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Associations between reproductive factors and biliary tract cancers in women from the Biliary Tract Cancers Pooling Project

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Abstract

Background & Aims: Gallbladder cancer (GBC) is known to have a female predominance while other biliary tract cancers (BTCs) have a male predominance. However, the role of female reproductive factors in BTC etiology remains unclear.

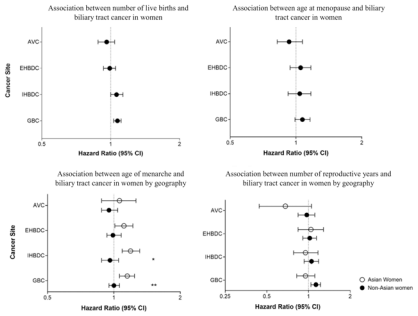
Methods: We pooled data from 19 studies of >1.5 million women participating in the Biliary Tract Cancers Pooling Project to examine the associations of parity, age at menarche, reproductive years, and age at menopause with BTC. Associations for age at menarche and reproductive years

with BTC were analyzed separately for Asian and non-Asian women. Hazard ratios (HRs) and 95% CIs were estimated using Cox proportional hazards models, stratified by study.

Results: During 21,681,798 person-years of follow-up, 875 GBC, 379 IHBDC, 450 EHBDC, and 261 AVC cases occurred. High parity was associated with risk of GBC (HR ≥5 vs. 0 births: 1.72, 95% CI: 1.25, 2.38). Age at menarche (HR per year increase: 1.15, 95% CI: 1.06, 1.24) was associated with GBC risk in Asian women while reproductive years were associated with GBC risk (HR per 5 years: 1.13, 95% CI: 1.04, 1.22) in non-Asian women. Later age at menarche was associated with IHBDC (HR: 1.19, 95% CI: 1.09, 1.31) and EHBDC HR: 1.11, 95% CI: 1.01, 1.22) in Asian women only.

Conclusion: We observed an increased risk of GBC with increasing parity. Among Asian women, older age at menarche was associated with increased risk for GBC, IHBDC, and EHBDC, while increasing reproductive years was associated with GBC in non-Asian women. These results suggest sex hormones may have distinct effects on cancers across the biliary tract and vary by geography.

Graphical Abstract



Lay Summary:

Our findings show that risk of gallbladder cancer (GBC) is increased among women who have given birth (especially women with 5 or more children). In women from Asian countries, later age at menarche increases the risk of GBC, intrahepatic bile duct cancer (IHBDC), extrahepatic bile duct cancer. We did not see this same association in women from Western countries. Age at menopause was not associated with the risk of any biliary tract cancers.

Keywords

Reproductive factors; parity; biliary tract cancer; gallbladder cancer

Introduction

Rare but lethal, biliary tract cancers (BTCs) include cancers of the gallbladder (GBC), intrahepatic bile duct (IHBDC), extrahepatic bile duct (EHBDC), and ampulla of Vater (AVC). GBC has a female predominance with a worldwide female-to-male incidence rate ratio of 2:1 [1, 2]. However, this ratio varies greatly by geography, ranging from 1:1 in the Far East to 4:1 in Spain [2]. Conversely, incidence rates of IHBDC, EHBDC, and AVC are higher in men worldwide [2, 3].

This sex ratio suggests that sex hormones may be involved in gallbladder carcinogenesis. High parity is associated with gallstones, often the precursor to gallbladder dysplasia [4]. During pregnancy gallbladder volume increases and bile flow decreases [5–7]. Elevated estrogen levels during pregnancy lead to an increase in cholesterol saturation of the bile [6, 8, 9]. Progesterone, also elevated during pregnancy, contributes to biliary stasis by impairing the smooth muscle contractility of the biliary tract leading to the formation of cholesterol gallstones [6, 8–10]. Gallstones are also risk factors for cholangiocarcinoma and evidence suggests that estrogen promotes tumor growth in the biliary tract [11, 12]. However, because the pronounced female predominance is absent for these cancers, the role of female reproductive factors in carcinogenesis across the biliary tract is unclear. Further, given that the sex ratio of gallbladder cancer in East Asia is closer to 1, the role of female sex hormones may vary by geographic region [13].

The rarity of BTCs make conducting large prospective studies of their etiology difficult, and much of the evidence to date is obtained from studies with small sample sizes lacking in geographic variability [14–17]. Few studies have examined female reproductive factors in the development of these cancers separately by site, other than the gallbladder [18, 19]. Further, many studies lacked information on important covariates, such as use of oral contraceptives and age at menarche [14, 16]. To address these shortcomings, we examined the associations of parity, age at menarche, reproductive years, and age at menopause with BTC risk using a large pooling project.

Methods

Study Population

Data for this analysis were obtained from 19 studies participating the Biliary Tract Cancers

Pooling Project (BiTCaPP), containing information on female reproductive factors (Table 1). BiTCaPP consists of 16 prospective cohort studies, one case-cohort study, one randomized controlled trial, and one cancer screening trial (Supplemental Table 1). We harmonized individual-level data from these studies for pooling into one analytic dataset. BiTCaPP is exempt from Institutional Review Board review by the National Cancer Institute’s Office of Human Subjects Research, though all component studies within BiTCaPP received approval from their respective institutions.

Outcome

Incident BTC was classified as primary GBC, IHBDC, EHBDC, or AVC as defined by the International Classification of Diseases codes (Supplemental Table 2).Diagnoses were verified by linkage to local, state/provincial, or national cancer registries, review of medical records, pathology reports, or death certificates, or a combination of these methods.

Exposures

All reproductive factors examined were reported by participants at baseline. Parity, defined as the number of live births, was analyzed continuously and in pre-specified categories (0, 1 – 2, 3 – 4, ≥5 births). Age at first birth and age at menopause (among menopausal women)

were analyzed continuously and categorically (≤22, 23 – 29, or ≥30 years old and <45 45 – 49, 50 – 54, or ≥55 years old, respectively). We calculated reproductive years at baseline by subtracting age at menarche from 1) age at menopause for women who were post-menopausal at baseline; or 2) age of study entry for pre-menopausal women. See Supplemental Table 1 for details on data collection of the exposure variables in each study. Improbable values for age at first birth (<10 or >55 years), age at menarche (<7 or >20 years), and age at menopause (>65 years) were set to missing.

Covariates

We categorized self-reported race as: white, black, Asian/Pacific Islander, and other; and education level as: some college, high school graduate or equivalent, or less than high school graduate. Oral contraceptive use was categorized as ever or never use. Because oral contraceptive use was not legal in Japan until 1999 [20], all participants in the JPHC were coded as never users in this study. Body mass index (BMI) was categorized according to the World Health Organization International Classification for Western women as follows: underweight (15.0 to <18.5 kg/m^2), normal weight (18.5 to <25 kg/m^2), overweight (25 to <30 kg/m^2), and obese (≥30kg/m^2) [21]. BMI for Asian women was categorized as underweight (15.0 to <18.5 kg/m^2), normal weight (18.5 to <23 kg/m^2), overweight (23 to <27.5 kg/m^2), obese (≥27.5 kg/m^2) [22]. Smoking and alcohol use were categorized as ever or never use.

BiTCaPP is comprised of 1,614,944 women. We excluded women under the age of 18 years (n=3), missing age at baseline or exit from the study (n= 3,908), with prior cancer diagnoses reported at baseline (n=43,908), with incident cancers categorized as being at other, unknown sites, or overlapping lesion of biliary tract (n=167), and unknown BTC status (n=9). We also excluded those with missing parity data (n=66,763), who constituted 4% of the total sample. We performed stochastic regression to impute the missing value of parity for these women. This imputation did not materially affect the results and so was not used for the primary analyses (Supplemental Table 3). Data from the remaining 1,500,198 individuals comprised the analytic dataset.

Statistical Analyses

Baseline demographics and reproductive factors were summarized using descriptive statistics. We evaluated associations of parity, age at menarche, reproductive years, and age at menopause with incident BTC using weighted Cox proportional hazards regression models to account for the case-cohort design of one study, with age as the time scale and left truncation at study entry to estimate site-specific hazard ratios (HRs) and 95% confidence intervals (95% CIs).

Directed acyclic graphs were used to identify the minimally sufficient set of covariates for confounding control (Supplemental Figures 1 – 3) and confounder selection was based on a ≥10% change in the estimate [23, 24]. Due to temporal and geographic differences in parity [25–27], ages at menarche, and age at menopause [28–30], all models were adjusted for participant birth year, race, and education, with the baseline hazard stratified by study. Models for parity were additionally adjusted for oral contraceptive use and age at menarche;

models for reproductive years and age at menopause were also adjusted for parity, BMI, and a history of smoking and alcohol use. We tested for linear trends across parity and age at menopause categories with the Wald test with 1 degree of freedom. For the age at menarche and reproductive years models we ran separate models for women from studies conducted in Asian countries and women from studies conducted in the West to examine the geographic variability of this association because East-Asian women have a lower BMI and later age at menarche than Non-Asian women [31–33]. We were unable to adjust the age of menarche model for BMI directly because this variable was collected at baseline (many years after menarche). We tested for heterogeneity in the association between Asian and Non-Asian women using the likelihood ratio test.

Sensitivity analyses

We also performed a random-effects meta-analysis for the continuous predictors because many of the studies lacked sufficient events for analysis of the categorical measures. We used Cochrane's I^2 statistic [34] to assess the statistical heterogeneity of results between the studies. Study-specific models were adjusted for the same covariates as in the pooled analysis where appropriate. To account for the fact that women who had children may be different from those who did not (either by choice or due to infertility), analyses were restricted to parous women, where we also examined the association of age of first birth with BTC risk. These models were adjusted for participant birth year, education level and race, with the baseline hazard stratified by study. Age at first birth was not available from 3 of the cohorts so these studies were excluded from these models.

The presence of gallstones, a strong risk factor for GBC and cholangiocarcinoma [35], were collected by self-report in a subset of BiTCaPP studies (n=15), typically at baseline. To assess whether the association of reproductive factors with incident BTC risk is materially different when controlling for gallstones, we compared estimated hazard ratios with and without adjustment for participant-reported history of gallstones. The analyses for GBC were repeated using the subset of studies that collected cholecystectomy history (n=7) to compare the estimated risk of GBC when restricted to women with a gallbladder. To examine the possible impact of reverse causation, we also conducted a sensitivity analysis in which the first two years of follow-up after baseline were excluded.

The proportional hazards assumption was assessed visually by plotting the scaled Schoenfeld residuals against time; the assumption was met for all models. All statistical tests were two-sided with a type I error rate of α=0.05. Data management and measures of association for the pooled and study-specific estimates were conducted using SAS Software (v9.4, Cary, NC); Stata (v.14) software was used for meta-analyses; and R Studio (v. 3.5.0) for the proportional hazards assumptions.

Results

As shown in Table 1, 875 GBC, 379 IHBDC, 450 EHBDC, and 261 AVC cases were diagnosed during 21,681,798 person-years of follow-up. The characteristics of the participants are presented by study in Table 2. The mean age at baseline was 56 years (standard deviation [SD] =10), the mean number of live births was 2.5 (SD=2), the mean age

at menarche was 13 years (SD=2), and mean age at menopause was 47 years (SD=6). In addition, 80% of women were white and 57% had some college education. Within the studies that collected relevant medical history, 12% of participants reported a history of gallstones and 13% reported a cholecystectomy.

Gallbladder cancer

As shown in Figure 1A, GBC is associated with an increasing number of live births (HR per live birth: 1.07, 95% CI: 1.03, 1.11). The risk of GBC was highest for women with 5 or more children compared to nulliparous women (HR: 1.72, 95% CI: 1.25, 2.38) (Table 3). Age at menopause was associated with increased GBC risk (Figure 1B), especially for women in the 50 – 54 years age group compared to those 45 – 49 years (HR: 1.26, 95% CI: 1.02, 1.56) and there was a borderline trend across age groups (*P*-trend=0.08) (Table 3). Figure 2B illustrates that in non-Asian women, there was no association between age at menarche and GBC. However, among women of Asian ancestry the risk of GBC increased with increasing age at menarche (HR per year: 1.15, 95% CI: 1.06, 1.24). Duration of reproductive years was associated with GBC in non-Asian women (HR per 5 years: 1.13, 95% CI: 1.04, 1.22).

Other biliary tract cancers

As illustrated in Figure 1A, increasing number of live births was associated with risk of IHBDC (HR per live birth: 1.06, 95% CI: 1.00, 1.13), but not EHBDC (HR per live birth: 0.99, 95% CI: 0.93, 1.05) or AVC (HR per live birth: 0.96, 95% CI: 0.88, 1.04). Age at menopause was associated with increased risk of AVC in the youngest age group (HR <45 vs. 45 – 49 years: 1.81, 95% CI: 1.13, 2.88), but this trend was not significant across age groups (P-trend=0.65) (Table 3). There was no association between age at menarche and any BTC among non-Asian women. Among women of Asian ancestry the risk of IHBDC and EHBDC was elevated with increasing age at menarche (IHBDC HR per year: 1.19, 95% CI: 1.09, 1.31; and EHBDC HR per year: 1.11, 95% CI: 1.01, 1.22) (Figure 2B).

Sensitivity analyses

Results from the random-effects meta-analysis were similar to those from the main pooled analysis (Supplemental Table 4). In the analyses restricted to parous women the results were not substantially different from those seen for all women (Supplemental Table 5). Age at first childbirth was not significantly associated with any BTC. The associations between reproductive factors and BTC risks did not change substantially when models were adjusted for self-reported gallstones (Supplemental Table 6). However, in seven studies with information on cholecystectomy, the association with GBC in the highest parity category was stronger than the associations where cholecystectomy status was ignored (Supplemental Table 7). Compared to nulliparous women, the HR for women with 5 or more live births without cholecystectomy was 1.86 (95% CI: 1.11, 3.09) and 1.60 (95% CI: 1.05, 2.43) without this restriction. There were no noteworthy differences in the associations between the main pooled analyses and those from the sensitivity analyses that excluded diagnoses that occurred in the first two years of follow-up (Supplemental Table 8).

Discussion

In this large pooled analysis of 19 longitudinal studies, we found that parity was associated with increased risk for GBC and IHBDC, but not EHBDC or AVC. We also found support for the potential role of exposure to lifetime endogenous sex hormones as measured by reproductive years in the development of GBC among non-Asian women. Later age at menarche was associated with GBC, IHBDC, and EHBDC among Asian women, highlighting the potential difference in BTC etiology by region.

Our finding that increasing parity is associated with increased risk of GBC is consistent with other studies[14–17, 19] (Supplemental Table 9). We found a 72% increased risk of GBC for the highest parity category (≥5 live births) compared to nulliparous women. These results suggest that exposure to high levels of hormones during pregnancy may increase women's risk for GBC. Increased cholesterol saturation of the bile and reduced emptying of the gallbladder is observed in the second and third trimesters of pregnancy due to increases in estrogen and progesterone [6, 7, 10]. The inhibition of gallbladder contractility can induce gallbladder stasis, leading to the formation of gallstones [5, 6, 8, 10]. The gallbladder is sensitive to changes in hormonal concentrations as it contains both estrogen and progesterone receptors [36]. High circulating levels of these sex hormones have been found in women with GBC and cholelithiasis [36–38]. Thus, continued exposure to elevated levels of female sex hormones through multiple full-term pregnancies may result in gallstone formation and serve as a potential mechanism for our findings of higher GBC risk.

We also saw some evidence for an association between increased parity and risk of IHBDC suggesting estrogens may play an important role in the development of cholangiocarcinoma as well. Cholangiocytes in a healthy liver lack estrogen receptors, but liver samples from patients with IHBDC are positive for ER-α and ER-β subtypes [11, 12]. 17β-estradiol can stimulate neoplastic cell proliferation by upregulating ER-α and downregulating ER-β [39]. Estrogens can also modulate the production of COX-2, an important mechanism in cholangiocarcinoma cell growth [12]. However, the results of the continuous analysis should be interpreted with caution as they are not consistent with the categorical analysis which did not demonstrate an increased risk of IHBDC with increased parity. Parity was not associated with EHBDC or AVC in any of our analyses, consistent with results of previous studies (Supplemental Table 9) [19, 40]. Kilander and colleagues reported a slight increased risk in the incidence of these cancers with increasing parity in women [18]. However, they observed a similar association with increasing offspring in men, suggesting possible unmeasured confounding rather than a true effect of female sex hormones on carcinogenesis [18].

Later age at menarche was associated with an increased risk of GBC, IHBDC, and EHBDC among Asian, but not non-Asian women, in our study. These findings are in line with observations from three studies conducted in Asian countries [17, 19, 41], that found older age at menarche was associated with BTC risk. Conversely, no association between age at menarche and BTC was found in studies conducted in Western Europe or the United States (Supplemental Table 9) [15, 16, 40, 42]. Asian women have a lower BMI than women of other ethnicities which may delay puberty onset [31–33]. That later age of menarche was only associated with increased BTC risk in Asian women suggests a different etiology for

BTC from non-Asian women. For instance, brown pigment stones, rather than cholesterol stones, are the predominant gallstone in some parts of Asia and are a result of parasitic infection (e.g. liver flukes) [43]. This difference in gallstone etiology may help explain why the sex disparity seen in the West is much smaller, or reversed, in many East Asian countries [13].

Previous research has also indicated that later age at menopause may be associated with BTC, though these studies did not examine this association by biliary tract site (Supplemental Table 9) [15, 16]. Though this trend was non-significant, increasing duration of reproductive years in non-Asian women was associated with GBC suggests that greater length of exposure to female sex hormones may increase this risk. On the other hand, two studies that examined GBC specifically did not find an association with age at menopause, contrary to our results [19, 41]. However, these studies were unable to adjust for all factors that may influence menopause, such as parity, age at menarche, previous oral contraceptive use, alcohol consumption, and smoking [44]. Moreover, to our knowledge, ours is the first study to examine this association with AVC. That age at menopause is associated with increased risk in the youngest age group may indicate a protective role for female hormones on AVC risk. Alternatively, younger age at menopause is also associated with decreased overall health, fertility, and longevity, which may be strong influences on cancer risk [44, 45].

The strengths of our analysis include its prospective design and large sample size. We were able to examine associations by anatomic site within the biliary tract with over 1,900 BTC cases. Though the sample size was small, BiTCaPP includes one of the largest collections of AVC, a rare and understudied cancer. This site-specific analysis is important given that the etiology of BTC varies by anatomic site [46, 47]. We were able to study these rare cancers across several lower risk populations globally. These hypotheses should also be tested in high risk populations, such as Chile, when data become available from newly formed cohorts [48]. We were able to account for the presence of gallstones and a history of cholecystectomy in some studies, factors which have been absent from previous studies on reproductive factors and GBC [14, 15, 17, 49]. Though we could not account for the presence of asymptomatic gallstones, inclusion of self-reported gallstones (largely symptomatic gallstones) did not substantively impact the results in sensitivity analyses. Similarly, excluding women with cholecystectomy in studies with data on cholecystectomy did not materially affect the results. That our results were consistent across multiple sensitivity analyses support the robustness of our findings.

A limitation of this pooled analysis is the variation in the way questions were ascertained across studies and lack of data on age at first birth, gallstones, and cholecystectomy in every study. Results from these analyses may appear more homogeneous if the excluded studies had the potential to induce heterogeneity. We were unable to examine the association of breastfeeding with risk of BTCs, for which there is some evidence that longer duration may be associated with a reduced the risk of cholangiocarcinoma and gallstones [19, 50]. We were also not able to account for exposure to menopausal hormone therapy, though the evidence for an increased risk in BTC is mixed [15, 51, 52]. We lacked information on BMI before age at menarche and pregnancy, and thus could not adjust for it. BMI is a potentially

important confounder as body fatness has an influence on age at puberty onset [53–56], is associated with gallstone formation [57], and has been associated with GBC and IHBDC risk later in life [46, 58–60]. Our inability to adjust for BMI and other unmeasured confounders that may be positively associated with BTC risk in some models may have resulted in an overestimation of the associations in our analysis. All exposures were collected by participant self-report instead of objective measures like medical records. Accurate recall may be an issue as these exposures may have occurred decades before baseline for some participants. Despite these concerns, validation studies have shown that self-reported compared to interviewer-assisted questionnaire or medical record-based measures are reliable, with the greatest reproducibility for parity [61–63]. Finally, women with missing parity data were likely to be women without children or those who had lost children. We used regression imputation to assess the possible impact on our results and found little difference as was expected with <5% missingness [64]. Yet, we acknowledge the lack of adequate methods for data missing not at random like these [64, 65].

Our study suggests that increased parity is associated with risk of GBC, and to a lesser extent, IHBDC. Other reproductive factors such as increased reproductive years among non-Asian women, and age at menopause, are also associated with GBC. These findings support a role for female sex hormones in the etiology of some BTCs in the West. Among Asian women, we observed increased risk of GBC, IHBDC, and EHBDC with increasing age at menarche, suggesting an alternate etiology for BTC among these women. Research should also consider cohorts from South American countries to verify these associations in women of Hispanic and Amerindian ancestry. We did not see associations for EHBDC and AVC with endogenous hormonal exposures, highlighting the variation in risk factors for cancer across the biliary tract. This study used proxy measures for hormones and future studies should focus on measuring endogenous estrogens and progesterone in the serum, gallbladder, and biliary tract to clarify the role of sex hormones in the development of these cancers.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Highlights:

- We pooled data from 19 longitudinal studies to estimate the associations between several female reproductive factors and BTC.
- The risk of GBC was increased with increasing number of live births in all women.
- The risk of GBC, IHBDC, and EHBDC were increased with later age of menarche among women from Asian countries only.
- Age of menopause was not associated with increased risk any BTC.

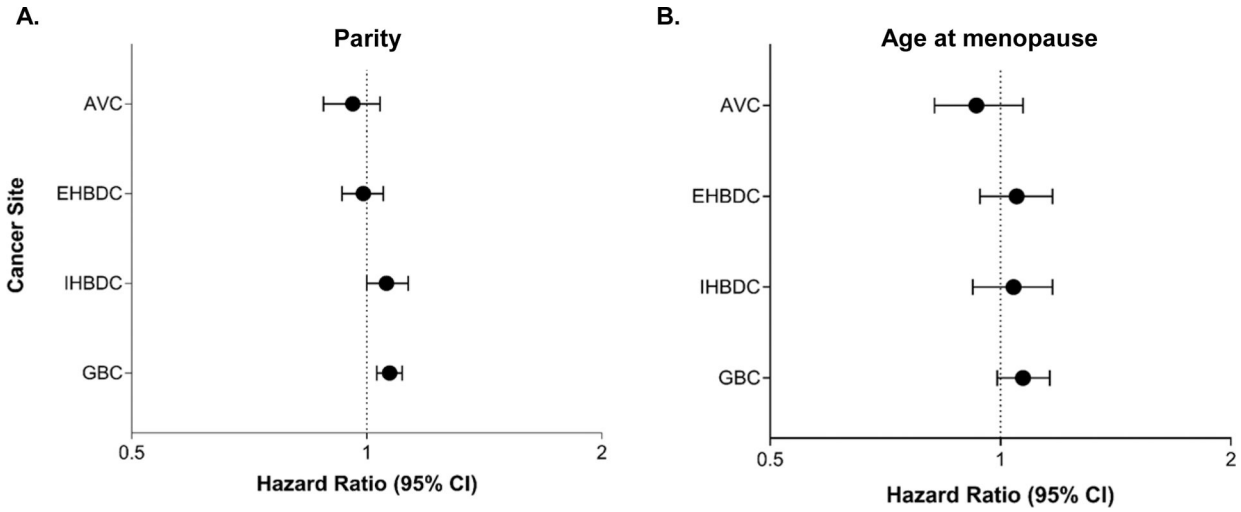

Figure 1.

Hazard ratios and 95% confidence intervals for the relationship between biliary tract cancer site and A) parity and B) age at menopause.

Abbreviations: AVC, ampulla of Vater cancer; CI, confidence interval; EHBDC, extrahepatic bile duct cancer; IHBDC, intrahepatic bile duct cancer; and GBC, gallbladder cancer.

Cox proportional hazard models for parity as a continuous predictor used age as the time scale and were adjusted for participant birth year, use of oral contraceptives (ever/never), age at menarche, race (white, black, Asian/Pacific Islander, other), education (<high school graduate, high school graduate, some college/post-high school training), and the baseline hazard was stratified by study.

Cox proportional hazard models for age at menopause as a continuous predictor used age as the time scale and were adjusted for participant birth year, age at menarche, education (<high school graduate, high school graduate, some college/post-high school training), parity, use of oral contraceptives (ever/never), smoking (ever/never), alcohol use (ever/never), body mass index (<18.5, 18.5 – <25, 25 – <30, ≥30 kg/m^2 for non-Asian women and <18.5, 18.5 – <23, 23 – <27.5, ≥27.5 kg/m^2 for Asian women), and the baseline hazard was stratified by study.

*P-interaction = 0.001; **P-interaction = 0.002

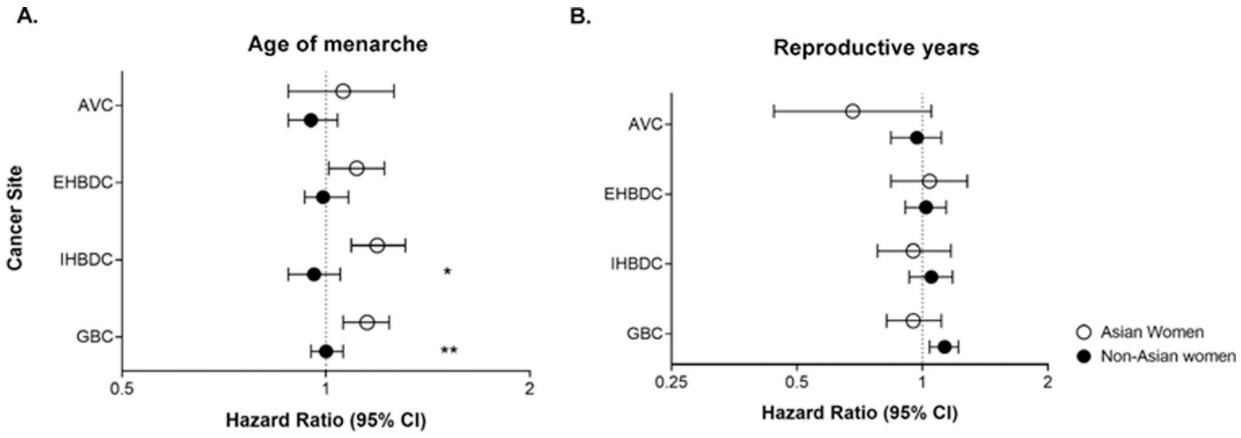

Figure 2.

Hazard ratios and 95% confidence intervals for the relationship between biliary tract cancer site and A) age of menarche and B) reproductive years by geographic region.

Abbreviations: AVC, ampulla of Vater cancer; CI, confidence interval; EHBDC, extrahepatic bile duct cancer; IHBDC, intrahepatic bile duct cancer; and GBC, gallbladder cancer.

Cox proportional hazard models for age of menarche as a continuous predictor used age as the time scale and were adjusted for participant birth year, education (<high school graduate, high school graduate, some college/post-high school training), and the baseline hazard was stratified by study.

Cox proportional hazard models for reproductive years as a continuous predictor used age as the time scale and were adjusted for participant birth year, age at menarche, education (<high school graduate, high school graduate, some college/post-high school training), parity, use of oral contraceptives (ever/never), smoking (ever/never), alcohol use (ever/never), body mass index (<18.5, 18.5 – <25, 25 – <30, ≥30 kg/m^2 for non-Asian women and <18.5, 18.5 – <23, 23 – <27.5, ≥27.5 kg/m^2 for Asian women), and the baseline hazard was stratified by study.

*P-interaction = 0.001; **P-interaction = 0.002

Table 1.

Summary of study characteristics with female participants contributing to the Biliary Tract Cancers Pooling Project[a]

Study (Acronym)	Study Population	Follow-Up Period	Baseline Sample *N* (%)	Total Person-Time	GBC Cases *N* (%)	IHBDC Cases *N* (%)	EHBDC Cases *N* (%)	AVC Cases *N* (%)
AgHealth	U.S.A.	1993–2013	18,712 (1.3)	310,597	8 (0.9)	2 (0.5)	5 (1.1)	2 (0.8)
AHS-2	U.S.A.	2002–2015	62,278 (4.2)	656,422	11 (1.3)	8 (2.2)	10 (2.2)	4 (1.5)
BCDDP	U.S.A.	1980–1999	47,214 (3.2)	361,833	11 (1.3)	6 (1.6)	7 (1.6)	8 (3.1)
CPS-II NC	U.S.A.	1992–2011	80,003 (5.4)	1,147,536	49 (5.6)	21 (5.5)	23 (5.1)	16 (6.2)
CSDLH	Canada	1992–2010	2,331 (0.2)	29,560	7 (0.8)	5 (1.3)	2 (0.4)	2 (0.8)
CSP	Taiwan	1991–2012	10,661 (0.7)	206,806	4 (0.5)	23 (6.1)	5 (1.1)	2 (0.8)
EPIC	Europe	1992–2010	320,904 (21.4)	4,462,700	96 (11.1)	67 (17.7)	48 (10.8)	48 (18.4)
JPHC I JPHC II	Japan	1990–2011 1993–2011	48,345 (3.2)	851,331	108 (12.4)	44 (11.6)	62 (13.8)	14 (5.4)
MCCS	Australia	1990–2009	23,500 (1.6)	411,868	27 (3.1)	10 (2.6)	11 (2.4)	2 (0.8)
MEC	U.S.A.	1993–2010	100,993 (6.7)	1,499,562	71 (8.1)	27 (7.1)	47 (10.4)	29 (11.1)
NHS	U.S.A.	1980–2012	98,678 (6.6)	2,458,524	52 (5.9)	17 (4.5)	34 (7.6)	17 (6.5)
NIH-AARP	U.S.A.	1995–2011	220,028 (14.7)	2,912,836	116 (13.3)	39 (10.3)	70 (15.6)	44 (16.9)
PLCO	U.S.A.	1993–2009	75,508 (5.0)	840,806	31 (3.5)	8 (2.1)	22 (4.9)	10 (3.8)
Sisters	U.S.A.	2003–2017	47,781 (3.2)	437,222	4 (0.5)	5 (1.3)	1 (0.2)	5 (1.9)
SMC	Sweden	1997–2008	37,151 (2.5)	359,221	42 (4.8)	3 (0.8)	6 (1.3)	1 (0.4)
SWHS	China	1996–2014	73,378 (4.9)	1,121,955	107 (12.2)	52 (13.8)	52 (11.6)	6 (2.3)
WHI	U.S.A.	1993–2014	145,711 (9.7)	2,055,805	110 (12.6)	29 (7.7)	40 (8.9)	39 (14.9)
WHS	U.S.A.	1992–2010	39,630 (2.6)	583,593	9 (1.0)	7 (1.9)	1 (0.2)	11 (4.2)
WLHS	Norway, Sweden	1991–2012 2003–2012	47,392 (3.2)	973623	12 (1.4)	6 (1.6)	4 (0.9)	1 (0.4)
Total			**1,500,198**	**21,681,798**	**875**	**379**	**450**	**261**

Abbreviations: Agricultural Health Study (AgHealth), Seventh-day Adventist Health Study 2 (AHS-2), Breast Cancer Detection Demonstration Project (BCDDP), Cancer Prevention Study-II, Nutrition Cohort (CPS-II NC), The Canadian Study of Diet, Lifestyle and Health (CSDLH), Cancer Screening Project (CSP, which includes the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/Cancer-Hepatitis B Virus and Hepatitis C Studies), European Prospective Investigation into Cancer and Nutrition (EPIC), Japan Public Health Center-based prospective Study I & II (JPHC), Melbourne Collaborative Cohort Study (MCCS), Multiethnic Cohort Study (MEC), National Institutes of Health-American Association of Retired Persons Diet and Health Study (NIH-AARP), Nurses' Health Study (NHS), Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial,, Swedish Mammography Cohort (SMC), Shanghai Women's Health Study (SWHS), Sister Study (Sisters), Women's Health Initiative (WHI), Women's Health Study (WHS), and Women's Lifestyle and Health Study (WLHS).

[a] WHI and WHS are randomized controlled trials, CSDLH is a case-cohort study, and PLCO is a screening trial. The remaining studies included in BiTCaPP are prospective cohort studies.

Table 2.

Summary of Participant Characteristics by Cohort Included in the Biliary Tract Cancer Pooling Project

Study	Baseline age Mean (SD)	Race/Ethnicity[a] %				Some college[b] %	Parity Mean (SD)	Age at menarche[c] Mean (SD)	Age at menopause[d] Mean (SD)	Gallstones[e] %	Cholecystectomy[f] %
		White	Black	Asian/ Pacific Islander	Other						
AgHealth	48 (12)	99	1	<1	<1	53	2.7 (1)	13 (1)	45 (8)	N/A	N/A
AHS-2	58 (14)	65	30	3	2	77	2.2 (2)	13 (2)	46 (8)	4	N/A
BCDDP	62 (8)	90	4	5	1	45	2.4 (2)	13 (1)	47 (6)	N/A	N/A
CPS-II NC	62 (7)	98	2	<1	<1	63	2.9 (2)	13 (1)	48 (6)	15	16
CSDLH	60 (14)	97	<1	1	1	97	2.7 (1)	13 (1)	49 (6)	N/A	N/A
CSP	46 (10)	0	0	100	0	1	3.8 (2)	16 (2)	49 (4)	4	N/A
EPIC	51 (10)	100	0	0	0	46	1.9 (1)	13 (2)	49 (5)	9	N/A
JPHC	53 (8)	0	0	100	0	11	2.8 (2)	15 (2)	48 (5)	3	N/A
MCCS	55 (9)	100	0	0	0	22	2.4 (2)	13 (2)	47 (6)	12	10
MEC	60 (9)	24	20	34	22	24	2.8 (2)	13 (2)	44 (4)	9	9
NHS	47 (7)	94	1	1	4	100	3.0 (2)	13 (1)	448 (5)	2	8
NIH-AARP	62 (5)	93	6	1	<1	67	2.5 (2)	13 (1)	46 (7)	14	20
PLCO	63 (5)	88	6	4	2	66	2.9 (1)	13 (2)	48 (5)	16	N/A
Sisters	55 (9)	87	9	1	4	85	1.9 (1)	13 (1)	49 (6)	15	13
SMC	62 (9)	100	0	0	0	18	2.2 (1)	13 (1)	50 (4)	20	N/A
SWHS	52 (9)	0	0	100	0	14	1.8 (1)	15 (2)	48 (4)	11	N/A
WHI	63 (7)	83	9	3	6	77	3.0 (2)	13 (1)	48 (6)	17	13
WHS	55 (7)	96	2	1	<1	100	2.5 (2)	12 (1)	47 (6)	10	N/A
WLHS	40 (6)	100	0	0	0	41	1.9 (1)	13 (1)	41 (6)	N/A	N/A
Total	**56 (10)**	**80**	**5**	**12**	**3**	**57**	**2.5 (2)**	**13 (2)**	**47 (6)**	**12**	**13**

Abbreviations: Agricultural Health Study (AgHealth), Seventh-day Adventist Health Study 2 (AHS-2), Breast Cancer Detection Demonstration Project (BCDDP), Cancer Prevention Study-II, Nutrition Cohort (CPS-II NC),The Canadian Study of Diet, Lifestyle and Health (CSDLH),Cancer Screening Project (CSP, which includes the Risk Evaluation of Viral Load Elevation and Associated Liver Disease/ Cancer-Hepatitis B Virus and Hepatitis C Studies), European Prospective Investigation into Cancer and Nutrition (EPIC), Japan Public Health Center-based prospective Study I & II (JPHC), Melbourne Collaborative Cohort Study (MCCS), Multiethnic Cohort Study (MEC), National Institutes of Health-American Association of Retired Persons Diet and Health Study (NIH-AARP), Nurses' Health Study (NHS), Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Trial, Sister Study (Sisters), Swedish Mammography Cohort (SMC), Shanghai Women's Health Study (SWHS), Women's Health Initiative (WHI), and Women's Health Study (WHS), and Women's Lifestyle and Health Study (WLHS).

Variables are missing for the following numbers of participants out of the studies reporting these variables:

[a] Race – 12,025

[b] Education – 55,173;

[c] Age at menarche – 13,459;

[d] Age at menopause – 75,964;

[e] History of gallstones – 197,896;

[f] Cholecystectomy – 129,927. N/A indicates these data were not available.

Table 3.

Associations between reproductive factors and biliary tract cancers among all women in the Biliary Tract Cancer Pooling Project

Reproductive factor	Non-cases[a]	GBC Cases	GBC HR (95% CI)	IHBDC Cases	IHBDC HR (95% CI)	EHBDC Cases	EHBDC HR (95% CI)	AVC Cases	AVC HR (95% CI)
Parity category[b]									
0	162,444	52	1.00 (Reference)	25	1.00 (Reference)	31	1.00 (Reference)	27	1.00 (Reference)
1 – 2	639,333	307	1.32 (0.98, 1.77)	137	1.13 (0.73, 1.73)	168	1.18 (0.80, 1.73)	96	0.88 (0.57, 1.36)
3 – 4	483,876	280	1.25 (0.93, 1.69)	131	1.21 (0.79, 1.85)	146	1.05 (0.71, 1.55)	86	0.80 (0.52, 1.24)
≥5	135,649	138	**1.72 (1.25, 2.38)**	50	1.39 (0.86, 2.25)	49	0.97 (0.62, 1.53)	30	0.82 (0.49, 1.40)
P-trend[c]			**0.006**		0.12		0.45		0.38
Age at menopause (among postmenopausal women)category[d]									
<45 years	179,812	109	1.02 (0.79, 1.32)	45	0.88 (0.61, 1.28)	61	1.11 (0.78, 1.56)	45	**1.81 (1.13, 2.88)**
45 – 49 years	206,441	136	1.00 (Reference)	69	1.00 (Reference)	70	1.00 (Reference)	29	1.00 (Reference)
50 – 54 years	286,777	226	**1.26 (1.02, 1.56)**	87	1.00 (0.73, 1.37)	113	1.31 (0.97, 1.78)	62	1.50 (0.96, 2.35)
≥55 years	65,820	49	1.15 (0.83, 1.59)	17	0.90 (0.52, 1.54)	19	0.98 (0.58, 1.63)	15	1.47 (0.78, 2.77)
P-trend[c]			0.08		0.73		0.51		0.65

Abbreviations: AVC, ampulla of Vater cancer; EHBDC, extrahepatic bile duct cancer; GBC, gallbladder cancer; and IHBDC, intrahepatic bile duct cancer.

[a]Non-cases: The same non-case group was used for all analyses.

[b]Models used age as the time scale and adjusted for participant birth year, use of oral contraceptives (ever/never), age at menarche, race (white, black, Asian/Pacific Islander, other), education (<high school graduate, high school graduate, some college/post-high school training), and the baseline hazard was stratified by study.

[c]The Wald test was used to test for a linear trend across categories of exposure and biliary tract cancer site.

[d]Models used age as the time scale and were adjusted for participant birth year, age at menarche, education (<high school graduate, high school graduate, some college/post-high school training), parity, use of oral contraceptives (ever/never), smoking (ever/never), alcohol use (ever/never), body mass index (<18.5, 18.5 – <25, 25 – <30, ≥30 kg/m^2 for non-Asian women and <18.5, 18.5 – <23, 23 – <27.5, ≥27.5 kg/m^2 for Asian women), and the baseline hazard was stratified by study.

Risk estimates with *P*-values <0.05 are shown in bold.