Coffee and Alcohol Consumption and the Risk of Pancreatic Cancer in Two Prospective United States Cohorts[1]

Dominique S. Michaud,[2] Edward Giovannucci, Walter C. Willett, Graham A. Colditz, and Charles S. Fuchs

Departments of Nutrition [D. S. M., E. G., W. C. W.] and Epidemiology [E. G., W. C. W., G. A. C.], Harvard School of Public Health; Channing Laboratory, Department of Medicine, Brigham and Women's Hospital and Harvard Medical School [E. G., W. C. W., G. A. C., C. S. F.]; and Department of Adult Oncology, Dana-Farber Cancer Institute [C. S. F.], Boston, Massachusetts 02115

Abstract

Although most prospective cohort studies do not support an association between coffee consumption and pancreatic cancer, the findings for alcohol are inconsistent. Recently, a large prospective cohort study of women reported statistically significant elevations in risk of pancreatic cancer for both coffee and alcoholic beverage consumption. We obtained data on coffee, alcohol, and other dietary factors using semiquantitative food frequency questionnaires administered at baseline (1986 in the Health Professionals Follow-Up Study and 1980 in the Nurses' Health Study) and in subsequent follow-up questionnaires. Data on other risk factors for pancreatic cancer, including cigarette smoking, were also available. Individuals with a history of cancer at study initiation were excluded from all of the analyses. During the 1,907,222 person-years of follow-up, 288 incident cases of pancreatic cancer were diagnosed. The data were analyzed separately for each cohort, and results were pooled to compute overall relative risks (RR). Neither coffee nor alcohol intakes were associated with an increased risk of pancreatic cancer in either cohort or after pooling the results (pooled RR, 0.62; 95% confidence interval, 0.27–1.43, for >3 cups of coffee/day *versus* none; and pooled RR, 1.00; 95% confidence interval, 0.57–1.76, for ≥30 grams of alcohol/day *versus* none). The associations did not change with analyses examining different latency periods for coffee and alcohol. Similarly, no statistically significant associations were observed for intakes of tea, decaffeinated coffee, total caffeine, or alcoholic beverages. Data from these two large cohorts do not support any overall association between coffee intake or alcohol intake and risk of pancreatic cancer.

Received 10/12/00; revised 1/31/01; accepted 3/2/01.
The costs of publication of this article were defrayed in part by the payment of page charges. This article must therefore be hereby marked *advertisement* in accordance with 18 U.S.C. Section 1734 solely to indicate this fact.
[1] Supported by research Grants CA 40356, CA 55075, and CA 86102.
[2] To whom requests for reprints should be addressed, at National Cancer Institute, 6120 Executive Boulevard, EPS Room 7026, Rockville, MD 20852. Phone: (301) 594-6545; Fax: (301) 496-6829; E-mail: michaudd@mail.nih.gov.

Introduction

Cancer of the pancreas represents the fifth leading cause of cancer-related mortality in the United States (1). Nonetheless, other than cigarette smoke, few environmental factors have been linked to the risk of pancreatic cancer (2). Numerous prospective and case-control studies have been conducted to determine whether coffee, tea, or alcohol increases pancreatic cancer risk, but results have been inconsistent (findings are summarized in Ref. 3). Many factors may contribute to these inconsistent results. Pancreatic cancer is particularly difficult to study in case-control studies because poor survival leads to reduced participation rates for direct interviews with cases, thus the studies rely more on interviews with surrogates, particularly next-of-kin. Moreover, in population-based case-control studies, heavy alcohol and coffee drinkers may have lower participation rates than nondrinkers, and in hospital-based case-control studies, alcohol and coffee may be related to the health conditions afflicting controls that are included for study.

Prospective studies could potentially avoid these selection biases in case or control participation, as well as potential recall bias. However, previous prospective studies (4–11) on alcohol or coffee intake have generally been limited by the small number of incident cases, which have ranged from 21 to 66, with the exception of two studies (12, 13) based on over 400 pancreatic cancer cases each. To date, 10 prospective studies have examined the relation between coffee intake and pancreatic cancer risk, and all but two of these (4, 12) found no association (5–11, 13). Additionally, seven prospective studies have examined the influence of alcohol intake in nonalcoholic populations, and the results are largely inconsistent (4–8, 12, 13). Three of seven of these studies (4, 5, 8) have reported a direct relationship between alcohol intake and risk of pancreatic cancer, and a fourth found an increase in risk among whiskey drinkers (12). Of the remaining three studies, one reported a strong but statistically nonsignificant positive association among past drinkers (7), and only two observed no associations between alcohol and pancreatic cancer (6, 13).

Despite the lack of association for coffee intake and pancreatic cancer in most previous cohort studies, a recent cohort study of 33,976 United States women reported statistically significant elevations in risk of pancreatic cancer for coffee consumption, independent of age and cigarette smoking (4). In that study, consumption of 18+ cups of coffee/week was associated with a 2-fold elevation in pancreatic cancer risk when compared with <7 cups/week. Alcohol was also observed to increase risk in the same study, although the association was not statistically significant (more than two drinks of alcohol/week increased pancreatic cancer risk by 65% when compared with nondrinkers).

We examined the relationships of coffee and alcohol intakes and pancreatic cancer risk in the HPFS[3], a prospective

[3] The abbreviations used are: HPFS, Health Professionals Follow-Up Study; NHS, Nurses' Health Study; FFQ, food frequency questionnaire; BMI, body mass index; CI, confidence interval; RR, relative risk; IWHS, Iowa Women's Health Study.

cohort of men, and in the NHS, a prospective cohort of women. The long follow-up period, the substantial number of cases ($n = 288$), and the availability of repeated dietary assessments allowed for alternative analyses to examine temporal relationships between coffee and alcohol and the risk of pancreatic cancer. In addition, we examined the intakes of decaffeinated coffee, tea, caffeine, and alcoholic beverage type in relation to pancreatic cancer risk.

Materials and Methods

Study Population. Two ongoing cohort studies provided data for our analyses, the HPFS and the NHS. The HPFS was initiated in 1986 when 51,529 United States men 40–75 years of age responded to a mailed questionnaire. Fifty-eight percent of the men in the HPFS cohort are dentists, and the other professions include optometrists, osteopaths, podiatrists, pharmacists, and veterinarians. The NHS began in 1976 when 121,700 female registered nurses 30–55 years of age responded to a mailed questionnaire. Detailed information on individual characteristics and habits such as age, marital status, weight, height, medical history, medication use, smoking status, and physical activity was obtained through the mailed questionnaires at baseline and subsequently every 2 years.

For each of the follow-up questionnaires, up to six mailings were sent to nonrespondents. Most of the deaths in this cohort were reported by family members or by the postal service in response to the follow-up questionnaires. In addition, the National Death Index was searched for nonrespondents; this method has been shown to have a sensitivity (the probability that a deceased person is found in the Index, given that the person is deceased) of 98% (14).

Dietary Assessment. In 1986, the baseline questionnaire for the HPFS cohort included a 131-item semiquantitative FFQ. In the NHS, a 61-item FFQ was mailed to all of the participants of the study in 1980. Both the HPFS and the NHS initial FFQs included questions on intakes of coffee and alcohol (wine, beer, and liquor) at baseline. On the initial questionnaires, we also inquired if a participant's alcohol use (and coffee in the NHS) had greatly increased or decreased over the past 10 years. In 1984, a more comprehensive FFQ (116-items) was mailed to the NHS cohort. This questionnaire resembled the FFQ administered to the HPFS in 1986 and included a question on decaffeinated coffee consumption (which was not asked on the 1980 questionnaire). In addition, both cohorts completed detailed FFQs in 1986, 1990, and 1994.

On the questionnaire, participants were asked to report their average frequency of intake over the previous year for a specified serving size of each food. Individual nutrient intakes were calculated by multiplying the frequency of each food consumed by the nutrient content of the specified portion size (obtained from the United States Department of Agriculture and supplemented by other publications) and then by summing the contributions from all of the foods. Total alcohol intake was the sum of the values for all of the three beverages; a 12-oz can or bottle of beer was assumed to contain 13.2 g of alcohol, a 4-oz glass of wine, 10.8 g, and a standard drink of liquor, 15.1 g (United States Department of Agriculture). Total caffeine intake was calculated by summing the amount of caffeine in coffee (77%), tea (13%), soda (6.6%), decaffeinated coffee (3%), chocolate (0.3%), and candies (0.1%) consumed by the study participants.

Validity studies of the FFQ, compared with 1-week diet records, among 127 men from the HPFS and 173 women from the NHS indicated that most foods and beverages are reported reasonably well. These studies are reported in detail elsewhere (15, 16). Correlations between the average intake assessed by two 1-week diet records completed 6 months apart and 1-FFQ were 0.93 and 0.77 for coffee and tea, respectively, in the HPFS (15), and 0.78 and 0.93 for coffee and tea, respectively, in the NHS (16). For alcohol intake, the correlation between multiple dietary records and a FFQ was 0.90 in the NHS and 0.86 in the HPFS (17).

Smoking History and Other Risk Factors. Smoking status and history of smoking were obtained at baseline and in all of the subsequent questionnaires in both cohorts. Current smokers also reported intensity of smoking (average number of cigarettes smoked/day) on each questionnaire. Past smokers reported when they last smoked on the baseline questionnaire. The time since quitting was also calculated for those who quit during follow-up. On the 1976 questionnaire, the NHS participants were asked at what age they started smoking. In the HPFS, each participant reported on the baseline questionnaire the average number of cigarettes smoked/day for each decade of life. From these data, categories were derived for age at start of smoking, based on the earliest decade where smoking was recorded, because there was no question (on the HPFS questionnaires) asking at what specific age the participant had initiated smoking.

Participants were asked about history of diabetes at baseline and in all of the subsequent questionnaires. In 1986 (HPFS) and in 1982 (NHS), and biennially thereafter, participants were asked about their history of cholecystectomy. BMI (kg/m^2) was calculated from self-reported height and weight (asked at baseline).

Identification of Pancreatic Cancer Cases. In both cohorts, participants were asked to report specified medical conditions including cancers that were diagnosed in the 2-year period between each follow-up questionnaire. Whenever a participant (or next of kin for decedents) reported a diagnosis of pancreatic cancer, we asked for permission to obtain related medical records or pathology reports. If permission to obtain records was denied, we attempted to confirm the self-reported cancer with an additional letter or phone call to the participant. If the primary cause of death as reported by a death certificate was a previously unreported pancreatic cancer case, we contacted a family member to obtain permission to retrieve medical records or at least to confirm the diagnosis of pancreatic cancer. In the participants included in these analyses, 130 new cases of pancreatic cancer were diagnosed in the HPFS between 1986 and 1998, and 158 pancreatic cancer cases were diagnosed in the NHS between 1980 and 1996.

Statistical Analysis. Of the surviving 121,700 NHS cohort members, 98,770 responded to the 1980 dietary questionnaire. We excluded participants with cancer (other than nonmelanoma skin cancer) diagnosed before baseline (1986 for the HPFS; 1980 for the NHS) and all of the individuals with implausibly high or low scores for total energy intake on the baseline questionnaires. As a result, 47,794 men and 88,799 women were eligible for analysis. For men and women, we computed person-time of follow-up for each participant from the return date of the baseline questionnaire to the date of pancreatic cancer diagnosis, death from any cause, or the end of follow-up (January 31, 1998 for men and June 30, 1996 for women), whichever came first. Incidence rates of pancreatic cancer were calculated by dividing the number of incident cases by the number of person-years in each category of dietary exposure. We computed the RR for each of the upper categories of intake

by dividing the rates in these categories by the rate in the lowest category of intake.

For each cohort, RRs adjusting for potential confounders were estimated using pooled logistic regression analyses with 2-year time increments (18). This approach is asymptotically equivalent to the Cox regression model with time-dependent covariates, given short time intervals and low probability of the outcome within the interval (18). In these models, age was categorized into 5-year age groups, total energy intake and BMI were divided into quintiles, and cigarette smoking was categorized as follows (based on a previous analysis of these cohorts; Ref. 19): never-smoker, quit ≥15 years ago, quit <15 years ago and smoked ≤25 pack-years in past 15 years, quit <15 years ago and smoked >25 pack-years in past 15 years, current smoker with ≤25 pack-years in past 15 years, and current smoker with >25 pack-years in past 15 years. In addition, we controlled for history of diabetes and cholecystectomy because they have been previously associated with pancreatic cancer risk in other studies (20–22). We also repeated our analyses, updating the exposure of interest cumulatively, using data from follow-up questionnaires. For the cumulative updated analyses in the NHS, we used data from the 1980 questionnaire to allocate person-time to each of the quintiles of exposure between 1980 and 1984, the average of 1980 and 1984 for the interval from 1984 to 1986, and the average of 1980, 1984, and 1986 for the interval from 1986 to 1990, and so forth. Cumulative updating was similarly performed in the HPFS. Tests for trend were performed using continuous variables, and two-sided *P*s are reported.

We pooled the data from the two cohorts using a random-effects model for the log of the RRs (23). Tests of heterogeneity using the Q statistic (23) were obtained for the main exposures (as continuous variables) to evaluate the overall trend in each cohort (and thus by gender) before pooling.

Results

In the HPFS and the NHS cohorts, 288 incident cases of pancreatic cancer were documented during 1,907,222 person-years of follow-up. Compared with nondrinkers of coffee, men and women who had a high intake of coffee (four or more cups/day) were more likely to be current smokers, had higher lifetime cigarette use (pack-years), and drank more alcohol. However, heavy coffee drinkers were less likely to have a history of diabetes or cholecystectomy (Table 1). Similarly, men and women with a high alcohol intake (30 or more grams of alcohol/day) smoked more and drank more coffee but had a lower prevalence of diabetes or history of cholecystectomy (Table 1).

Consumption of caffeinated coffee was not associated with an increased risk of pancreatic cancer in the pooled analysis of the two cohorts. Among men in the HPFS, caffeinated coffee drinkers had a significantly lower risk of pancreatic cancer than those who did not drink any coffee, after adjusting for smoking and other pancreatic risk factors (*P* for continuous variable, 0.04; Table 2). Among women in the NHS, the multivariate RR for intake of four or more cups of coffee a day, compared with none, was 0.88 (95% CI, 0.56–1.38). The pooled RR between both cohorts was 0.62 (95% CI, 0.27–1.43) for four or more cups of regular coffee a day, compared with none (Table 2). Intakes of decaffeinated coffee and tea were not related to the risk of pancreatic cancer in either cohort (Table 2). Compared with nondrinkers of coffee or tea, the pooled RR was 0.93 (95% CI, 0.45–1.91) for four or more cups of decaffeinated coffee and 1.04 (95% CI, 0.71–1.54) for more than one cup of tea/day. Controlling for alcohol intake in these multivariate models did not alter the RRs presented in Table 2.

Total caffeine intake (which includes coffee, tea, other caffeinated drinks, and caffeine from food sources) was also examined in relation to the risk of pancreatic cancer. Compared with the bottom quintile of intake, the top quintile was associated with a weak inverse association in the men, which was not statistically significant (Table 2). In the NHS, no association was apparent between total caffeine intake and risk of pancreatic cancer (Table 2). The pooled RR of pancreatic cancer for the highest quintile of caffeine intake, compared with the lowest, was 0.82 (95% CI, 0.57–1.17).

We examined possible differences in the associations of specific coffee brewing methods with the risk of pancreatic cancer. The coffee brewing method used was asked on the 1990 questionnaires in both the cohorts, and, consequently, the follow-up periods for these analyses start in 1990. We observed no association with the type of brewing method (filtered, instant, or expresso), controlling for amount of coffee consumed (data not shown).

Caffeinated soda consumption was also examined in these cohorts. No significant association was observed for sugared or artificially sweetened caffeinated soda and the risk of pancreatic cancer (≥1 can of regular soda/day compared with none: multivariate RR, 1.32; 95% CI, 0.47–3.67 in the NHS; and RR, 1.19; 95% CI, 0.43–3.30 in the HPFS; ≥1 can of low calorie soda/day compared with none: multivariate RR, 0.83; 95% CI, 0.40–1.73 in the NHS; and RR, 0.67; 95% CI, 0.27–1.66 in the HPFS).

We examined the association between alcohol intake and pancreatic cancer in both cohorts. In the HPFS, the multivariate RRs of pancreatic cancer were nonsignificantly elevated for each category of alcohol intake compared with abstinence (Table 3). In the NHS, no association was observed for alcohol intake. In the pooled analysis of both cohorts, alcohol intake was not associated with risk of pancreatic cancer (continuous *P*, 0.94; Table 3). In addition to these analyses of intakes of total alcohol intake, we examined individual alcoholic beverages, including wine, beer, and liquor. No associations were observed between these specific beverages and risk of pancreatic cancer in either cohort (data not shown). Multivariate RRs for every additional drink/day in the pooled analyses were 1.08 (95% CI, 0.88–1.33) for beer, 0.91 (95% CI, 0.70–1.19) for wine, and 0.96 (95% CI, 0.81–1.15) for hard liquor. Additional control for coffee intake in the multivariate analyses did not change the RRs presented in Table 3.

We excluded from all of our analyses those men and women who abstained from alcohol and who had reported at baseline having substantially reduced their alcohol intake in the previous decade. In another analysis, we created two separate categories for current abstainers: those who reported past heavy drinking, and those who never drank alcohol. In both cohorts, past heavy alcohol drinking was not significantly associated with risk of pancreatic cancer (compared with never drinkers, multivariate RR, 1.62; 95% CI, 0.75–3.50; and multivariate RR, 1.11; 95% CI, 0.52–2.36 in the HPFS and NHS, respectively).

We performed alternative analyses in addition to the baseline analyses for the intakes of coffee and alcohol (Table 4). If recent intake of coffee or alcohol was of greatest etiological importance, then we would expect a stronger association in the analyses in which intake is updated every 4 years with the most recent food frequency questionnaires (simple update); however, this pattern was not observed for either coffee or alcohol. The cumulative update analyses average all of the previous FFQs

Table 1 Baseline characteristics among men in the HPFS and women in the NHS cohorts (1986 and 1980, respectively) comparing highest with lowest intakes of coffee and alcohol[a]

	Coffee intake (cups/day)			
	HPFS		NHS	
	None (n = 15,074)	⩾4 (n = 5,027)	None (n = 20,664)	⩾4 (n = 21,985)
Age (yr)	54	53	46	47
BMI (kg/m^2)	25	26	25	24
MET-h/week[b]	25	21	14	13
Diabetes mellitus (%)	3.0	2.6	3.0	1.8
Cholecystectomy (%)	2.9	2.5	8.2	6.6
Current smokers (%)	5.6	22	19	46
Pack-yr of cigarettes[c]	10	23	3	8
Daily intakes				
Calories (kcal)	1925	2127	1566	1588
Total fat (g)	69	76	69	71
Saturated fat (g)	24	27	28	29
Carbohydrates (g)	245	221	161	151
Dietary fiber (g)[d]	24	20	17	16
Alcohol (g)	8.0	14.7	4.5	7.1
	Alcohol intake (g/day)			
	HPFS		NHS	
	None (n = 4,923)	⩾30 (n = 5,659)	None (n = 25,577)	⩾30 (n = 4,506)
Age (yr)	53	56	47	48
BMI (kg/m^2)	26	26	25	24
MET-h/week[b]	23	23	12	13
Diabetes mellitus (%)	3.2	2.1	3.4	1.3
Cholecystectomy (%)	3.0	1.8	8.5	4.6
Current smokers (%)	5	20	21	53
Pack-yr of cigarettes[c]	6	22	4	11
Dietary intakes (/day)				
Calories (kcal)	1942	2220	1568	1759
Total fat (g)	74	65	71	60
Saturated fat (g)	26	22	28	24
Carbohydrates (g)	251	196	164	123
Dietary fiber (g)[d]	23	18	17	13
Coffee (cups)	0.8	1.9	1.9	2.6

[a] All variables (except age) are age-standardized. Additionally, total fat, saturated fat, carbohydrates, and dietary fiber are energy-adjusted using the nutrient-density method.
[b] MET-h/week, sum of the average time/week spent in each activity × MET value of each activity. MET, metabolic equivalent; Met value = (caloric need/kilogram body weight per hour activity)/(caloric need/kilogram body weight per hour at rest).
[c] Pack-years are calculated for current and past smokers.
[d] Based on Southgate values.

for the subsequent follow-up period and minimize the measurement error for long-term average consumption. For these analyses, we observed similar estimates to those obtained using baseline diet (data not shown).

Although we excluded participants with cancer at baseline, individuals could have altered their dietary patterns because of preclinical manifestations of disease. To address this issue, we repeated our analyses (using baseline diet) after excluding the first 2 years of follow-up. Such lag analyses did not lead to substantially different findings for coffee or alcohol. Similarly, removing women in the NHS who reported having changed their coffee intake substantially in the previous decade (on the 1980 dietary questionnaire) did not change the findings for coffee intake (this question was not asked in the HPFS). In an additional analysis in the NHS, we added an 8-year lag period between diet (1980) and follow-up period (1988–1996), but we observed no association for either coffee or alcohol intake and risk of pancreatic cancer (data not shown).

We assessed the effect of consistent coffee or alcohol use over a 4-year induction period using two consecutive questionnaires (1986 and 1990 in the HPFS; 1980 and 1984 in the NHS). In each analysis, we excluded individuals who changed their frequency of coffee or alcohol intake and started follow-up after the second questionnaire was returned. No associations were observed using these analyses for coffee intake and risk of pancreatic cancer. For alcohol, the association was inverse when using consistent drinkers in the HPFS.

We examined intakes of coffee and alcohol stratified by age (<55 and ≥55 years of age), BMI (less than median and equal or above median), and smoking status (never, past, and current; Table 5). BMI, age, and smoking status did not modify the associations between coffee and pancreatic cancer. A nonsignificant elevation in risk of pancreatic cancer was observed among alcohol consumers less than 55 years old; however, no similar elevation in risk was observed among those 55 or more years old. Although RRs of pancreatic cancer were different by BMI strata for alcohol intake, these differences were not statistically significant, and no trend was apparent for the increased risk among those in the low BMI stratum. The alcohol intake and pancreatic cancer associations were similar for nev-

Table 2 Coffee, decaffeinated coffee, tea, and caffeine intakes (measured at baseline) and risk of pancreatic cancer in the NHS and HPFS[a]

	Coffee intake					*P*, trend test
	None	<1/day	1/day	2–3/day	>3/day	
HPFS						
No. of cases	47	36	10	31	6	
Person-yr	165,891	116,053	68,956	120,793	56,025	
Age-adjusted RR	1.0	1.07	0.50	0.95	0.44	0.10
Multivariate RR	1.0	1.04	0.48	0.89	0.37	0.04
(95% CI)	Reference	(0.67–1.61)	(0.24–0.95)	(0.56–1.40)	(0.16–0.88)	
NHS						
No. of cases	39	10	14	52	43	
Person-yr	320,609	116,465	152,839	448,476	341,115	
Age-adjusted RR	1.0	0.71	0.68	0.88	1.01	0.50
Multivariate RR	1.0	0.72	0.71	0.88	0.88	0.92
(95% CI)	Reference	(0.36–1.44)	(0.38–1.30)	(0.58–1.34)	(0.56–1.38)	
Pooled						
Multivariate RR	1.0	0.94	0.60	0.88	0.62	0.35
(95% CI)	Reference	(0.65–1.36)	(0.38–0.94)	(0.65–1.21)	(0.27–1.43)	

	Decaffeinated coffee intake				*P*, trend test
	None	<1/day	1–3/day	>3/day	
HPFS					
No. of cases	58	41	26	5	
Person-yr	254,010	147,998	107,121	18,319	
Age-adjusted RR	1.0	1.10	0.88	1.08	0.88
Multivariate RR	1.0	1.13	0.89	0.99	0.73
(95% CI)	Reference	(0.76–1.70)	(0.56–1.42)	(0.39–2.47)	
NHS[b]					
No. of cases	67	14	31	3	
Person-yr	515,117	114,501	204,283	24,771	
Age-adjusted RR	1.0	0.88	1.02	0.85	0.57
Multivariate RR	1.0	0.95	1.07	0.85	0.60
(95% CI)	Reference	(0.53–1.69)	(0.70–1.64)	(0.28–2.71)	
Pooled					
Multivariate RR	1.0	1.07	0.98	0.93	0.54
(95% CI)	Reference	(0.77–1.49)	(0.72–1.35)	(0.45–1.91)	

	Tea intake				*P*, trend test
	None	<5/week	5/week–1/day	>1/day	
HPFS					
No. of cases	61	45	13	11	
Person-yr	230,246	121,883	72,158	41,356	
Age-adjusted RR	1.0	0.95	0.66	1.09	0.74
Multivariate RR	1.0	1.02	0.72	1.17	0.61
(95% CI)	Reference	(0.69–1.50)	(0.40–1.32)	(0.61–2.22)	
NHS					
No. of cases	48	51	34	25	
Person-yr	422,844	391,096	283,955	281,610	
Age-adjusted RR	1.0	1.19	1.06	0.84	0.26
Multivariate RR	1.0	1.33	1.22	0.98	0.49
(95% CI)	Reference	(0.90–1.98)	(0.79–1.90)	(0.60–1.60)	
Pooled					
Multivariate RR	1.0	1.16	0.98	1.04	0.77
(95% CI)	Reference	(0.88–1.53)	(0.59–1.63)	(0.71–1.54)	

	Caffeine intake (quintiles)					*P*, trend test
	1	2	3	4	5	
HPFS						
No. of cases	30	35	22	19	24	
Age-adjusted RR	1.0	1.24	0.75	0.69	0.93	0.48
Multivariate RR	1.0	1.23	0.72	0.69	0.74	0.12
(95% CI)	Reference	(0.75–2.00)	(0.41–1.24)	(0.38–1.23)	(0.42–1.28)	
NHS						
No. of cases	36	26	31	27	38	
Age-adjusted RR	1.0	0.72	0.83	0.74	1.09	0.34
Multivariate RR	1.0	0.75	0.86	0.71	0.89	0.96
(95% CI)	Reference	(0.45–1.24)	(0.53–1.39)	(0.43–1.17)	(0.55–1.42)	
Pooled						
Multivariate RR	1.0	0.96	0.79	0.70	0.82	0.39
(95% CI)	Reference	(0.59–1.56)	(0.55–1.14)	(0.48–1.02)	(0.57–1.17)	

[a] Multivariate relative risks are adjusted for age in 5-year categories, pack-years of smoking (past 15 years; current and past smokers separately), BMI (quintiles at baseline), history of diabetes mellitus, history of cholecystectomy, energy intake (quintiles), and period.
[b] Decaffeinated coffee intake was first assessed on the 1984 NHS questionnaire.

Table 3 Intake of alcohol and the risk of pancreatic cancer in the NHS and the HPFS[a]

	Alcohol intake (g/day)[b]					*P*, trend test
	0	0.1–1.4	1.5–4.9	5.0–29.9	≥30	
HPFS						
No. of cases	9	6	24	48	18	
Person-yr	54,697	30,753	97,305	213,867	61,709	
Age-adjusted RR	1.0	1.08	1.51	1.29	1.50	0.43
Multivariate RR	1.0	1.01	1.44	1.23	1.34	0.55
(95% CI)	Reference	(0.36–2.83)	(0.67–3.12)	(0.59–2.53)	(0.58–3.08)	
NHS						
No. of cases	48	15	34	45	8	
Person-yr	396,683	173,220	288,437	403,553	68,905	
Age-adjusted RR	1.0	0.74	1.04	0.91	0.87	0.61
Multivariate RR	1.0	0.72	1.07	0.93	0.78	0.49
(95% CI)	Reference	(0.41–1.30)	(0.68–1.67)	(0.61–1.42)	(0.36–1.68)	
Pooled						
Multivariate RR	1.0	0.78	1.15	1.00	1.00	0.94
(95% CI)	Reference	(0.47–1.30)	(0.78–1.69)	(0.69–1.44)	(0.57–1.76)	

[a] Controlling for age in 5-year categories, pack-years of smoking (past 15 years; current and past smokers separately), BMI (quintiles at baseline), history of diabetes mellitus, history of cholecystectomy, energy intake (quintiles), and period.
[b] Individuals who at baseline reported abstinence and had decreased their alcohol intake substantially in previous 10 years were excluded.

er-smokers and past smokers. Among current smokers, those men who drank more than 5 g of alcohol a day had an elevated risk of pancreatic cancer, but these associations were statistically nonsignificant (compared with <5 g of alcohol/day, multivariate RRs, 3.98; 95% CI, 0.8–18.9; and multivariate RR, 2.14; 95% CI, 0.4–10.5 for 5–14.9 g/day and ≥15 g/day, respectively). In the NHS, a nonsignificant increase in risk was also observed among current smokers drinking alcohol (RR, 1.65; 95% CI, 0.77–3.54 for 15 or more g/day of alcohol, compared with nondrinkers).

Discussion

We found no statistically significant associations for intakes of coffee or alcohol and the risk of pancreatic cancer in men and women living throughout the United States. Our findings were similar whether we used baseline, current, or cumulative-averaged intakes of alcohol or coffee, as well as after we removed the first 2 years of follow-up or restricted the analyses to those with consistent intakes during two consecutive dietary questionnaires. Furthermore, no associations were observed for intakes of caffeine, decaffeinated coffee, tea, or different types of alcoholic beverages. Although there was a suggestion that alcohol may increase the risk of pancreatic cancer among current smokers, we had limited statistical power to examine this relationship.

The lack of an association between coffee intake and risk of pancreatic cancer in this study is consistent with most previous data. Reviewing the available studies that have assessed the influence of coffee or alcohol consumption (24, 25), the IARC concluded that there was little evidence to support a causal relation between coffee or alcohol and risk of pancreatic cancer.

Because we had repeated dietary assessments over time, we were able to examine the effects of recent and long-term coffee intake and confirm that neither one yielded a significant effect on pancreatic cancer. In contrast to the recent prospective study of women in Iowa, we did not confirm a positive association between coffee intake and pancreatic cancer in our cohort of women (4). In addition, no positive association was observed in the age strata of 55 years and older, which most closely resembles the ages of women found in the Iowa Study (4). The RR reported for 18 or more cups of coffee a week in the Iowa study (RR, 2.15; 95% CI, 1.08–4.30) is significantly different to our finding for a similar coffee intake (RR, 0.62; 95% CI, 0.27–1.43). The IWHS findings (4) are based on a total of 66 cases of pancreatic cancer. In contrast, our results are based on 288 cases (158 women). The IWHS also reported an elevated risk of pancreatic cancer among alcohol drinkers; however, this finding was not statistically significant, and it was statistically compatible with our findings. Given that the elevated risks observed in the IWHS were also present in analyses restricted to never-smokers, it is unlikely that inadequate control of smoking is responsible for their results. Although a FFQ very similar to ours was used in the IWHS, alcohol intake appeared to be poorly reported in the IWHS ($r = 0.32$ in validation study), and no validation information was provided for coffee intake (4). Given the very high correlations observed in our validation studies for alcohol and coffee, it is unlikely that measurement error is responsible for the lack of associations in this study, although this cannot be ruled out completely. A longer follow-up with additional cases should help elucidate whether the findings of the IWHS are the result of chance.

In this study, we had data on regular *versus* decaffeinated coffee and also on the method typically used for brewing coffee. Because the brewing method may affect the concentration of certain compounds found in coffee, such as methylglyoxal (26) and caffeine (27), it may be an important aspect of coffee intake. *In vitro* studies show that caffeine can inhibit DNA repair (28, 29) and induce mitotic events before DNA replication is completed (30). Human physiological studies indicate that moderate caffeine consumption is unlikely to have an effect on health (27). The brewing method was not related to risk of pancreatic cancer, and we did not observe any effect of total caffeine intake (calculated from all of the caffeinated beverages and foods).

In previous prospective studies, findings have been less consistent for alcohol than for coffee intake. Prospective studies that have reported a relation between alcohol (or an alcoholic beverage) and pancreatic cancer tended to have longer follow-up periods (8, 12, 17, and 20 years; Refs. 4, 5, 12, 13) than those studies reporting no associations (6, 9, and 12 years; Refs. 6–8). Because dietary exposures in case-control studies mostly

Table 4 RRs and 95% CIs of pancreatic cancer for coffee and alcohol intakes in the NHS and HPFS, comparing different methods of analyses[a]

	Coffee intake					
	None	<1/day	1/day	2–3/day	>3/day	(95% CI)[a]
HPFS						
Baseline diet	1.0	1.04	0.48	0.89	0.37	(0.16–0.88)
Simple update[b]	1.0	0.95	0.78	0.65	0.56	(0.25–1.28)
Cumulative update[c]	1.0	1.11	0.46	0.86	0.47	(0.21–1.02)
2-yr lag[d]	1.0	1.07	0.42	0.83	0.39	(0.16–0.93)
Consistent intake[e]	1.0	1.01	0.44	0.76	0.46	(0.10–2.00)
NHS						
Baseline	1.0	0.72	0.71	0.88	0.88	(0.56–1.38)
Simple update[b]	1.0	1.08	0.92	1.22	1.10	(0.61–1.97)
Cumulative update[c]	1.0	1.20	0.71	1.23	0.96	(0.55–1.67)
2-yr lag[d]	1.0	0.76	0.64	0.90	0.84	(0.53–1.34)
Consistent intake[e]	1.0	1.97	1.42	1.95	1.57	(0.70–3.56)
Exclude Δs coffee[f]	1.0	1.08	0.84	1.15	0.99	(0.58–1.70)
	Alcohol intake (g/day)[g]					
	0	0.1–1.4	1.5–4.9	5.0–29.9	⩾30	(95% CI)[a]
HPFS						
Baseline	1.0	1.01	1.44	1.23	1.34	(0.58–3.08)
Simple update[b]	1.0	1.15	1.43	1.61	1.24	(0.52–2.93)
Cumulative update[c]	1.0	0.52	1.19	1.18	1.28	(0.55–2.98)
2-yr lag[d]	1.0	1.14	1.49	1.23	1.31	(0.54–3.16)
Consistent intake[e]	1.0	1.39[h]		0.79	0.56	(0.18–1.74)
NHS						
Baseline diet	1.0	0.72	1.07	0.93	0.78	(0.36–1.68)
Simple update[b]	1.0	0.99	0.54	0.97	0.77	(0.36–1.64)
Cumulative update[c]	1.0	0.86	0.84	0.98	0.93	(0.42–2.04)
2-yr lag[d]	1.0	0.66	1.07	0.99	0.63	(0.27–1.52)
Consistent intake[e]	1.0	1.18[h]		0.70	0.80	(0.27–2.33)

[a] Controlling for age in 5-year categories, pack-years of smoking (past 15 years; current and past smokers separately), BMI (quintiles at baseline), history of diabetes mellitus, history of cholecystectomy, energy intake (quintiles), and period; 95% CIs are for top *vs.* bottom category comparisons.
[b] Simple updating uses the most recent dietary questionnaire.
[c] Cumulative updating averages dietary questionnaires; see statistical section for detailed explanation.
[d] 2-year lag removes the first 2 years of follow-up (and uses baseline diet).
[e] Consistent users reported the same frequency of coffee or alcohol intake over two consecutive questionnaires (*i.e.*, 1980 and 1984 for the NHS; 1986 and 1990 for the HPFS). Follow-up in these analyses start in 1984 for the NHS and 1990 for the HPFS.
[f] Excludes women who reported having changed their coffee consumption in decade before beginning of follow-up (this question was not asked in the HPFS).
[g] Individuals who at baseline reported abstinence and having decreased their alcohol intake substantially in previous 10 years were excluded.
[h] Collapsed categories 2 and 3 because of insufficient numbers.

reflect recent diet, the lack of association for alcohol intake might suggest that alcohol plays a role at an early stage in carcinogenesis (*e.g.*, initiation). However, our data do not support an early or late effect of alcohol intake on risk of pancreatic cancer. Past heavy users of alcohol were not at an elevated risk of pancreatic cancer in either the NHS or the HPFS cohorts. Moreover, allowing for an 8-year induction period did not demonstrate any significant association with alcohol intake.

In a previous case-control study (31), an interaction was observed between smoking status and alcohol intake such that alcohol drinking did not increase risk of pancreatic cancer among nonsmokers or low-dose smokers, but it did substantially increase risk among cigarette smokers. Alcohol intake was not associated with risk of pancreatic cancer overall in this study, but RRs were nonsignificantly elevated in both cohorts among current smokers drinking alcohol, compared with smokers not drinking. Because of the relatively small number of cases in this subset of participants and, thus, lack of statistical power, these findings should be interpreted with caution, and we cannot exclude a moderate increase in these groups.

The null relationship between tea intake and risk of pancreatic cancer is consistent with data from most prospective studies (4–7, 32, 33), with the exception of one study that reported a significant inverse association (34). Similarly, case-control studies have consistently found no association between tea and pancreatic cancer risk (3).

The lack of associations reported here are unlikely to be the result of misclassification of exposure. Validation studies of the dietary assessment questionnaires (FFQ) used in these two cohorts have demonstrated that coffee and alcohol are highly correlated with reports from detailed dietary records (15, 16). In addition, we observed similar results in those analyses that used the average of the multiple dietary assessments, minimizing measurement error. Furthermore, findings were similar after restricting analyses to those who reported consistent coffee or alcohol intake over consecutive questionnaires. Given the high response rates obtained in the NHS and HPFS cohorts, neither nonresponse rates nor differential follow-up are likely to account for our observations.

In conclusion, the risk of pancreatic cancer was not elevated with increasing consumption of alcohol, coffee, decaffeinated coffee, or tea in two large prospective cohort studies of

Table 5 Pooled RRs of pancreatic cancer for coffee and alcohol intakes in the NHS and HPFS cohorts, by strata of BMI, age, and smoking[a]

	Coffee intake					
	None	<1/day	1/day	2–3/day	>3/day	(95% CI)[a]
BMI (<median)[b]	1.0	0.89	0.90	1.28	0.89	(0.44–1.78)
BMI (≥median)[b]	1.0	0.95	0.52	0.71	0.63	(0.27–1.50)
Age <55 years	1.0	1.15	1.00	1.23	0.87	(0.23–3.26)
Age ≥55 years	1.0	0.90	0.38	0.69	0.51	(0.28–0.91)
Never-smoker	1.0	1.25	0.72	1.01[c]	—	(0.61–1.66)
Past smoker	1.0	0.95	0.46	0.75	0.52	(0.24–1.10)
Current smoker	1.0	0.35	0.56	0.74	0.43	(0.07–2.69)
	Alcohol intake (g/day)[d]					
	0	0.1–4.9	5.0–14.9	≥15.0	(95% CI)[a]	
BMI (<median)[b]	1.0	1.42	1.10	1.46	(0.72–2.96)	
BMI (≥median)[b]	1.0	0.82	0.98	0.97	(0.54–1.76)	
Age <55 years	1.0	1.05	1.13	1.69	(0.93–3.07)	
Age ≥55 years	1.0	0.87	0.83	0.76	(0.33–1.72)	
Never-smoker	1.0	0.95	0.77	0.96	(0.43–2.16)	
Past smoker	1.0	0.82	0.74	0.72	(0.29–1.78)	
Current smoker[e]	1.0	1.28	1.25	1.65	(0.77–3.54)	

[a] Controlling for age in 5-year categories, history of diabetes mellitus, history of cholcysectomy, energy intake (quintiles), and period. In addition, adjustments for pack-years of smoking were also made in the BMI and age strata (pack-years) and in past and current smokers strata. Similarly, BMI was adjusted in age and smoking strata; 95% CIs are for top *vs.* bottom category comparisons.
[b] BMI medians: NHS, 23.4; HPFS, 25.2. Models further adjusted for smoking in pack-years.
[c] Collapsed categories 4 and 5 because of few cases in those categories (in the HPFS).
[d] Individuals who at baseline reported abstinence and having decreased their alcohol intake substantially in previous 10 years were excluded.
[e] RRs for the NHS only; HPFS only had 17 cases and no cases were present in the bottom category.

men and women living in the United States. Specifically, the associations did not change whether examining distant or recent past intakes of alcohol or coffee or when allowing for a lag between diet assessment and cancer diagnosis. Similarly, total caffeine intake from beverages and diet was not associated with the risk of pancreatic cancer. With fewer than 100 pancreatic cancer cases who are current smokers, our findings are still inadequate to offer a strong conclusion for the potential interaction between smoking and alcohol. Ultimately, our data are consistent with conclusions of the IARC Working Group (24, 25) that neither coffee nor alcohol intakes are associated with an increase in pancreatic cancer risk.

Acknowledgments

We thank the participants of the HPFS and the NHS for their continuing outstanding dedication and commitment to the study and Alvin Wing, Kathleen Markham, and Mildred Wolff for their assistance.

References

1. American Cancer Society. Cancer Facts and Figures-2000. Atlanta: American Cancer Society, Inc., 2000.

2. Ahlgren, J. D. Epidemiology and risk factors in pancreatic cancer. Semin. Oncol., *23:* 241–250, 1996.

3. World Cancer Research Fund and American Institute for Cancer Research. Food, Nutrition and the Prevention of Cancer: a Global Perspective. *In:* Pancreas, pp. 176–197. Washington, DC: American Institute for Cancer Research, 1997.

4. Harnack, L. J., Anderson, K. E., Zheng, W., Folsom, A. R., Sellers, T. A., and Kushi, L. H. Smoking, alcohol, coffee, and tea intake and incidence of cancer of the exocrine pancreas: the Iowa Women's Health Study. Cancer Epidemiol. Biomark. Prev., *6:* 1081–1086, 1997.

5. Zheng, W., McLaughlin, J. K., Gridley, G., Bjelke, E., Schuman, L. M., Silverman, D. T., Wacholder, S., Co-Chien, H. T., Blot, W. J., and Fraumeni, J. F., Jr. A cohort study of smoking, alcohol consumption, and dietary factors for pancreatic cancer (United States). Cancer Causes Control, *4:* 477–482, 1993.

6. Shibata, A., Mack, T. M., Paganini-Hill, A., Ross, R. K., and Henderson, B. E. A prospective study of pancreatic cancer in the elderly (see comments). Int. J. Cancer, *58:* 46–49, 1994.

7. Hiatt, R., Klatsky, A., and Armstrong, M. A. Pancreatic cancer, blood glucose and beverage consumption. Int. J. Cancer, *41:* 794–797, 1988.

8. Heuch, I., Kvale, G., Jacobsen, B. K., and Bjelke, E. Use of alcohol, tobacco and coffee, and risk of pancreatic cancer. Br. J. Cancer, *48:* 637–643, 1983.

9. Stensvold, I., and Jacobsen, B. K. Coffee and cancer: a prospective study of 43,000 Norwegian men and women. Cancer Causes Control, *5:* 401–408, 1994.

10. Nomura, A., Heilbrun, L., and Stemmermann, G. Prospective study of coffee consumption and the risk of cancer. J. Natl. Cancer Inst. (Bethesda), *76:* 587–590, 1986.

11. Mills, P. K., Beeson, W. L., Abbey, D. E., Fraser, G. E., and Phillips, R. L. Dietary habits and past medical history as related to fatal pancreas cancer risk among Adventists. Cancer (Phila.), *61:* 2578–2585, 1988.

12. Hirayama, T. Epidemiology of pancreatic cancer in Japan. Jpn. J. Clin. Oncol., *19:* 208–215, 1989.

13. Friedman, G. D., and van den Eeden, S. K. Risk factors for pancreatic cancer: an exploratory study. Int. J. Epidemiol., *22:* 30–37, 1993.

14. Rich-Edwards, J. W., Corsano, K. A., and Stampfer, M. J. Test of the National Death Index and Equifax Nationwide Death Search. Am. J. Epidemiol., *140:* 1016–1019, 1994.

15. Feskanich, D., Rimm, E. B., Giovannucci, E. L., Colditz, G. A., Stampfer, M. J., Litin, L. B., and Willett, W. C. Reproducibility and validity of food intake measurements from a semiquantitative food frequency questionnaire. J. Am. Diet. Assoc., *93:* 790–796, 1993.

16. Salvini, S., Hunter, D. J., Sampson, L., Stampfer, M. J., Colditz, G. A., Rosner, B., and Willett, W. C. Food-based validation of a dietary questionnaire: the effects of week-to-week variation in food consumption. Int. J. Epidemiol., *18:* 858–867, 1989.

17. Giovannucci, E., Colditz, G., Stampfer, M. J., Rimm, E. B., Litin, L., Sampson, L., and Willett, W. C. The assessment of alcohol consumption by a simple self-administered questionnaire. Am. J. Epidemiol., *133:* 810–817, 1991.

18. D'Agostino, R. B., Lee, M. L. T., Belanger, A. J., Cupples, L. A., Anderson, K., and Kannel, W. B. Relation of pooled logistic regression to time dependent Cox regression analysis: The Framingham Heart Study. Stat. Med., *9:* 1501–1515, 1990.

19. Fuchs, C., Colditz, G., Stampfer, M., Giovannucci, E., Hunter, D., Rimm, E., Willett, W., and Speizer, F. A prospective study of cigarette smoking and the risk of pancreatic cancer. Arch. Intern. Med., *156:* 2255–2260, 1996.

20. Everhart, J., and Wright, D. Diabetes mellitus as a risk factor for pancreatic cancer. A meta-analysis. JAMA, *273:* 1605–1609, 1995.

21. Silverman, D., Schiffman, M., Everhart, J., Goldstein, A., Lillemoe, K., Swanson, G., Schwartz, A., Brown, L., Greenberg, R., Schoenberg, J., Pottern, L., Hoover, R., and Fraumeni, J. J. Diabetes mellitus, other medical conditions and familial history of cancer as risk factors for pancreatic cancer. Br. J. Cancer, *80:* 1830–1837, 1999.

22. Chow, W. H., Johansen, C., Gridley, G., Mellemkjaer, L., Olsen, J. H., and Fraumeni, J. F., Jr. Gallstones, cholecystectomy and risk of cancers of the liver, biliary tract and pancreas. Br. J. Cancer, *79:* 640–644, 1999.

23. DerSimonian, R., and Laird, N. Meta-analysis in clinical trials. Control. Clin. Trials, *7:* 177–188, 1986.

24. IARC. Alcohol drinking. IARC Monograph Evaluations of Carcinogenic Risks in Humans. Lyon, France: IARC, 1988.

25. IARC. Coffee, tea, mate methylxanthines, and methylglyoxal. IARC Monograph Evaluations of Carcinogenic Risks in Humans. Lyon, France: IARC, 1991.

26. Kasai, H., Kumeno, K., Yamaizumi, Z., Nishimura, S., Nagao, M., Fujita, Y., Sugimura, T., Nukaya, H., and Kosuge, T. Mutagenicity of methylglyoxal in coffee. Gann, *73:* 681–683, 1982.

27. Leonard, T. K., Watson, R. R., and Mohs, M. E. The effects of caffeine on various body systems: a review. J. Am. Diet. Assoc., *87:* 1048–1053, 1987.

28. Kuhlmann, W., Fromme, H. G., Heege, E. M., and Ostertag, W. The mutagenic action of caffeine in higher organisms. Cancer Res., *28:* 2375–2389, 1968.

29. Selby, C. P., and Sancar, A. Molecular mechanisms of DNA repair inhibition of caffeine. Proc. Natl. Acad. Sci. USA, *87:* 3522–3525, 1990.

30. Schlegel, R., and Pardee, A. B. Caffeine-induced uncoupling of mitosis from the completion of DNA replication in mammalian cells. Science (Wash. DC), *232:* 1264–1266, 1986.

31. Cuzick, J., and Babiker, A. Pancreatic cancer, alcohol, diabetes mellitus and gall-bladder disease. Int. J. Cancer, *43:* 415–421, 1989.

32. Heilbrun, L. K., Nomura, A., and Stemmermann, G. N. Black tea consumption and cancer risk: a prospective study. Br. J. Cancer, *54:* 677–683, 1986.

33. Kinlen, L. J., and McPherson, K. Pancreas cancer and coffee and tea consumption: a case-control study. Br. J. Cancer, *49:* 93–96, 1984.

34. Whittemore, A., Paffenbarger, R., Jr., Anderson, K., and Halpern, J. Early precursors of pancreatic cancer in college men. J. Chronic Dis., *36:* 251–256, 1983.