

# Survival of patients with primary liver cancer in central and northern Denmark, 1998–2009

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**Objective:** Primary liver cancer (PLC) is a serious disease with high mortality. During the last decade, improvements in the diagnostic procedures and treatment of PLC may have improved survival. However, few updated longitudinal studies examined this issue. In a population-based setting, we studied changes in the prognoses over time.

**Methods:** Between 1998 and 2009, we identified all patients with PLC in the central and northern Denmark regions, with a combined population of 1.8 million. We determined age- and period-stratified survival, and computed mortality rate ratios (MRRs) with 95% confidence intervals (CIs), using Cox proportional hazard regression to assess changes over time, while controlling for age and gender. We conducted the analyses for PLC overall and separately for hepatocellular carcinoma (HCC) and cholangiocarcinoma, respectively.

**Results:** We included 1064 patients with PLC. Their median age was 69 years (range 17–94 years). The number of patients diagnosed with PLC in the period 2007–2009 was approximately 40% higher than the number in 1998–2000. One-year survival increased from 16% in 1998–2000 to 28% in 2007–2009, corresponding to an adjusted 1-year MRR of 0.65 (95% CI: 0.54–0.79). In patients aged <60 years, we found the most pronounced increase in 1-year survival, from 14% to 49% in women and from 19% to 41% in men. The 3- and 5-year survival in the entire cohort increased from 5% to a predicted 11% and from 2% to a predicted 7% during our study period, respectively. Accordingly, the expected 3- and 5-year adjusted MRRs were 0.68 (95% CI: 0.57–0.82) and 0.68 (95% CI: 0.57–0.81), respectively. One-, 3-, and 5-year survival improved during the study period for both HCC and cholangiocarcinoma.

**Conclusion:** PLC survival remains poor in the Danish population, although we observed an increase over the period 1998–2009, particularly in young people.

**Keywords:** liver neoplasm, prognosis, mortality, epidemiology

## Introduction

Primary liver cancer (PLC) encompasses hepatocellular carcinoma, intrahepatic cholangiocarcinoma, and a few other rare histological types. PLC is the fifth most common cancer in the world and the third most common cause of cancer death worldwide. Yet, almost 85% of liver cancer cases occur in developing countries, and the incidence in men is more than two-fold higher than in women.<sup>1</sup> In high-incidence parts of the world, chronic liver disease caused by persistent infection with hepatitis B or C viruses is the most common underlying cause, whereas alcohol-related liver diseases are more common in Denmark and other Nordic countries.<sup>2,3</sup>

During the last 20 years, diagnostic procedures like contrast-enhanced ultrasound, computer tomography, magnetic resonance, and new serologic markers have been

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introduced in order to detect PLC at an earlier stage.<sup>4,5</sup> More advanced treatments, including surgical resection, minimal invasive ablation treatments, chemotherapy, and biological targeted drugs have also become available in recent decades.<sup>6–9</sup>

Despite these efforts, survival remains very poor. A minimal improvement in 5-year survival was reported in the period 1964–2003 among PLC patients in the Nordic countries.<sup>2</sup> However, among Nordic patients diagnosed in 1999–2003, Danish patients had the lowest 5-year relative survival, 3% in men and 5% in women.<sup>2</sup> A previous study from northern Denmark reported a median survival of PLC of 3 months in 2000–2004.<sup>10</sup> Few other previous population-based studies on PLC prognosis exist.

Therefore, we used the Danish National Patient Registry (DNPR) to examine changes in the 1-, 3-, and 5-year survival after PLC diagnosis in the 1998–2009 period.

## Material and methods

We conducted this study in the central and the northern Denmark regions, with a combined population of 1.8 million persons. The National Health Service provides tax-supported health care for all inhabitants of Denmark, guaranteeing free access to hospitals. Virtually no PLC patients were treated in private hospitals during the study period.

### Identification of primary liver cancer patients

Through the DNPR, we identified all patients who had a first-time hospitalization with PLC in the period January 1, 1998 through December 31, 2009. The DNPR contains information about all admissions from nonpsychiatric hospitals in Denmark since 1977.<sup>11</sup> Outpatient and emergency room visits at hospitals have been included since 1995. This registry includes information on civil registration number, dates of admission and discharge, surgical procedure(s) performed, and up to 20 diagnoses from each hospital contact. Diagnoses have been classified according to the International Classification of Diseases (ICD) 8th edition until the end of 1993 and 10th edition (ICD-10) thereafter. We included the following diagnoses: hepatocellular carcinoma (HCC) (ICD-10 code: C22.0), cholangiocarcinoma (ICD-10 code: C22.1), and other liver cancers (other specified carcinomas of liver: [ICD-10 code: C22.7] and unspecified malignant neoplasm of the liver [ICD-10 code: C22.9]).

### Survival

Since 1968, the Central Office of Civil Registration has assigned a unique 10-digit personal identification number

to all Danish citizens.<sup>12</sup> This number, unique to each Danish resident, is used in all Danish registries, allowing unambiguous individual-level data linkage. From the Civil Registration System we also obtained information on vital status (dead or alive), date of death, and residence for all cancer patients.

### Statistical analysis

We followed each patient from date of cancer diagnosis until emigration, death, or June 25, 2010, whichever came first. To visualize crude survival we constructed Kaplan–Meier curves stratified according to period of diagnosis (1998–2000, 2001–2003, 2004–2006, and 2007–2009). We estimated 1-, 3-, and 5-year survival. In the latter periods, we estimated 3- and 5-year survival using a hybrid analysis in which we included the actual survival for as long as possible and then estimated the conditional probability of surviving thereafter based on the corresponding survival experience of patients in the previous periods (ie, using a period analysis technique).<sup>13</sup> To compare mortality over time, we used Cox proportional hazards regression analysis with 1998–2000 as the reference period to estimate 1-, 3-, and 5-year mortality rate ratios (MRRs) and corresponding 95% confidence intervals (CIs), adjusting for age group and gender. We included age in three age groups (15–59 years, 60–79 years, and 80+). In two separate models, we additionally included age as a continuous variable and as a cubic spline curve with three knots, respectively. These models did not change our MRR estimates.

In an additional analysis, we stratified the patients by type of liver cancer in the four periods.

Analyses were performed using SAS version 9.2 (SAS Institute Inc, Cary, NC).

## Results

Of the 1064 PLC patients diagnosed in the 1998–2009 period, 39% were women. The median age at diagnosis was 69 years (range 17–94 years) (Table 1 and Figure 1).

The annual number of PLC patients increased during the study period, from 225 patients diagnosed in 1998–2000 to 316 diagnosed in the period 2007–2009. This increase covered a 10% increase in patients aged 15–59 years at PLC diagnosis, a 48% increase in the group aged 60–79, and a 75% increase in patients aged 80 years or older. Among patients aged 60–79, the increase was mainly seen among men (Table 2), while the increase in patients aged more than 80 years was mainly seen in women (Table 3).

**Table 1** Survival and MRRs with 95% confidence intervals according to year of primary liver cancer diagnosis, central and northern Denmark 1998–2009

	Year of diagnosis			
	1998–2000	2001–2003	2004–2006	2007–2009
Number of cancer patients	225	255	268	316
Median age (years)	68	69	68	69
<b>1 year</b>				
Survival	16% (12%–22%)	22% (17%–28%)	21% (16%–26%)	28% (23%–34%)
MRR	1 (reference)	0.83 (0.68–1.01)	0.86 (0.71–1.05)	0.67 (0.55–0.82)
Adjusted MRR <sup>a</sup>	1 (reference)	0.83 (0.68–1.01)	0.87 (0.71–1.05)	0.65 (0.54–0.79)
<b>3 year</b>				
Survival	5% (3%–9%)	12% (9%–16%)	9% (6%–13%)	11% (8%–15%) <sup>b</sup>
MRR	1 (reference)	0.79 (0.65–0.95)	0.85 (0.71–1.02)	0.69 (0.58–0.83) <sup>b</sup>
Adjusted MRR <sup>a</sup>	1 (reference)	0.79 (0.66–0.96)	0.85 (0.71–1.03)	0.68 (0.57–0.82) <sup>b</sup>
<b>5 year</b>				
Survival	2% (1%–4%)	6% (3%–9%)	6% (4%–9%) <sup>b</sup>	7% (4%–11%) <sup>b</sup>
MRR	1 (reference)	0.79 (0.66–0.95)	0.83 (0.69–0.99) <sup>b</sup>	0.69 (0.58–0.82) <sup>b</sup>
Adjusted MRR <sup>a</sup>	1 (reference)	0.79 (0.66–0.95)	0.83 (0.70–1.00) <sup>b</sup>	0.68 (0.57–0.81) <sup>b</sup>

**Notes:** <sup>a</sup>adjusted for age and gender; <sup>b</sup>predicted values.

**Abbreviation:** MRR, mortality rate ratio.

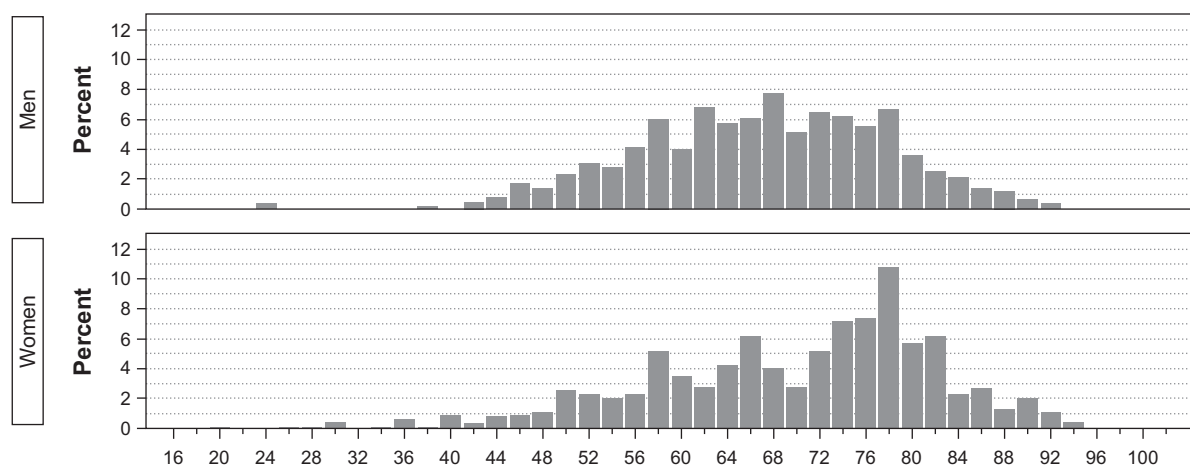
The 1-year survival improved from 16% (1998–2000) to 28% (2007–2009). Accordingly, the 1-year crude MRR was 0.67 (95% CI 0.55–0.82) in 2007–2009, using 1998–2000 as reference. Adjustment for age and sex did not change the MRR substantially (Table 1 and Figure 2).

The largest increase in 1-year survival was seen in patients aged 15–59 years (Tables 2 and 3). The 3-year survival improved from 5% in 1998–2000 to about 10% in the other periods. The crude MRR declined to 0.85 (95% CI 0.71–1.02) in 2004–2006, while the estimated crude MRR in the 2007–2009 period was 0.69 (95% CI 0.58–0.83). Again, the adjustments did not notably change the results. The 5-year survival improved from 2% (1998–2000) to estimated 7% (2007–2009) over the study period corresponding to a 2007–2009 crude MRR of 0.69 (95% CI 0.58–0.82) (Table 1).

Table 4 shows the distribution of the type of PLC during the study periods.

Survival improved both in patients with HCC and in those with cholangiocarcinoma during the study period (Tables 5 and 6). Among HCC patients, 1-, 3-, and 5-year survival increased from 24% to 37%, from 5% to estimated 12% and from 3% to estimated 9%, respectively, in the period 2007–2009, compared with 1998–2000. The crude and adjusted MRRs showed a corresponding decrease in the mortality of about 30% in the period 2007–2009 relative to the period 1998–2000 (Table 5).

Among patients with cholangiocarcinoma 1-, 3-, and 5-year survival increased from 19% to 27%, from 3% to estimated 11% and from 0% to estimated 4%, respectively (Table 6). The crude and adjusted MRRs showed a



**Figure 1** The age distribution of men and women at primary liver cancer diagnosis, central and northern Denmark 1998–2009.

**Table 2** Survival and 95% confidence intervals in men with primary liver cancer, according to age and year of diagnosis, central and northern Denmark 1998–2009

Men		Year of diagnosis			
		1998–2000	2001–2003	2004–2006	2007–2009
Age (years)					
15–59					
	Number of cancer patients	42	49	45	42
	1-year survival	19% (9%–32%)	29% (17%–41%)	22% (11%–35%)	41% (26%–56%)
	3-year survival	7% (2%–17%)	18% (9%–30%)	11% (4%–22%)	24% (12%–39%) <sup>a</sup>
	5-year survival	2% (0%–11%)	6% (2%–15%)	9% (3%–19%) <sup>a</sup>	20% (9%–35%) <sup>a</sup>
60–79					
	Number of cancer patients	75	82	114	132
	1-year survival	19% (11%–28%)	27% (18%–37%)	12% (7%–19%)	27% (19%–35%)
	3-year survival	7% (2%–14%)	15% (8%–23%)	3% (1%–7%)	9% (4%–16%) <sup>a</sup>
	5-year survival	3% (1%–8%)	5% (2%–11%)	0% <sup>a</sup>	–
80+					
	Number of cancer patients	16	16	19	19
	1-year survival	13% (2%–33%)	0%	16% (4%–35%)	32% (13%–52%)
	3-year survival	0%	0%	5% (0%–21%)	6% (0%–25%) <sup>a</sup>
	5-year survival	0%	0%	–	–

Note: <sup>a</sup>predicted values.

corresponding decrease in mortality a little below 30% in the period 2007–2009 relative to 1998–2000, although the CIs are rather wide.

## Discussion

In this population-based study the 1-, 3-, and 5-year mortality decreased approximately 30% among PLC patients between 1998 and 2009. Still, their life expectancy remained poor.

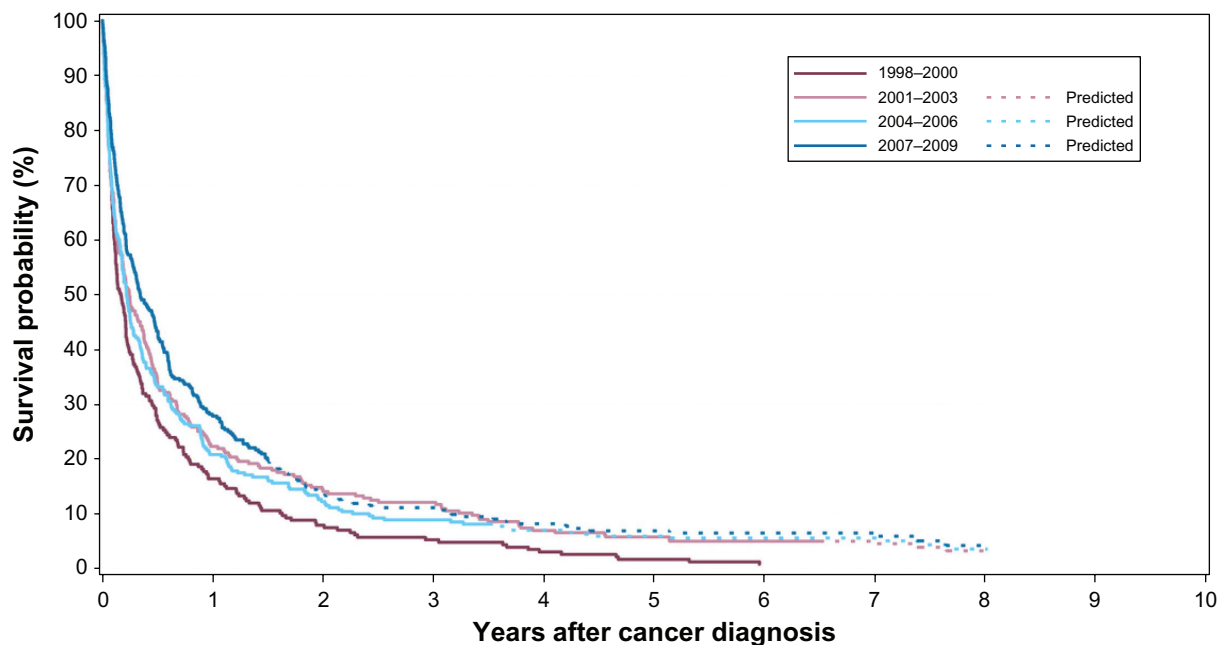
The results from this present study extend the findings from a previous study by our group<sup>10</sup> by adding data from an

additional 5 years and, moreover, by calculating the estimated 3- and 5-year survival for patients diagnosed in the most recent years. We affirmed that while the survival continued to increase in Denmark, it is still poor compared with that in other developed countries. The latest EURO CARE report (which did not include PLC data from Denmark), covering the period 2000–2002, reported 1-, 5-, and 10-year relative survival rates for PLC of 33.5%, 9.8%, and 6.3%, respectively.<sup>14</sup> Similar results were reported in the United States with 5-year relative survival rates of 8.3% in the period 1995–2000.<sup>15</sup> Recent data on PLC prognosis in other settings confirm improvement of

**Table 3** Survival and 95% confidence intervals in women with primary liver cancer, according to age and year of diagnosis, central and northern Denmark 1998–2009

Women		Year of diagnosis			
		1998–2000	2001–2003	2004–2006	2007–2009
Age (years)					
15–59					
	Number of cancer patients	21	23	28	27
	1-year survival	14% (4%–32%)	35% (17%–54%)	43% (25%–60%)	49% (29%–67%)
	3-year survival	10% (2%–26%)	26% (11%–45%)	29% (14%–46%)	20% (8%–37%) <sup>a</sup>
	5-year survival	0%	26% (11%–45%)	21% (9%–38%) <sup>a</sup>	14% (5%–28%) <sup>a</sup>
60–79					
	Number of cancer patients	59	60	46	66
	1-year survival	15% (8%–26%)	17% (9%–27%)	33% (20%–46%)	21% (12%–31%)
	3-year survival	3% (1%–10%)	5% (1%–13%)	15% (7%–27%)	6% (2%–13%) <sup>a</sup>
	5-year survival	2% (0%–8%)	3% (1%–10%)	12% (5%–24%) <sup>a</sup>	5% (2%–12%) <sup>a</sup>
80+					
	Number of cancer patients	12	25	16	30
	1-year survival	8% (1%–31%)	12% (3%–28%)	13% (2%–33%)	13% (4%–28%)
	3-year survival	0%	4% (0%–17%)	0%	–
	5-year survival	0%	0%	0%	–

Note: <sup>a</sup>predicted values.



**Figure 2** Survival curves for patients with primary liver cancer according to year of diagnosis, central and northern Denmark 1998–2009.

survival during the last decades, although their results vary for country, sex, and age group,<sup>2,16,17</sup> whereas others focus entirely on hepatocellular carcinoma or consider previous time periods.<sup>18–20</sup>

Our study design had both strengths and limitations. The study was large, population-based, with a well defined primary catchment area, complete registration, and long-term follow-up. Thus, selection bias was negligible. Nevertheless, the quality of the diagnosis coding in the DNPR is crucial. In a previous publication, we compared the PLC survival from the DNPR to that from the Danish Cancer Registry (DCR), which is almost 100% complete and valid,<sup>21</sup> and found similar results.<sup>22</sup> Moreover, in two other studies from our region, the completeness of both ovarian cancer diagnosis and prostate cancer diagnosis in the DNPR compared with the DCR were 96%, and the positive predictive values were among 95% and 97%.<sup>23,24</sup>

**Table 4** Distribution of liver cancer types in the different study periods in central and northern Denmark 1998–2009

Type of liver cancer				
Year diagnosis	HCC (%)	Cholangiocarcinoma (%)	Other (%)	Total
1998–2000	79 (35.1%)	31 (13.8%)	115 (52.1%)	225
2001–2003	103 (40.4%)	41 (16.1%)	111 (43.5%)	255
2004–2006	114 (42.5%)	50 (18.7%)	104 (38.8%)	268
2007–2009	151 (47.8%)	58 (18.4%)	107 (33.8%)	316
Total	447 (42.0%)	180 (16.9%)	437 (41.1%)	1064

**Notes:** Other liver cancers include unspecified liver cancers as well as specified types other than HCC and cholangiocarcinoma.

**Abbreviation:** HCC, hepatocellular carcinoma.

Although the overall quality of the PLC diagnosis in the DNPR was found to be good, the quality of specific types of PLC diagnoses was poorer. Indeed, approximately 40% of the patients had an unspecified type of liver cancer. Since HCC accounts for approximately 85% of primary liver cancer worldwide,<sup>25</sup> the possibility of HCC coded as “other liver cancers” is more than plausible. Nevertheless, patients coded with HCC and cholangiocarcinoma are likely to have these diseases (ie, high positive predictive value), and we therefore believe that our survival estimates for these subgroups are valid.

Another limitation is our lack of data on cancer stage and treatment. Furthermore, information on alcohol consumption, coexistence of liver cirrhosis and hepatitis virus infection, and other comorbidities were not available. Changes over time in these factors could have provided further evidence of the underlying reason for the observed improvement in survival.

One of the possible explanations, at least among patients with hepatocellular carcinoma, of the poorer survival in Denmark compared with the other developed countries could be related to the high prevalence of cirrhosis due to alcohol abuse in Denmark.<sup>26,27</sup> In fact, unlike several other Western countries where immigration from developing areas with endemic hepatitis B and spread of hepatitis C are suggested to play a major role in PLC developing, the hepatitis C prevalence in Denmark is approximately 0.3%, and it has remained low during the study period while alcoholism remained the most frequent cause of cirrhosis.<sup>28,29</sup>

**Table 5** Survival and 95% confidence intervals in patients with hepatocellular carcinoma, according to age and year of diagnosis, central and northern Denmark 1998–2009

	Year of diagnosis			
	1998–2000	2001–2003	2004–2006	2007–2009
Number of cancer patients	79	103	114	151
Median age (years)	67	68	66	69
<b>1 year</b>				
Survival	24% (15%–34%)	28% (20%–37%)	22% (15%–30%)	37% (29%–45%)
MRR	1 (reference)	0.94 (0.67–1.33)	1.05 (0.76–1.45)	0.67 (0.49–0.93)
Adjusted MRR <sup>a</sup>	1 (reference)	0.93 (0.66–1.31)	1.04 (0.75–1.45)	0.65 (0.47–0.91)
<b>3 year</b>				
Survival	5% (2%–11%)	17% (11%–25%)	9% (4%–15%)	12% (7%–19%) <sup>b</sup>
MRR	1 (reference)	0.81 (0.59–1.10)	0.97 (0.72–1.31)	0.71 (0.53–0.94) <sup>b</sup>
Adjusted MRR <sup>a</sup>	1 (reference)	0.80 (0.59–1.09)	0.97 (0.72–1.31)	0.70 (0.52–0.93) <sup>b</sup>
<b>5 year</b>				
Survival	3% (0%–8%)	7% (3%–13%)	6% (3%–12%) <sup>b</sup>	9% (5%–16%) <sup>b</sup>
MRR	1 (reference)	0.84 (0.62–1.14)	0.96 (0.72–1.29) <sup>b</sup>	0.70 (0.53–0.93) <sup>b</sup>
Adjusted MRR <sup>a</sup>	1 (reference)	0.83 (0.61–1.13)	0.95 (0.71–1.27) <sup>b</sup>	0.69 (0.52–0.92) <sup>b</sup>

Notes: <sup>a</sup>adjusted for age and gender; <sup>b</sup>predicted values.

Abbreviation: MRR, mortality rate ratio.

Alcohol abuse may have strong negative impact on PLC survival for two main reasons. First, among patients with alcohol abuse, liver cirrhosis is almost always present at the time of hepatocellular carcinoma diagnosis, which is not the case in patients with hepatitis C-related hepatic cancer.<sup>30</sup> Since liver cirrhosis is known to be associated with poor prognosis,<sup>26</sup> patients with hepatitis C related PLC probably have a better survival after resection. Second, chronic alcohol abuse in itself is known to increase both overall mortality among cirrhotic patients<sup>31</sup> and postoperative mortality in the general population.<sup>32</sup> Alcoholic

liver cirrhosis with severe compromised liver function is therefore often considered a contraindication for surgical resection for liver cancer.<sup>33</sup> Moreover, we found the largest survival improvement among patients <60 years, and Jepsen et al reported that alcoholic cirrhosis prevalence and incidence in the Danish population have decreased in people <45 years from 1996 to 2005 and have only slightly increased in people aged 45–64 years in the same period.<sup>34</sup> This evidence could support the hypothesis that alcohol abuse could be related to the higher mortality among patients with HCC.

**Table 6** Survival and 95% confidence intervals in patients with cholangiocarcinoma, according to age and year of diagnosis, central and northern Denmark 1998–2009

	Year of diagnosis			
	1998–2000	2001–2003	2004–2006	2007–2009
Number of cancer patients	31	41	50	58
Median age (years)	64	68	69	67
<b>1 year</b>				
Survival	19% (8%–35%)	22% (11%–35%)	24% (13%–36%)	27% (16%–39%)
MRR	1 (reference)	0.87 (0.52–1.47)	0.82 (0.50–1.37)	0.74 (0.45–1.22)
Adjusted MRR <sup>a</sup>	1 (reference)	0.91 (0.54–1.56)	0.84 (0.51–1.39)	0.73 (0.44–1.20)
<b>3 year</b>				
Survival	3% (0%–14%)	5% (1%–15%)	8% (3%–18%)	11% (4%–20%) <sup>b</sup>
MRR	1 (reference)	0.86 (0.54–1.39)	0.79 (0.50–1.26)	0.73 (0.46–1.15) <sup>b</sup>
Adjusted MRR <sup>a</sup>	1 (reference)	0.88 (0.53–1.43)	0.79 (0.49–1.25)	0.72 (0.46–1.15) <sup>b</sup>
<b>5 year</b>				
Survival	0% (0%–14%)	2% (0%–11%)	3% (0%–11%) <sup>b</sup>	4% (0%–14%) <sup>b</sup>
MRR	1 (reference)	0.83 (0.52–1.34)	0.76 (0.48–1.21) <sup>b</sup>	0.70 (0.45–1.10) <sup>b</sup>
Adjusted MRR <sup>a</sup>	1 (reference)	0.88 (0.53–1.47)	0.74 (0.47–1.18) <sup>b</sup>	0.70 (0.44–1.10) <sup>b</sup>

Notes: <sup>a</sup>adjusted for age and gender; <sup>b</sup>predicted values.

Abbreviation: MRR, mortality rate ratio.

Several factors may explain the improved prognosis of PLC patients reported in our study. Recent advances in surgical and medical therapy such as radio-frequency ablation, stereotactic radiotherapy, biological targeted therapy, and chemo-embolization could lead to improved survival.<sup>35–37</sup> In addition, better diagnostic tests including radiology and serology have the potential for detecting PLC at an earlier stage and thereby increasing the likelihood of effective treatment.<sup>4,5</sup> However, earlier diagnosis of PLC owing to increased accuracy of diagnostic tests may result in prolonged survival, even without any prognostic changes (ie, lead time bias), and we cannot exclude that this could partly explain our results. Nonetheless, the median age at diagnosis did not decrease during the study period, providing some evidence that the improvement in survival was not caused solely by earlier diagnosis.

In conclusion, in Denmark, PLC survival increased over the study period, but it still remains poor.

## Disclosure

The authors report no conflict of interest in this work.

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