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ORIGINAL ARTICLE

Reproductive factors and risk of biliary tract cancer in a population-based study

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ABSTRACT

Background. The strong female predominance of biliary tract cancer (BTC) may be related to reproductive factors. We aimed to clarify whether parity or age at first birth influence the risk of BTC.
Methods. This was a population-based, case-control study including Swedish female and male cases of cancer of the gallbladder (GBC), extra hepatic bile ducts (EHCC), or the ampulla of Vater (AVC) between 1960 and 2008. For each case, 10 age- and sex-matched controls were randomly selected. Conditional logistic regression was used to calculate odds ratios (ORs) with 95% confidence intervals (CIs), adjusted for potential confounders.
Results. In total, 1169 cases of GBC, 432 cases of EHCC and 295 cases of AVC were included. Multi- and nulliparous women and men had an increased risk of all tumor locations in the biliary tract compared to uniparous women and men, respectively. Whereas higher age at first birth was associated with a decreased risk of GBC in women, no such association was found in men. There were no clear differences in the risk of EHCC and AVC between women and men.
Conclusion. Sex hormones may play a role in the etiology of GBC. The associations between reproductive factors and EHCC and AVC are similar in women and men, which do not support the sex hormone hypothesis.

Biliary tract cancer (BTC), including cancers of the gallbladder (GBC), extra hepatic bile ducts (EHCC), and the ampulla of Vater (AVC), is characterized by a dismal prognosis and poor survival [1,2]. There are only a few established risk factors of which gallstone disease, primary sclerosing cholangitis, diabetes and certain biliary infections may be the most prominent [3–6]. There are intriguing sex differences in the incidence of BLC. GBC, the most common type of BLC, is characterized by a female-to-male ratio of 3–4:1 in Sweden and even higher in some countries [7–9]. For EHCC and AVC, the female-to-male ratio is closer to one, but a male predominance has rather been observed [10]. The mechanisms behind these associations are poorly understood, but an influence of sex hormones has been suggested [11]. Serum levels of estrogens increase greatly during pregnancy and reproductive factors, including factors such as parity (number of live births) and age at first birth,

correlate with endogenous estrogen levels and have been used as proxy to study the effects of endogenous estrogen exposure on the development of BTC etiology previously [12,13]. Most studies have shown an increased risk of BTC with increasing exposure to sex hormones, however, a majority of these studies have been small and seldom population-based [14–16]. Additionally, older studies rarely differentiate between different tumor locations, which may indeed affect any conclusions drawn from these studies. Furthermore, if exposure to sex hormones does in fact increase the risk of BTC, a measurable difference between females and males is expected because the levels of sex hormones in males are not likely to be affected by parity and age at first birth in a similar way as in females.

Thus, with the aim to clarify the role of parity and age at first birth in the development of GBC, EHCC, and AVC, we conducted a nationwide

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Swedish population-based study of women and men using register data from nationwide Swedish healthcare registers.

Methods

Study design

The study was a nationwide, population-based, case-control study, nested within the Swedish Multi-Generation Register during the study period 1960–2008. Subjects aged older than 15 years were included in the study. The study population included approximately 10 million individuals. Information of potential confounding comorbidities was collected from the Swedish Patient Register. Individual record linkage was possible using the Swedish Personal Identity Number, uniquely identifying each resident in Sweden [17]. The study outcomes were any cancer of the biliary tract. Censoring was made at death, migration or end of study period, whichever occurred first. The Regional Ethical Review Board in Stockholm, Sweden approved the study.

Data sources

The Multi-Generation Register contains all persons born in 1932 or later, registered as a Swedish resident at some point since 1961. The register contains valid data of parenthood, siblings and children of each index person [18].

The Register of the Total Population provides individual characteristics on all Swedish residents since 1968, including age, sex, dates of migration, country of birth, marital status, and residence [19].

The Swedish Cancer Register has information on incident cancers in Sweden since 1958. The register contains information of cancer site, histological subtype and date of diagnosis. Both clinicians and pathologists are required to report all newly diagnosed cases of cancer to this register, resulting in an overall completeness of at least 96% [20]. However, a recent study from our group suggested a less complete coverage for BTC specifically [21].

The Causes of Death Register contains complete information on date of death for all deceased Swedish residents since 1952 and the data on cause-specific death is 99.2% complete [22].

The Patient Register has collected information on in-hospital care since 1965, with 100% nationwide coverage since 1987, and is of excellent overall quality [23].

The Education Register annually updates information on the highest formal education attained (from elementary to postgraduate level) by each Swedish resident since 1985 [24].

Cases

Females and males with a diagnosis of BTC, reported to the Swedish Cancer Register between 1960 and 2008, were identified using the seventh version of the International Classification of Disease (ICD-7). The ICD-7 codes for GBC, EHCC and AVC were 1551, 1552, and 1553, respectively. Additionally, to ensure uniform tumor biology, only adenocarcinomas were included using the histology code "096" from the C24 WHO classification of histology. Adenocarcinoma is the dominating histological type of malignancy in the biliary tract [25]. Cases with a history of prior gastrointestinal malignancy or those with a first diagnosis of BTC at autopsy were excluded from the study.

Control subjects

For every incident case of BTC, 10 controls were randomly selected from the source population using density-based sampling, matched for age (calendar year) and sex [26]. Eligible controls were resident in Sweden, alive at the time of cancer diagnosis of the corresponding case, and had no history of gastrointestinal malignancy. Specifically for GBC, 608 controls that had undergone cholecystectomy (gallbladder removal) prior to cancer diagnosis of the corresponding case were excluded.

Study exposures

The two study exposures were parity (number of live births) and age at first birth. Parity was defined as number of live births up to the date of cancer diagnosis for the cases, and up to the date of cancer diagnosis of the corresponding case for the controls. Parity was categorized into four predefined groups: 0, 1, 2, or ≥ 3 children. Age at the birth of the first child was categorized into three predefined groups: ≤ 22, 23–29, or ≥ 30 years.

Statistical analyses

Conditional logistic regression was used to estimate the association between parity and age at first birth in relation to the risk of developing GBC, EHCC, and AVC. Odds ratios (ORs) with 95% confidence intervals (95% CI) were calculated. Persons with one child and persons ≤ 22 years old at the birth of their first child were used as the reference categories, respectively. Two models were constructed: Model 1 included the matching variable age only. Model 2

was further adjusted for the level of education (categorized into four groups: elementary school, secondary school, university, or missing), country of birth (Sweden or outside Sweden), and comorbidities (yes or no). The included comorbidities were diabetes, alcohol abuse, tobacco smoking-related diseases, i.e. chronic obstructive pulmonary disease or peripheral vascular disease (see Appendix for included diagnosis codes, available online at http://www.informahealthcare.com). Due to a small number of cases with primary sclerosing cholangitis (one case of EHCC, no case of AVC, and seven cases of GBC), no adjustment was performed for primary sclerosing cholangitis.

To detect any influence of menopausal status, the analyses were stratified for age < 50 and ≥ 50 years at cancer diagnosis or index date. This cut-off represents a median age of menopause and is in agreement with previous studies [27,28]. As a result of a limited sample size of cases with EHCC and AVC, only the analysis for GBC is shown.

All analyses were performed with the SAS Statistical Package, version 9.2 (SAS Institute Inc, Cary, NC, USA).

Results

Study participants

Altogether, 1169 cases of GBC, 432 cases of EHCC, and 295 cases of AVC were identified. Mean age at

diagnosis was between 56 and 57 years. Some characteristics are shown in Table I. Female cases were more often multiparous and were younger at first birth compared to controls. A similar result was observed for men, however less prominent. Diabetes was more common in cases compared to controls in all groups.

Reproductive factors and GBC

Nulliparous women had a similar risk of GBC compared to women with one child (Table II). Increasing parity increased the risk of GBC (OR 2.06, 95% CI 1.68–2.51 for women with ≥ 3 children). Furthermore, older age at first birth decreased the risk of GBC (OR 0.54, 95% CI 0.41–0.70 for women ≥ 30 years of age at first birth). Whereas parity was not associated with GBC in women < 50 years at time of diagnosis, this risk was increased in women ≥ 50 years at the time of GBC diagnosis (Table III). Postmenopausal women diagnosed with GBC who had ≥ 3 children had a more than two-fold (OR 2.34; 95% CI 1.87–2.93) increased risk of GBC compared to uniparous postmenopausal women. Stratification for age at diagnosis did not change the estimates for age at first birth (Table III).

Men with three or more children had an increased risk for GBC, similar to what was observed in women (OR 1.70, 95% CI 1.20–2.40). However, in contrast to women, there was no decrease in the risk of GBC for men with increasing age at the birth of the first

Table I. Characteristics of cases of extra hepatic bile duct cancer (EHCC), cancer of ampulla of Vater (AVC) and gallbladder cancer (GBC) and matched controls.

	EHCC – women		AVC – women		GBC – women		EHCC – men		AVC – men		GBC – men	
	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)	Cases N (%)	Controls N (%)
Total	217	2170	115	1150	878	8238	215	2150	180	1800	291	2844
Risk factors												
Diabetes	17 (8)	46 (2)	11 (10)	27 (2)	43 (5)	145 (2)	24 (11)	77 (4)	21 (12)	66 (4)	23 (8)	78 (3)
Alcohol use	3 (1)	29 (1)	0 (0)	21 (2)	8 (1)	112 (1)	14 (7)	74 (3)	13 (7)	66 (4)	11 (4)	120 (4)
Smoking	5 (2)	33 (2)	3 (3)	16 (1)	18 (2)	105 (1)	10 (5)	51 (2)	10 (6)	33 (2)	6 (2)	105 (1)
Education												
Primary	61 (28)	679 (31)	40 (35)	374 (33)	303 (34)	2495 (30)	75 (35)	720 (33)	69 (38)	593 (33)	90 (31)	947 (33)
Secondary	70 (32)	646 (30)	36 (31)	397 (34)	281 (32)	2740 (33)	75 (35)	700 (33)	52 (9)	631 (35)	99 (34)	923 (33)
University	29 (14)	361 (17)	19 (17)	241 (21)	98 (11)	1489 (18)	25 (12)	403 (19)	26 (15)	329 (18)	38 (13)	523 (18)
Missing	57 (26)	484 (22)	20 (17)	138 (12)	196 (22)	1514 (19)	40 (18)	327 (15)	33 (18)	247 (14)	64 (22)	451 (16)
Birth country												
Not Sweden	21 (10)	292 (14)	15 (13)	165 (14)	95 (11)	1037 (13)	28 (13)	277 (13)	35 (19)	197 (11)	30 (10)	343 (12)
Number of children												
0	32 (15)	312 (14)	8 (7)	169 (14)	85 (10)	1094 (13)	42 (20)	382 (18)	40 (22)	362 (20)	53 (18)	527 (18)
1	37 (17)	585 (27)	24 (21)	306 (27)	162 (18)	2325 (28)	34 (16)	598 (28)	21 (12)	529 (29)	63 (22)	871 (31)
2	85 (39)	737 (34)	45 (39)	388 (34)	317 (36)	2736 (33)	70 (32)	699 (32)	73 (40)	531 (30)	91 (31)	819 (29)
≥ 3	63 (29)	536 (25)	38 (33)	287 (25)	314 (36)	2083 (26)	69 (32)	469 (22)	46 (26)	378 (21)	84 (29)	627 (22)
Age at first birth in years												
≤ 22	100 (46)	759 (35)	47 (41)	401 (35)	420 (48)	2917 (35)	44 (20)	323 (15)	32 (18)	236 (13)	48 (17)	433 (15)
23–29	66 (30)	863 (40)	44 (38)	436 (38)	306 (35)	3253 (40)	87 (40)	908 (42)	69 (38)	761 (42)	128 (44)	1248 (44)
≥ 30	19 (9)	236 (11)	16 (14)	144 (12)	67 (7)	974 (12)	42 (20)	535 (25)	39 (22)	441 (25)	62 (21)	636 (22)
No children	32 (15)	312 (14)	8 (7)	169 (15)	85 (10)	1094 (13)	42 (20)	384 (18)	40 (22)	362 (20)	53 (18)	527 (19)

Table II. Association of reproductive factors and risk of extra hepatic bile duct cancer (EHCC), cancer of ampulla of Vater (AVC) and gallbladder cancer (GBC) in men and women, expressed as odds rations (OR) and 95% confidence intervals (95% CI).

	EHCC OR (95% CI)*	AVC OR (95% CI)*	GBC OR (95% CI)*
Women			
Number of children			
0	1.40 (0.84–2.33)	0.47 (0.20–1.13)	1.00 (0.76–1.32)
1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
2	1.64 (1.09–2.46)	1.51 (0.88–2.60)	1.59 (1.30–1.94)
≥3	1.65 (1.07–2.55)	1.56 (0.89–2.73)	2.06 (1.68–2.51)
Age at first birth (years)			
≤22	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
23–29	0.60 (0.43–0.84)	0.97 (0.61–1.53)	0.71 (0.60–0.83)
≥30	0.61 (0.36–1.04)	0.86 (0.45–1.64)	0.54 (0.41–0.70)
Men			
Number of children			
0	1.87 (1.15–3.01)	2.42 (1.39–4.23)	1.26 (0.85–1.87)
1	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
2	1.78 (1.16–2.73)	3.32 (1.98–5.54)	1.43 (1.01–2.01)
≥3	2.57 (1.65–3.98)	2.77 (1.61–4.77)	1.70 (1.20–2.40)
Age at first birth (years)			
≤22	1.00 (Reference)	1.00 (Reference)	1.00 (Reference)
23–29	0.75 (0.50–1.11)	0.71 (0.45–1.13)	1.03 (0.72–1.48)
≥30	0.67 (0.42–1.06)	0.73 (0.44–1.23)	1.05 (0.69–1.59)

*Model is adjusted for diabetes, alcohol use, smoking, birth country and educational level.

Table III. Association of reproductive factors and risk of extra hepatic bile duct cancer (EHCC), cancer of ampulla of Vater (AVC), and gallbladder cancer (GBC) in cancer of ampulla Vater (AVC), and gallbladder cancer (GBC) in women and men stratified for age at cancer women and men stratified for age at cancer.

	GBC	
	<50 years OR (95% CI)*	≥50 years OR (95% CI)*
Women		
Number of children		
0	1.01 (0.58–1.76)	0.99 (0.72–1.37)
1	1.00 (Reference)	1.00 (Reference)
2	1.11 (0.72–1.71)	1.72 (1.37–2.16)
≥3	1.16 (0.73–1.84)	2.34 (1.87–2.93)
Age at first birth (years)		
≤22	1.00 (Reference)	1.00 (Reference)
23–29	0.65 (0.46–0.94)	0.72 (0.60–0.86)
≥30	0.46 (0.23–0.90)	0.55 (0.41–0.75)
Men		
Number of children		
0	0.85 (0.37–1.95)	1.39 (0.89–2.17)
1	1.00 (Reference)	1.00 (Reference)
2	0.97 (0.46–2.06)	1.55 (1.05–2.28)
≥3	1.12 (0.51–2.46)	1.86 (1.26–2.75)
Age at first birth (years)		
≤22	1.00 (Reference)	1.00 (Reference)
23–29	0.80 (0.40–1.60)	1.14 (0.75–1.75)
≥30	0.61 (0.24–1.51)	1.23 (0.76–1.98)

*Model is adjusted for diabetes, alcohol use, smoking, birth country and educational level.

child (Table II). When stratified for age at GBC diagnosis, the increased risk of parity and GBC remained unchanged among men diagnosed at ≥50 years, but no such association was found for men diagnosed <50 years (Table III). There was an inverse but not statistically significant association between age at the birth of the first child and GBC in men diagnosed <50 years of age (Table III).

Reproductive factors and EHCC

As presented in Table II, multiparous (2 children or more) women were at an increased risk of EHCC compared to uniparous women (OR 1.65, 95% CI 1.07–2.55 for women with ≥3 children). Childlessness also increased the risk of EHCC, but the effect was not statistically significant (OR 1.40, 95% CI 0.84–2.33). Older age at first birth suggested a decreased risk of EHCC (OR 0.60, 95% CI 0.43–0.84 for women aged 23–29 years old). A similar association was observed for women ≥30 years of age at first birth, but this association was not statistically significant (Table II).

All results were similar in men compared to women (Table II). Childlessness increased the risk of EHCC, similarly to women (OR 2.07, 95% CI 1.13–3.78).

Reproductive factors and AVC

The risk of AVC was increased, but not statistically significantly, comparing women with three or more children to women with one child (OR 1.56, 95% CI 0.89–2.73). Nulliparous women were at a seemingly reduced risk compared to uniparous women (OR 0.47, 95% CI 0.20–1.13). Older age at first birth indicated a slightly decreased risk (Table II).

There was a more pronounced increase in risk of AVC in men with more than one child compared to men with one child (OR 3.32, 95% CI 1.98–5.54 for men with two children; OR 2.77; 95% CI 1.61–4.77). Similarly to what was observed in women a decreased, but not statistically significantly, risk was observed with older age at birth of the first child (Table II).

Discussion

This large population-based study did find some support for a role of sex hormones in the etiology of GBC. However, based on the similar findings for both men and women regarding EHCC and AVC, this study does not support the hormonal hypothesis in the etiology of these cancers.

Strengths of the present study include a large sample size and the nationwide, population-based design,

counteracting random error and selection bias, respectively. Additionally, complete follow-up further minimizes information bias. The distinction between different tumor sites in the study is an important design characteristic because EHCC and AVC may different risk factors compared to GBC. Furthermore, exposure and outcome was recorded independently of one another, avoiding information bias. The Swedish Cancer Register may suffer from lack of coverage of BTC, as we have shown in a previous study [21]. However, it is unlikely that any systematic underreporting of BTC to the Cancer Register is related to parity or age at first birth. Thus, the resulting non-differential misclassification because of such underreporting will only attenuate the observed findings. Another limitation was the inability to control for factors such as age at menarche, use of hormone replacement therapy (HRT) or oral contraceptives and age at menopause, due to lack of this information. However, none of these factors would, reasonably, alter the findings in men. Additionally, the role of HRT and oral contraceptives in biliary tract cancer remains a matter of debate (29–32). Furthermore, there was no information on stillbirths, but the proportion of stillbirths in Sweden is low (1.7% in 1955 and 0.4% in 1985) and should therefore not affect the overall results considerably [33]. Lack of information of obesity represents an additional limitation to the study. A recent systematic review showed that high body mass index was a risk factor for GBC, but there was no difference between the sexes [34]. The same study failed to show an association of obesity and EHCC or AVC. Thus, it is not certain that differences in BMI between men and women accounts for the difference in results shown in the present study for women and men regarding GBC, however lack of information of body mass or obesity do represent an important limitation. In the present study, as in most register-based reports where potentially important information simply is not available, lack of information may introduce important limitations and should be considered before any conclusions are drawn from the results. In the present study, although the statistical analyses were adjusted for some potential confounders, such as diabetes and alcohol abuse, residual confounding by known or unknown factors cannot be ruled out and should be considered.

The rarity of BTC has limited the number of large epidemiological studies. Concerning the association with reproductive factors specifically, the available literature has provided shifting results. The present study is, by far, the largest study addressing this particular hypothesis and few previous studies have been population based. A previous Swedish study showed no clear association of parity or age at first birth with risk of EHCC, but a positive association with GBC [35]. A small Italian study, including 29 cases of GBC, found a positive association with parity but not with age at first birth [36]. Similar results were shown in a slightly larger Indian study [37]. A second Italian study, where tumor location was disregarded, reported a non-significant, positive association with parity but found no clear association of BTC and age at first birth [38]. However, in that study the age at first birth was dichotomized with a cut-off of 27 years of age, which make comparisons to our results dubious. An older study from Czechoslovakia used mortality in cancer as the outcome and showed an increased mortality in GBC with increasing parity [39]. A Norwegian study also addressed the association of parity and risk of BTC, but showed no effect [40]. An international, fairly large study showed a clear connection between reproductive factors and risk of GBC [41]. The results of our study are in agreement with a more recent study from China, demonstrating a positive association between reproductive factors and GBC, whereas no such effects were observed for EHCC [42]. An American study focusing on EHCC and AVC did not show any association between cancer risk and reproductive factors [43]. Additionally, the similar results for men, compared to women, in the present study indicates possible confounding by an unknown factor rather than a true hormonal effect in EHCC and AVC. The higher risk observed in men without children could reflect residual confounding by environmental factors in this group. The observed association for age at birth of the first child and GBC in women, but not in men suggests a possible association between hormonal factors and this cancer. Compared to the previous studies of BTC risk, the inclusion of men in a separate analysis allowed additional assessment of potential biological effects of sex hormones and effects of unknown confounding and is a novel aspect of this study providing interesting results. The previous literature combined with the results from our study supports a possible association of hormonal factors and GBC specifically, but not for BTC collectively.

We did observe a higher risk of GBC in postmenopausal, multiparous women compared to premenopausal, multiparous women. For age at first birth, however, there were no clear differences depending on menopausal status. Interestingly, when men were analyzed in the same manner, the results were similar to what was observed for women for parity. For age at the birth of the first child, men older than 50 years old seemed to have a reduced risk compared to men aged less than 50 years. These findings suggest a role of unknown confounding in the analysis of menopausal status and risk of GBC rather than a true biological effect.

We did not adjust for gallstone disease in the analyses. Gallstone disease is considered a risk factor

for BTC, but has been shown to be dependent on estrogen exposure [3,44]. Gallstone disease should rather be considered an important mediator, through which estrogen affects the biliary tree and potentially drives the oncogenic process, rather than a confounder. Adjusting for gallstone disease would disregard an important pathway of the potential oncogenic effects of estrogen on the biliary tree.

An increasing amount of literature is supporting the hypothesis that hormonal influences are important in BTC etiology and, in extension, the possibility of hormonally active treatment of BTC. In vitro data have demonstrated a presence of estrogen and progesterone receptors in BTC tissue and yet other studies have demonstrated an increased risk of BTC with estrogen receptor polymorphisms [45,46]. Furthermore, in vivo studies have shown reduced growth of BTC cell lines treated with anti-estrogenic substances [47]. A thorough understanding of the molecular mechanisms involved in BTC etiology is essential to devise the new treatment options desperately needed for these cancers. Hormonal factors are proving to be one aspect in which to invest more resources in future research, making the results of the present study and similar work an important foundation for future research.

In conclusion, this study suggests that reproductive factors are associated with GBC, supporting a possible hormonal mechanism in the etiology of this cancer. In contrast, the similar results in women and men for EHCC and AVC do not support the hormonal hypothesis. More detailed large population-based studies are needed to fully scrutinize the research question.

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Declaration of interest: The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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