Androgen Receptor CAG Repeat Length and Risk of Biliary Tract Cancer and Stones

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Abstract

Biliary tract cancers, encompassing cancers of the gallbladder, extrahepatic bile ducts, and ampulla of Vater, are rare but highly fatal. Gallstones represent the major risk factor for biliary tract cancer, and share with gallbladder cancer a female predominance and an association with reproductive factors and obesity. Although estrogens have been implicated in earlier studies of gallbladder cancer, there are no data on the role of androgens. Because intracellular androgen activity is mediated through the androgen receptor (AR), we examined associations between AR CAG repeat length [(CAG)n] and the risk of biliary tract cancers and stones in a population-based study of 331 incident cancer cases, 837 gallstone cases, and 750 controls from Shanghai, China, where the incidence rates for biliary tract cancer are rising sharply. Men with (CAG)n >24 had a significant 2-fold risk of gallbladder cancer [odds ratio (OR), 2.00; 95% confidence interval (CI), 1.07-3.73], relative to those with (CAG)n ≤ 22. In contrast, women with (CAG)n >24 had reduced gallbladder cancer risk (OR, 0.69; 95% CI, 0.43-1.09) relative to those with (CAG)n ≤ 22; P interaction sex = 0.01, which was most pronounced for women aged 68 to 74 (OR, 0.48; 95% CI, 0.25-0.93; P interaction age = 0.02). No associations were found for bile duct cancer or gallstones. Reasons for the heterogeneity of genetic effects by gender and age are unclear but may reflect an interplay between AR and the levels of androgen as well as estrogen in men and older women. Further studies are needed to confirm these findings and clarify the mechanisms involved.

Introduction

Biliary tract cancers, encompassing cancers of the gallbladder, extrahepatic bile duct, and ampulla of Vater, are rare but highly fatal (1). Gallstones represent a major predisposing factor, especially for gallbladder cancer, the most common type of biliary cancer (1, 2). Gallstones and gallbladder cancer are twice as common in women as in men (1, 2), and it is thought that sex hormones, in particular estrogens, may explain part of their female excess (1). In females, both gallbladder cancer and gallstones have been linked to reproductive factors, including parity, age at menarche, and age at menopause, providing support for an etiologic role for estrogens (1). Bile duct cancers, which are slightly more common in men, seem more related to smoking and inflammatory processes (1, 2), and any hormonal involvement is unclear.

Intracellularly, sex hormone activity is mediated through the androgen receptor (AR) as well as the estrogen receptors (ESR1 and ESR2; ref. 3). We recently showed that variation in ESR1 and ESR2 genes is associated with cancers of the bile duct and ampulla of Vater;11 yet there are currently no reports on the association between biliary tract cancers and variation in the AR gene.

After binding androgen, the AR-hormone complex regulates the transcription of androgen-responsive genes (4). The AR gene, present on the X chromosome, contains a highly polymorphic CAG repeat that normally varies between 9 and 37 repeats in length (5). CAG length [(CAG)n] is inversely associated with the transcriptional activity

Note: Supplementary data for this article are available at Cancer Epidemiology, Biomarkers & Prevention Online (http://cebp.aacrjournals.org/).

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of the AR such that having longer (CAG)$_n$ reduces the transcriptional activity of the AR and subsequent intracellular androgenic activity (5, 6). (CAG)$_n$ greater than ~37 repeats in length is associated with pathologic conditions related to reduced androgenicity such as gynecomastia and ineffective spermatogenesis (5). Although AR (CAG)$_n$ has been associated with the risk of hormone-related cancers, such as breast and prostate cancers (7, 8), there is no data on (CAG)$_n$ and biliary tract cancers. In this report, we examined the association between (CAG)$_n$ and the risk of biliary tract cancers and stones in a population-based case-control study from Shanghai, China to further clarify the etiologic role of sex hormones on biliary tract cancers.

Materials and Methods

Study Population

Details of the study have been described elsewhere (9). Briefly, incident cancers were ascertained from 38 hospitals in Shanghai, China with >95% capture of cases during the study period. Cases were confirmed using histology and imaging results. Gallstone cases were frequency-matched to cancer cases on age, sex, and hospital and were confirmed using medical records, pathology reports, and imaging data. Subjects without cancer were randomly selected from the Shanghai Resident Registry and were frequency-matched to cases on age, sex, and hospital histology and imaging results. Within 3 mo of the primary interview, 5% of subjects were randomly selected for re-interview; reproducibility was >90%.

Data Collection

Information on demographic characteristics, smoking, drinking, medical history, and reproductive history was collected within 3 wk of case diagnosis. Trained nurses measured height and weight, and collected fasting blood samples. Participation was 95% for cases and 82% for controls. Within 3 mo of the primary interview, 5% of subjects were randomly selected for re-interview; reproducibility was >90%.

Genotyping

(CAG)$_n$ was chosen because of its known functional effect on AR transcriptional activity (6). For genotyping, we used an automated fragment analysis method described elsewhere (10, 11). Briefly, DNA samples were amplified by PCR before automated fragment analysis on an ABI Prism Model 310 Genetic Analyzer. Samples were run on a capillary containing POP-4 polymer and the data were analyzed with GeneScan analysis software, version 2.0.2. The accuracy of the automated fragment analysis method was confirmed by direct sequencing (11). In all quality control samples, sequencing confirmed the (CAG)$_n$ by automated fragment analysis. In this study, reproducibility across 20 aliquots of five samples was >90%.

Statistical Methods

Body mass index (kg/m$^2$) was categorized using WHO classification for obesity in Asians. Age at menarche was categorized into tertiles based on the distribution among controls. Distributions of putative risk factors including age, sex, smoking, drinking, hypertension, diabetes, gallstones, and body mass index, as well as parity, menopausal status, and age at menarche among women by case-control status are presented in Supplementary Table S1.

Because one copy of the X chromosome is randomly inactivated in female cells such that women generally have a 50:50 expression of the paternal/maternal X chromosomes (12), we used the biallelic mean for (CAG)$_n$ in women. Distributions of (CAG)$_n$ allele frequencies by case status were plotted for men and women separately and overlaid with smoothed kernel densities. Tertiles of (CAG)$_n$ were defined based on the distribution among controls ($\leq$22, 22-24, >24). Odds ratios (OR) and 95% confidence intervals (CI) were estimated from unconditional logistic regression models minimally adjusted for age and sex and from models fully adjusted for risk factors (Supplementary Table S1). Linear trends in genetic effects across tertiles were evaluated using the Wald $P$ for trend. Bile duct cancer cases were compared with all controls (n = 750), gallbladder cancer cases with controls without cholecystectomy (n = 704), and gallstone cases with controls without stones (n = 562). Heterogeneity of genetic effects by factors listed in Supplementary Table S1 was evaluated using the likelihood ratio test.

Results

The mean (CAG)$_n$ in controls was 23.1 (range, 8-33), with a similar distribution among men and women. Among cases, the means of (CAG)$_n$ were 23.1, 23.5, and 23.2 for gallbladder cancer, bile duct cancer, and gallstones, respectively. Male gallbladder cancer cases and controls had a bimodal (CAG)$_n$ distribution (Fig. 1A), but there was no significant difference in mean or median (CAG)$_n$ (data not shown). In women, there was no difference in the continuous distribution of (CAG)$_n$ between cases and controls (Fig. 1B), but an inverse association of borderline significance was seen when (CAG)$_n$ was categorized as tertiles ($P$ trend = 0.09; Table 1). Specifically, women with (CAG)$_n$ >24 had reduced gallbladder cancer risk (OR, 0.69; 95% CI, 0.43-1.09), relative to those with (CAG)$_n$ <23. In contrast, men with (CAG)$_n$ >24 had significantly increased gallbladder cancer risk (OR, 2.00; 95% CI, 1.07-3.73), relative to those with (CAG)$_n$ <23, and a significant linear trend ($P$ trend = 0.04; Table 1). Heterogeneity of genetic effects by gender was statistically significant ($P$ interaction = 0.01). There were no case-control differences in the distribution of (CAG)$_n$ for bile duct cancer or gallstones using (CAG)$_n$ as a continuous variable or in tertiles (Supplementary Figs. S1A-S2B; Table 1). Further adjustment for factors in Supplementary Table S1 did not materially change results (data not shown).
We found a significant interaction between (CAG)$_n$ and tertiles of age in women ($P$ interaction = 0.02) but not in men. The interaction between (CAG)$_n$ and age in women was also apparent using age modeled as quartiles ($P$ interaction = 0.01) and as a continuous variable ($P$ interaction = 0.10). There was an inverse association between (CAG)$_n$ and gallbladder cancer risk among women in the oldest age group (68-74 years; $P$ trend = 0.02), but not in the younger age groups. Older women with (CAG)$_n$ >24 had a reduced risk of gallbladder cancer (OR, 0.48; 95% CI, 0.25-0.93) relative to those with (CAG)$_n$ <23 (Table 2). The age interaction persisted after adjustment for parity, body mass index, and menopausal status (data not shown). There were too few cases of

**Figure 1.** A, distribution of AR CAG repeat allele frequencies by gallbladder cancer case-control status in men. One case with an extreme value of AR CAG repeat length 50 was excluded from the plot in males. Only controls without cholecystectomy are included. B, distribution of AR CAG repeat allele frequencies by gallbladder cancer case-control status in women. The biallelic mean AR (CAG)$_n$ is reported among women; only controls without cholecystectomy are included.
gallbladder cancer among premenopausal women ($n = 14$) to test the potentially more biologically relevant interaction between menopausal status and tertiles of (CAG)$_n$. However, the interaction between (CAG)$_n$ and age persisted in postmenopausal women ($P$ interaction = 0.03 for tertiles of age). Heterogeneity of genetic effects by the other factors in Supplementary Table S1 was not statistically significant.

**Discussion**

In this population-based study, we showed that longer AR (CAG)$_n$ is associated with increased gallbladder cancer risk in men but reduced risk in women, especially those at older ages. In contrast, no association was found between (CAG)$_n$ and bile duct cancer or gallstones.

Confounding by putative risk factors (Supplementary Table S1) is unlikely to explain our findings because adjustment did not materially change the effect. It is also unlikely that genotyping errors could explain our findings because the genotyping method used in the study was validated against sequencing results with good concordance (11). Furthermore, the (CAG)$_n$ distribution in our subjects was similar to the distribution in a previous study in Shanghai males using direct sequencing (13). Measurement of (CAG)$_n$ in women is more complex because only one copy of the AR is expressed (12), leading to a 50:50 paternal/maternal AR copy expression (14). Using the mean of two CAG repeats might not have captured the true expression of AR in women. Such measurement error, if any, would bias the association toward the null and would not explain the opposite effects in men and women. Furthermore, we saw a similar reduction in gallbladder cancer risk in older women across (CAG)$_n$ tertiles using the shorter or longer copy of (CAG)$_n$ (data not shown).

Given the known association between longer (CAG)$_n$ and reduced AR transcriptional activity (6), the lower risk associated with longer (CAG)$_n$ in women suggests that lower intracellular androgenic activity decreases gallbladder cancer risk in older women. Longer (CAG)$_n$ has been linked with lower testosterone levels in both premenopausal and postmenopausal women in some (15-17) but not all (18-20) studies. Lower testosterone

| Table 1. OR and 95% CIs for biliary tract cancer and stones in relation to AR CAG repeat length |
|---------------------------------|-----------------|-----------------|-----------------|-----------------|-----------------|
|                                | Total n         | AR (CAG)$_n < 23^*$ n | AR (CAG)$_n = 23-24^*$ n | AR (CAG)$_n > 24^*$ n | P for trend†     |
|                                |                 | OR‡               | OR (95% CI)‡         | OR (95% CI)‡         |                 |
| Men and women                  |                 |                  |                  |                  |                 |
| Control set 1§                 | 750             | 288              | 260              | 195              | 202             |
| Control set 2†                 | 704             | 269              | 240              |                  | 159             |
| Control set 3¶                 | 562             | 211              | 192              |                  |                  |
| Gallbladder cancer             | 215             | 90               | Reference        | 59               | 0.68 (0.46-0.99)| 66               | 0.99 (0.69-1.44)| 0.83             |
| Bile duct cancer               | 116             | 42               | Reference        | 38               | 1.15 (0.71-1.85)| 36               | 1.31 (0.81-2.14)| 0.27             |
| Gallstones                     | 837             | 317              | Reference        | 273              | 0.91 (0.70-1.18)| 247             | 1.05 (0.80-1.38)| 0.77             |
| Men                            |                 |                  |                  |                  |                 |
| Control set 1§                 | 293             | 131              | 84               |                  | 78              |
| Control set 2†                 | 281             | 128              | 77               |                  | 76              |
| Control set 3¶                 | 242             | 105              | 70               |                  | 67              |
| Gallbladder cancer             | 58              | 23               | Reference        | 8                | 0.58 (0.25-1.37)| 27               | 2.00 (1.07-3.73)| 0.04             |
| Bile duct cancer               | 70              | 30               | Reference        | 20               | 1.04 (0.56-1.96)| 20               | 1.13 (0.60-2.12)| 0.72             |
| Gallstones                     | 313             | 130              | Reference        | 80               | 0.92 (0.61-1.40)| 103             | 1.26 (0.84-1.88)| 0.30             |
| Women                          |                 |                  |                  |                  |                 |
| Control set 1§                 | 457             | 157              | 176              |                  | 124             |
| Control set 2†                 | 423             | 141              | 163              |                  | 119             |
| Control set 3¶                 | 320             | 106              | 122              |                  | 92              |
| Gallbladder cancer             | 157             | 67               | Reference        | 51               | 0.66 (0.43-1.01)| 39               | 0.69 (0.43-1.09)| 0.09             |
| Bile duct cancer               | 46              | 12               | Reference        | 18               | 1.35 (0.63-2.89)| 16               | 1.66 (0.75-3.64)| 0.21             |
| Gallstones                     | 524             | 187              | Reference        | 193              | 0.88 (0.63-1.23)| 144             | 0.92 (0.64-1.32)| 0.61             |

*AR (CAG)$_n$ tertiles based on the distribution among all controls for one allele in men and the mean of two alleles in women.
†P for trend is based on a Wald test for the linear trend in effect across tertiles of AR (CAG)$_n$.
‡Adjusted for age and sex.
§All controls used for comparison with bile duct cancer cases.
∥Controls without cholecystectomy used for comparison with gallbladder cancer cases.
¶Controls without gallstones used for comparison with gallstone cases.
levels have also been noted in women treated with AR antagonists (21-24). Together, these data suggest that androgenic activity may play a role in gallbladder cancer in women, although estrogens have long been implicated in the etiology of gallbladder cancer due to the higher rates in women and the association between gallbladder cancer and reproductive factors (1). The observation that (CAG)n is associated with gallbladder cancer risk in women does not seem to implicate estrogen directly because there does not seem to be a correlation between (CAG)n and estrogen levels in women (15, 17), and because there does not seem to be a correlation between (CAG)n and age on gallbladder cancer risk persisted among postmenopausal women who generally have lower estrogen levels than men (25). However, because we do not have measurements of serum testosterone or estrogen levels in our study, it is difficult to tease out whether the observed association is related to reduced androgenic activity or the imbalance of estrogen and androgen.

The decreased gallbladder cancer risk associated with lower androgenic activity or imbalance of estrogen and androgen is biologically plausible because androgens are involved in regulating cell cycle control and differentiation in hormone-responsive tissues (26), which are likely to include the gallbladder (1). Furthermore, our recent finding that variants in the CYP19A1 gene, encoding aromatase that converts androgen to estrogen (27, 28), are associated with gallbladder cancer risk (29), further suggests that an imbalance of androgens and estrogens may be involved in gallbladder cancer.

In contrast with women, the positive association between gallbladder cancer risk and (CAG)n in men suggests that, in men, lower intracellular androgenic activity may increase the risk of gallbladder cancer. The divergent results in men and women may seem paradoxical at first, but is consistent with the apparent sex-specific differences in the relationship between (CAG)n and testosterone levels in men and women, and the hypothesis that androgen-estrogen imbalance may also have a role in gallbladder cancer pathogenesis. Contrary to the relationship in women, some (30-33), but not all (34-38) studies have shown that (CAG)n is positively correlated with levels of testosterone in men, and clinical studies show a clear increase in testosterone levels in men treated with AR antagonists (39). Currently, the positive correlation between (CAG)n and serum androgen levels is thought to be part of a feedback loop to compensate for lower AR-mediated androgenic activity in men with longer (CAG)n (refs. 30, 31). Although longer (CAG)n has been associated with increased estrogen levels in men in two studies (31, 34), most studies have not shown a correlation between estrogen levels and (CAG)n in men (30, 35, 37, 38). Thus, similar to the results in women, our results in men provide further support for a possible role of androgens in gallbladder cancer. However, a full understanding of the divergent direction of association between AR (CAG)n and risk of gallbladder cancer in men and women will require a prospective study with sufficient size and measurements of serum androgen and estrogen as well as their respective receptors to clarify the specific contribution of androgens, estrogen, and imbalance of estrogen and androgen in gallbladder cancer etiology.

Our null finding for bile duct cancer is not unexpected because risk is not as closely related to gallstones, reproductive factors, and obesity (1, 2). However, we found

<p>| Table 2. ORs and 95% CIs for gallbladder cancer in relation to AR CAG repeat length by tertiles of age in women |
|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|---------------------------------------------------------------|
| Total | AR (CAG)n &lt;23* | AR (CAG)n 23-24* | AR (CAG)n &gt;24* | P for trend† |</p>
<table>
<thead>
<tr>
<th>n</th>
<th>OR</th>
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<th>OR (95% CI)</th>
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<tbody>
<tr>
<td>Age, 34-61</td>
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<tr>
<td>Controls†</td>
<td>129</td>
<td>42</td>
<td>Reference</td>
<td>56</td>
<td>0.70 (0.30-1.61)</td>
<td>31</td>
<td></td>
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<tr>
<td>Gallbladder cancer</td>
<td>40</td>
<td>15</td>
<td>Reference</td>
<td>14</td>
<td>0.99 (0.40-2.46)</td>
<td>0.92</td>
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<tr>
<td>Age, 62-67</td>
<td></td>
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<tr>
<td>Controls†</td>
<td>125</td>
<td>51</td>
<td>Reference</td>
<td>45</td>
<td>0.70 (0.25-2.01)</td>
<td>0.80</td>
<td></td>
</tr>
<tr>
<td>Gallbladder cancer</td>
<td>43</td>
<td>15</td>
<td>Reference</td>
<td>22</td>
<td>1.66 (0.77-3.59)</td>
<td>6</td>
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<tr>
<td>Age, 68-74</td>
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<tr>
<td>Controls†</td>
<td>169</td>
<td>48</td>
<td>Reference</td>
<td>62</td>
<td>0.31 (0.15-0.64)</td>
<td>22</td>
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<tr>
<td>Gallbladder cancer</td>
<td>74</td>
<td>37</td>
<td>Reference</td>
<td>15</td>
<td>0.48 (0.25-0.93)</td>
<td>0.02</td>
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NOTE: P interaction for tertiles of AR (CAG)n and age for women were as follows: P = 0.10 for continuous age, P = 0.01 for quartiles of age, and P = 0.02 for tertiles of age. Results are shown for tertiles of age because the number of cases by (CAG)n tertiles within quartiles of age were too small for valid estimates.

AR (CAG)n tertiles based on the distribution among all controls for one allele in men and the mean of two alleles in women.‡
P for trend is based on a Wald test for the linear trend in effect across tertiles of AR (CAG)n.†

Population controls without cholecystectomy.

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that ESR variation is associated with bile duct cancer in a previous report, so our null finding should be confirmed. The lack of association between (CAG), and gallstones is surprising because gallstones are closely related to the pathogenesis of gallbladder cancer (1). This finding suggests that androgenic activity may contribute to gallbladder cancer risk through mechanisms independent of stones.

The strengths of this study include its relatively large size and the population-based design with validation procedures designed to minimize misclassification of exposure and outcome. Limitations are the case-control design and lack of information on circulating hormones, which is needed to understand the individual and combined effects of sex hormones and nuclear receptors.

In summary, our population-based case-control study showed that (CAG), was positively associated with gallbladder cancer risk in men but inversely associated with gallbladder cancer in older women. The gender differences may reflect interactions between AR-influenced androgenic activity and circulating levels of sex hormones. The findings should inform prospective studies into the role of sex hormones and genetic modifiers in the etiology of biliary tract cancer and stones.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

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