Published in final edited form as:

J Hepatol. 2020 October ; 73(4): 863–872. doi:10.1016/j.jhep.2020.04.046.

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

Sarah S. Jackson¹, Hans-Olov Adami², Gabriella Andreotti¹, Laura E. Beane-Freeman¹, Amy Berrington de González¹, Julie E. Buring^{3,4}, Gary E. Fraser⁵, Neal D. Freedman¹, Susan M. Gapstur⁶, Gretchen Gierach¹, Graham G. Giles^{7,8,9}, Francine Grodstein³, Patricia Hartge¹, Mazda Jenab¹⁰, Victoria Kirsh^{11,12}, Synnove F. Knutsen⁵, Qing Lan¹, Susanna C. Larsson^{13,14}, I-Min Lee^{3,4}, Mei-Hsuan Lee¹⁵, Linda M. Liao¹, Roger L. Milne^{7,8,9}, Kristine R. Monroe¹⁶, Marian L. Neuhouser¹⁷, Katie M. O'Brien¹⁸, Jessica L. Petrick¹⁹, Mark P. Purdue¹, Thomas E. Rohan²⁰, Sven Sandin², Dale P. Sandler¹⁸, Norie Sawada²¹, Aladdin H. Shadyab²², Tracey G. Simon^{23,24}, Rashmi Sinha¹, Rachael Stolzenberg-Solomon¹, Shoichiro Tsugane²¹, Elisabete Weiderpass²⁵, Alicja Wolk^{13,14}, Hwai-I Yang^{26,15}, Wei Zheng²⁷, Katherine A. McGlynn¹, Peter T. Campbell⁶, Jill Koshiol¹

¹Division of Cancer Epidemiology and Genetics, National Cancer Institute, Rockville, MD, USA,

²Department of Medical Epidemiology and Biostatistics, Karolinska Institutet, Stockholm, Sweden,

³Department of Epidemiology, Harvard T.H. Chan School of Public Health, Boston, MA, USA,

⁴Division of Preventive Medicine, Department of Medicine, Brigham and Women's Hospital, Boston, MA, USA,

⁵School of Public Health, Loma Linda University, Loma Linda, CA, USA,

⁶Behavioral and Epidemiology Research Group, American Cancer Society, Inc., Atlanta, GA, USA,

⁷Cancer Epidemiology Division, Cancer Council Victoria, Melbourne, Australia,

⁸Centre for Epidemiology and Biostatistics, Melbourne School of Population and Global Health, University of Melbourne, Parkville, Victoria, Australia,

⁹Precision Medicine, School of Clinical Sciences at Monash Health, Monash University, Clayton, Victoria, Australia,

Corresponding Author: Sarah S. Jackson, PhD, MPH, Postdoctoral Research Fellow, Infections and Immunoepidemiology Branch, National Cancer Institute, Division of Cancer Epidemiology and Genetics, 9609 Medical Center Drive, Bethesda, MD 20879, Phone: 240-276-7814, Fax: 240-276-7806, sarah.jackson@nih.gov.

Authors contributions: SSJ conducted the analyses and prepared the first draft of the paper. JK, KAM, and PTC jointly conceived the study and contributed to the interpretation of the results. All authors were responsible for the data collection in their respective studies or the pooled analyses and critically reviewed the manuscript.

Publisher's Disclaimer: This is a PDF file of an unedited manuscript that has been accepted for publication. As a service to our customers we are providing this early version of the manuscript. The manuscript will undergo copyediting, typesetting, and review of the resulting proof before it is published in its final form. Please note that during the production process errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

Publisher's Disclaimer: Disclaimer: Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization, the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

Conflict of Interest: The authors declare no potential conflicts of interest.

- ¹⁰Section of Nutrition and Metabolism, International Agency for Research on Cancer (IARC-WHO), Lyon, France,
- ¹¹Ontario Institute for Cancer Research, Toronto, Ontario, Canada,
- ¹²Dalla Lana School of Public Health, University of Toronto, Toronto, Ontario, Canada,
- ¹³Unit of Cardiovascular and Nutritional Epidemiology, Institute of Environmental Medicine, Karolinska Institutet, Stockholm, Sweden,
- ¹⁴Department of Surgical Sciences, Uppsala University, Uppsala, Sweden,
- ¹⁵Institute of Clinical Medicine, National Yang-Ming University, Taipei, Taiwan,
- ¹⁶Department of Preventive Medicine, Keck School of Medicine, University of Southern California, Los Angeles, CA, USA,
- ¹⁷Cancer Prevention Program, Division of Public Health Sciences, Fred Hutchinson Cancer Research Center, Seattle, WA, USA,
- ¹⁸Epidemiology Branch, National Institute of Environmental Health Sciences, Research Triangle Park, NC, USA,
- ¹⁹Slone Epidemiology Center, Boston University, Boston, MA, USA,
- ²⁰Department of Epidemiology and Population Health, Albert Einstein College of Medicine, Bronx, NY, USA,
- ²¹Epidemiology and Prevention Group, Center for Public Health Sciences, National Cancer Center, Tokyo, Japan,
- ²²Department of Family Medicine and Public Health, University of California San Diego School of Medicine, La Jolla, CA, USA,
- ²³Division of Gastroenterology, Department of Medicine, Massachusetts General Hospital, Boston, MA, USA,
- ²⁴Clinical and Translational Epidemiology Unit, Massachusetts General Hospital and Harvard Medical, Boston, MA, USA,
- ²⁵International Agency for Research on Cancer (IARC), Lyon, France,
- ²⁶Genomics Research Center, Academia Sinica, Taipei, Taiwan,
- ²⁷Division of Epidemiology, Department of Medicine, Vanderbilt Epidemiology Center, Vanderbilt-Ingram Cancer Center, Vanderbilt University, Nashville, TN, USA

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/m²), normal weight (18.5 to <25 kg/m²), overweight (25 to <30 kg/m²), and obese (30kg/m²) [21]. BMI for Asian women was categorized as underweight (15.0 to <18.5 kg/m²), normal weight (18.5 to <23 kg/m²), overweight (23 to <27.5 kg/m²), obese (27.5 kg/m²) [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 $\alpha=0.05$. 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]. 17 β -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.

Funding

BiTCaPP: This cohort consortium was funded by the Intramural Program of the National Institutes of Health, National Cancer Institute (Z1A CP010218-01).

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 and World Cancer Research Fund International (UK) grant 2009/93.

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

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

CSP: This work was supported by Academia Sinica [AS-TP-108-L09-3; AS-SUMMIT-108] and Ministry of Science and Technology [108-2314-B-001-008; 107-0210-01-19-01].

EPIC: The coordination of 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 Generale de l'Education Nationale, France; Institut National de la Sante et de la Recherche Medicale, France; Deutsche Krebsshilfe, 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 Andalusia, 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 Skane and Vasterbotten, Sweden; Cancer Research United Kingdom; Medical Research Council, United Kingdom; Stroke Association, United Kingdom, British Heart Foundation, United Kingdom; Department of Health, Food Standards Agency, United Kingdom; and Wellcome Trust; United Kingdom. We thank Bertrand Hemon for his precious help with the EPIC database. The principle investigators and funders corresponding to each of the EPIC centers that contributed cases were Kim Overvad, Anne Tjønneland (Denmark); Francoise Clavel-Chapelon (France); Heiner Boeing, Rudolf Kaaks (Germany); Antonia Trichopoulou (Greece); Vittorio Krogh, Domenico Palli, Paolo Vineis, Salvatore Panico, Rosario Tumino (Italy); Eiliv Lund (Norway); Antonio Agudo, Maria Jose Sanchez, J. Ramón Quirós, Carmen Navarro, Aurelio Barricarte, Miren Dorronsoro (Spain); Mattias Johansson, Jonas Manjer (Sweden); H. Bas Bueno-de-Mesquita, Petra H. Peeters (The Netherlands); Timothy Key, Nick Wareham (UK); The coordination of European Prospective Investigation into Cancer and Nutrition is financially supported by the European Commission (DG-SANCO) and the International Agency for Research on Cancer. The national cohorts are supported by the French National Cancer Institute (L'Institut National du Cancer; INCA); Ligue contre le Cancer, Institut Gustave Roussy, Mutuelle Générale de l'Éducation Nationale, Institut National de la Santé et de la Recherche Médicale (INSERM) (France); German Cancer Aid; German Cancer Research Center (DKFZ); German Federal Ministry of Education and Research; Danish Cancer Society; Health Research Fund (FIS) of the Spanish Ministry of Health (RTICC (DR06/0020/0091)); the participating regional governments from Asturias, Andalusia, Murcia, Navarra and Vasco Country and the Catalan Institute of Oncology of Spain; Cancer Research UK; Medical Research Council, UK; the Stroke Association, UK; British Heart Foundation; Department of Health, UK; Food Standards Agency, UK; the Wellcome Trust, UK; the Hellenic Health Foundation; Italian Association for Research on Cancer; Compagnia San Paolo, Italy; Dutch Ministry of Public Health, Welfare and Sports; Dutch Ministry of Health; Dutch Prevention Funds; LK Research Funds; Dutch ZON (Zorg Onderzoek Nederland); World Cancer Research Fund (WCRF); Statistics Netherlands (The Netherlands); Swedish Cancer Society; Swedish Scientific Council; Regional Government of Skane, Sweden; Nordforsk—Centre of Excellence programme.

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 cohort recruitment was funded by VicHealth and Cancer Council Victoria. The MCCS was further augmented by Australian National Health and Medical Research Council grants 209057, 396414 and 1074383 and by infrastructure provided by Cancer Council Victoria.

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

NHS: Data used in this study was 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, WY. The authors assume full responsibility for analyses and interpretation of these data.

NIH-AARP: This research was supported [in part] by the Intramural Research Program of the NIH, 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, Georgia. Cancer incidence data from California were collected by the California Cancer Registry, California Department of Public Health's Cancer Surveillance and Research Branch, Sacramento, California. Cancer incidence data from the Detroit metropolitan area were collected by the Michigan Cancer Surveillance Program, Community Health Administration, Lansing, Michigan. The Florida cancer incidence data used in this report were collected by the Florida Cancer Data System (Miami, Florida) under contract with the Florida Department of Health, Tallahassee, Florida. The views expressed herein are solely those of the authors and do not necessarily reflect those of the FCDC or FDOH. Cancer incidence data from Louisiana were collected by the Louisiana Tumor Registry, Louisiana State University Health Sciences Center School of Public Health, New Orleans, Louisiana. Cancer incidence data from New Jersey were collected by the New Jersey State Cancer Registry, The Rutgers

Cancer Institute of New Jersey, New Brunswick, New Jersey. Cancer incidence data from North Carolina were collected by the North Carolina Central Cancer Registry, Raleigh, North Carolina. Cancer incidence data from Pennsylvania were supplied by the Division of Health Statistics and Research, Pennsylvania Department of Health, Harrisburg, Pennsylvania. 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, Arizona. Cancer incidence data from Texas were collected by the Texas Cancer Registry, Cancer Epidemiology and Surveillance Branch, Texas Department of State Health Services, Austin, Texas. 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, Nevada.

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

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). Support for data collection and study and data management are provided by Social & Scientific Systems, Inc., and Westat, Inc., Durham, NC.

SMC: This cohort is supported by the Swedish Research Council (Research Infrastructure SIMPLER, 2017-00644), the Swedish Cancer Foundation, and by Strategic Funds from Karolinska Institutet, Stockholm, Sweden.

SWHS: This project was supported by grants from the U.S. National Institutes of Health (R37 CA070867 to W.Z., and R01 CA082729 and UM1 CA173640 to X.-O.S.) and by the Intramural Research Program (contract N02 CP1101066).

WHI: The WHI program is funded by the National Heart, Lung, and Blood Institute, National Institutes of Health, U.S. Department of Health and Human Services through contracts, HHSN268201600018C, HHSN268201600001C, HHSN268201600002C, HHSN268201600003C, and HHSN268201600004C. WHI would like to additionally acknowledge the following short list of WHI investigators: **Program Office:** (National Heart, Lung, and Blood Institute, Bethesda, Maryland) Jacques Rossouw, Shari Ludlam, Joan McGowan, Leslie Ford, and Nancy Geller; **Clinical Coordinating Center:** (Fred Hutchinson Cancer Research Center, Seattle, WA) Garnet Anderson, Ross Prentice, Andrea LaCroix, and Charles Kooperberg; **Investigators and Academic Centers:** (Brigham and Women's Hospital, Harvard Medical School, Boston, MA) JoAnn E. Manson; (MedStar Health Research Institute/Howard University, Washington, DC) Barbara V. Howard; (Stanford Prevention Research Center, Stanford, CA) Marcia L. Stefanick; (The Ohio State University, Columbus, OH) Rebecca Jackson; (University of Arizona, Tucson/Phoenix, AZ) Cynthia A. Thomson; (University at Buffalo, Buffalo, NY) Jean Wactawski-Wende; (University of Florida, Gainesville/Jacksonville, FL) Marian Limacher; (University of Iowa, Iowa City/Davenport, IA) Jennifer Robinson; (University of Pittsburgh, Pittsburgh, PA) Lewis Kuller; (Wake Forest University School of Medicine, Winston-Salem, NC) Sally Shumaker; (University of Nevada, Reno, NV) Robert Brunner; and **Women's Health Initiative Memory Study:** (Wake Forest University School of Medicine, Winston-Salem, NC) Mark Espeland. For a list of all the investigators who have contributed to WHI science, please visit: <https://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Long%20List.pdf>

WHS: WHS was supported by grants CA047988, CA182913, 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.

References

- [1]. Edgren G, Liang L, Adami HO, Chang ET. Enigmatic sex disparities in cancer incidence. *Eur J Epidemiol* 2012;27:187–196. [PubMed: 22212865]
- [2]. Randi G, Malvezzi M, Levi F, Ferlay J, Negri E, Franceschi S, et al. Epidemiology of biliary tract cancers: an update. *Annals of Oncology* 2008;20:146–159. [PubMed: 18667395]
- [3]. Florio AA, Ferlay J, Znaor A, Ruggieri D, Alvarez CS, Laversanne M, et al. Global trends in intrahepatic and extrahepatic cholangiocarcinoma incidence from 1993 to 2012. *Cancer* 2020.
- [4]. Thijs C, Knipschild P, Leffers P. Pregnancy and gallstone disease: an empiric demonstration of the importance of specification of risk periods. *Am J Epidemiol* 1991;134:186–195. [PubMed: 1862802]
- [5]. Everson GT. Gallbladder function in gallstone disease. *Gastroenterol Clin North Am* 1991;20:85–110. [PubMed: 2022427]

- [6]. Everson GT, McKinley C, Lawson M, Johnson M, Kern F Jr. Gallbladder function in the human female: effect of the ovulatory cycle, pregnancy, and contraceptive steroids. *Gastroenterology* 1982;82:711–719. [PubMed: 7060890]
- [7]. Hahm JS, Park JY, Song SC, Cho YJ, Moon KH, Song YH, et al. Gallbladder motility change in late pregnancy and after delivery. *Korean J Intern Med* 1997;12:16–20. [PubMed: 9159032]
- [8]. Kern F Jr., Everson GT, DeMark B, McKinley C, Showalter R, Erfling W, et al. Biliary lipids, bile acids, and gallbladder function in the human female. Effects of pregnancy and the ovulatory cycle. *J Clin Invest* 1981;68:1229–1242. [PubMed: 7298849]
- [9]. Kern F Jr., Everson GT, DeMark B, McKinley C, Showalter R, Braverman DZ, et al. Biliary lipids, bile acids, and gallbladder function in the human female: effects of contraceptive steroids. *The Journal of laboratory and clinical medicine* 1982;99:798–805. [PubMed: 7077124]
- [10]. Braverman DZ, Johnson ML, Kern F Jr. Effects of pregnancy and contraceptive steroids on gallbladder function. *N Engl J Med* 1980;302:362–364. [PubMed: 7351927]
- [11]. Alvaro D, Barbaro B, Franchitto A, Onori P, Glaser SS, Alpini G, et al. Estrogens and insulin-like growth factor 1 modulate neoplastic cell growth in human cholangiocarcinoma. *Am J Pathol* 2006;169:877–888. [PubMed: 16936263]
- [12]. Alvaro D, Mancino MG, Onori P, Franchitto A, Alpini G, Francis H, et al. Estrogens and the pathophysiology of the biliary tree. *World journal of gastroenterology* 2006;12:3537–3545. [PubMed: 16773710]
- [13]. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA: A Cancer Journal for Clinicians* 2018;68:394–424. [PubMed: 30207593]
- [14]. Lambe M, Trichopoulos D, Hsieh CC, Ekblom A, Adami HO, Pavia M. Parity and cancers of the gall bladder and the extrahepatic bile ducts. *International journal of cancer* 1993;54:941–944. [PubMed: 8335402]
- [15]. Moerman CJ, Berns MP, Bueno de Mesquita HB, Runia S. Reproductive history and cancer of the biliary tract in women. *International journal of cancer* 1994;57:146–153. [PubMed: 8157350]
- [16]. Tavani A, Negri E, La Vecchia C. Menstrual and reproductive factors and biliary tract cancers. *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)* 1996;5:241–247. [PubMed: 8894561]
- [17]. Pandey M, Shukla VK. Lifestyle, parity, menstrual and reproductive factors and risk of gallbladder cancer. *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)* 2003;12:269–272. [PubMed: 12883378]
- [18]. Kilander C, Mattsson F, Lu Y, Ljung R, Lagergren J, Sadr-Azodi O. Reproductive factors and risk of biliary tract cancer in a population-based study. *Acta Oncol* 2015;54:1152–1158. [PubMed: 25752973]
- [19]. Andreotti G, Hou L, Gao YT, Brinton LA, Rashid A, Chen J, et al. Reproductive factors and risks of biliary tract cancers and stones: a population-based study in Shanghai, China. *British journal of cancer* 2010;102:1185–1189. [PubMed: 20216539]
- [20]. Dhont M History of oral contraception. *Eur J Contracept Reprod Health Care* 2010;15 Suppl 2:S12–18. [PubMed: 21091163]
- [21]. World Health Organization. Report of a WHO Consultation on Obesity Obesity: preventing and managing the global epidemic. Geneva: World Health Organization; 2000 WHO Technical Report Series;894.
- [22]. Appropriate body-mass index for Asian populations and its implications for policy and intervention strategies. *Lancet (London, England)* 2004;363:157–163.
- [23]. Rothman KJ, Greenland S, Lash TL. *Modern epidemiology*, 3rd ed. Philadelphia: Wolters Kluwer Health/Lippincott Williams & Wilkins; 2008.
- [24]. Greenland S, Pearce N. Statistical foundations for model-based adjustments. *Annual review of public health* 2015;36:89–108.
- [25]. Jalovaara M, Neyer G, Andersson G, Dahlberg J, Dommermuth L, Fallesen P, et al. Education, Gender, and Cohort Fertility in the Nordic Countries. *European journal of population = Revue europeenne de demographie* 2019;35:563–586. [PubMed: 31372105]

- [26]. Van Bavel J, Klesment M, Beaujouan E, Brzozowska Z, Puur A, Reher D, et al. Seeding the gender revolution: Women's education and cohort fertility among the baby boom generations. *Population studies* 2018;72:283–304. [PubMed: 30280973]
- [27]. Kirmeyer SE, Hamilton BE. Transitions between childlessness and first birth: three generations of U.S. women. *Vital and health statistics Series 2, Data evaluation and methods research* 2011;1–18.
- [28]. Nichols HB, Trentham-Dietz A, Hampton JM, Titus-Ernstoff L, Egan KM, Willett WC, et al. From menarche to menopause: trends among US Women born from 1912 to 1969. *Am J Epidemiol* 2006;164:1003–1011. [PubMed: 16928728]
- [29]. Kono S, Sunagawa Y, Higa H, Sunagawa H. Age of menopause in Japanese women: trends and recent changes. *Maturitas* 1990;12:43–49. [PubMed: 2333036]
- [30]. Dratva J, Gomez Real F, Schindler C, Ackermann-Liebrich U, Gerbase MW, Probst-Hensch NM, et al. Is age at menopause increasing across Europe? Results on age at menopause and determinants from two population-based studies. *Menopause* 2009;16:385–394. [PubMed: 19034049]
- [31]. Huen KF, Leung SS, Lau JT, Cheung AY, Leung NK, Chiu MC. Secular trend in the sexual maturation of southern Chinese girls. *Acta paediatrica (Oslo, Norway : 1992)* 1997;86:1121–1124.
- [32]. Frisch RE, Revelle R. Height and Weight at Menarche and a Hypothesis of Critical Body Weights and Adolescent Events. *Science* 1970;169:397–399. [PubMed: 5450378]
- [33]. Meng X, Li S, Duan W, Sun Y, Jia C. Secular Trend of Age at Menarche in Chinese Adolescents Born From 1973 to 2004. *Pediatrics* 2017;140.
- [34]. Higgins JP, Thompson SG. Quantifying heterogeneity in a meta-analysis. *Statistics in Medicine* 2002;21:1539–1558. [PubMed: 12111919]
- [35]. Diehl AK, Stern MP, Ostrower VS, Friedman PC. Prevalence of clinical gallbladder disease in Mexican-American, Anglo, and black women. *South Med J* 1980;73:438–441, 443. [PubMed: 7367932]
- [36]. Chen A, Hummer D. The role of estrogen receptors in the development of gallstones and gallbladder cancer. *Med Hypotheses* 1991;36:259–260. [PubMed: 1787822]
- [37]. Gupta P, Agarwal A, Gupta V, Singh PK, Pantola C, Amit S. Expression and clinicopathological significance of estrogen and progesterone receptors in gallbladder cancer. *Gastrointest Cancer Res* 2012;5:41–47. [PubMed: 22690257]
- [38]. Baskaran V, Vij U, Sahni P, Tandon RK, Nundy S. Do the progesterone receptors have a role to play in gallbladder cancer? *Int J Gastrointest Cancer* 2005;35:61–68. [PubMed: 15722575]
- [39]. Mancinelli R, Onori P, Demorrow S, Francis H, Glaser S, Franchitto A, et al. Role of sex hormones in the modulation of cholangiocyte function. *World J Gastrointest Pathophysiol* 2010;1:50–62. [PubMed: 21607142]
- [40]. Chow WH, McLaughlin JK, Menck HR, Mack TM. Risk factors for extrahepatic bile duct cancers: Los Angeles County, California (USA). *Cancer causes & control : CCC* 1994;5:267–272. [PubMed: 8061176]
- [41]. Makiuchi T, Sobue T, Kitamura T, Sawada N, Iwasaki M, Sasazuki S, et al. Reproductive factors and gallbladder/bile duct cancer: a population-based cohort study in Japan. *European journal of cancer prevention : the official journal of the European Cancer Prevention Organisation (ECP)* 2017;26:292–300. [PubMed: 27164185]
- [42]. Petrick J, McMenamin Ú, Zhang X, Zeleniuch-Jacquotte A, Wactawski-Wende J, Simon T, et al. Exogenous Hormone Use, Reproductive Factors and Risk of Intrahepatic Cholangiocarcinoma among Women: Results from the Liver Cancer Pooling Project and UK Biobank. *British journal of cancer* 2020.
- [43]. Stinton LM, Shaffer EA. Epidemiology of gallbladder disease: cholelithiasis and cancer. *Gut Liver* 2012;6:172–187. [PubMed: 22570746]
- [44]. Shadyab AH, Macera CA, Shaffer RA, Jain S, Gallo LC, Gass MLS, et al. Ages at menarche and menopause and reproductive lifespan as predictors of exceptional longevity in women: the Women's Health Initiative. *Menopause (New York, NY)* 2017;24:35–44.

- [45]. Shadyab AH, Gass MLS, Stefanick ML, Waring ME, Macera CA, Gallo LC, et al. Maternal Age at Childbirth and Parity as Predictors of Longevity Among Women in the United States: The Women's Health Initiative. *American journal of public health* 2017;107:113–119. [PubMed: 27854529]
- [46]. Jackson SS, Van Dyke AL, Zhu B, Pfeiffer RM, Petrick JL, Adami HO, et al. Anthropometric Risk Factors for Cancers of the Biliary Tract in the Biliary Tract Cancers Pooling Project. *Cancer Res* 2019;79:3973–3982. [PubMed: 31113819]
- [47]. McGee EE, Jackson SS, Petrick JL, Van Dyke AL, Adami HO, Albanes D, et al. Smoking, Alcohol, and Biliary Tract Cancer Risk: A Pooling Project of 26 Prospective Studies. *J Natl Cancer Inst* 2019.
- [48]. Ferreccio C, Roa JC, Bambs C, Vives A, Corvalan AH, Cortes S, et al. Study protocol for the Maule Cohort (MAUCO) of chronic diseases, Chile 2014–2024. *BMC Public Health* 2016;16:122. [PubMed: 26847446]
- [49]. Guo P, Xu C, Zhou Q, Zhou J, Zhao J, Si Z, et al. Number of parity and the risk of gallbladder cancer: a systematic review and dose-response meta-analysis of observational studies. *Arch Gynecol Obstet* 2016;293:1087–1096. [PubMed: 26408005]
- [50]. Liu B, Beral V, Balkwill A, Million Women Study C. Childbearing, breastfeeding, other reproductive factors and the subsequent risk of hospitalization for gallbladder disease. *Int J Epidemiol* 2009;38:312–318. [PubMed: 18775873]
- [51]. Kilander C, Lagergren J, Konings P, Sadr-Azodi O, Brusselaers N. Menopausal hormone therapy and biliary tract cancer: a population-based matched cohort study in Sweden. *Acta Oncol* 2019;58:290–295. [PubMed: 30656997]
- [52]. Gallus S, Negri E, Chatenoud L, Bosetti C, Franceschi S, La Vecchia C. Post-menopausal hormonal therapy and gallbladder cancer risk. *International journal of cancer* 2002;99:762–763. [PubMed: 12115514]
- [53]. Bratke H, Bruserud IS, Brannsether B, Assmus J, Bjerknes R, Roelants M, et al. Timing of menarche in Norwegian girls: associations with body mass index, waist circumference and skinfold thickness. *BMC pediatrics* 2017;17:138. [PubMed: 28587648]
- [54]. Wagner IV, Sabin MA, Pfaffle RW, Hiemisch A, Sergeyev E, Korner A, et al. Effects of obesity on human sexual development. *Nature reviews Endocrinology* 2012;8:246–254.
- [55]. Kaplowitz PB. Link between body fat and the timing of puberty. *Pediatrics* 2008;121 Suppl 3:S208–217. [PubMed: 18245513]
- [56]. Johnston FE, Malina RM, Galbraith MA, Frisch RE, Revelle R, Cook S. Height, weight and age at menarche and the “critical weight” hypothesis. *Science* 1971;174:1148–1149. [PubMed: 5133734]
- [57]. Maclure KM, Hayes KC, Colditz GA, Stampfer MJ, Speizer FE, Willett WC. Weight, diet, and the risk of symptomatic gallstones in middle-aged women. *N Engl J Med* 1989;321:563–569. [PubMed: 2761600]
- [58]. Campbell PT, Newton CC, Kitahara CM, Patel AV, Hartge P, Koshiol J, et al. Body Size Indicators and Risk of Gallbladder Cancer: Pooled Analysis of Individual-Level Data from 19 Prospective Cohort Studies. *Cancer epidemiology, biomarkers & prevention : a publication of the American Association for Cancer Research, cosponsored by the American Society of Preventive Oncology* 2017;26:597–606.
- [59]. Petrick JL, Thistle JE, Zeleniuch-Jacquotte A, Zhang X, Wactawski-Wende J, Van Dyke AL, et al. Body Mass Index, Diabetes and Intrahepatic Cholangiocarcinoma Risk: The Liver Cancer Pooling Project and Meta-analysis. *The American journal of gastroenterology* 2018.
- [60]. Kyrgiou M, Kalliala I, Markozannes G, Gunter MJ, Paraskevaides E, Gabra H, et al. Adiposity and cancer at major anatomical sites: umbrella review of the literature. *Bmj* 2017;356:j477. [PubMed: 28246088]
- [61]. Goodman MT, Nomura AM, Wilkens LR, Kolonel LN. Agreement between interview information and physician records on history of menopausal estrogen use. *Am J Epidemiol* 1990;131:815–825. [PubMed: 2321625]
- [62]. Lucas R, Azevedo A, Barros H. Self-reported data on reproductive variables were reliable among postmenopausal women. *J Clin Epidemiol* 2008;61:945–950. [PubMed: 18468857]

- [63]. Hunter DJ, Manson JE, Colditz GA, Chasan-Taber L, Troy L, Stampfer MJ, et al. Reproducibility of oral contraceptive histories and validity of hormone composition reported in a cohort of US women. *Contraception* 1997;56:373–378. [PubMed: 9494771]
- [64]. Allison PD. *Missing data*. Thousand Oaks, Calif.: Sage Publications; 2002.
- [65]. Sterne JAC, White IR, Carlin JB, Spratt M, Royston P, Kenward MG, et al. Multiple imputation for missing data in epidemiological and clinical research: potential and pitfalls. *BMJ* 2009;338:b2393. [PubMed: 19564179]

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/m² for non-Asian women and <18.5, 18.5 – <23, 23 – <27.5, 27.5 kg/m² 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/m² for non-Asian women and <18.5, 18.5 – <23, 23 – <27.5, 27.5 kg/m² 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 (%)	EBHDC 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)	973,623	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).

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.

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

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 INC	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).

Author Manuscript

Author Manuscript

Author Manuscript

Author Manuscript

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)	EHBD C Cases	EHBD C 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)
<i>P</i> -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)
<i>P</i> -trend ^c			0.08		0.73		0.51		0.65

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

^aNon-cases: The same non-case group was used for all analyses.

^bModels 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.

^cThe Wald test was used to test for a linear trend across categories of exposure and biliary tract cancer site.

^dModels 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/m² for non-Asian women and <18.5, 18.5 – <23, 23 – <27.5, 27.5 kg/m² for Asian women), and the baseline hazard was stratified by study.

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