A prospective study of coffee intake and pancreatic cancer: results from the NIH-AARP Diet and Health Study

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Background: Evidence evaluating the association between type of coffee intake (caffeinated, decaffeinated) and risk of pancreatic cancer is limited.

Methods: In the US NIH-AARP Diet and Health Study, we used Cox proportional hazards regression to estimate hazard ratios and 95% confidence intervals (CIs) for coffee intake and risk of pancreatic cancer among 457,366 US adults.

Results: Over 4,155,256 person-years of follow-up, 1,541 incident first primary pancreatic cancers occurred. Following detailed adjustment for tobacco smoking history, risk estimates for coffee drinking were not statistically significant; compared with never drinkers of coffee, the hazard ratios (95% CI) were 1.05 (0.85–1.30), 1.06 (0.86–1.31), 1.03 (0.85–1.25), 1.00 (0.79–1.25), and 1.24 (0.93–1.65) for 0, 1, 1, 2–3, 4–5, and ≥6 cups per day, respectively (P-value for trend 0.46). The observed null association was consistent across all examined strata (sex, smoking status, coffee caffeination, and prevalent diabetes).

Conclusions: In a prospective study of coffee intake with the largest number of pancreatic cancer cases to date, we did not observe an association between total, caffeinated, or decaffeinated coffee intake and pancreatic cancer.

Pancreatic cancer is highly lethal, with a 5-year survival rate of 7% (Howlader, 2015). As there is currently no screening test for this disease, identification of modifiable factors that may lower disease risk is important. Coffee, a common dietary exposure in the United States and worldwide, contains bioactive compounds that may alter cancer risk (Cornelis, 2015; Guertin and Loftfield et al, 2015); however, evidence evaluating the association between type of coffee intake (caffeinated, decaffeinated) and risk of pancreatic cancer is limited.

In 2012, the American Institute of Cancer Research concluded that a substantial effect of coffee on risk of pancreatic cancer was unlikely (World Cancer Research Fund and American Institute for Cancer Research, 2012). However, results from prior meta-analyses are conflicting (Nishi et al, 1996; Dong et al, 2011; Turati et al, 2012). Additionally, a recent pooled analysis of prospective studies concluded that there was no association between coffee intake and risk of pancreatic cancer (Genkinger et al, 2012), but interpretation of these results is difficult due to the appreciable heterogeneity between the 14 included international studies.

Although smoking status and caffeine are important considerations in the association between coffee intake and pancreatic cancer, most previous studies had insufficient case numbers to examine associations stratified by smoking status and lacked information on caffeine type. Smoking is a risk factor for pancreatic cancer (Maisonneuve and Lowenfels, 2014) and is highly correlated with coffee drinking (Nomura et al, 1986; Nilsson et al, 2010; Ren et al, 2010). The European Prospective Study into Nutrition and Cancer (EPIC) recently reported no overall association for high coffee drinking (fourth quartile vs...
non-drinking) and pancreatic cancer, but did observe increased risk among moderately low drinkers (those in the second quartile) of caffeinated coffee (Bhoo-Pathy et al., 2013).

We sought to clarify the association between coffee drinking and pancreatic cancer risk in a large US cohort. With 1541 incident pancreatic cancers, the NIH-AARP Diet and Health Study (http://dietandhealth.cancer.gov/) includes more than two times the number of cases as compared with the largest single prospective study to date (Bhoo-Pathy et al., 2013), and allows for further investigation of potential differences in risk between caffeinated and decaffeinated coffee.

**MATERIALS AND METHODS**

**Study population.** The NIH-AARP Diet and Health Study, detailed elsewhere (http://dietandhealth.cancer.gov/) (Schatzkin et al., 2001), included 566,398 participants who responded to the mailed study questionnaire, which collected data on demographics, health-related behaviours, and diet. At baseline, participants were aged 50–71 years and resided in one of six US states or two metropolitan areas. We included 457,366 participants with non-missing data on coffee intake and smoking who had plausible dietary intakes, did not have prevalent cancer at baseline (except non-melanoma skin cancer), were not proxy respondents, and were still alive upon receipt of the study questionnaire. The Special Studies Institutional Review Board at the National Cancer Institute approved this study, and all participants provided informed consent.

**Ascertainment of pancreatic cancer cases.** Cancer cases were identified by linkage of the NIH-AARP cohort to 11 state cancer registries and the National Death Index; it is estimated that ~90% of cancers in the NIH-AARP cohort are captured by these cancer registries (Michaud et al., 2005). Our analyses were limited to first primary cancers of the exocrine pancreas, defined as codes C25.0–C25.3 and C25.7–C25.9 in the International Classification of Diseases for Oncology, third edition (World Health Organization, 2010); we excluded non-exocrine pancreatic cancers (histology types 8150–8155, 8240, 8246, and 8502) as the etiology of these cancers is thought to differ.

**Assessment of coffee intake and covariates.** At study baseline, participants reported their typical coffee intake and whether they predominantly (more than half the time) drank caffeinated or decaffeinated coffee on a food frequency questionnaire. Covariates that were also assessed at baseline included age, sex, smoking, alcohol use, education, diabetes, and race.

**Statistical analysis.** We used Cox proportional hazards regression to estimate hazard ratios and 95% confidence intervals for pancreatic cancer, using non-drinkers of coffee (reported never drinking coffee during the past year) as the referent group and person-years as the time metric; person-years were calculated beginning on the date the questionnaire was returned until the date of cancer diagnosis or the date of censoring, which included movement out of the registry area, loss to follow-up, death, or the end of follow-up (31 December 2006), whichever came first. In our primary models, we adjusted for age, sex, and comprehensive tobacco smoking status; details on smoking categories and additional covariates in the multivariate-adjusted models are provided in Table 1.

In secondary analyses, we examined the association between coffee intake and pancreatic cancer across prespecified subgroups, including sex, smoking status, type of coffee predominantly consumed (caffeinated or decaffeinated), and prevalent diabetes. We tested the proportional hazards assumption by testing for an interaction between coffee intake and person-years. To examine possible effects of reverse causation, namely whether preclinical disease might alter coffee intake, we conducted lag analyses that started follow-up 2 years after the baseline time point. We conducted all analyses using SAS 9.3 (SAS Institute, Cary, NC, USA) with two-sided tests of statistical significance; P-values <0.05 were interpreted as statistically significant.

**RESULTS**

The mean age of our cohort at baseline was 62 years, and the sample was largely comprised of non-Hispanic whites. Approximately 90% of the study sample reported drinking coffee (Supplementary Table 1). Among the 457,366 participants in our study, 57% primarily drank caffeinated coffee and 30% primarily drank decaffeinated coffee. Compared with non-drinkers and low coffee consumers, high coffee consumers were more likely to be male, non-Hispanic White, married, less well educated, and smokers. They consumed greater amounts of alcohol, dietary fats, and total calories but lower amounts of fruits, vegetables, and foods with folic acid (Supplementary Table 1). Among these 457,366 participants, 1541 cancers of the exocrine pancreas occurred over ~4.2 million person-years of follow-up (Supplementary Table 1). Although models adjusted only for age and sex suggested a statistically significant higher risk of pancreatic cancer with higher coffee intake, the association was substantially attenuated after extensive adjustment for smoking (Table 1). Adjustment for additional covariates did not appreciably alter risk estimates (change <1%). The interaction term between coffee intake and person-years, which tested the proportional hazards assumption, was not statistically significant (P = 0.52). Similar results were observed when we used coffee drinkers of <1 cup per day as the referent group.

The association did not differ by sex (Table 1), tobacco smoking (Table 2), or self-reported history of diabetes (data not shown). Lastly, the association did not differ appreciably between participants drinking predominantly caffeinated and decaffeinated coffee (Table 3), or in analyses that excluded the first 2 years of follow-up (Supplementary Table 2).

**DISCUSSION**

In this large US prospective study, there was no association between total, caffeinated, or decaffeinated coffee intake and risk of pancreatic cancer following adjustment for smoking. Similarly, null findings were observed in never, former, and current cigarette smokers, among men and women, and by stratum of self-reported diabetes at baseline.

The significant association we observed in age- and sex-adjusted models, which suggested increased risk of pancreatic cancer at higher coffee intakes, is likely because of residual confounding by smoking. Smoking is an important risk factor for pancreatic cancer (Bosetti et al., 2012; Klein et al., 2013), and as smoking and coffee drinking are highly correlated behaviours in NIH-AARP (Guertin et al., 2015) and other (Nomura et al., 1986; Nilsson et al., 2010; Ren et al., 2010) study populations, it is particularly important to consider smoking status and dose when considering the risk of disease in association with coffee consumption.

Ours is the largest prospective study of coffee intake and pancreatic cancer to date, with 1541 incident pancreatic cancer cases, and larger than the sum total from the recent Continuous Update Project (CUP) meta-analysis, which included 1460 cases identified from 13 prospective cohorts (World Cancer Research Fund and American Institute for Cancer Research, 2012). In addition to studies considered by the 2012 CUP, the totality of the evidence includes two recently reported prospective cohort
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Table 1. Hazard ratios (95% confidence intervals) for pancreatic cancer according to coffee intake in the NIH-AARP Diet and Health Study (N = 457,366)

| Model adjustments | None (ref.) | <1 | 1 | 2–3 | 4–5 | ≥6 |
|-------------------|------------|----|---|-----|-----|----|
| (n = 46,369)      | (n = 74,796) |   |   |     |     |    |
| All participants  |            |    |   |     |     |    |
| No. of cases      | 129        | 234| 258| 645 | 195 | 80 |
| Age, sex          | 1.00       | 1.07 (0.87–1.33) | 1.10 (0.89–1.36) | 1.15 (0.95–1.38) | 1.24 (0.99–1.55) | 1.77 (1.34–2.34) |
| Age, smoking      | 1.00       | 1.05 (0.85–1.30) | 1.06 (0.86–1.31) | 1.03 (0.85–1.26) | 1.01 (0.80–1.27) | 1.26 (0.94–1.69) |
| Multivariate      | 1.00       | 1.05 (0.84–1.30) | 1.06 (0.86–1.31) | 1.03 (0.85–1.26) | 1.01 (0.80–1.27) | 1.26 (0.94–1.69) |
| Men (n = 275,328) |            |    |   |     |     |    |
| No. of cases      | 71         | 153| 146| 427 | 142 | 54 |
| Age               | 1.00       | 1.18 (0.89–1.56) | 1.07 (0.81–1.43) | 1.19 (0.93–1.53) | 1.34 (1.01–1.78) | 1.74 (1.22–2.48) |
| Age, smoking      | 1.00       | 1.16 (0.87–1.53) | 1.03 (0.77–1.37) | 1.08 (0.84–1.39) | 1.08 (0.81–1.45) | 1.21 (0.84–1.75) |
| Multivariate      | 1.00       | 1.14 (0.86–1.52) | 1.02 (0.76–1.35) | 1.05 (0.81–1.36) | 1.06 (0.79–1.43) | 1.21 (0.84–1.75) |
| Women (n = 182,038) |         |    |   |     |     |    |
| No. of cases      | 58         | 81 | 112| 218 | 53  | 24 |
| Age               | 1.00       | 0.92 (0.66–1.29) | 1.11 (0.84–1.58) | 1.08 (0.81–1.45) | 1.08 (0.75–1.57) | 1.90 (1.19–3.01) |
| Age, smoking      | 1.00       | 0.90 (0.65–1.27) | 1.12 (0.81–1.54) | 0.97 (0.72–1.30) | 0.85 (0.58–1.24) | 1.34 (0.83–2.16) |
| Multivariate      | 1.00       | 0.91 (0.65–1.28) | 1.12 (0.82–1.55) | 1.01 (0.75–1.35) | 0.89 (0.60–1.30) | 1.38 (0.85–2.22) |

Abbreviations: BMI = body mass index; NIH-AARP = National Institutes of Health–AARP. All models were adjusted for age at study baseline (continuous), and sex (with the exception of gender-stratified models). Detailed adjustment for smoking included current cigarette smoking status (current, former, never), number of cigarettes smoked per day among current and former smokers (1–10, 11–20, 21–30, 31–40, 41–60, >60), time of smoking cessation among former smokers (<1, <5, <10, >10 years before study baseline), and whether a participant ever smoked pipe/cigars (yes/no). Multivariate models were additionally adjusted for diabetes (yes/no), race/ethnicity (non-Hispanic white, non-Hispanic black, other), BMI (as (18.5, 18.5–25, 25–30, >30), highest level of education (≤11 years, high school graduate, some college, college graduate), alcohol consumption (0, <1, 1–2, 3–4 drinks per day), health status (good/excellent, good, poor/fair), use of nutritional supplements (yes/no), current marital status (married/not married, physical activity (never/rarely, 1–3x per week, 1–3x per week, 3–4x per week, or >5x per week), history of cardiovascular disease (yes/no), family history of cancer (yes/no), total energy intake (kcal, continuous), and the nutrient density-adjusted intakes (continuous) of the following dietary items: fruits, vegetables, folate, protein, saturated fat, and total fat. Bold values are statistically significant (P-values < 0.05). *P < 0.001. **P < 0.001.

*Participants reported never drinking coffee during the past year.

Table 2. HRs and 95% CIs for pancreatic cancer according to coffee intake in the NIH-AARP Diet and Health Study, stratified by smoking status (n = 442,280)

| Model adjustments | None (ref.) | <1 | 1 | 2–3 | 4–5 | ≥6 |
|-------------------|------------|----|---|-----|-----|----|
| (n = 46,369)      | (n = 150,179) |   |   |     |     |    |
| Current smokers   |            |    |   |     |     |    |
| No. of cases      | 15         | 70 | 147| 147 | 103 | 67 |
| HR (95% CI)       | 1.00       | 1.15 (0.66–2.01) | 1.10 (0.65–1.88) | 1.10 (0.65–1.88) | 1.03 (0.60–1.77) | 0.57 |
| Former smokers    | 228,875    |    |   |     |     |    |
| No. of cases      | 43         | 244| 329| 127 |     |    |
| HR (95% CI)       | 1.00       | 1.16 (0.84–1.60) | 1.08 (0.78–1.48) | 1.18 (0.83–1.67) | 0.83 |
| Never smokers     | 147,706    |    |   |     |     |    |
| No. of cases      | 17         | 160| 141| 31  |     |    |
| HR (95% CI)       | 1.00       | 0.95 (0.71–1.26) | 0.98 (0.73–1.31) | 0.97 (0.63–1.48) | 0.93 |

Abbreviations: CI = confidence intervals; HR = hazard ratios; NIH-AARP = National Institutes of Health–AARP. Participants who reported that they never smoked cigarettes but smoked pipe/cigars are excluded from these analyses (n = 150,179). All models were adjusted for age at study baseline (continuous), sex, number of cigarettes smoked per day among current and former smokers (1–10, 11–20, 21–30, 31–40, 41–60, >60), time of smoking cessation among former smokers (<1, <5, <10, >10 years before study baseline), and whether a participant ever smoked pipe/cigars (yes/no). P-values < 0.05 were considered to be statistically significant.

*Participants reported never drinking coffee during the past year.

**Never smokers of any tobacco product (cigarettes, pipes, or cigars).**

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Three previous studies from prospective cohorts have investigated associations by caffeinated and decaffeinated coffee separately (Michaud et al, 2001; Turati et al, 2012; Bhoo-Pathy et al, 2013). Our findings are consistent with those recently reported by EPIC (Bhoo-Pathy et al, 2013), with one exception; EPIC detected a small positive association between moderately low drinkers of caffeinated coffee and pancreatic cancer, compared with non-drinkers, which we did not observe in NIH-AARP. However, the authors acknowledged that the observed association among low caffeinated coffee drinkers in EPIC may be because of chance or residual confounding.

Several limitations in our study should be acknowledged. Our sample was largely Caucasian, which precluded examination of associations by race/ethnicity; our results may not be generalizable to populations with different characteristics. Coffee intake was only measured once at study baseline; however, previous studies suggest that coffee consumption is relatively stable over time (Nilsson et al, 2010; Hildebrand et al, 2012). Our results are most likely reflective of the association between filtered coffee and pancreatic cancer risk, given that this is the type of coffee predominantly consumed in the United States. Type of coffee preparation (i.e. filtered vs boiled) may affect the concentration and types of constituents present in a cup of coffee and may be relevant for pancreatic cancer risk (Nilsson et al, 2010). NIH-AARP queries...
Table 3. HRs and 95% CIs for pancreatic cancer according to caffeinated and decaffeinated coffee intake in the NIH-AARP Diet and Health Study (n = 441,363)

| Caffeinated coffee drinkers (n = 259,908) | Coffee intake (cups per day) | None (ref.)* | ≤1 | 2–3 | ≥4 | P-value for trend |
|-----------------------------------------|------------------------------|---------------|----|-----|----|------------------|
| No. of cases                           | 129                          | 264           | 449| 212 |    |                  |
| HR (95% CI)                            | 1.00                         | 1.13 (0.92–1.40)| 1.04 (0.86–1.27)| 1.07 (0.85–1.34)| 0.85 |

| Decaffeinated coffee drinkers (n = 135,088) | Coffee intake (cups per day) | None (ref.)* | ≤1 | 2–3 | ≥4 | P-value for trend |
|------------------------------------------|------------------------------|---------------|----|-----|----|------------------|
| No. of cases                             | 129                          | 204           | 180| 52  |    |                  |
| HR (95% CI)                              | 1.00                         | 0.98 (0.79–1.23)| 1.02 (0.81–1.28)| 0.96 (0.69–1.33)| 0.50 |

Abbreviations: CI = confidence intervals; HR = hazard ratios; NIH-AARP = National Institutes of Health–AARP. Participants who reported drinking coffee were classified as drinkers of caffeinated coffee or decaffeinated coffee (mutually exclusive) based on which type of coffee they reported drinking more than half the time; 16,001 coffee drinkers were missing caffeine data. All models were adjusted for age at study baseline (continuous), sex, number of cigarettes smoked per day among current and former smokers (<1, 1–5, 5–10, 10–20, 21–30, 31–40, 41–60, ≥60), time of smoking cessation among former smokers (<1, 1–5, 5–10, or ≥10 years before study baseline), and whether a participant ever smoked pipe/organ (yes/no). P-values < 0.05 were considered to be statistically significant.

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CONFLICT OF INTEREST

The authors declare no conflict of interest.

REFERENCES

Bhoo-Pathy N, Uiterwaal CS, Dik VK, Jeurnink SM, Bech BH, Overvad K, Halkjær J, Tjønneland A, Boutron-Ruault MC, Fagherazzi G, Racine A, Katze KA, Li K, Boeing H, Floegel A, Androulidaki A, Bamia C, Trichopoulou A, Masala G, Panico S, Cossignani P, Tumino R, Vinies P, Peeters PH, Gavrilyuk O, Skeie G, Weiderpass E, Duell EJ, Arguèlles M, Molina-Montes E, Navarro C, Ardanaz E, Dornonsoro M, Lindkvist B, Wallström P, Sund M, Ye W, Khaw KT, Wareham N, Key TJ, Travis RC, Duarte-Salles T, Freisling H, Lica JL, Gallou V, Michaëlas DS, Riboli E, Bueno-De-Mesquita HB (2013) Intake of coffee, decaffeinated coffee, or tea does not affect risk for pancreatic cancer: results from a European prospective Investigation into Nutrition and Cancer Study. *Clin Gastroenterol Hepatol* 11: 1486–1492.

Bidel S, Hu G, Jousilahti P, Pukkala E, Hakulinen T, Tuomilehto J (2013) Coffee consumption and risk of gastric and pancreatic cancer—a prospective cohort study. *Int J Cancer* 132: 1631–1639.

Caffeinated Coffee Drinkers (Maisonneuve and Lowenfels, 2014) and is highly correlated with smoking. Smoking is an established risk factor for pancreatic cancer (Maisonuneuve and Lowenfels, 2014) and is highly correlated with coffee intake. The prospective design is a significant strength of our study as it limits the potential that disease status influenced the self-report of coffee intake. The majority of prior evidence is limited to case-control studies or hospital-based cohorts, reviewed elsewhere (World Cancer Research Fund and American Institute for Cancer Research, 2007), which are vulnerable to recall bias. As compared with previous studies, we were able to more comprehensively adjust for smoking status by incorporating data on time since cessation among former smokers, which may have any effects of residual confounding by smoking on our estimates. Smoking is an established risk factor for pancreatic cancer (Maisonuneuve and Lowenfels, 2014) and is highly correlated with coffee intake in the NIH-AARP Study (Guertin and Loffeld et al, 2015) and elsewhere (Nomura et al, 1986; Nilsson et al, 2010; Ren et al, 2010). Although we did not find evidence for an association, we had excellent statistical power. Our cohort included approximately two times the number of pancreatic cancer cases compared with the largest study to date (Bhoo-Pathy et al, 2013). The large size of the NIH-AARP cohort and the availability of data on coffee consumption preferences also allowed us to investigate whether effects differed between primarily caffeinated and primarily decaffeinated coffee drinkers.

This study, in addition to the previous literature, supports the 2012 conclusion of the American Institute of Cancer Research in that there is little epidemiologic evidence of an association between coffee intake and pancreatic cancer risk (World Cancer Research Fund and American Institute for Cancer Research, 2012). Our study provides evidence to extend this conclusion to both caffeinated and decaffeinated coffee drinking.

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