Recent studies from several countries, including the United States, have indicated that the incidence rate of intrahepatic cholangiocarcinoma is increasing while that of extrahepatic cholangiocarcinoma is decreasing. We examined whether such opposing trends could be confirmed in Danish data. We computed the nationwide Danish incidence rates of intra- and extrahepatic cholangiocarcinomas from January 1, 1978, through December 31, 2002, with data from the high-quality Danish Cancer Registry. Incidence rates were standardized to the US population in 2000. The study included 1335 patients with intrahepatic cholangiocarcinoma and 1269 with extrahepatic cholangiocarcinoma. The Danish incidence rates of intra- and extrahepatic cholangiocarcinomas were nearly identical throughout the study period. From 1978 through 2002, the incidence rate of intrahepatic cholangiocarcinoma decreased from 1.27 (95% confidence interval [CI] = 0.96 to 1.58) to 0.46 (95% CI = 0.29 to 0.62) per 100,000 people, and the rate of extrahepatic cholangiocarcinoma decreased from 1.05 (95% CI = 0.77 to 1.34) to 0.74 (95% CI = 0.53 to 0.95). The median age at diagnosis decreased during the study period, and the proportion of localized cancers increased. The decrease in cholangiocarcinoma incidence rates cannot be explained by time trends in known risk factors (e.g., inflammatory bowel disease, diabetes, smoking, or thorotrast), but our findings are consistent with a common etiology for intra- and extrahepatic cholangiocarcinomas.

**Affiliations of authors:** Department of Clinical Epidemiology (PJ, HTS) and Department of Medicine V (Hepatology and Gastroenterology) (HV), Aarhus University Hospital, Aarhus, Denmark; International Epidemiology Institute, Rockville, MD (RET); Institute of Cancer Epidemiology, The Danish Cancer Society, Copenhagen, Denmark (SF).

**Correspondence to:** Peter Jepsen, MD, Department of Clinical Epidemiology, Aarhus University Hospital, Ole Worms Allé 1150, DK-8000 Aarhus C, Denmark (e-mail: pj@dce.au.dk).

See “Notes” following “References.”

DOI: 10.1093/jnci/djk201

© The Author 2007. Published by Oxford University Press. All rights reserved. For Permissions, please e-mail: journals.permissions@oxfordjournals.org.
years or older had the largest decrease in incidence (Table 1), and so the median age at diagnosis fell from 70 years (range = 24–95 years) in the period from 1978 through 1982 to 67 years (range = 30–92 years) in the period from 1998 through 2002 for intrahepatic cholangiocarcinoma and from 71 years (range = 30–96 years) to 68.5 years (range = 18–95 years) for extrahepatic cholangiocarcinoma.

In the period from 1978 through 1982, 22% (95% CI = 16% to 28%) of intrahepatic cholangiocarcinomas were localized compared with 31% (95% CI = 23% to 40%) in the period from 1998 through 2002. A similar improvement was observed for extrahepatic cholangiocarcinomas, from 20% (95% CI = 15% to 27%) localized in the period from 1978 through 1982 to 32% (95% CI = 24% to 42%) in that from 1998 through 2002.

The primary strength of this study is the quality of the Danish Cancer Registry. The registry is notified of all cancers diagnosed by general practitioners, practicing specialists, or hospital doctors or in institutes of pathology or forensic medicine, and registration is virtually complete (5). Accuracy of a cancer diagnosis is ensured by cross-checking the information from the clinician’s notification with the information from the pathologist’s notification, and contacting them if the information is not consistent (5). A limitation of our study was that cholangiocarcinoma topography may have been incorrectly reported by clinicians, but it is unlikely that misclassification between intra- and extrahepatic cholangiocarcinomas had a major systematic impact on incidence rates or on time trends in incidence rates.

We designed our study to allow direct comparisons with the US incidence rates presented by Welzel et al. (3). The extrahepatic cholangiocarcinoma rates for the United States and Denmark were nearly identical throughout the period from 1978 through 2002. The intrahepatic

Table 1. Incidence rates for intra- and extrahepatic cholangiocarcinomas in Denmark*

<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Women</td>
<td>Intrahepatic</td>
<td>1.16 (0.98 to 1.33)</td>
<td>1.07 (0.91 to 1.23)</td>
<td>0.95 (0.80 to 1.10)</td>
<td>0.58 (0.47 to 0.70)</td>
<td>0.54 (0.43 to 0.65)</td>
<td>0.84 (0.78 to 0.91)</td>
</tr>
<tr>
<td></td>
<td>Extrahepatic</td>
<td>1.03 (0.86 to 1.20)</td>
<td>1.03 (0.87 to 1.19)</td>
<td>0.90 (0.75 to 1.04)</td>
<td>0.64 (0.52 to 0.76)</td>
<td>0.57 (0.48 to 0.69)</td>
<td>0.82 (0.76 to 0.88)</td>
</tr>
<tr>
<td>Men</td>
<td>Intrahepatic</td>
<td>1.12 (0.93 to 1.31)</td>
<td>1.34 (1.13 to 1.56)</td>
<td>0.91 (0.74 to 1.07)</td>
<td>0.79 (0.64 to 0.94)</td>
<td>0.73 (0.58 to 0.87)</td>
<td>0.97 (0.89 to 1.05)</td>
</tr>
<tr>
<td></td>
<td>Extrahepatic</td>
<td>1.03 (0.84 to 1.21)</td>
<td>0.99 (0.79 to 1.18)</td>
<td>0.88 (0.72 to 1.04)</td>
<td>0.81 (0.66 to 0.96)</td>
<td>0.74 (0.59 to 0.89)</td>
<td>0.88 (0.80 to 0.95)</td>
</tr>
<tr>
<td>Age, y</td>
<td>&lt;60</td>
<td>Intrahepatic</td>
<td>0.32 (0.24 to 0.40)</td>
<td>0.30 (0.22 to 0.37)</td>
<td>0.23 (0.17 to 0.30)</td>
<td>0.21 (0.15 to 0.27)</td>
<td>0.23 (0.17 to 0.29)</td>
</tr>
<tr>
<td></td>
<td>Extrahepatic</td>
<td>0.30 (0.22 to 0.38)</td>
<td>0.26 (0.19 to 0.33)</td>
<td>0.27 (0.20 to 0.34)</td>
<td>0.20 (0.15 to 0.26)</td>
<td>0.16 (0.11 to 0.20)</td>
<td>0.23 (0.20 to 0.26)</td>
</tr>
<tr>
<td></td>
<td>60–79</td>
<td>Intrahepatic</td>
<td>4.69 (4.02 to 5.35)</td>
<td>4.67 (4.02 to 5.32)</td>
<td>3.99 (3.39 to 4.60)</td>
<td>2.70 (2.20 to 3.20)</td>
<td>2.59 (2.10 to 3.07)</td>
</tr>
<tr>
<td></td>
<td>Extrahepatic</td>
<td>3.99 (3.38 to 4.60)</td>
<td>4.26 (3.64 to 4.88)</td>
<td>3.62 (3.04 to 4.19)</td>
<td>3.13 (2.59 to 3.67)</td>
<td>3.36 (2.80 to 3.91)</td>
<td>3.67 (3.41 to 3.93)</td>
</tr>
<tr>
<td></td>
<td>≥80</td>
<td>Intrahepatic</td>
<td>8.02 (5.88 to 10.17)</td>
<td>9.87 (7.72 to 12.02)</td>
<td>6.84 (5.12 to 8.56)</td>
<td>4.31 (3.03 to 5.59)</td>
<td>2.60 (1.64 to 3.57)</td>
</tr>
<tr>
<td></td>
<td>Extrahepatic</td>
<td>8.06 (5.88 to 10.24)</td>
<td>6.94 (4.98 to 8.91)</td>
<td>6.16 (4.57 to 7.76)</td>
<td>4.56 (3.20 to 5.93)</td>
<td>2.30 (1.38 to 3.23)</td>
<td>5.32 (4.63 to 6.01)</td>
</tr>
<tr>
<td>Total</td>
<td>Intrahepatic</td>
<td>1.15 (1.02 to 1.28)</td>
<td>1.19 (1.06 to 1.32)</td>
<td>0.95 (0.84 to 1.06)</td>
<td>0.67 (0.58 to 0.77)</td>
<td>0.62 (0.53 to 0.71)</td>
<td>0.90 (0.86 to 0.95)</td>
</tr>
<tr>
<td></td>
<td>Extrahepatic</td>
<td>1.05 (0.92 to 1.17)</td>
<td>1.01 (0.89 to 1.13)</td>
<td>0.91 (0.80 to 1.02)</td>
<td>0.74 (0.64 to 0.83)</td>
<td>0.65 (0.56 to 0.74)</td>
<td>0.86 (0.81 to 0.90)</td>
</tr>
</tbody>
</table>

* Rates are standardized to the US population in 2000.
† Total refers to the years from 1978 through 2002.
cholangiocarcinoma rates, however, were three times higher in Denmark than in the United States until the mid-1980s, when the US rate started to increase and the Danish rate started to decrease. From approximately 1990, rates in the United States and Denmark were nearly identical. Thus, we found no signs of opposite incidence trends for intra- and extrahepatic cholangiocarcinomas in Denmark, unlike those in the United States and several other regions of the world (2).

Changes in diagnostic methods are unlikely to explain our findings. New diagnostic tools improve sensitivity and/or specificity, and higher sensitivity cannot explain a lower cholangiocarcinoma incidence. We included only diagnoses that were based on histologic examination; although not all histology codes in our cholangiocarcinoma definition were specific to cholangiocarcinoma, there was no sign that the less specific codes were more frequent in the beginning of the study period. Also, the decrease in autopsies could not explain the decreasing cholangiocarcinoma incidence.

A limitation of our study was that we had only partial information on the prevalence of cholangiocarcinoma risk factors. The most important risk factors for cholangiocarcinoma in a Western population include primary sclerosing cholangitis and other biliary diseases, inflammatory bowel disease, infection with hepatitis C virus, diabetes, smoking, thorotrust (i.e., a mixture containing radioactive thorium dioxide particles that was used as a contrast medium for x-ray diagnostics between 1930 and 1950), alcoholism, and liver cirrhosis (6–9). The prevalence of smoking has decreased in Denmark, although primarily among men (10), so other factors must be responsible for the larger cholangiocarcinoma incidence decrease among women. In addition, smoking prevalence has decreased in countries with increasing cholangiocarcinoma incidence (11). The prevalence of thorotrust exposure has also decreased, but only 1000 Danes were exposed, with none of them exposed after 1947 (12). The prevalence of inflammatory bowel disease and diabetes has increased (13,14), and there is no indication that the prevalence of the remaining risk factors has decreased. Thus, none of the known cholangiocarcinoma risk factors can explain our findings.

In conclusion, intra- and extrahepatic cholangiocarcinomas may share the same biology. It remains unclear why the incidence rates have decreased in Denmark and are now similar to those in the United States.

References

Notes
The authors had full responsibility for the collection of the data, the analysis and interpretation of the data, the decision to submit the manuscript for publication, and the writing of the manuscript.

Funding for this research was from the Karen Elise Jensen Foundation and the Western Danish Research Forum for Health Sciences.

Manuscript received November 1, 2006; revised March 19, 2007; accepted March 20, 2007.