JNCI J Natl Cancer Inst (2019) 111(12): djz103

doi: 10.1093/jnci/djz103
First published online May 25, 2019
Review

REVIEW

Smoking, Alcohol, and Biliary Tract Cancer Risk: A Pooling Project of 26 Prospective Studies

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Abstract

Background: Tobacco and alcohol are well-established risk factors for numerous cancers, yet their relationship to biliary tract cancers remains unclear.
Methods: We pooled data from 26 prospective studies to evaluate associations of cigarette smoking and alcohol consumption with biliary tract cancer risk. Study-specific hazard ratios (HRs) and 95% confidence intervals (CIs) for associations with smoking and alcohol consumption were calculated. Random-effects meta-analysis produced summary estimates. All statistical tests were two-sided.
Results: Over a period of 38 369 156 person-years of follow-up, 1391 gallbladder, 758 intrahepatic bile duct, 1208 extrahepatic bile duct, and 623 ampulla of Vater cancer cases were identified. Ever, former, and current smoking were associated with increased extrahepatic bile duct and ampulla of Vater cancers risk (eg, current vs never smokers HR = 1.69, 95% CI = 1.34 to 2.13 and 2.22, 95% CI = 1.69 to 2.92, respectively), with dose-response effects for smoking pack-years, duration, and intensity (all $P_{trend} < .01$). Current smoking and smoking intensity were also associated with intrahepatic bile duct cancer (eg, >40 cigarettes per day vs never smokers HR = 2.15, 95 % CI = 1.15 to 4.00; $P_{trend} = .001$). No convincing association was observed between smoking and gallbladder cancer. Alcohol consumption was only associated with intrahepatic bile duct cancer, with increased risk for individuals consuming five or more vs zero drinks per day (HR = 2.35, 95%CI = 1.46 to 3.78; $P_{trend} = .04$). There was evidence of statistical heterogeneity among several cancer sites, particularly between gallbladder cancer and the other biliary tract cancers.

Received: December 7, 2018; **Revised:** April 13, 2019; **Accepted:** May 15, 2019

Conclusions: Smoking appears to increase the risk of developing all biliary tract cancers except gallbladder cancer. Alcohol may increase the risk of intrahepatic bile duct cancer. Findings highlight etiologic heterogeneity across the biliary tract.

Biliary tract cancers, which include cancers of the gallbladder, intrahepatic bile duct, extrahepatic bile duct, and ampulla of Vater, are relatively rare but highly fatal malignancies (1–3). Although incidence rates of biliary tract cancers are low globally, they are substantially higher in certain geographic regions and among some ethnic and racial subgroups (1,2,4). Increasing incidence rates of intrahepatic and extrahepatic bile duct cancers have also been reported in the United States (1,5). Yet, because of the rarity of biliary tract cancers and a paucity of published data, the etiology of these malignancies remains poorly understood.

Tobacco and alcohol are established risk factors for several cancers (6) and have been classified as group 1 carcinogens by the International Agency for Research on Cancer (7). Tobacco smoking is the leading cause of cancer worldwide. Alcohol consumption accounts for a smaller proportion of new cancer cases; however, the global prevalence of alcohol use is high, with approximately 38% of the world's population age 15 years or older regularly consuming alcohol (7,8).

Despite a large body of tobacco- and alcohol-related research, the relationship of these exposures to biliary tract cancers remains unclear. Prior studies investigating associations of tobacco smoking and alcohol consumption with biliary tract cancer risk have yielded inconsistent or inconclusive results (6,9–22). Most prior studies have been relatively small, retrospective case-control studies, limiting their ability to detect modest associations and to perform analyses individually by anatomic site. Prior meta-analyses relied primarily on case-control data and almost exclusively evaluated ever vs never smoking and alcohol consumption (23–28). With the exception of one pooled analysis of intrahepatic bile duct cancer (29), previous meta-analyses have relied on published literature and have often been limited by publication biases and an inability to control for important confounders (23–28).

To address these limitations, we pooled individual-level data from 26 prospective cohort studies and trials to evaluate associations of cigarette smoking and alcohol consumption with primary biliary tract cancer risk. We evaluated all associations separately by anatomic cancer.

Methods

Study Population

We used data from the Biliary Tract Cancers Pooling Project (BiTCaPP), which includes prospective information from more than 2.8 million participants. Studies were identified for potential inclusion via the National Cancer Institute Cancer Cohort Consortium and individual research collaborations. Eligible studies were prospective studies with at least one biliary tract cancer case. Deidentified individual-level datasets were requested electronically and successfully received from all studies. Study-specific datasets were then harmonized (ie, formatted uniformly across studies to allow for inferential equivalence) (30) and compiled in a pooled dataset. All data used in this analysis were checked for consistency and completeness using logical queries and comparisons with published data. No major data quality issues were identified.

Each study received ethical approval from its respective institutional review board and all study participants provided written informed consent. BiTCaPP was exempted from additional ethical review by the National Cancer Institute's Office of Human Subjects Research.

We included in this analysis 26 BiTCaPP studies with information both on cigarette smoking and alcohol consumption. Details on the included studies are described in Table 1. Briefly, this sample included 21 prospective cohort studies (31–51), four randomized control trials (52–55), and one cancer screening trial (56). Studies were conducted in North America (n = 16) (31–33,35,37,38,41–44,48,49,53–56), Europe (n = 5) (34,36,50–52), Asia (n = 4) (39,45–47), and Australia (n = 1) (40).

We excluded individuals younger than 18 years (n = 130) and/or for whom entry or exit age was missing (n = 5044). We also excluded participants with prior cancer diagnoses other than nonmelanoma skin cancer at study entry (n = 61 232), biliary tract cancers of undefined and/or unknown site or overlapping lesions (n = 329), and participants with missing biliary tract cancer status (n = 11). The final analytic sample thus included 2 724 982 individuals.

Ascertainment of Outcomes

Outcomes of interest for this study were primary biliary tract cancers occurring as incident, first cancers. Each study provided data on primary biliary tract cancers by anatomic site using International Classification of Disease codes (Supplementary Table 1, available online). Cancer diagnoses were ascertained via linkage to a local, state, provincial, or national cancer registry (Agricultural Health Study [AgHealth]; Adventist Health Study-2 [AHS-2]; Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study [ATBC]; Cohort of Swedish Men [COSM]; Iowa Women's Health Study [IWHS]; Melbourne Collaborative Cohort Study [MCCS]; Multiethnic Cohort Study [MEC]; National Institutes of Health-American Association of Retired Persons Diet and Health Study [NIH-AARP]; Radiation Effects Research Foundation Life Span Study [RERF]; Singapore Chinese Health Study [SCHS]; Swedish Mammography Cohort [SMC]; VITamins and Lifestyle Study [VITAL]; Women's Lifestyle and Health Study [WLHS]); self-report verified by medical record, pathology report, cancer registry linkage, or death certificate (Health Professionals Follow-Up Study [HPFS]; Nurses' Health Study [NHS]; Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial [PLCO]; Physicians' Health Study [PHS]; Sister Study [SISTER]; Women's Health Initiative [WHI]; Women's Health Study [WHS]); or a combination of methods (Breast Cancer Detection Demonstration Project [BCDDP]; Cancer Prevention Study II Nutrition Cohort [CPS-II NC]; European Prospective Investigation into Cancer and Nutrition [EPIC]; Japan Public Health Center-based prospective Study 1 and 2 [JPHC]; New York University Women's Health Study [NYUWHS]; Shanghai Cohort Study [SCS]).

Ascertainment of Exposures

All studies provided self-reported data on demographic and epidemiologic characteristics, including data on smoking and alcohol, which was obtained via questionnaires and/or in-person

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Table 1. Summary of studies included in the smoking and alcohol analyses of the Biliary Tract Cancers Pooling Project

Study (abbreviation)	Period	No. in baseline sample*	Age at baseline, median (IQR), y	Female sex, † %	Current smokers, ‡ %	Alcoholic drinks per day, § median (IQR)	Gallstones, ‖ %	Cholecystectomy, ¶ %	No. of biliary tract cancer cases			
									GBC	IHBDC	EHBDC	AVC
Agricultural Health Study (AgHealth) (31)	1993–2013	89 009	45.0 (37.0–56.0)	37.7	14.5	0.1 (0.0–0.6)	—	—	23	19	18	11
Adventist Health Study-2 (AHS-2) (32)	2002–2015	95 942	57.0 (47.0–69.0)	64.9	1.1	0.4 (0.1–0.7)	3.3	—	16	9	11	7
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC) (52)	1985–2010	29 127	57.0 (53.0–61.0)	0	100	1.0 (0.4–2.0)	5.6	4.9	17	38	42	16
Breast Cancer Detection Demonstration Project (BCDDP) (33)	1980–1998	47 224	61.5 (56.0–67.7)	100	12.5	0.2 (0.1–0.7)	—	—	12	6	7	8
Cohort of Swedish Men (COSM) (34)	1998–2008	45 801	59.5 (52.5–68.5)	0	25.0	0.7 (0.3–1.4)	11.7	—	13	6	15	3
Cancer Prevention Study II Nutrition Cohort (CPS-II NC) (35)	1992–2011	155 077	63.0 (58.0–68.0)	52.6	8.9	0.6 (0.2–1.3)	11.6	12.7	70	54	57	36
European Prospective Investigation into Cancer and Nutrition (EPIC) (36)	1992–2010	490 466	51.5 (45.1–58.3)	70.0	22.9	0.5 (0.1–1.2)	6.3	—	134	119	111	86
Health Professionals Follow-Up Study (HPFS) (37)	1986–2012	51 375	54.0 (45.0–62.0)	0	10.0	0.7 (0.3–1.4)	—	3.2	11	8	23	10
Iowa Women's Health Study (IWHS) (38)	1986–2013	37 977	61.0 (58.0–65.0)	100	14.8	0.3 (0.1–0.8)	—	—	69	14	30	12
Japan Public Health Center-based prospective Study 1 and 2 (JPHC) (39)	1990–2011	99 595	52.9 (46.2–58.9)	52.4	28.1	1.8 (0.8–3.4)	2.9	—	172	120	199	38
Melbourne Collaborative Cohort Study (MCCS) (40)	1990–2009	39 992	55.5 (47.6–62.8)	58.8	11.4	0.8 (0.3–1.6)	9.1	7.6	35	20	22	6
Multiethnic Cohort Study (MEC) (41)	1993–2010	187 414	60.0 (52.0–67.0)	54.5	16.5	0.5 (0.1–1.6)	6.7	6.4	110	60	117	64
Nurses' Health Study (NHS) (42)	1980–2010	100 667	47.0 (41.0–53.0)	100	29.0	0.2 (0.1–0.8)	1.6	7.7	54	17	34	18
National Institutes of Health-American Association of Retired Persons Diet and Health Study (NIH-AARP) (43)	1995–2011	556 036	63.0 (58.0–67.0)	40.2	12.5	0.3 (0.1–1.2)	9.6	14.2	218	134	242	151
New York University Women's Health Study (NYUWHS) (44)	1985–2007	13 350	51.0 (43.0–58.0)	100	18.1	0.6 (0.3–1.2)	5.0	—	7	6	9	0
Physicians' Health Study (PHS) (53)	1982–2009	28 426	54.3 (47.6–61.4)	0	9.3	0.4 (0.1–1.0)	3.7	—	7	9	9	7
Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO) (56)	1993–2009	116 583	65.7 (61.0–70.0)	50.8	9.5	0.3 (0.1–1.1)	11.6	—	34	13	31	24

(continued)

Table 1. (continued)

Study (abbreviation)	Period	No. in baseline sample*	Age at baseline, median (IQR), y	Female sex, † %	Current smokers, ‡ %	Alcoholic drinks per day, § median (IQR)	Gallstones, ‖ %	Cholecystectomy, ¶ %	No. of biliary tract cancer cases			
									GBC	IHBDC	EHBDC	AVC
Radiation Effects Research Foundation Life Span Study (RERF) (45)	1950–2005	51 302	51.4 (41.5–62.0)	61.4	31.1	0.1 (0.0–0.1)	—	—	148	—	120	25
Singapore Chinese Health Study (SCHS) (46)	1993–2008	61 320	55.0 (49.0–62.0)	55.5	19.7	0.5 (0.5–0.5)	—	—	29	26	14	22
Shanghai Cohort Study (SCS) (47)	1986–2012	18 075	56.0 (52.0–60.0)	0	50.5	1.5 (0.5–1.5)	—	—	15	13	21	15
Sister Study (SISTER) (48)	2003–2012	47 798	55.4 (48.9–62.0)	100	8.1	0.2 (0.0–0.7)	14.5	12.8	4	4	0	4
Swedish Mammography Cohort (SMC) (51)	1998–2008	37 151	60.5 (54.5–69.5)	100	23.2	0.3 (0.1–0.6)	19.9	—	42	3	6	1
VITamins and Lifestyle Study (VITAL) (49)	2000–2009	77 011	61.0 (55.0–68.0)	51.9	8.4	0.5 (0.1–1.2)	—	—	16	15	15	5
Women's Health Initiative (WHI) (54)	1993–2014	161 081	63.0 (57.0–69.0)	100	7.0	0.3 (0.1–0.8)	16.3	12.9	113	32	50	42
Women's Health Study (WHS) (55)	1992–2010	39 788	53.0 (49.0–59.0)	100	13.1	0.3 (0.1–0.9)	9.9	—	10	7	1	11
Women's Lifestyle and Health Study (WLHS) (50)	1991–2011	47 392	40.0 (35.0–45.0)	100	21.3	0.2 (0.1–0.4)	—	—	12	6	4	1
Total		2 724 982	58.0 (51.0–65.0)	59.5	16.9	0.4 (0.1–1.1)	8.9	10.5	1391	758	1208	623

*No. in baseline sample: Baseline sample size is calculated after excluding individuals who were younger than 18 years, had missing entry or exit age, had prior cancer diagnoses other than nonmelanoma skin cancer at study entry, had biliary tract cancers of undefined and/or unknown site or overlapping lesions, and/or had missing biliary tract cancer status. —indicates the study did not report this variable; AVC = ampulla of Vater cancer; EHBDC = extrahepatic bile duct cancer; GBC = gallbladder cancer; IHBDC = intrahepatic bile duct cancer; IQR = interquartile range.

†Variables are missing for 38 participants (0.001%).

‡Variables are missing for 54 426 participants (2.0%).

§Variables are missing for 118 605 participants (4.4%).

‖Variables are missing for 162 690 participants (7.2%).

¶Variables are missing for 327 588 participants (24.7%).

interviews. We assessed self-reported ever vs never smoking, smoking status (never, former, current), duration of smoking (years), smoking intensity (cigarettes per day), and smoking pack-years. Detailed information on the ascertainment of smoking information for each study is provided in Supplementary Table 2 (available online). Briefly, all 26 studies provided information on ever smoking and smoking status; however, one study (ATBC) included only current smokers by design and thus was excluded from the smoking analyses. Most studies defined ever smoking as "regular smoking" (n = 7) or having smoked at least 100 cigarettes (n = 7). Current smoking was usually defined as any cigarette smoking reported at the time of data collection (n = 23). A total of 25 and 21 studies provided information on cigarette smoking duration and intensity, respectively. For 15 studies, smoking duration was calculated by subtracting the age at initiation of smoking from either the age at which the subject quit (former smokers) or the age at baseline (current smokers). The remaining 10 studies collected self-reported total years smoked at baseline. Nine studies reported smoking duration excluding intermittent periods of cessation. For smoking intensity, studies provided either the average number of cigarettes smoked per day over the lifetime smoking period (n = 12) or the average smoked per day at the time of data collection or last smoking period (n = 9). We calculated smoking pack-years (cigarettes per day divided by 20, multiplied by duration in years) for 21 studies.

For all 26 studies, we assessed self-reported number of alcoholic drinks consumed per day (Supplementary Table 3, available online). Studies provided either grams of alcohol (n = 22) or alcoholic drinks (n = 4) consumed per day. For the purposes of these analyses, one alcoholic drink was defined as 14 g of ethanol (57). Most studies (n = 17) reported average alcohol consumption over the past 12 months.

Ever smoking and smoking status were analyzed categorically, with never smokers as the reference group. Smoking and alcohol dose variables were analyzed 1) categorically using a priori cut points (smoking pack-years: never smokers [reference], >0–20, >20–40, >40; smoking duration [years] and intensity [cigarettes per day]: never smokers [referent], >0–10, >10–20, >20–40, >40; alcoholic drinks per day: 0 [referent], >0–0.5, >0.5–1, 1–<3, 3–<5, ≥5) and 2) continuously (analyzed per 10-unit increase [smoking variables] or per one drink [alcohol]).

Statistical Analysis

We assessed associations of cigarette smoking and alcohol consumption with biliary tract cancer risk using Cox proportional hazards regression with age as the timescale and left truncation at baseline. Visual and statistical examination of the scaled Schoenfeld residuals for the main exposures (smoking status and alcoholic drinks per day [categorical]) in the pooled dataset showed no evidence of proportional hazards assumption violation (58). All global *P* values for potential violations of the proportional hazards assumption for the multivariable models as a whole were greater than .10. Participant follow-up time began at baseline and ended at the time of first primary cancer diagnosis (other than nonmelanoma skin cancer), loss to follow-up, death, or study-specific end date, whichever occurred first.

We performed our primary analyses using a two-stage approach. In the first stage, we calculated site- and study-specific hazard ratios (HRs) and 95% confidence intervals (CIs) adjusted for a priori confounders identified based on directed acyclic graphs: sex (male, female), race (white, black, Asian and Pacific Islander, other), educational attainment (<high school graduate, high school graduate, some college or post-high school training), body mass index in kg/m^2 (<18.5, 18.5–<25, 25–<30, ≥30), history of diabetes (ever vs never diagnosed), and birth cohort (1870–1899, 1900–1909, 1910–1919, 1920–1929, 1930–1939, 1940–1949, 1950–1959, 1960–1982). Smoking models were additionally adjusted for alcoholic drinks per day (0, >0–0.5, >0.5–1, 1–<3, ≥3), and alcohol models were additionally adjusted for smoking status (never, former, current). Results were not materially altered after excluding body mass index and diabetes, which could be potential confounders or causal mediators depending on temporal relationships (data not shown). In the second stage, we performed a random-effects meta-analysis of the study-specific estimates and assessed statistical heterogeneity between studies using the I^2 statistic (59). We also repeated these analyses using a one-stage approach, calculating hazard ratios in the aggregate, pooled dataset and stratifying the baseline hazard by study. We evaluated heterogeneity by biliary tract cancer site in the pooled dataset using a data duplication method for competing risks, testing for heterogeneity via the Wald test (60). Heterogeneity analyses were conducted for the associations with smoking status and alcoholic drinks per day (categorical).

We performed several prespecified sensitivity analyses in the pooled dataset. We analyzed smoking and alcohol dose-response variables restricting to ever smokers and individuals who consumed more than 0 alcoholic drinks per day, with the lowest exposure group as the reference group. For smoking intensity and duration, we also conducted analyses adjusting for smoking pack-years (categorical) to assess if associations with intensity or duration persisted after accounting for the effect of total exposure (61). We evaluated potential multiplicative effect-measure modification by sex and race for the associations with smoking status and alcoholic drinks consumed per day (categorical). Effect-measure modification was assessed using likelihood ratio tests comparing models with and without a multiplicative term (62). In a subset of 17 studies with information on prior gallstone diagnoses (Table 1), we also compared risk estimates with and without adjustment for history of gallstones to explore whether the associations with smoking and alcohol might be mediated by gallstones, a key risk factor for biliary tract cancers (63). Finally, for all analyses of gallbladder cancer, we compared overall risk estimates with estimates that were generated after restricting to participants who had no history of cholecystectomy (ie, only individuals who were at risk for gallbladder cancer at baseline). This analysis was restricted to nine studies that provided information on cholecystectomies (Table 1).

Analyses were performed in SAS software version 9.4 (SAS Institute Inc, Cary, NC), Stata software version 15.0 (StataCorp LLC, College Station, TX), and R software version 3.5.1 (R Development Core Team, Vienna, Austria). Participants with missing data were case-deleted. All statistical tests were two-sided and *P* values less than .05 were considered statistically significant.

Results

Of the 2 724 982 people in the BiTCaPP sample, 1391 (0.05%) developed gallbladder cancer, 758 (0.03%) developed intrahepatic bile duct cancer, 1208 (0.04%) developed extrahepatic bile duct cancer, and 623 (0.02%) developed ampulla of Vater cancer over a total of 38 369 156 person-years of follow-up. The median time

to diagnosis of any biliary tract cancer was 10.6 years (interquartile range [IQR] = 5.6–14.5 years), and the median age at biliary tract cancer diagnosis was 71.8 years (IQR = 65.0–78.5 years), with no substantial variations by anatomic site.

Characteristics of the participants and studies are shown in Table 1. The percentage of current smokers ranged from 1.1% in AHS-2 to 50.5% in SCS (in ATBC, 100% of participants were current smokers by design), whereas median alcoholic drinks per day ranged from 0.1 in AgHealth and the RERF to 1.8 in the JPHC.

Summary risk estimates for the associations of cigarette smoking and alcohol consumption with biliary tract cancer risk are shown in Tables 2 and 3. There was low to moderate between-study heterogeneity for most risk estimates, with 66% of I^2 lower than 10%, and 91% lower than 40%.

Ever, former, and current smokers were at increased risk of extrahepatic bile duct and ampulla of Vater cancers when compared never smokers (HR for current vs never smokers = 1.69, 95% CI = 1.34 to 2.13 and 2.22, 95% CI = 1.69 to 2.92, respectively; Table 2 and Figure 1). Current smokers were also at increased risk of intrahepatic bile duct cancer (HR = 1.30 , 95% CI = 1.00 to 1.69). Increasing levels of smoking pack-years, duration, and intensity were associated with extrahepatic bile duct and ampulla of Vater cancers (eg, HR = 1.96, 95% CI = 1.47 to 2.63, and HR = 2.18, 95% CI = 1.56 to 3.06, for smoking duration >40 years vs never smokers, respectively). In contrast, only smoking intensity was consistently associated with intrahepatic bile duct cancer risk (eg, HR = 2.15, 95% CI = 1.15 to 4.00, for >40 cigarettes per day vs never smokers). We observed no convincing evidence of an association between cigarette smoking and gallbladder cancer risk. Although a few estimates were suggestive of an increased risk (eg, HR = 1.75, 95% CI = 1.00 to 3.06, for >40 cigarettes per day vs never smokers), there was no consistent pattern or evidence of a dose-response relationship, and some estimates were based on a small number of cases (eg, <20).

Results for smoking dose variables were fairly consistent when analyzed continuously, although effect sizes were smaller given these analyses evaluated the average impact of a 10-unit increase and assumed a linear relationship. In addition, smoking pack-years was associated with intrahepatic bile duct cancer when analyzed continuously, which may suggest a loss of power in the categorical analysis (given marginal associations observed in high categories) or a chance finding. We saw evidence for a dose-response relationship of smoking pack-years, duration, and intensity with extrahepatic bile duct and ampulla of Vater cancers (all $P_{trend} < .01$). There was also evidence of a dose-response relationship between smoking intensity and intrahepatic bile duct cancer ($P_{trend} = .001$). When we analyzed associations using the aggregate, pooled dataset, results were consistent, although most associations were attenuated (Supplementary Table 4, available online). Risk estimates restricted to ever smokers were also generally consistent (Supplementary Table 5, available online), as were the estimates for smoking intensity and duration when additionally adjusted for smoking pack-years (Supplementary Table 6, available online).

Drinkers who reported drinking at least five alcoholic drinks per day were at increased risk of intrahepatic bile duct cancer compared with participants who consumed zero alcoholic drinks per day (HR = 2.35, 95% CI = 1.46 to 3.78), and there was evidence of a dose-response trend ($P_{trend} = .04$; Table 3 and Figure 2). Individuals consuming three to fewer than five drinks per day were at marginally increased risk of extrahepatic bile duct cancer (HR = 1.82, 95% CI = 0.98 to 3.39); however, there was no evidence of a dose-response relationship ($P_{trend} = .84$), there was high between-study heterogeneity ($I^2 = 57.2\%$), and these results were not robust to sensitivity analyses. No associations between alcohol consumption and gallbladder or ampulla of Vater cancer were observed. In the pooled dataset, the pattern of results was similar, but some of the associations did not reach statistical significance (Supplementary Table 4, available online). Results were similar when we analyzed drinks per day as a continuous variable (Table 3). When restricting to individuals who consumed alcohol, the pattern of results was consistent (Supplementary Table 5, available online).

For the associations with smoking status and alcoholic drinks per day, there was evidence of potential heterogeneity between several biliary tract cancers, particularly gallbladder cancer (all $P_{heterogeneity} < .001$ for comparisons with gallbladder cancer; alcoholic drinks per day $P_{heterogeneity} = .03$ for ampulla of Vater vs intrahepatic bile duct cancer; smoking status $P_{heterogeneity} = .08$ for ampulla of Vater vs intrahepatic bile duct cancer; and smoking status $P_{heterogeneity} = .09$ for extrahepatic bile duct cancer vs intrahepatic bile duct cancer). There was little evidence of heterogeneity between ampulla of Vater and extrahepatic bile duct cancer (smoking status $P_{heterogeneity} = .77$; alcoholic drinks per day $P_{heterogeneity} = .22$). For the associations with alcoholic drinks per day, there was also little evidence of heterogeneity between extrahepatic and intrahepatic bile duct cancers ($P_{heterogeneity} = .33$).

There was evidence of possible multiplicative effect-measure modification by race for the association of smoking status with extrahepatic bile duct cancer (likelihood ratio test $P = .05$) and intrahepatic bile duct cancer (likelihood ratio test $P = .09$). For extrahepatic bile duct cancer, the associations with smoking status appeared to be stronger for whites and blacks than for Asians and Pacific Islanders, and there was limited evidence of an association with individuals of other races (Supplementary Table 7, available online). However, sample sizes were small for some comparisons (eg, <40 cases). For intrahepatic bile duct cancer, the association with current smoking was strongest for Asians and Pacific Islanders and individuals of other races. Race was not a multiplicative effect modifier of the associations between alcohol consumption and biliary tract cancer risk (all likelihood ratio test $P \geq .98$). There was also no evidence of multiplicative effect-measure modification by sex at any cancer site (all likelihood ratio test $P \geq .38$).

When we additionally adjusted for history of gallstones in 17 studies, risk estimates were not materially altered (Supplementary Table 8, available online). In nine studies, we restricted the pooled analyses of gallbladder cancer to individuals without a prior cholecystectomy. As shown in Supplementary Table 9 (available online), results were consistent after restriction, although some risk estimates for cigarette smoking were slightly stronger among those without a prior cholecystectomy.

Discussion

In this large, prospective study, we evaluated associations of cigarette smoking and alcohol consumption with the risk of biliary tract cancers by anatomic site. Cigarette smoking was associated with approximately 1.3- to 3.0-fold higher risks of intrahepatic bile duct, extrahepatic bile duct, and ampulla of Vater cancers. Associations with smoking were strongest and most consistent with extrahepatic bile duct and ampulla of Vater cancers, whereas associations with intrahepatic bile duct cancer appeared to be more modest and most apparent at

Table 2. Adjusted hazard ratios and 95% confidence intervals for associations of cigarette smoking with biliary tract cancer risk by anatomic site in the Biliary Tract Cancers Pooling Project–summary risk estimates from the random-effects meta-analysis*

Cigarette smoking	No. of noncases†,‡	Gallbladder cancer			Intrahepatic bile duct cancer			Extrahepatic bile duct cancer			Ampulla of Vater cancer		
		No. of cases‡	HR (95% CI)	I^2, %	No. of cases‡	HR (95% CI)	I^2, %	No. of cases‡	HR (95% CI)	I^2, %	No. of cases‡	HR (95% CI)	I^2, %
Ever smoking													
No	1 084 270	596	(Referent)	—	263	(Referent)	—	348	(Referent)	—	189	(Referent)	—
Yes	1 191 039	493	1.02 (0.89 to 1.17)	0.0	315	1.11 (0.93 to 1.33)	0.0	541	1.38 (1.17 to 1.62)	6.1	317	1.52 (1.24 to 1.86)	0.0
Smoking status													
Never smoker	1 084 270	596	(Referent)	—	263	(Referent)	—	348	(Referent)	—	189	(Referent)	—
Former smoker	827 061	332	0.98 (0.84 to 1.14)	0.0	211	1.06 (0.87 to 1.30)	0.0	351	1.29 (1.09 to 1.53)	0.0	209	1.38 (1.11 to 1.72)	0.0
Current smoker	362 313	161	1.18 (0.98 to 1.43)	0.0	104	1.30 (1.00 to 1.69)	0.0	190	1.69 (1.34 to 2.13)	15.1	108	2.22 (1.69 to 2.92)	0.0
Smoking pack-years													
Never smoker	984 603	545	(Referent)	—	246	(Referent)	—	333	(Referent)	—	174	(Referent)	—
>0–20	385 482	165	0.95 (0.79 to 1.14)	0.0	78	0.89 (0.67 to 1.19)	0.0	146	1.16 (0.93 to 1.45)	4.0	94	1.41 (1.07 to 1.85)	0.0
>20–40	223 798	112	1.19 (0.93 to 1.51)	10.6	76	1.35 (0.97 to 1.89)	16.2	126	1.53 (1.12 to 2.10)	38.4	72	1.84 (1.27 to 2.66)	22.0
>40	148 402	68	1.16 (0.88 to 1.52)	0.0	48	1.29 (0.92 to 1.81)	0.0	93	1.76 (1.24 to 2.51)	37.7	46	1.79 (1.11 to 2.90)	30.8
P_{trend}§			.39			.08			<.001			.005	
Continuous per 10 pack-years	—	—	1.03 (0.99 to 1.07)	0.0	—	1.06 (1.02 to 1.11)	3.1	—	1.10 (1.05 to 1.16)	39.5	—	1.09 (1.02 to 1.16)	36.6
Smoking duration (years)													
Never smoker	1 070 496	594	(Referent)	—	258	(Referent)	—	345	(Referent)	—	187	(Referent)	—
>0–10	164 873	56	1.07 (0.80 to 1.43)	0.0	41	1.46 (1.02 to 2.09)	0.0	51	1.46 (1.07 to 1.99)	0.0	30	1.53 (1.01 to 2.31)	0.0
>10–20	194 455	57	0.93 (0.67 to 1.30)	15.2	39	1.23 (0.85 to 1.79)	0.0	56	1.20 (0.88 to 1.64)	0.0	37	1.81 (1.18 to 2.76)	6.5
>20–40	501 925	227	1.11 (0.94 to 1.32)	0.0	128	1.06 (0.82 to 1.36)	5.9	225	1.29 (1.03 to 1.62)	20.5	126	1.57 (1.15 to 2.14)	20.3
>40	127 3389	64	1.06 (0.72 to 1.55)	44.1	41	1.29 (0.89 to 1.87)	3.2	93	1.96 (1.47 to 2.63)	13.5	55	2.18 (1.56 to 3.06)	0.0
P_{trend}§			.86			.57			.008			<.001	
Continuous per 10 years	—	—	1.00 (0.96 to 1.05)	7.1	—	1.02 (0.94 to 1.10)	25.9	—	1.10 (1.02 to 1.19)	47.8	—	1.14 (1.07 to 1.21)	0.0
Smoking intensity (cigarettes/day)													
Never smoker	984 603	545	(Referent)	—	246	(Referent)	—	333	(Referent)	—	174	(Referent)	—
>0–10	316 037	166	1.06 (0.88 to 1.28)	0.0	60	0.86 (0.61 to 1.22)	13.1	128	1.20 (0.97 to 1.49)	0.0	87	1.49 (1.14 to 1.96)	0.0
>10–20	336 669	151	1.13 (0.93 to 1.37)	0.0	108	1.33 (1.03 to 1.72)	0.0	185	1.62 (1.21 to 2.17)	41.6	97	1.87 (1.20 to 2.91)	50.8
>20–40	230 576	91	1.13 (0.88 to 1.45)	0.0	77	1.46 (1.09 to 1.95)	0.0	135	1.74 (1.39 to 2.19)	0.0	78	1.76 (1.29 to 2.40)	0.0
>40	46 656	17	1.75 (1.00 to 3.06)	8.0	19	2.15 (1.15 to 4.00)	17.7	24	3.00 (1.17 to 7.73)	60.4	13	2.02 (0.92 to 4.43)	17.9
P_{trend}§			.34			.001			<.001			.001	
Continuous per 10 cigarettes	—	—	1.04 (0.98 to 1.10)	0.0	—	1.12 (1.05 to 1.20)	0.0	—	1.17 (1.10 to 1.24)	11.1	—	1.13 (1.05 to 1.21)	0.0

*Adjusted for sex (male, female), race (white, black, Asian and Pacific Islander, other), education (less than high school graduate, high school graduate, some college or post-high school training), body mass index in kg/m^2 (<18.5, 18.5–<25, 25–<30, ≥30), history of diabetes (ever vs never diagnosed), birth cohort (1870–1899, 1900–1909, 1910–1919, 1920–1929, 1930–1939, 1940–1949, 1950–1959, 1960–1982), and alcoholic drinks per day (0, >0–0.5, >0.5–1, 1–<3, ≥3). CI = confidence interval; HR= hazard ratio.

†No. of noncases: The same noncase group was used for all analyses, except for analyses of intrahepatic bile duct cancer. The Radiation Effects Research Foundation Life Span Study (RERF) did not provide information on intrahepatic bile duct cancer diagnoses, so this study was excluded from these analyses and the maximum noncase group was thus n = 2 267 501.

‡No. of noncases and No. of cases: Some counts do not add to totals because of missing data. Numbers represent the maximum possible number of participants included in each analysis.

§P_{trend}: Two-sided *P* value for the ordinal variable, calculated using the Wald test.

Table 3. Adjusted hazard ratios and 95% confidence intervals for associations of alcohol consumption with biliary tract cancer risk by anatomic site in the Biliary Tract Cancers Pooling Project–summary risk estimates from the random-effects meta-analysis*

Alcohol consumption	No. of noncases†,‡	Gallbladder cancer			Intrahepatic bile duct cancer			Extrahepatic bile duct cancer			Ampulla of Vater cancer		
		No. of cases‡	HR (95% CI)	I^2, %	No. of cases‡	HR (95% CI)	I^2, %	No. of cases‡	HR (95% CI)	I^2, %	No. of cases‡	HR (95% CI)	I^2, %
Alcoholic drinks/day													
0	716 188	456	(Referent)		230	(Referent)		326	(Referent)		161	(Referent)	
>0–0.5	865 648	408	1.07 (0.91 to 1.26)	0.0	173	0.79 (0.62 to 1.00)	0.0	292	0.87 (0.68 to 1.12)	30.8	181	1.08 (0.80 to 1.45)	13.7
>0.5–<1	269 152	99	1.10 (0.87 to 1.39)	0.0	59	0.91 (0.65 to 1.26)	0.0	103	1.14 (0.82 to 1.58)	28.4	52	0.99 (0.69 to 1.41)	0.0
1–<3	338 965	112	0.94 (0.74 to 1.21)	0.0	95	0.98 (0.73 to 1.31)	0.0	140	1.08 (0.74 to 1.58)	48.3	95	1.33 (0.99 to 1.80)	0.0
3–<5	68 509	20	1.16 (0.69 to 1.94)	0.0	32	1.25 (0.77 to 2.02)	8.5	45	1.82 (0.98 to 3.39)	57.2	18	1.16 (0.66 to 2.01)	0.0
≥5	42 166	9	2.39 (0.63 to 9.12)	64.9	24	2.35 (1.46 to 3.78)	0.0	22	1.02 (0.64 to 1.62)	0.0	14	1.59 (0.85 to 2.98)	0.0
P_{trend}§			.31			.04			.84			.35	
Continuous per 1 drink	—	—	0.98 (0.92 to 1.05)	12.0	—	1.03 (1.01 to 1.06)	0.0	—	1.03 (0.98 to 1.08)	25.3	—	1.00 (0.95 to 1.04)	0.0

*Adjusted for sex (male, female), race (white, black, Asian and Pacific Islander, other), education (less than high school graduate, high school graduate, some college or post-high school training), body mass index in kg per m^2 (<18.5, 18.5–<25, 25–<30, ≥30), history of diabetes (ever vs never diagnosed), birth cohort (1870–1899, 1900–1909, 1910–1919, 1920–1929, 1930–1939, 1940–1949, 1950–1959, 1960–1982), and smoking status (never, former, current). CI = confidence interval; HR = hazard ratio.

†No. of noncases: The same noncase group was used for all analyses, except for analyses of intrahepatic bile duct cancer. The Radiation Effects Research Foundation Life Span Study (RERF) did not provide information on intrahepatic bile duct cancer diagnoses, so this study was excluded from these analyses and the maximum noncase group was thus n = 2 267 501.

‡No. of noncases and No. of cases: Some counts do not add to totals because of missing data. Numbers represent the maximum possible number of participants included in each analysis.

§P_{trend}: Two-sided P value for the ordinal variable, calculated using the Wald test.

higher levels of smoking intensity. In contrast, there was no convincing evidence of an association between cigarette smoking and gallbladder cancer. High levels of alcohol consumption (ie, ≥5 alcoholic drinks per day) were associated with a 2.4-fold higher risk of intrahepatic bile duct cancer, but no associations were observed with other biliary tract cancers. These findings highlight etiologic heterogeneity across the biliary tract.

Prior studies investigating the associations of cigarette smoking and alcohol consumption with biliary tract cancer risk have been largely inconclusive or conflicting. Relatively limited research exists on the association of tobacco smoking with intrahepatic bile duct cancer, and both null (10,24) and positive (9,16,18,19,28,29) associations have been reported. For extrahepatic bile duct cancer, some prior studies have reported positive associations with tobacco smoking (11,12,18,25,28), but other studies have reported null (9,10,17) or inverse associations (15). Reasons for the inconsistencies in these associations may include the small sample sizes of some prior studies (eg, <100 cases), variability in study design, or inability to control for important confounders. Regarding associations with ampulla of Vater cancer, ever smoking was associated with increased risk in one prior case-control study; however, risk estimates were based on a small number of cases (<50) (11). We have demonstrated this association in a well-powered prospective study and have additionally shown associations with smoking pack-years, intensity, and duration.

Our findings are consistent with the proven carcinogenicity of tobacco smoke (7) and the well-established associations between cigarette smoking and other cancers, including cancers of the lung, bladder, liver, pancreas, and stomach (6). Mechanisms for the association between smoking and intrahepatic bile duct, extrahepatic bile duct, and ampulla of Vater cancers likely include direct or indirect toxic effects of carcinogens (eg, polycyclic aromatic hydrocarbons, N-nitrosamines, aromatic amines, and volatile organics) (64), some of which may be concentrated in bile (65), and/or cell-mediated and humoral immunological changes (eg, T-cell unresponsiveness and modulations in the production of proinflammatory cytokines) (66). We observed moderate to high between-study heterogeneity for some associations, particularly associations with extrahepatic bile duct cancer. One possible explanation for this heterogeneity is that extrahepatic bile duct cancer diagnosis criteria may vary among study populations, and adjudication of rare cancers is a challenge. Other potential sources of heterogeneity include etiologic differences across different populations and/or variations in study design and smoking ascertainment.

In some studies, tobacco smoking has been associated with an increased risk of gallbladder cancer incidence (12,26) and mortality (14), yet other studies have observed no association (20–22). Overall, evidence for a clear pattern in these associations is still lacking, and there may be preferential reporting of positive associations (6). In our analyses, we observed no convincing association between cigarette smoking and gallbladder cancer risk. We observed a few marginal associations, and risk estimates tended to be slightly stronger when restricted to individuals without a prior cholecystectomy, suggesting a possible attenuation of gallbladder cancer risk estimates by the presence of people with cholecystectomy. However, marginal associations were weak and tended to be inconsistent. We also observed no evidence of a dose-response relationship with smoking pack-years, duration, or intensity. Taken together, our results do not provide strong evidence for an association between cigarette smoking and gallbladder cancer risk.

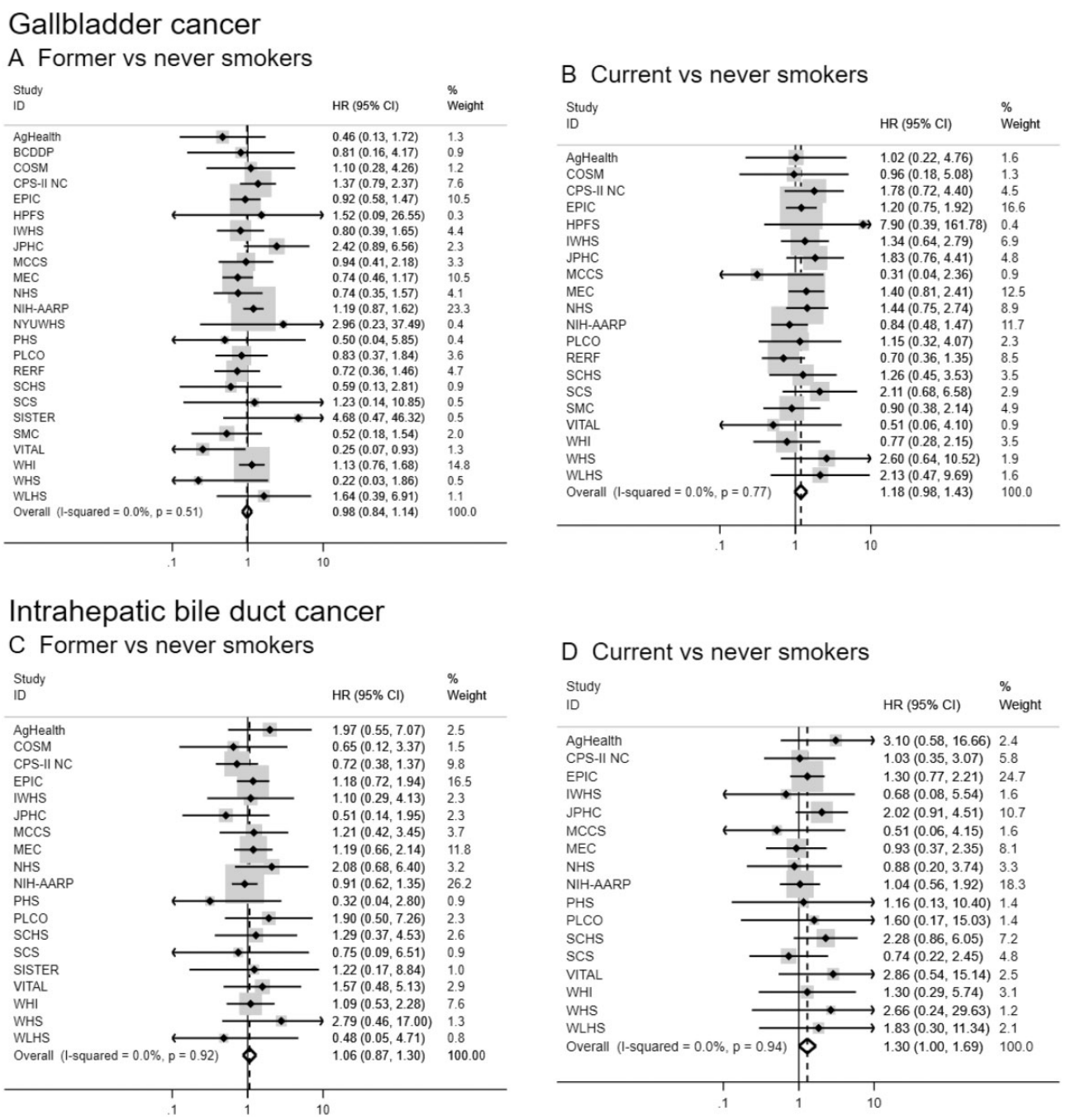

Figure 1. Forest plots for associations between cigarette smoking status and biliary tract cancer risk by anatomic site in the Biliary Tract Cancers Pooling Project. Hazard ratios for former vs never smoking (**A, C, E, G**) and current vs never smoking (**B, D, F, H**) are adjusted for sex (male, female), race (white, black, Asian and Pacific Islander, other), education (less than high school graduate, high school graduate, some college or post-high school training), body mass index in kg per m^2 (<18.5, 18.5–<25, 25–<30, ≥30), diabetes (ever vs never diagnosed), birth cohort (1870–1899, 1900–1909, 1910–1919, 1920–1929, 1930–1939, 1940–1949, 1950–1959, 1960–1982), and alcoholic drinks per day (0, >0–0.5, >0.5–1, 1–<3, ≥3). Small **black-filled diamonds** represent the point estimates for each study. **Horizontal lines** represent 95% confidence intervals; if ending in an **arrow**, the interval transcends the region plotted. % weight describes the weight (inverse variance) each study contributed to the summary hazard ratio. Study weight is also represented by the **shaded gray region** around each study-specific point estimate. I^2 is the percentage of variation due to between-study heterogeneity. Summary hazard ratios (**dotted lines**) and 95% confidence intervals (**hollow diamonds**) were estimated via random-effects meta-analysis. All statistical tests were two-sided. *P* values were calculated using the Wald test. Some additional studies collected information on cigarette smoking status but could not contribute to this meta-analysis because they did not have a sufficient number of biliary tract cancer patients who were former or current smokers. AgHealth = Agricultural Health Study; BCDDP = Breast Cancer Detection Demonstration Project; CI = confidence interval; COSM = Cohort of Swedish Men; CPS–II NC = Cancer Prevention Study II Nutrition Cohort; EPIC = European Prospective Investigation into Cancer and Nutrition; HR = hazard ratio; HPFS = Health Professionals Follow–Up Study; IWHS = Iowa Women's Health Study; JPHC = Japan Public Health Center-based prospective Study 1 and 2; MCCS = Melbourne Collaborative Cohort Study; MEC = Multiethnic Cohort Study; NHS = Nurses' Health Study; NIH-AARP = National Institutes of Health-American Association of Retired Persons Diet and Health Study; NYUWHS = New York University Women's Health Study; PHS = Physicians' Health Study; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; RERF = Radiation Effects Research Foundation Life Span Study; SCHS = Singapore Chinese Health Study; SCS = Shanghai Cohort Study; SISTER = Sister Study; SMC = Swedish Mammography Cohort; VITAL = VITamins and Lifestyle Study; WHI = Women's Health Initiative; WHS = Women's Health Study; WLHS = Women's Lifestyle and Health Study.

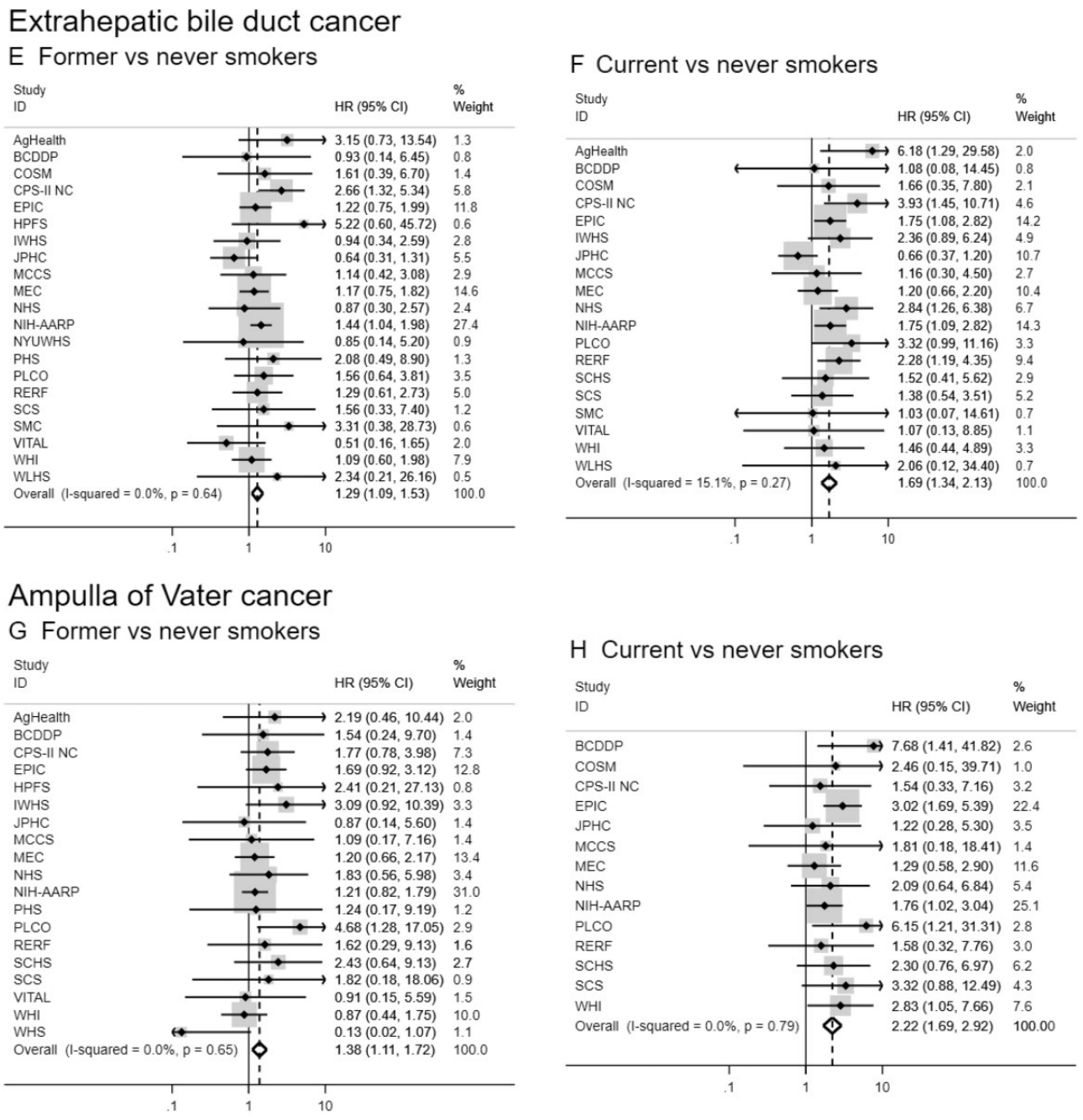

Figure 1. Continued

Studies investigating the association between alcohol consumption and biliary tract cancer risk have also been mixed. Positive (10,23,24,29) as well as null (11,15,19,23,25) associations of alcohol consumption with extrahepatic and intrahepatic bile duct cancer risk have been reported, and the International Agency for Research on Cancer has deemed the epidemiologic evidence for an association insufficient (6). Null associations between alcohol consumption and ampulla of Vater cancer have been reported by prior studies (11,23), which is consistent with our findings. Associations between alcohol consumption and gallbladder cancer, however, have often been contradictory (12–14,23,27). These contradictory findings may be partially attributed to the potential protective effects of alcohol intake on gallstone formation (67) due to inhibition of gallbladder water absorption and alterations in the composition of biliary lipids (68). Nonetheless, in the present study, our results were robust to additional adjustment for history of gallstones.

We observed positive associations between high levels of alcohol consumption and intrahepatic bile duct cancer risk. Possible mechanisms for the positive association with alcohol consumption include genotoxic effects of acetaldehyde, production of reactive oxygen and nitrogen species, DNA methylation, reduced immune surveillance, and inflammatory responses (69). In the present study, alcohol consumption was not associated with gallbladder, extrahepatic bile duct, or ampulla of Vater cancers. It is possible that we did not have sufficient

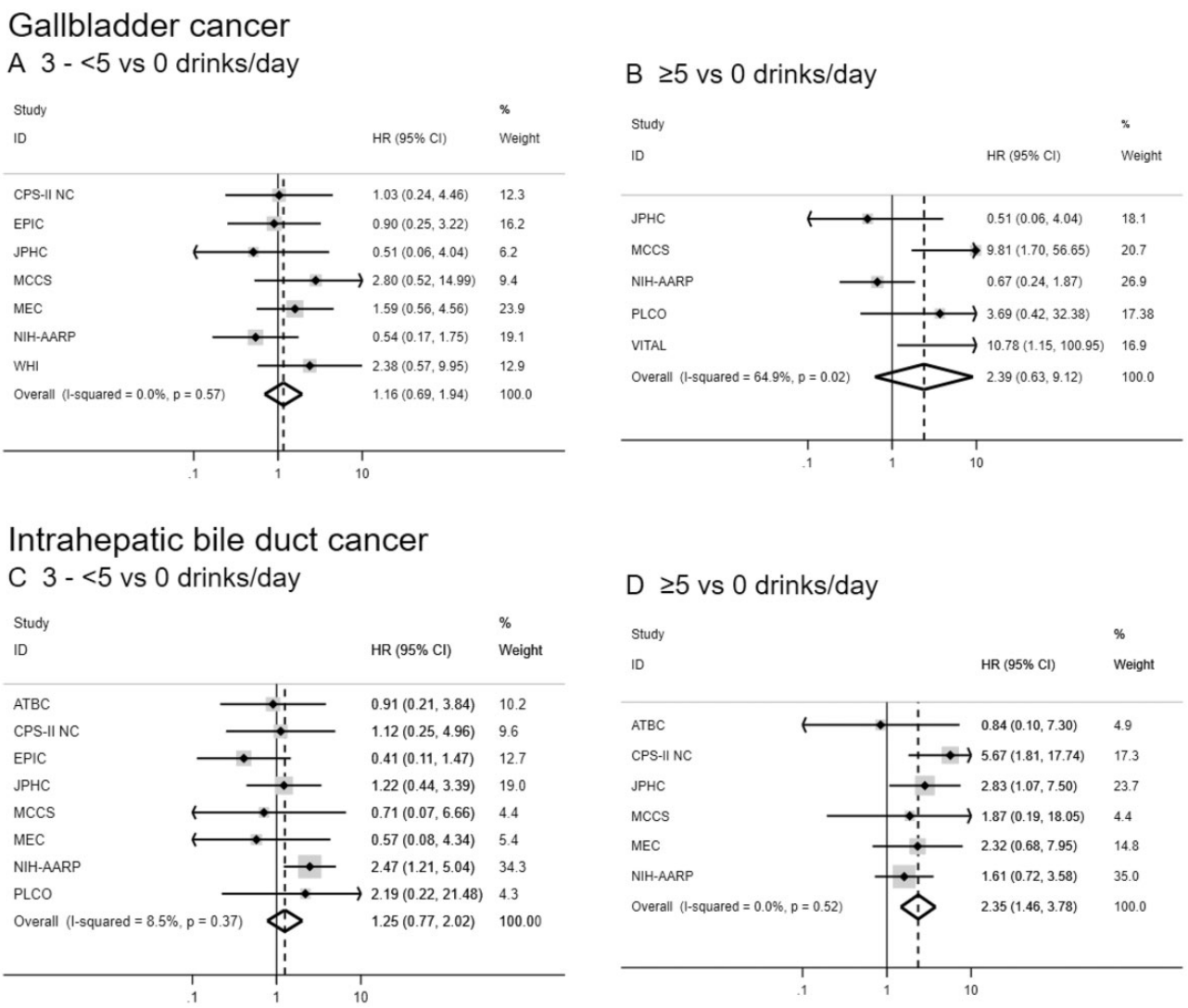

Figure 2. Forest plots for associations between alcohol consumption (drinks per day) and biliary tract cancer risk by anatomic site in the Biliary Tract Cancers Pooling Project. Hazard ratios for three to fewer than five vs zero drinks per day (**A, C, E, G**) and five or more vs zero drinks per day (**B, D, F, H**) are adjusted for sex (male, female), race (white, black, Asian and Pacific Islander, other), education (less than high school graduate, high school graduate, some college or post-high school training), body mass index in kg per m^2 (<18.5, 18.5–<25, 25–<30, ≥30), diabetes (ever vs never diagnosed), birth cohort (1870–1899, 1900–1909, 1910–1919, 1920–1929, 1930–1939, 1940–1949, 1950–1959, 1960–1982), and cigarette smoking status (never, former, current). Small **black-filled diamonds** represent the point estimates for each study. **Horizontal lines** represent 95% confidence intervals; if ending in an **arrow**, the interval transcends the region plotted. % weight describes the weight (inverse variance) each study contributed to the summary hazard ratio. Study weight is also represented by the **shaded gray region** around each study-specific point estimate. I^2 is the percentage of variation due to between-study heterogeneity. Summary hazard ratios (**dotted lines**) and 95% confidence intervals (**hollow diamonds**) were estimated via random-effects meta-analysis. All statistical tests were two-sided. *P* values were calculated using the Wald test. Some additional studies collected information on alcoholic drinks per day but could not contribute to this meta-analysis because they did not have a sufficient number of biliary tract cancer patients consuming three to fewer than five or five or more drinks per day. ATBC = Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study; CI = confidence interval; COSM = Cohort of Swedish Men; CPS-II NC = Cancer Prevention Study II Nutrition Cohort; EPIC = European Prospective Investigation into Cancer and Nutrition; HR = hazard ratio; IWHS = Iowa Women's Health Study; JPHC = Japan Public Health Center-based prospective Study 1 and 2; MCCS = Melbourne Collaborative Cohort Study; MEC = Multiethnic Cohort Study; NHS = Nurses' Health Study; NIH-AARP = National Institutes of Health-American Association of Retired Persons Diet and Health Study; PLCO = Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial; VITAL = VITamins and Lifestyle Study; WHI = Women's Health Initiative.

statistical power to detect associations at the highest levels of alcohol consumption, where there were fewer than 25 cases and estimates were based on a subset of studies with a sufficient number of high consumers. It is also possible that alcohol consumption is not an important risk factor for these cancers.

There was evidence of effect-measure modification by race for the association of smoking status with extrahepatic and intrahepatic bile duct cancers. Results suggested that the strength of the associations may vary by race (eg, the association between smoking status and extrahepatic bile duct cancer was stronger among whites and blacks than among other racial groups, whereas the association with intrahepatic bile duct cancer was strongest among Asians and Pacific Islanders and individuals of other races). Although we were underpowered to detect associations in some subgroups, these variations in associations by race for some but not all anatomic sites point to potential etiologic differences among biliary tract cancers despite their anatomic proximity.

Gallstones is one of the primary known risk factors for biliary tract cancers (63), and it may act as a mediator in the

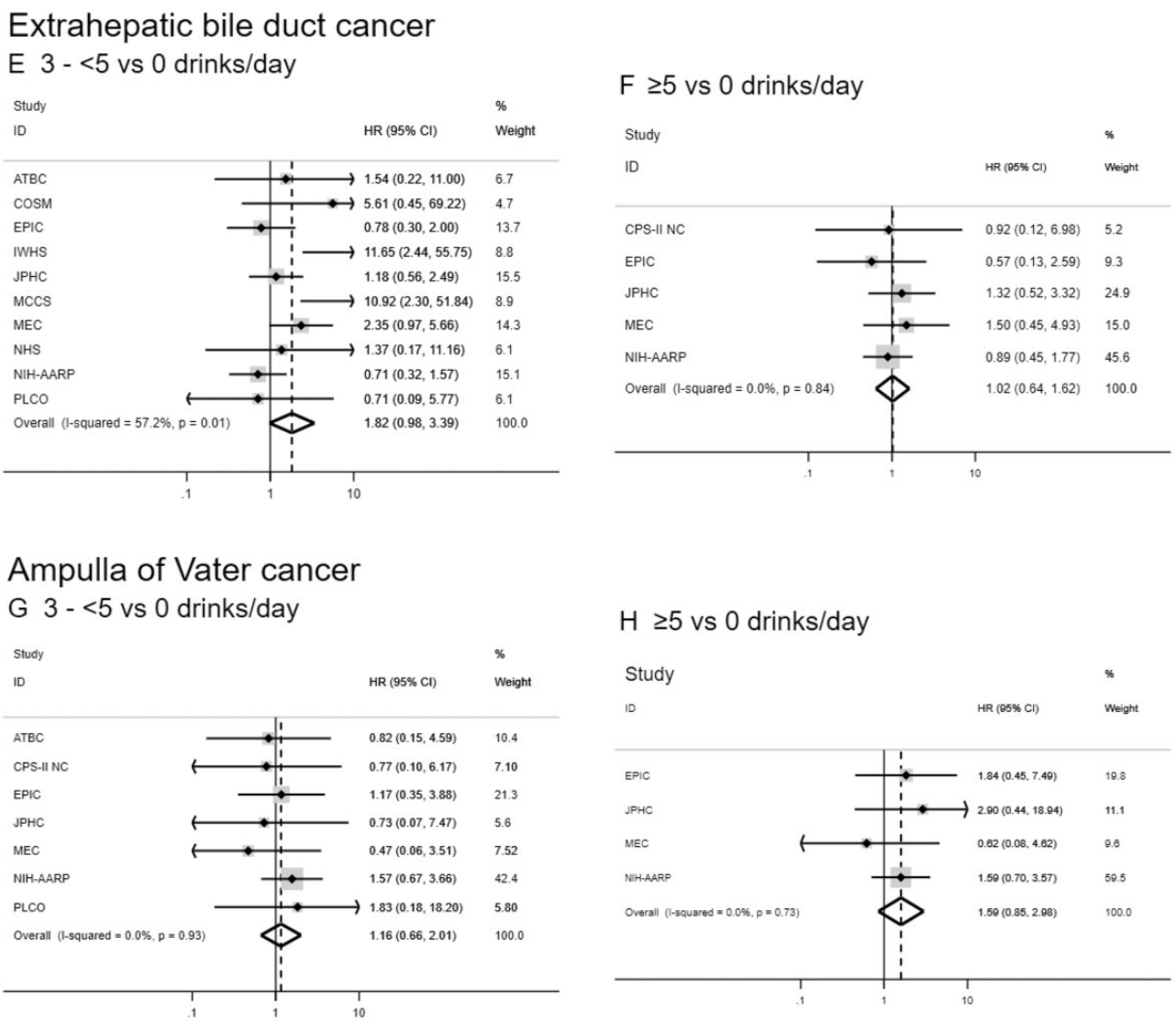

Figure 2. Continued

associations we observed. Nevertheless, when we additionally adjusted for history of gallstones, there were no appreciable changes in risk estimates, suggesting that the associations we observed were likely not mediated by gallstones.

Strengths of our study include its prospective design, diversity of included studies, large sample size, and long follow-up period, which provided unprecedented statistical power to assess associations with rare biliary tract cancer by anatomic site. Meta-analyses of individual participant data offer several advantages over meta-analyses of the published literature (70). For example, by pooling individual-level data, we were able to standardize adjustments for multiple potential confounders, mitigate publication bias, and decrease the variability in effect estimates that is caused by inconsistencies in analytic modeling. For two-thirds of the associations assessed, we observed low heterogeneity ($I^2 < 10\%$) and a similar pattern of risk estimates across studies that differed substantially in design, population, and geographic location, lending greater confidence to these findings. The robustness of our findings to multiple sensitivity analyses also lends greater credence to these associations.

Our study also has several limitations. Smoking and alcohol data were provided at a single timepoint for most studies, so we were unable to assess changes in these exposures over the course of follow-up, and approaches to measuring these exposures varied across studies. Data on cigarette smoking and alcohol consumption were ascertained via self-report and may be subject to under- or misreporting. Regarding alcohol exposure, definitions of standard drink measures and sizes often vary substantially among and within countries (71), which may have introduced some misclassification in the assessment of alcoholic drinks consumed per day. We were also unable to assess duration of drinking, total alcohol exposure, or differences by beverage type. In addition, findings for heavy alcohol consumption should be interpreted with caution given modest sample sizes and few studies contributing to the highest exposure categories. There may be residual or unmeasured confounding, particularly from other lifestyle factors (eg, diet or physical

activity). Finally, there may have been some histological misclassification of cancers.

In this pooled analysis of 26 studies, we assessed associations between two potentially modifiable lifestyle factors and biliary tract cancer risk in a well-powered, prospective study. Our findings provide evidence that smoking is associated with intrahepatic bile duct, extrahepatic bile duct, and ampulla of Vater cancers, suggesting that tobacco may be a risk factor for even more cancers than previously appreciated. High levels of alcohol consumption were also associated with intrahepatic bile duct cancer risk. Findings suggest etiologic heterogeneity across the biliary tract, particularly for gallbladder cancer, underscoring the importance of analyzing biliary tract cancers individually by anatomic site to understand the unique factors contributing to each of these malignancies. More broadly, our findings provide insight into the etiology of these rare, understudied cancers and support ongoing public health efforts to mitigate cigarette smoking and heavy alcohol consumption.

Funding

AgHealth: This study was funded by the Intramural Program of the National Institutes of Health, National Cancer Institute (Z01 P010119). and the National Institute of Environmental Health Sciences (Z01 ES 049030–11).

AHS-2: Project support was obtained from National Cancer Institute grant 1U01CA152939.

ATBC: The ATBC Study is supported by the Intramural Research Program of the US National Cancer Institute, National Institutes of Health, and by US Public Health Service contract HHSN261201500005C from the National Cancer Institute, Department of Health and Human Services.

BCDDP: The BCDDP Follow-up Study was supported by the Intramural Research Program of the National Institutes of Health, National Cancer Institute.

COSM: This cohort is supported by the Swedish Research Council (Research Infrastructure SIMPLER), the Swedish Cancer Foundation, and by Strategic Funds from Karolinska Institutet, Stockholm, Sweden.

CPS-II NC: The American Cancer Society funds the creation, maintenance, and updating of the Cancer Prevention Study-II cohort.

EPIC: The coordination of the EPIC is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by Danish Cancer Society, Denmark; Ligue Contre le Cancer, France; Institut Gustave Roussy, France; Mutuelle Générale de l'Education Nationale, France; Institut National de la Santé et de la Recherche Médicale, France; Deutsche Krebshilfe, Germany; Deutsches Krebsforschungszentrum and Federal Ministry of Education and Research, Germany; Hellenic Health Foundation, Greece; Italian Association for Research on Cancer; National Research Council, Italy; Dutch Ministry of Public Health, Welfare and Sports, the Netherlands; Netherlands Cancer Registry, the Netherlands; LK Research Funds, the Netherlands; Dutch Prevention Funds, the Netherlands; Dutch ZON (Zorg Onderzoek Nederland), the Netherlands; World Cancer Research Fund, London, UK; Statistics Netherlands, the Netherlands; European Research Council, Norway; Health Research Fund, Regional Governments of Andalucía, Asturias, Basque Country, Murcia (project no. 6236) and Navarra, ISCIII RETIC (RD06/0020/0091), Spain; Swedish Cancer Society, Sweden; Swedish Scientific Council, Sweden; Regional Government of Skåne and Västerbotten, Sweden; Cancer Research, UK; Medical Research Council, UK; Stroke Association, UK; British Heart Foundation, UK; Department of Health, Food Standards Agency, UK; and Wellcome Trust, UK.

HPFS: This work was supported by grants from the National Institutes of Health (UM1 CA167552, P01 CA55075), the Entertainment Industry Foundation, and the National Colorectal Cancer Research Alliance. HPFS would like to thank the participants and staff of the HPFS for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, and WY. The authors assume full responsibility for analyses and interpretation of these data.

IWHS: IWHS was funded by a grant from the National Cancer Institute (R01 CA39742).

JPHC: This work was supported by the National Cancer Center Research and Development Fund (since 2011) and a grant-in-aid from Cancer Research (1989–2010) from the Ministry of Health, Labor, and Welfare of Japan.

MCCS: MCCS receives core funding from Cancer Council Victoria and is additionally supported by grants from the Australian National Health and Medical Research Council (209057, 251533, 396414, and 504715).

MEC: This work was supported by the National Institutes of Health (P01 CA33619 and U01 CA164973).

NHS: Data used in this study were supported by an infrastructure grant (UM1 CA186107) and a program project grant that funds cancer research (P01 CA87969). NHS would like to thank the participants and staff of the NHS for their valuable contributions as well as the following state cancer registries for their help: AL, AZ, AR, CA, CO, CT, DE, FL, GA, ID, IL, IN, IA, KY, LA, ME, MD, MA, MI, NE, NH, NJ, NY, NC, ND, OH, OK, OR, PA, RI, SC, TN, TX, VA, WA, and WY. The authors assume full responsibility for analyses and interpretation of these data.

NIH-AARP: This study was supported (in part) by the Intramural Research Program of the National Institutes of Health, National Cancer Institute. Cancer incidence data from the Atlanta metropolitan area were collected by the Georgia Center for Cancer Statistics, Department of Epidemiology, Rollins School of Public Health, Emory University, Atlanta, GA. Cancer incidence data from California were collected by the California Cancer Registry, California Department of Public Health's Cancer Surveillance and Research Branch, Sacramento, CA. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, Lansing, MI. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (Miami, FL) under contract with the Florida Department of Health, Tallahassee, FL. The views expressed herein are solely those of the authors and do not necessarily reflect those of the Florida Cancer Data System or the Florida Department of Health. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Health Sciences Center School of Public Health, New Orleans, LA. Cancer incidence data from New

Jersey were collected by the New Jersey State Cancer Registry, Rutgers Cancer Institute of New Jersey, New Brunswick, NJ. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry, Raleigh, NC. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, PA. The Pennsylvania Department of Health specifically disclaims responsibility for any analyses, interpretations, or conclusions. Cancer incidence data from Arizona were collected by the Arizona Cancer Registry, Division of Public Health Services, Arizona Department of Health Services, Phoenix, AZ. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, TX. Cancer incidence data from Nevada were collected by the Nevada Central Cancer Registry, Division of Public and Behavioral Health, State of Nevada Department of Health and Human Services, Carson City, NV. The study authors are indebted to the participants in the NIH-AARP Diet and Health Study for their outstanding cooperation. Additional acknowledgments can be found https://dietandhealth.cancer.gov/acknowledgement.html.

NYUWHS: The NYUWHS is supported by grants UM1 CA182934 and P30 CA16087 from the National Cancer Institute and by grant P30 ES000260 from the National Institute of Environmental Health Sciences.

PHS: PHS is supported by grants from the National Cancer Institute (CA-34933, CA-40360, and CA-097193) and from the National Heart, Lung, and Blood Institute (HL-26490 and HL-34595), National Institutes of Health, Bethesda, MD.

PLCO: The PLCO Cancer Screening Trial is supported by contracts from the National Cancer Institute.

RERF: The Radiation Effects Research Foundation (RERF), Hiroshima and Nagasaki, Japan, is a public interest foundation funded by the Japanese Ministry of Health, Labour and Welfare and the US Department of Energy (DOE). The research was also funded in part through DOE award DE-HS0000031 to the National Academy of Sciences. This publication was supported by RERF Research Protocol A2-13. The views of the authors do not necessarily reflect those of the two governments.

SCHS: This study is supported by the National Cancer Institute (R01CA080205, R01CA144034, and UM1CA182876).

SCS: The Shanghai Cohort Study is supported by the National Cancer Institute (R01CA043092, R01CA144034, and UM1CA182876).

SISTER: The Sister Study is supported by the Intramural Research Program of the National Institutes of Health, National Institute of Environmental Health Sciences (ZO1-ES-044005).

SMC: This cohort is supported by the Swedish Research Council (Research Infrastructure SIMPLER), the Swedish Cancer Foundation, and by Strategic Funds from Karolinska Institutet, Stockholm, Sweden.

VITAL: The VITAL study was supported by the National Institutes of Health grant K05-CA154337 (National Cancer Institute and Office of Dietary Supplements).

WHI: The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, US Department of Health and Human Services through contracts, HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. The authors thank the WHI investigators and staff for their dedication, and the study participants for making the program possible. A listing of WHI investigators can be found at http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf.

WHS: WHS was supported by grants CA047988, HL043851, HL080467, and HL099355.

WLHS: The WLHS project was supported by the Swedish Research Council (grant number 521–2011-295) and a Distinguished Professor Award at Karolinska Institutet to Hans-Olov Adami, grant number 2368/10–221.

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The funders had no role in the design of the study, the collection, analysis, and interpretation of the data, writing of the manuscript, or the decision to submit it for publication.

Potential competing interests: None.

Author contributions: Study concept and design (all authors); acquisition of data (all authors); statistical analysis (McGee, Jackson, Zhu, Koshiol); interpretation of data (McGee, Koshiol); drafting of manuscript (McGee); critical review and approval of final manuscript (all authors).

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