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ORIGINAL ARTICLE

Exogenous estrogen and the risk of biliary tract cancer – a population-based study in a cohort of Swedish men treated for prostate cancer

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ABSTRACT

Background: To assess the role of exogenous estrogen in the etiology of biliary tract cancer, a nationwide population-based cohort study in Sweden was performed. **Methods**: The study included all men in Sweden with prostate cancer diagnosed in 1961–2008. Due to treatment standards, patients diagnosed in 1961–1980 were considered more exposed to estrogen, while those diagnosed in 1981–2008 were regarded less exposed. Standardized incidence ratios (SIRs) with 95% confidence intervals (CIs) were calculated to estimate the risk of biliary tract cancer in cohort members compared to the corresponding Swedish male population. **Results**: After 849 307 person-years of follow-up in 203 131 prostate cancer patients, there were 41 incident gallbladder cancers and 36 cancers of the extra-hepatic bile ducts. In overall, there were no apparent differences in the risk of gallbladder cancer or bile duct cancer between patients diagnosed in 1961–1980 and patients diagnosed in 1981–2008. However, in patients diagnosed in 1961–1980, there was a statistically non-significant increased risk of gallbladder cancer (SIR 1.34; 95% CI 0.71–2.29) and extra-hepatic bile duct cancer (SIR 1.20; 95% CI 0.55–2.28) >5 years of follow-up after the prostate cancer diagnosis. No such association was found for patients diagnosed in 1981–2008. Sensitivity analyses excluding prostate cancer patients exposed to potential confounding factors did not change the SIRs. **Conclusions**: Long exposure to high doses of exogenous estrogen might increase the risk of biliary tract cancer. However, any potential excess risk of bile duct cancer resulted by prolonged exposure to high doses of exogenous estrogen seems to be small.

Biliary tract cancer (BTC), including cancers of the extra-hepatic bile duct (EHCC), the ampulla of Vater (AVC) and the gallbladder (GBC), is a group of highly lethal tumors with poor five-year survival rates [1]. The etiology of BTC is insufficiently understood. Only a few risk factors have been established, including gallstone disease [2], primary sclerosing cholangitis [3], certain hepato-biliary infections [4], and diabetes [5].

A strong female predominance is an interesting characteristic of BTC, particularly in GBC where the female to male ratio ranges from 2.4 to 1 [6,7]. The mechanism behind this sex difference is unknown but it has been hypothesized that exposure to female sex hormones, such as estrogen, might increase this risk [8]. Previous epidemiologic studies addressing this hypothesis have mainly investigated reproductive factors or menstrual history in women, and it seems that high parity and young age at the first birth may increase the risk of BTC [8–12]. However, a recent study by our research group did not support this hypothesis for EHCC, but the role of sex hormones in the risk of GBC could not be ruled out [13].

If the female predominance of BTC, particularly GBC, is explained of estrogen exposure, medical treatment that increases the level of estrogen in males may also increase this risk. To test this hypothesis, we identified men treated for prostate cancer in Sweden; a group of patients exposed to high doses of exogenous estrogen. Between the years 1961 and 1980, high doses of estrogen was the mainstay of treatment regime, whereas treatment involved much lower estrogen doses after 1980 [14–16]. We assessed the risk of BTC in a cohort of men with prostate cancer compared to men in the entire corresponding Swedish population.

Materials and methods

Design

The design of this cohort study has been described previously [17]. Briefly, we conducted a retrospective, nationwide, population-based cohort study in Sweden between 1 January 1961 and 31 December 2008. The cohort consisted of all patients with histologically verified prostate cancer identified in the Swedish Cancer Register during the study period. The prostate cancer patients were identified by the diagnosis code 177 in the seventh version of the International Classification of

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Diseases (ICD-7). Only adenocarcinomas were included, defined by the histology code 096 from the C24 WHO classification of histology. This will minimize the risk of mistakenly detecting metastases of prostate cancer as new cases of BTC. The personal identity number, a 10-digit code uniquely identifying every Swedish resident, was used for record linkage to other nationwide registers, which enabled complete follow-up [18].

The outcome was histologically verified BTC assessed from the Cancer Register (ICD-7: 1551 for GBC and 1552–1553 for EHCC including AVC). Only adenocarcinomas were included (histology code 096) to ensure uniform tumor biology. Information on potential confounders was retrieved from the Swedish Patient Register. The entire Swedish male population resident in Sweden during the study period was used as reference. The Ethics Committee at Karolinska Institutet approved the study.

Data sources

The Swedish Cancer Register collects information of all newly diagnosed cancers in Sweden from 1958 and onwards. However, the register did not encompass the entire Swedish population until 1960; therefore follow-up of this study was restricted to the years after 1960. Both pathologists and clinicians are required to report all new cancer cases to the register, and the overall completeness is at least 96% but for BTC specifically, the coverage may be less complete [19,20].

The Swedish Cause of Death Register was started in 1952 and contains information on causes and dates of death in all deceased Swedish residents with a completeness of 99.2% [21].

The Swedish Patient Register started in large parts of Sweden 1964 and covers all inpatient hospital care since 1987 and all outpatient specialist care since 2001 in Sweden, and is of excellent overall quality [22]. The register contains information on discharge diagnosis codes and performed surgical procedures.

The Swedish Register of the Total Population contains information on age, sex and migration status of the entire Swedish population. This register was used to extract information on date of emigration among members of the prostate cancer cohort.

Statistical analysis

Standardized incidence ratios (SIR) with 95% confidence intervals (CIs) were calculated by computing the ratio of the observed to expected number of newly diagnosed BTC in the study cohort. The expected number of BTC patients was calculated by multiplying the observed number of person-years by age- and calendar-year specific incidence rates in the entire Swedish male population using five-year intervals. Person-years were calculated from the date of entry into the cohort, i.e. date of prostate cancer diagnosis, until 1) diagnosis date of BTC; 2) emigration; 3) death; or 4) end of the study period, whichever occurred first. The first year of follow-up was excluded to counteract detection bias, i.e. earlier detection of a BTC because of regular contacts with the health care during prostate cancer diagnosis and treatment.

We performed separate analyses for the sub-sites GBC and EHCC combined with AVC due to the potential differences in their etiology. In the analyses of GBC specifically, all cases with cholecystectomy (gallbladder removal) prior to the diagnosis of prostate cancer were excluded. Additionally, cohort members in the GBC analyses were censored at cholecystectomy.

Lastly, a sensitivity analysis was performed, in an attempt to evaluate the effect of potential confounding factors. Cohort members with obesity, diabetes, primary sclerosing cholangitis, alcohol abuse or gallstone disease without cholecystectomy were excluded from the sensitivity analysis.

Study cohorts

The clinical management of prostate cancer changed markedly over the study period. A high-dose estrogen regimen was the mainstay therapy during the decades preceding 1980 [14,16]. Bilateral orchiectomy (removal of the testicles) was also performed internationally, but did not have much support in Sweden [15]. Radical prostatectomy, external radiation therapy and other treatments replaced systemic estrogen treatment in the years following 1980, which was hardly used at all after the mid-1990s [23,24]. The analyses were stratified a priori into an *exposed* cohort (patients diagnosed between 1961 and 1980) and a *less exposed* cohort (patients diagnosed between 1981 and 2008) to account for the differences in estrogen exposure resulting from changes in prostate cancer therapy during the study period. To evaluate any dose-response associations, the analyses were stratified for the latency time between diagnosis of prostate cancer and BTC diagnosis ($>1-\leq5$ years or >5 years). Both groups were followed up until December 2008.

Results
Study population

A total of 203 131 prostate cancer patients constituted the final cohort, rendering 849 307 person-years at risk after excluding the first year of follow-up (Table 1). The *exposed* cohort consisted of 45 744 prostate cancer patients (22.5%) and the *less exposed* cohort consisted of 157 387 such patients (77.5%). For the GBC analysis, 196 063 prostate cancer patients remained after exclusion of 7068 individuals with prior cholecystectomy, rendering a total of 810 110 person-years at risk after excluding the first year of follow-up (Table 1). The median follow-up was 3.8 years for all outcomes and mean age at entry (the age at prostate cancer diagnosis) was 72 years.

Risk of GBC

Altogether, 41 cases of GBC were identified in the prostate cancer cohort, compared to 49.2 expected cases after excluding the first year of follow-up (SIR 0.82; 95% CI 0.60–1.13). In the *exposed* cohort, 17 cases of GBC were observed compared to the 19.5 expected (SIR 0.87; 95% CI 0.51–1.39) and in the *less exposed* cohort, 24 cases of GBC were observed compared to the 29.7 expected (SIR 0.81; 95% CI 0.52–1.21). The mean follow-up time was 3.9 years in the *exposed* cohort and 3.2 years in the *less exposed* cohort. Most of the prostate cancer patients were followed for more than five years (Table 1). After exclusion of prostate cancer patients with potential confounders, all point SIR estimates were decreased, but there

was no clear difference between the *exposed* and the *less exposed* groups (Table 2). In the latency time analysis, the decreased risk of GBC remained early after prostate cancer diagnosis in both groups. There was a statistically non-significant increased risk of GBC in the *exposed* group >5 years after the prostate cancer diagnosis (SIR 1.34, 95% CI 0.71–2.29). In the *less exposed group*, there were no differences in the risk of GBC comparing the early to the late follow-up periods (Table 3).

Risk of EHCC

In total, 36 cases of EHCC were observed compared to the 45.5 expected cases after excluding the first year of follow-up (SIR 0.79; 95% CI 0.55–1.10). In the *exposed* group, 13 cases of EHCC were observed compared to the 14.4 expected (SIR 0.91; 95% CI 0.48–1.55) and in the *unexposed* group, 23 cases of EHCC were observed compared to the 31.1 expected (SIR 0.74; 95% CI 0.47–1.11). The mean follow-up time was 4.0 years in the *exposed* cohort and 3.3 years in the *less exposed* cohort. Most of the prostate cancer patients were followed for more than five years (Table 1). The results did not change considerably after exclusion of cohort members without potential confounders (Table 2). In the latency time analysis, there was no clear difference in risk between the two exposure level groups during the early follow-up. There was a statistically, non-significant increased risk of EHCC in the *exposed* group >5 years after the prostate cancer diagnosis (SIR 1.20, 95% CI 0.55–2.28).

Discussion

This population-based cohort study was designed to assess the role of exogenous estrogen in the development of BTC among men. The results indicate a possible role of exogenous sex hormones in the development of BTC after prolonged estrogen exposure.

Methodological strengths of this study include the population-based design and the large size of the cohort that counteract selection bias and random errors, respectively. Moreover, the availability of data from high quality, nationwide registers enabled a complete follow-up of all cohort members, which otherwise often constitutes a major concern in large cohort studies. The Swedish Cancer Register may suffer from limited coverage concerning BTC specifically, but the coverage should not be related to prostate cancer treatment and the effect of any such non-differential bias would thus only dilute results. There are, however, some limitations that need to be discussed. The lack of information about the specific estrogen exposure of individual cohort members may introduce exposure misclassification. However, the assumption that prostate cancer patients were exposed to estrogens, particularly during 1961–1980 is scientifically sound because the treatment of choice for prostate cancer between 1960 and 1980 in Sweden was estrogen treatment, typically continued until death. Orchiectomy, which was the predominating alternative treatment, did not gain much popularity in

Table 1. Characteristics of the cohort of Swedish men with prostate cancer between 1961 and 2008.

	Gallbladder cancer	Extra-hepatic bile ducts[a]
Number of individuals, total cohort	196 063	203 131
Number of individuals, early cohort	45 263	45 744
Number of individuals, late cohort	150 800	157 387
Median time of follow-up in years, total cohort (IQR)	3.8 (1.6–7.1)	3.8 (1.7–7.2)
Median time of follow-up in years, early cohort (IQR)	3.2 (1.1–7.3)	3.3 (1.1–7.4)
Median time of follow-up in years, late cohort (IQR)	3.9 (1.8–7.1)	4.0 (1.8–7.2)
Person-years at risk	988 153	1 034 078
Mean age at prostate cancer (standard deviation)	72 (8.7)	72 (8.7)
Mean age at biliary tract cancer diagnosis (range)	77 (63–90)	80 (65–89)

[a]Extra-hepatic bile ducts also included cancer of the ampulla of Vater.
IQR: inter-quartile range.

Table 3. Standardized incidence rates (SIR) with corresponding 95% confidence intervals (CIs) for gallbladder cancer and extra-hepatic bile ducts[a] in a cohort of Swedish men with prostate cancer by latency interval.

Sub-group	Time period	Latency time (years)	Observed	Expected	SIR (95% CI)
Gall bladder					
	1961–1980	>1–5	4	9.8	0.41 (0.11–1.04)
		>5	13	9.7	1.34 (0.71–2.29)
	1981–2008	>1–5	15	18.4	0.81 (0.46–1.34)
		>5	9	11.3	0.80 (0.36–1.52)
Extra-hepatic bile ducts					
	1961–1980	>1–5	4	5.6	0.71 (0.19–1.83)
		>5	9	7.5	1.20 (0.55–2.28)
	1981–2008	>1–5	13	15.1	0.86 (0.46–1.47)
		>5	10	12.7	0.78 (0.38–1.44)

[a]Extra-hepatic bile ducts also included cancer of the ampulla of Vater.

Table 2. Standardized incidence rates (SIR) with corresponding 95% confidence intervals (CIs) for gallbladder cancer and extra-hepatic bile ducts[a] in a cohort of Swedish men with prostate cancer between 1961 and 2008.

Cancer	Time period	Number of observed cases	Number of expected cases	SIR (95% CIs)	Sensitivity analysis[b] SIR (95% CIs)
Gallbladder					
	1961–2008	41	49.2	0.83 (0.60–1.13)	0.67 (0.44–0.97)
	1961–1980[c]	17	19.5	0.87 (0.51–1.39)	0.63 (0.31–1.13)
	1981–2008	24	29.7	0.81 (0.52–1.21)	0.69 (0.40–1.11)
Extra-hepatic bile ducts					
	1961–2008	36	45.5	0.79 (0.55–1.10)	0.73 (0.48–1.06)
	1961–1980[c]	13	14.4	0.91 (0.48–1.55)	0.80 (0.39–1.48)
	1981–2008	23	31.1	0.74 (0.47–1.11)	0.69 (0.40–1.10)

[a]Extra-hepatic bile ducts also included cancer of the ampulla of Vater;
[b]Cases with gallstone disease who did not undergo cholecystectomy or had diabetes, obesity, alcohol abuse or primary sclerosing cholangitis prior to prostate cancer diagnosis were excluded;
[c]More exposed to estrogen.

Sweden during this period. In the decades following 1980, the treatment of prostate cancer became more heterogeneous, including prostatectomy, radiotherapy and most notably androgen receptor blockers [15]. Thus, analogous to two previous studies from our group using a similar design, the analyses were stratified for these two time periods to account for this factor [25,26]. Another potential shortcoming of our study was the lack of adjustment for potential confounding factors. However, the sensitivity analysis excluding cohort members exposed to potential confounding factors did not alter the results considerably and there were no clear differences between the two different exposure categories. However, a potential effect of residual confounding cannot be completely ruled out.

The main analyses showed no increased risk estimates of BTC among men with prostate cancer compared to the background population, but rather a non-significant risk reduction. The reason for this is unknown, but given the relatively short mean follow-up of prostate cancer patients in the present study, there is a possibility that the estrogen exposure in the cohort was too short to be a significant element in the oncogenic process of BTC. This hypothesis is somewhat supported by the results in the latency time analyses where a decreased risk estimate of BTC in cases prostate cancer patients with a short latency time was observed. However, a marginally increased, albeit not statistically significant, risk of BTC was observed in the more exposed group with longer latency time, i.e. the group with the highest estrogen exposure. It is conceivable that estrogen exposure needs to be prolonged to significantly impact biliary tract carcinogenesis. The follow-up time did not differ between the different exposure groups, and should thus not be an important limitation. These results may indicate that prolonged exposure to exogenous estrogen in males may in fact increase the risk of BTC development. However, given the overlapping CIs between the two exposure groups, despite diverging point estimates, an effect of confounding or chance cannot be completely ruled out.

A reduced risk of GBC in prostate cancer patients has been reported previously [27]. As prostate cancer was suggested to be an androgen-driven disease, it was suggested that exposure to high levels androgens in prostate cancer patients might protect against the development of BTC. However, recent studies have failed to demonstrate any clear associations between high levels of male sex hormone levels and prostate cancer [28]. In this study, the main analyses showed that prostate cancer patients might have a lower risk of BTC compared to men without prostate cancer. This suggests that some common factor in men with prostate cancer may protect them against the development of BTC. This finding is interesting and further studies are warranted to assess the biological explanation of the observed association between prostate cancer and BTC.

The role of estrogens in the etiology of BTC has been debated over the past years. Most epidemiological studies assessing the association of endogenous estrogen and BTC have found that factors associated with prolonged exposure to estrogen, i.e. high parity, younger age at birth of the first child, younger age at menarche, increase the risk of BTC [8,9,12].

A recent report from our group demonstrated that the picture is somewhat more complicated, but that the risk of gallbladder cancer specifically may be affected by endogenous estrogen exposure [13]. To our knowledge, no previous study has investigated the association between exogenous estrogen exposure and BTC in males, making this report novel in that regard.

In conclusion, this population-based, nationwide, cohort study examined the hypothesis that exogenous estrogen exposure increases the risk of BTC in a new model of prostate cancer patients. The results indicated a possibly increased risk of BTC in men with prolonged exogenous estrogen exposure. However, any potential excess risk of BTC by prolonged exposure to exogenous estrogen seems to be small.

Disclosure statement

Funding information

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