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Family history of cancer and risk of biliary tract cancers: results from the Biliary Tract Cancers Pooling Project

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These co-first authors contributed equally to this manuscript.

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

Background—Although some familial cancer syndromes include biliary tract cancers (BTCs) (cancers of the gallbladder, intrahepatic and extrahepatic bile ducts, and ampulla of Vater), the few studies that have examined the relationships between family history of cancer (FHC) and BTCs have reported inconclusive findings. The objective of this study was to investigate the associations of FHC with risk of BTC in the Biliary Tract Cancers Pooling Project (BiTCaPP).

Methods—We used Cox proportional hazards regression models to estimate HRs and 95% confidence intervals for associations between FHC (any, 1st degree, in female relative, in male relative, relative with gastrointestinal cancer, and relative with hormonally-related cancer) and BTC risk by anatomic site within the biliary tract, adjusting for sex and race/ethnicity. Sensitivity analyses were conducted that restricted to studies reporting cholecystectomy data and to people without a history of cholecystectomy.

Results—Data on FHC were available from 12 prospective studies within BiTCaPP, which collectively contributed 2,246 cases (729 gallbladder, 345 intrahepatic and 615 extrahepatic bile duct, and 385 ampulla of Vater cancers) with 21,706,107 person-years of follow-up. A marginal, inverse association between FHC and gallbladder cancer was driven to the null when analysis was restricted to studies reporting cholecystectomy data and to people without a history of cholecystectomy. FHC was not associated with risk of BTC at the other anatomic sites.

Conclusions—These findings do not support an association between FHC and BTCs.

Impact—In a study of 1.5 million people, FHC is not a risk factor for BTCs.

Keywords
Biliary Tract; Cancer; Family History; Risk; Pooling Project

Introduction

Biliary tract cancers (BTCs), including gallbladder (GBC), intrahepatic (IHBDC) and extrahepatic (EHBDC) bile duct, and ampulla of Vater (AVC) cancers, have a poor prognosis (1). Previous studies found associations of familial cancer syndromes (familial adenomatous polyposis, Lynch syndrome, neurofibromatosis type 1) with BTC risk, suggesting they may have a heritable component (2).

While some studies suggest a higher risk of BTCs among individuals with a family history of cancer (FHC) compared to people without a FHC, most studies examined BTCs combined (3) or only at one anatomic site (4–6) or had small numbers of cases (3, 5–8). Also, it is unknown whether family history of gastrointestinal or hormonally-dependent cancers is associated with BTCs. We investigated associations of type of FHC with risk of BTC by anatomic site.
Materials and Methods

The Biliary Tract Cancers Pooling Project (BiTCaPP) combines data from 28 prospective studies involving over 2.8 million people. The National Cancer Institute has Office of Human Subjects Research Protection exemption for BiTCaPP. Contributing studies received institutional review board approval prior to data collection; participants gave written informed consent.

FHC was available from 12 BiTCaPP studies (Table 1) and was harmonized as: any FHC, first degree FHC, cancer history in a female relative, cancer history in a male relative, family history of gastrointestinal cancers (colorectum, esophagus, small intestine, stomach, liver, biliary tract, pancreas), and family history of hormonally-related cancers (breast, ovarian, prostate, endometrial/uterine). Exclusions were prevalent disease at baseline, missing person time, age at baseline, or case/non-case status and age <18 years at baseline.

Relationships between FHC and baseline characteristics were examined using $\chi^2$ tests for categorical variables and t-tests for continuous variables. We used Cox proportional hazards regression models with age as the time scale and left truncation at recruitment to estimate HRs and 95% confidence intervals (CI) for associations between FHC and BTCs, adjusting for sex and race/ethnicity, with baseline hazard stratified by study. Analyses were repeated restricting to studies reporting cholecystectomy and to people without a history of cholecystectomy. To address concerns that FHC may be associated with history of cholecystectomy, and thereby bias results toward the null, we evaluated these relationships using logistic regression adjusting for baseline age, sex, and race/ethnicity. All tests were two-sided ($\alpha=0.05$) and conducted using SAS software (Version 9.3, Cary, NC).

Results

Data were available for over 1.5 million people (58% of BiTCaPP) and 21,706,107 person-years (Table 1). Participants averaged 60 years-old at baseline and were mostly non-Hispanic white with slightly more women than men (Table 1). Compared with people without a FHC, people with a FHC were more likely to be women (59 vs. 53%, $P<0.0001$) and non-Hispanic white (87 vs. 79%, $P<0.0001$) and to have a college education (68 vs. 60%, $P<0.0001$). Differences in baseline age [mean (standard deviation) for with FHC vs. without FHC, $P$-value: 61 (8) vs. 60 (9), $<0.0001$] and history of diabetes or gallstones (with FHC vs. without FHC, $P$-value: 8 vs. 9%, $<0.0001$ for diabetes and 10 vs. 9%, $<0.0001$ for gallstones) between people with and without any FHC were statistically significant, but too small to be clinically meaningful. People with any FHC more frequently reported a cholecystectomy history [odds ratio (95% CI): 1.20 (1.18-1.21)].

FHC was not associated with IHBDC or EHBDC (Table 2). FHC was marginally, inversely associated with overall GBC, but the association was null after restricting to people who had not had a cholecystectomy. Having a relative with a hormonally-related cancer was marginally and inversely associated with AVC risk.
**Discussion**

In the largest study to date, we examined associations of FHC and BTC risk by anatomic site. We observed no association of FHC with IHBDC or EHBDC and marginal, inverse associations with GBC and with AVC. To address the concern that associations of FHC with GBC may reflect informative censoring by cholecystectomy rather than a true association, we restricted FHC-GBC analyses to studies reporting cholecystectomy and to people not reporting a history of a cholecystectomy, which drove associations between FHC and GBC to the null. The association between family history of hormonally-related cancer (upper CI of 0.99) and AVC may represent a false positive finding among many comparisons.

While most previous studies reported FHC associated with higher risk of BTCs overall (3), GBC (4, 5, 7), EHBDC or IHBDC (6, 7), or AVC (7), one study using FHC from the Utah pedigree database reported statistically nonsignificant, lower risks of BTCs with FHC (8). BiTCaPP was also predominantly comprised of non-Hispanic whites from the U.S. It is possible that the association of FHC with BTC risk may vary by population. Thus, FHC still may be an important predictor of BTC risk outside of the United States. Misclassification of self-reported FHC is possible but likely nondifferential.

In the largest prospective study, we found no associations between FHC and BTC risk. These results provide no support to the hypothesis that having a FHC is associated with higher BTC risk. As we were unable to examine associations of family history of BTCs with BTCs, the results do not preclude this potential association.

**Acknowledgments**

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The Melbourne Collaborative Cohort Study was made possible by the contributions of many people, including the original investigators, the recruiting teams, and the many thousands of Melbourne residents who participated in the study.

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For a list of the investigators who have contributed to the Women’s Health Initiative science, please visit the following website: [http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf](http://www.whi.org/researchers/Documents%20%20Write%20a%20Paper/WHI%20Investigator%20Short%20List.pdf)

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Abbreviations List

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>AARP</td>
<td>NIH-AARP Diet and Health Study</td>
</tr>
<tr>
<td>AgHealth</td>
<td>Agricultural Health Study</td>
</tr>
<tr>
<td>ATBC</td>
<td>Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study</td>
</tr>
<tr>
<td>AVC</td>
<td>ampulla of Vater cancer</td>
</tr>
<tr>
<td>BCDDP</td>
<td>Breast Cancer Detection Demonstration Project</td>
</tr>
<tr>
<td>BiTCaPP</td>
<td>Biliary Tract Cancers Pooling Project</td>
</tr>
<tr>
<td>BTC</td>
<td>biliary tract cancer</td>
</tr>
<tr>
<td>CI</td>
<td>confidence interval</td>
</tr>
<tr>
<td>CPS-II NC</td>
<td>Cancer Prevention Study II Nutrition Cohort</td>
</tr>
</tbody>
</table>
EHDBC  extrahepatic bile duct cancer
FHC    family history of cancer
GBC    gallbladder cancer
HPFS   Health Professionals Follow-Up Study
IHBDC  intrahepatic bile duct cancer
IRB    institutional review board
IWHS   Iowa Women’s Health Study
MCCS   Melbourne Collaborative Cohort Study
MEC    Multiethnic Cohort Study
NHS    Nurses’ Health Study
PLCO   Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial
SD     standard deviation
WHI    Women’s Health Initiative

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17264972]
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27655103]
Table 1

Participant characteristics by study included in family history of cancers and biliary tract cancers in the BiTCaPP\textsuperscript{a,b}

<table>
<thead>
<tr>
<th>Study</th>
<th>Follow-Up Period</th>
<th>Sample Size\textsuperscript{c} N (% of Pooled)</th>
<th>GBC N</th>
<th>IHBDC N</th>
<th>EHBDC N</th>
<th>AVC N</th>
<th>Women %</th>
<th>Age Mean (SD)</th>
<th>Non-Hispanic White %</th>
<th>Cholecystectomy %</th>
<th>Gallstones %</th>
</tr>
</thead>
<tbody>
<tr>
<td>AARP</td>
<td>1995-2011</td>
<td>547,369 (36)</td>
<td>213</td>
<td>150</td>
<td>219</td>
<td>147</td>
<td>40</td>
<td>62 (5)</td>
<td>93</td>
<td>14</td>
<td>10</td>
</tr>
<tr>
<td>AgHealth</td>
<td>1993-2013</td>
<td>43,934 (3)</td>
<td>6</td>
<td>8</td>
<td>5</td>
<td>3</td>
<td>47</td>
<td>47 (12)</td>
<td>98</td>
<td>N/C</td>
<td>N/C</td>
</tr>
<tr>
<td>ATBC</td>
<td>1985-2010</td>
<td>20,438 (1)</td>
<td>14</td>
<td>20</td>
<td>30</td>
<td>12</td>
<td>0</td>
<td>57 (5)</td>
<td>100</td>
<td>5</td>
<td>6</td>
</tr>
<tr>
<td>BCDDP</td>
<td>1980-1998</td>
<td>47,008 (3)</td>
<td>11</td>
<td>5</td>
<td>7</td>
<td>8</td>
<td>100</td>
<td>62 (8)</td>
<td>88</td>
<td>N/C</td>
<td>22</td>
</tr>
<tr>
<td>CPS-II NC</td>
<td>1992-2011</td>
<td>155,091 (10)</td>
<td>70</td>
<td>59</td>
<td>51</td>
<td>36</td>
<td>53</td>
<td>63 (6)</td>
<td>98</td>
<td>13</td>
<td>12</td>
</tr>
<tr>
<td>HPFS</td>
<td>1986-2012</td>
<td>51,395 (3)</td>
<td>11</td>
<td>8</td>
<td>23</td>
<td>10</td>
<td>0</td>
<td>54 (10)</td>
<td>97</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>IWHS</td>
<td>1986-2013</td>
<td>37,663 (2)</td>
<td>69</td>
<td>17</td>
<td>27</td>
<td>12</td>
<td>100</td>
<td>62 (4)</td>
<td>99</td>
<td>N/C</td>
<td>N/C</td>
</tr>
<tr>
<td>MCCS</td>
<td>1990-2009</td>
<td>39,695 (3)</td>
<td>35</td>
<td>20</td>
<td>22</td>
<td>6</td>
<td>59</td>
<td>55 (9)</td>
<td>100</td>
<td>8</td>
<td>9</td>
</tr>
<tr>
<td>MEC</td>
<td>1993-2010</td>
<td>190,565 (12)</td>
<td>111</td>
<td>N/A</td>
<td>110</td>
<td>64</td>
<td>55</td>
<td>60 (9)</td>
<td>25</td>
<td>6</td>
<td>7</td>
</tr>
<tr>
<td>NHS</td>
<td>1976-2012</td>
<td>100,693 (7)</td>
<td>54</td>
<td>17</td>
<td>34</td>
<td>18</td>
<td>100</td>
<td>47 (7)</td>
<td>94</td>
<td>8</td>
<td>2</td>
</tr>
<tr>
<td>PLCO</td>
<td>1993-2009</td>
<td>148,086 (10)</td>
<td>46</td>
<td>19</td>
<td>50</td>
<td>34</td>
<td>51</td>
<td>63 (5)</td>
<td>89</td>
<td>N/C</td>
<td>12</td>
</tr>
<tr>
<td>WHI</td>
<td>1993-2014</td>
<td>158,969 (10)</td>
<td>89</td>
<td>22</td>
<td>37</td>
<td>35</td>
<td>100</td>
<td>63 (7)</td>
<td>83</td>
<td>13</td>
<td>16</td>
</tr>
<tr>
<td>Total</td>
<td></td>
<td>1,540,906</td>
<td>729</td>
<td>345</td>
<td>615</td>
<td>385</td>
<td>56</td>
<td>60 (8)</td>
<td>84</td>
<td>10</td>
<td>10</td>
</tr>
</tbody>
</table>

\textsuperscript{a}Studies were conducted in the United States, except for ATBC (Finland) and MCCS (Australia). ATBC and WHI were randomized controlled trials; PLCO was a cancer screening trial. The remaining studies contributing to BiTCaPP were prospective cohort studies.

\textsuperscript{b}Data are missing for the following variables: race/ethnicity (\(N=11,145\)), cholecystectomy (\(N=319,423\)), gallstones (\(N=18,916\)).

\textsuperscript{c}Sample sizes presented are figures after people are excluded who were missing family history of any cancer (\(N=66,887\)), had prevalent disease (person time \(<0\)) or missing person time (\(N=30,706\)), and/or age at baseline \(\leq 18\) (\(N=166\)) or missing age at baseline (\(N=37\)).

Abbreviations: NIH-AARP Diet & Health Study (AARP), Agricultural Health Study (AgHealth), Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC), ampulla of Vater cancer (AVC), Biliary Tract Cancers Pooling Project (BiTCaPP), Breast Cancer Detection Demonstration Project (BCDDP), Cancer Prevention Study II Nutrition Cohort (CPS-II NC), extrahepatic bile duct cancer (EHBDC), gallbladder cancer (GBC), Health Professionals Follow-Up Study (HPFS), intrahepatic bile duct cancer (IHBDC), Iowa Women's Health Study (IWHS), Melbourne Collaborative Cohort Study (MCCS), Multiethnic Cohort Study (MEC), Nurses' Health Study (NHS), not available from study (N/A), not collected (N/C), Prostate, Lung, Colorectal and Ovarian Cancer Screening Trial (PLCO), standard deviation (SD), Women's Health Initiative (WHI).
Table 2

Family history of cancer and risk of biliary tract cancers: pooled HR estimates from the BiTCaPP

<table>
<thead>
<tr>
<th>FHC Variable</th>
<th>Biliary Tract Cancer Site</th>
<th>GBC</th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td>Overall</td>
<td></td>
<td>Restricted to Studies with Cholecystectomy Data</td>
<td>Restricted to People Not Reporting a Cholecystectomy</td>
<td></td>
</tr>
<tr>
<td></td>
<td>(12 Studies)</td>
<td></td>
<td>(8 Studies)</td>
<td>(8 Studies)</td>
<td></td>
</tr>
<tr>
<td>Any FHC&lt;sup&gt;a&lt;/sup&gt;</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Cases: n (%)</td>
<td>808,883 (60)</td>
<td></td>
<td>754,710 (60)</td>
<td>689,897 (60)</td>
<td></td>
</tr>
<tr>
<td>Cases: n (%)</td>
<td>206 (60)</td>
<td></td>
<td>339 (57)</td>
<td>322 (56)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.96 (0.77-1.19)</td>
<td></td>
<td>0.89 (0.75-1.05)</td>
<td>0.89 (0.75-1.05)</td>
<td></td>
</tr>
<tr>
<td>1&lt;sup&gt;st&lt;/sup&gt; Degree FHC</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Cases: n (%)</td>
<td>701,678 (52)</td>
<td></td>
<td>662,945 (53)</td>
<td>607,264 (52)</td>
<td></td>
</tr>
<tr>
<td>Cases: n (%)</td>
<td>183 (54)</td>
<td></td>
<td>295 (50)</td>
<td>279 (49)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.97 (0.78-1.20)</td>
<td></td>
<td>0.89 (0.75-1.04)</td>
<td>0.88 (0.75-1.04)</td>
<td></td>
</tr>
<tr>
<td>Female Relative with Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Cases: n (%)</td>
<td>524,406 (39)</td>
<td></td>
<td>448,724 (36)</td>
<td>408,640 (35)</td>
<td></td>
</tr>
<tr>
<td>Cases: n (%)</td>
<td>128 (37)</td>
<td></td>
<td>206 (35)</td>
<td>195 (34)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.89 (0.71-1.12)</td>
<td></td>
<td>0.99 (0.82-1.19)</td>
<td>1.00 (0.83-1.21)</td>
<td></td>
</tr>
<tr>
<td>Male Relative with Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Cases: n (%)</td>
<td>408,907 (31)</td>
<td></td>
<td>386,177 (31)</td>
<td>353,196 (31)</td>
<td></td>
</tr>
<tr>
<td>Cases: n (%)</td>
<td>107 (31)</td>
<td></td>
<td>156 (27)</td>
<td>147 (26)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.92 (0.72-1.16)</td>
<td></td>
<td>0.86 (0.71-1.04)</td>
<td>0.87 (0.71-1.06)</td>
<td></td>
</tr>
<tr>
<td>Relative with GI Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Cases: n (%)</td>
<td>225,826 (18)</td>
<td></td>
<td>222,961 (19)</td>
<td>200,930 (18)</td>
<td></td>
</tr>
<tr>
<td>Cases: n (%)</td>
<td>58 (19)</td>
<td></td>
<td>107 (19)</td>
<td>101 (19)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.96 (0.72-1.28)</td>
<td></td>
<td>0.97 (0.78-1.21)</td>
<td>0.97 (0.78-1.21)</td>
<td></td>
</tr>
<tr>
<td>Relative with Hormonally-Related Cancer</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Cases: n (%)</td>
<td>376,622 (30)</td>
<td></td>
<td>338,764 (28)</td>
<td>306,277 (28)</td>
<td></td>
</tr>
<tr>
<td>Cases: n (%)</td>
<td>83 (26)</td>
<td></td>
<td>145 (26)</td>
<td>137 (26)</td>
<td></td>
</tr>
<tr>
<td>HR (95% CI)</td>
<td>0.85 (0.66-1.10)</td>
<td></td>
<td>0.87 (0.72-1.05)</td>
<td>0.87 (0.71-1.06)</td>
<td></td>
</tr>
</tbody>
</table>

<sup>a</sup>Adjusted for sex and race/ethnicity without restrictions.
The baseline hazard was adjusted by including study in the strata statement.

Adjusted for sex, race/ethnicity and restricted to the 8 studies reporting history of cholecystectomy (AARP, ATBC, CPS-II NC, HPFS, MCCS, MEC, NHS, and WHI) without restricting to people who did not report a history of cholecystectomy.

Adjusted for sex, race/ethnicity and restricted to people who did not report a history of cholecystectomy (8 studies).

Any FHC includes data on second degree family history of cancer, which was available for BCDDP, IWHS, NHS, and WHI.

Abbreviations: ampulla of Vater cancer (AVC), Biliary Tract Cancers Pooling Project (BiTCaPP), confidence interval (CI), extrahepatic bile duct cancer (EHBDC), family history of cancer (FHC), gallbladder cancer (GBC), intrahepatic bile duct cancer (IHBD).