.89-1.59)	20%	0.28		0.37

¹ Multivariate relative risks (RR) were adjusted for smoking status (never smokers; past smokers, pack-years <15yrs; current smokers, pack-years <40yrs, current smokers, pack-years > 40yrs), alcohol intake (0.0-1-14.9, 15-29.9, 30g/day), history of diabetes (no, yes), body mass index (continuously) and energy intake (continuously); age in years and year of questionnaire return were included as stratification variables

² I^2 statistic, which describes percentage of total variation that is due to heterogeneity rather than chance, is based on the highest category of beverage intake

³ P value, test for between-studies heterogeneity is based on the highest category of beverage intake.

⁴ P value, test for between-studies heterogeneity due to sex is based on the highest category of beverage intake.

⁵ P value, test for trend.

⁶ The Breast Cancer Detection Demonstration Project Follow-up Cohort, the Cancer Prevention Study II Follow-up Cohort, and California Teacher's Study 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

⁷ The New York State Cohort (males and females) 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.

Table 3

Pooled Multivariate Relative Risks (95% CI) for consumption of coffee, tea, and sugar-sweetened carbonated soft drinks overall and by histological subtype and risk factors for pancreatic cancer

	Coffee ^{2,3} (Increment 237 g/day)			Tea ^{2,3} (Increment 237 g/day)			Sugar-Sweetened Carbonated Soft Drinks ^{2,4} (Increment 175 g/day)			
	No. of cases	RR (95% CI)	P Het ⁵	No. of cases	RR (95% CI)	P Het ⁵	No. of cases	RR (95% CI)	P Het ⁵	P Int ⁶
Total pancreatic CA	1595	1.01 (0.97-1.04)	0.05	1595	1.00 (0.96-1.05)	0.51	2047	1.06 (1.02-1.12)	0.70	
Females	758	1.04 (0.97-1.11)	0.01	758	0.98 (0.91-1.05)	0.20	1090	1.03 (0.93-1.13)	0.76	0.38
Males	837	0.98 (0.95-1.01)	0.90	837	1.02 (0.96-1.09)	0.84	957	1.08 (1.02-1.14)	0.41	
Adenocarcinoma ⁷	1149	1.01 (0.98-1.05)	0.12	1240	1.02 (0.96-1.08)	0.20	1556	1.08 (1.03-1.14)	0.84	
Non-diabetics ⁸	1244	0.98 (0.95-1.02)	0.23	1244	1.00 (0.95-1.06)	0.37	1689	1.07 (1.02-1.13)	0.64	
Smoking Status ⁹										
Never	525	1.04 (0.95-1.15)	<0.01	525	0.96 (0.88-1.03)	0.51	724	1.08 (0.98-1.19)	0.34	0.73
Former	442	0.94 (0.89-1.01)	0.19	442	1.02 (0.95-1.10)	0.55	667	1.10 (1.01-1.19)	0.88	
Current	591	1.00 (0.96-1.04)	0.62	591	1.09 (1.02-1.16)	0.71	633	1.06 (0.98-1.14)	0.94	
Alcohol Consumption										
0	405	1.06 (0.99-1.13)	0.03	405	1.05 (0.97-1.13)	0.43	626	1.14 (1.05-1.23)	0.40	0.23
0-15	811	1.00 (0.96-1.04)	0.30	811	0.98 (0.92-1.04)	0.48	967	1.06 (0.99-1.13)	0.90	
>=15	371	0.96 (0.89-1.04)	0.11	371	1.09 (1.01-1.18)	0.87	452	1.03 (0.93-1.15)	0.94	
Physical Activity ¹⁰										
Low	607	0.98 (0.94-1.02)	0.39	607	1.00 (1.00-1.00)	0.63	843	1.06 (0.99-1.14)	0.79	0.98
Medium	435	1.00 (0.94-1.06)	0.26	435	1.00 (0.99-1.00)	0.09	592	1.13 (1.04-1.22)	0.44	

	Coffee ^{2,3} (Increment 237 g/day)			Tea ^{2,3} (Increment 237 g/day)			Sugar-Sweetened Carbonated Soft Drinks ^{2,4} (Increment 175 g/day)		
	No. of cases	RR (95% CI)	P Int ⁶	No. of cases	RR (95% CI)	P Int ⁶	No. of cases	RR (95% CI)	P Int ⁶
High	303	0.99 (0.94-1.04)	0.59	303	1.00 (1.00-1.01)	0.54	476	1.09 (1.00-1.19)	0.90
Body Mass Index									
<25	671	1.03 (0.98-1.07)	0.19	671	1.03 (0.96-1.10)	0.21	872	1.12 (1.03-1.22)	0.26
>=25	892	0.98 (0.95-1.01)	0.43	892	0.98 (0.93-1.04)	0.78	1119	1.03 (0.97-1.10)	0.97
Age at diagnosis									
<69	817	1.01 (0.98-1.04)	0.55	814	1.01 (0.95-1.06)	0.80	1008	1.04 (0.96-1.12)	0.37
>=69	778	0.99 (0.94-1.05)	0.09	778	1.02 (0.96-1.08)	0.73	1039	1.10 (1.04-1.17)	0.68
Follow-up ^{1,1}									
<=5	487	0.99 (0.95-1.03)	0.71	502	1.00 (0.93-1.08)	0.31	663	1.05 (0.98-1.13)	0.70
>5	1093	1.02 (0.97-1.08)	0.01	1093	1.03 (0.97-1.09)	0.31	1369	1.08 (1.02-1.15)	0.96

¹ Multivariate relative risks (RR) were adjusted for smoking status (never smokers; past smokers, pack-years <15yrs; current smokers, pack-years 15yrs; current smokers, pack-years 40yrs, current smokers, pack-years > 40yrs), alcohol intake (0.0-1-14.9, 15-29.9, 30g/day), history of diabetes (no, yes), body mass index (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 (<15yrs, >15yrs for past smokers; <40yrs, 40yrs 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.

² For coffee and tea, 8 oz. weighs approximately 237g; for carbonated soft drinks, 12 oz. weighs approximately 355g

³ The Breast Cancer Detection Demonstration Project Follow-up Cohort, the Cancer Prevention Study II Follow-up Cohort, and California Teacher's Study 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

⁴ The New York State Cohort (males and females) were not included in these analyses because they did not measure consumption of this particular beverage or the beverage was not assessed as a separate item.

⁵ P value, test for between-studies heterogeneity.

⁶ P value, test for interaction.

⁷ The Health Professionals Follow-up Study was not included in the analysis on pancreatic adenocarcinoma as they did not have the histology data available.

⁸ Breast Cancer Detection Demonstration Project Follow-up Cohort, Canadian National Breast Screening Study and New York State Cohort were excluded from this analysis because they did not measure diabetes status at baseline.

⁹ Alpha-Tocopherol Beta-Carotene Cancer Prevention Trial was excluded from the never and past smoking analyses because this study only included current smokers. Due to the small case numbers ($n < 10$), The Netherlands Cohort Study male cohort was excluded from never smoking analysis, New York State female cohort was excluded from past smoking analysis, and Melbourne Collaborative Cohort Study (males and females) were excluded from current smoking analysis.

¹⁰ CNBSS was excluded from the physical activity analysis due to small case numbers ($n < 10$).

¹¹ The Melbourne Collaborative Cohort Study (males and females) were excluded from the follow-up less than 5 years analysis due to small case numbers (< 10).