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RESEARCH ARTICLE

Trends in cancer of the liver, gall bladder, bile duct, and pancreas in elderly in Denmark, 1980–2012

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ABSTRACT

Background Cancers of the liver, bile duct, gall bladder and pancreas (HPB-c) are a heterogeneous group, united almost exclusively by a poor prognosis. As the number of elderly in the Western world continues to rise and HPB-c are associated with age, we wanted to examine changes in incidence, mortality, prevalence and relative survival for these cancers.

Materials and methods HBP-c was defined as ICD-10 codes C22 (liver), C23-24 (gall bladder), and C25 (pancreas). Data derived from the NORDCAN database with comparable data on cancer incidence, mortality, prevalence and relative survival in the Nordic countries, where the Danish data were delivered from the Danish Cancer Registry and the Danish Cause of Death Registry with follow-up for death or emigration until the end of 2013.

Results The incidence and mortality rates of cancer of the liver and pancreas increased over time while the rates of cancer of the gall bladder and bile duct decreased. All HBP-c were more frequent in persons over the age of 70 than in younger persons. The relative one- and five-year survival rose in most HPB-c, but mainly occurring in the younger population of 0–69 years with only small to no gains in the 80 + group.

Conclusion As the number of persons aged 80 years or more will increase dramatically in the following years, and our results show a gap in relative survival, it is important to continue to study this population in order to improve management and outcome.

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Primary malignancies of the liver, bile duct, gall bladder and pancreas (HPB-c) present an enormous challenge to the modern healthcare system. HPB-c constitute a diverse group of cancers, but almost exclusively all are characterized by dismal prognosis [1]. In Europe, 197 000 new cases of HPB-c were diagnosed and with 187 000 deaths, HBP-c is only surpassed by lung and colorectal cancer in number of deaths [2].

For more than a hundred years, life expectancy in the Western world has increased with three months per year and it is expected that this increase will continue. As the incidence of most cancers will rise, the more elderly will require cancer-directed therapy [3]. For this reason it is becoming increasingly important to study the older population in order to gain knowledge on how to best treat these patients. The most fit should be treated as younger patients, some patients will not tolerate optimal therapy and some patients should only receive best supportive care. In general, there is less high quality data – i.e. randomized trials – in HPB-c compared to other primaries, such as breast and lung cancer, and especially there is very limited knowledge about optimal therapy in older HPB-c patients, as they are under-represented in clinical trials [4]. Older patients included in studies are selected on the basis of appropriate performance status and sufficient organ functions and these patients are not representative of the majority of older patients who are treated in every day practice.

This study examines the changes in incidence, mortality, prevalence as well as changes in short- and long-term relative survival of HPB-c patients with particular focus on the elderly.

Material and methods

HBP-c was defined as ICD-10 codes C22 (liver), C23-24 (gall bladder), and C25 (pancreas). ICD-10 codes for the liver includes intrahepatic bile duct cancers and more seldom tumors (e.g. hepatoblastoma and liver sarcomas), whereas ''gall bladder'' includes extrahepatic bile duct cancer as well as tumors of the ampulla of Vater. A more detailed description of the materials and methods appear elsewhere [5]. In brief, data were derived from the NORDCAN database, which include comparable data on cancer incidence, mortality, prevalence and relative survival in the Nordic countries, where the Danish data are delivered from the Danish Cancer Registry and the

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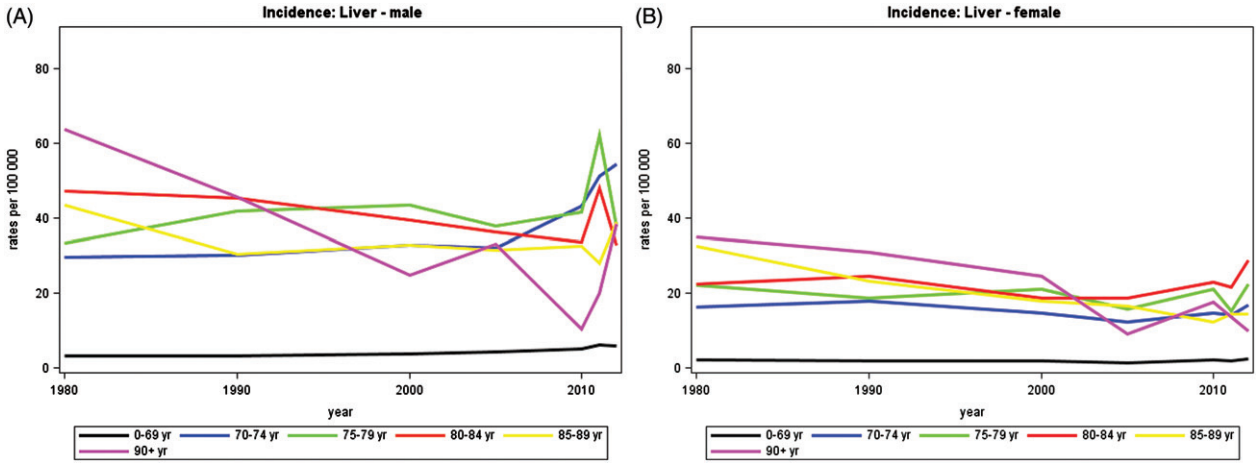

Figure 1. (A) Incidence rates of cancer of liver in males in Denmark, 1980–2012, by age group. (B) Incidence rates of cancer of liver in females in Denmark, 1980–2012, by age group.

Danish Cause of Death Registry with follow-up for death or emigration until the end of 2013. This study focuses on the elderly population with age categorized as 0–69, 70–79, 80–89 and 90 + years.

For incidence and mortality, age group specific numbers and rates per 100 000 person years are shown in graphs with calendar periods for time of diagnosis subdivided into the following periods: 1978–1982, 1988–1992, 1998–2002, 2003–2007, 2010, 2011 and 2012. Prevalence was defined as the number of cancer patients (including cured patients as well) with that specific diagnosis still alive and is shown in tables by the end of 1980, 1990, 2000, 2005, 2010, 2011 and 2012.

Sex- and age-specific one- and five-year relative survival proportion ratios were calculated for each of the diagnostic groups for the age groups 0–69, 70–79, 80–89 and 90 + years and for the five-year periods of diagnosis 1968–1972, 1973–1977, . . ., 2003–2007 and 2008–2012.

Relative survival for a group of cancer patients was calculated as the observed survival (where all causes of death are considered events) divided by the expected survival for a group from the Danish population with the same age and year of birth composition. The actuarial method was used for observed survival and the Ederer II method for the expected survival calculation [6]. Relative survival can be interpreted as the survival if the cancer was the only cause of death. For the most recent period, 2008–2012, not all patients could be followed up for death in five years, and we used hybrid methods where we supplemented data with survival experience from cancer patients diagnosed in earlier years. Survival was not calculated for cancer groups with less than five patients [indicated by (-) in tables and blank in the graphs]. If all patients died in the follow-up period resulting in zero survival this is indicated as 0 (-) and if calculation for a cell results in a relative survival higher than 100% the result is shown in tables, but restricted to 100% in graphs.

Results

Liver

The average annual number of new cancers in the liver rose from 257 in 1980 to 398 in 2012 and the number of deaths from 179 in 1980 to 398 in 2012. Figure 1 show that the incidence rates remained quite stable over this time period and that the rates were about four times higher among persons aged 70 years or more than in younger persons. Mortality rates (Figure 2) were also higher among older persons and these seemed to have increased since 1990. The relative one-year survival increased from about 5% to about 40% in persons aged less than 70 years and from about 2% to 20% in males and 25% in females aged 70–89 years. The relative five-year survival was 6% or less in all time periods and age groups, except for women aged less than 70 years in 2003–2012 where it was 14%. These numbers were reflected in the prevalence, with an increase from 63 in 1980 to 497 in 2012.

Gall bladder/bile duct

Cancer of the gall bladder and biliary tract is rare in Denmark with about 250 new cases per year and 138 deaths. It is more common in women than in men and the incidence rates are at least five times higher in persons aged more than 70 years compared with younger persons (Figure 3). While no particular time trend was observed in men, both incidence and mortality rates decreased with time since 1980 for women (Figures 3 and 4). The one-year relative survival increased with time for all age groups except those aged 90 + years while minor improvements were observed in the five-year relative survival from 6–9% to 13–16% in the last period (Figure 5).

Pancreas

There is considerable uncertainty in the diagnosis of pancreatic cancer with many new cases and deaths without a histological verification. This affects incidence, mortality as well as survival. In 1980, on average 740 persons were classified as having an incident pancreatic cancer or died from pancreatic cancer while this number increased to 973 in 2012. Figure 6 shows that the one-year relative survival increased from 10% to 30% in persons less than 70 years, to 22% in the age group 70–79, and to 12% in the age group 80–89 years. The five-year relative survival was less than 8% in all age groups and time periods.

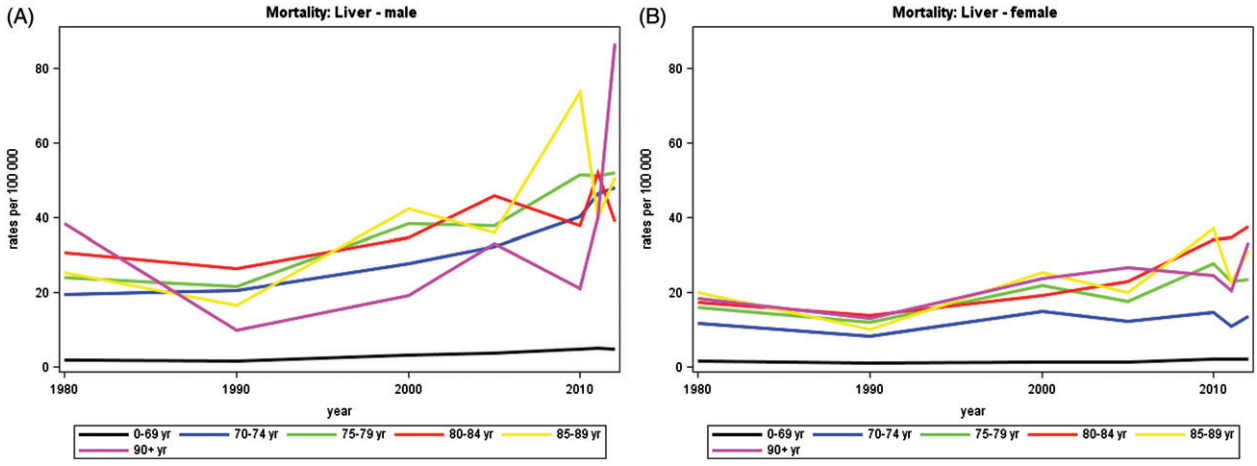

Figure 2. (A) Mortality rates of cancer of liver in males in Denmark, 1980–2012, by age group. (B) Mortality rates of cancer of liver in females in Denmark, 1980–2012, by age group.

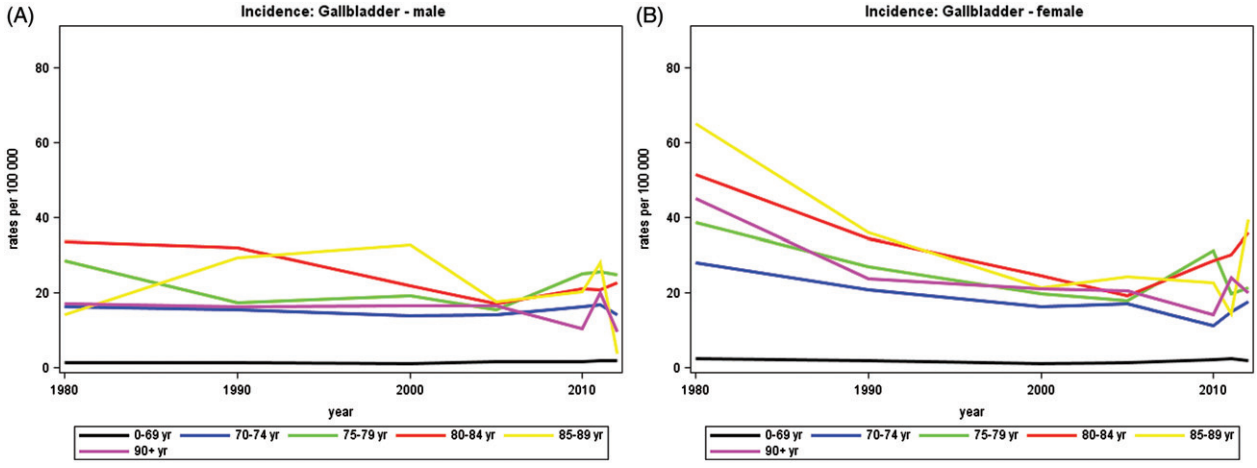

Figure 3. (A) Incidence rates of biliary cancer in males in Denmark, 1980–2012, by age group. (B). Incidence rates of biliary cancer in females in Denmark, 1980–2012, by age group.

Discussion

In our study we found the incidence increased over time for cancer of the liver and pancreas. The increase in pancreatic- and liver-cancers may be due to reductions in other ''lethal'' comorbidities, improved diagnostics, changes in individual behavior, and other yet unknown causes. In this respect it was somewhat surprising that the incidence rate of gall bladder and bile duct cancers decreased over time. Similar trends have been described in other registry-based studies [7–13], but the reasons for this decline are largely unknown [13].

For all HPB malignancies, we found lower survival rates in elderly compared to younger patients. This difference has been described earlier across Europe in a cohort from 1990 to 1994. This study described similar findings regarding survival, and especially noteworthy is the excess mortality found in the elderly during the first year after diagnosis [14].

Although elderly had lower survival rates across the study period, there was an increase in both short- and long-term survival for especially the 0–69 and 70–79 age groups. This increase was highest for the short-term survival, where the effect most likely is caused by earlier diagnosis, reduced perioperative mortality, and increased use of palliative chemotherapy/radiotherapy. However, long-term survival has also increased in all primaries, again isolated to the population between 0 and 79. The most likely reason for these changes is the increased use of surgery, potentially due to early detection and decreased surgical mortality.

HPB malignancies represent a diverse group of cancers distinct both by anatomical region and microscopic appearance. Though based on registry data from an entire population, this analysis has some limitations. We did not have information on morphological subtypes or on histological verification of the diagnosis. For the analysis of survival, also no information was available on stage of disease. However, the excellent coverage and quality of the Danish and Nordic cancer registries allow for analysis of whole populations and not only selected trial patients [15].

Microscopic verification is missing in a large percentage of patients with HPB cancers; especially pancreatic cancers with as many as 50% missing according to the EUROCARE-4

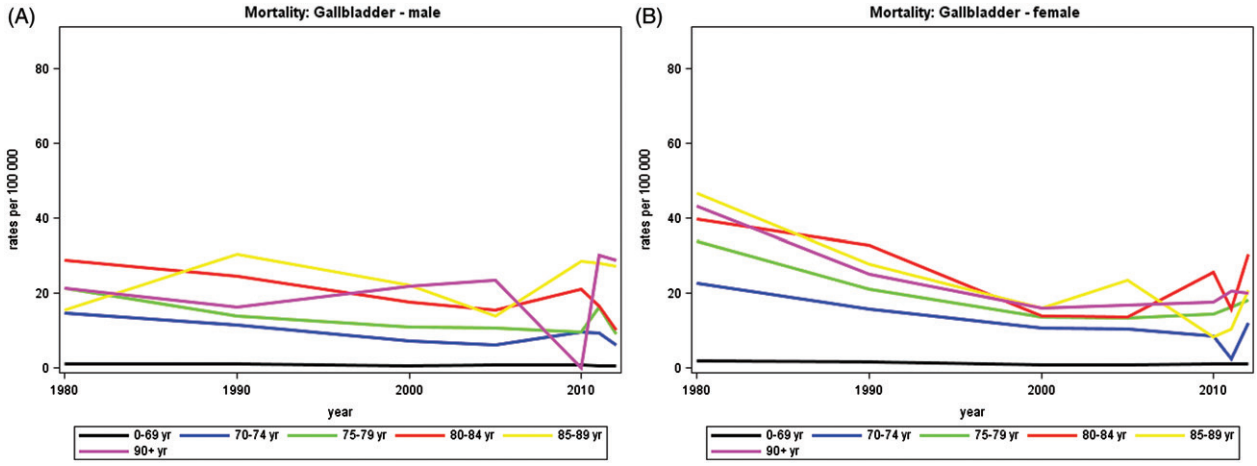

Figure 4. (A) Mortality rates of biliary cancer in males in Denmark, 1980–2012, by age group. (B) Mortality rates of biliary cancer in females in Denmark, 1980–2012, by age group.

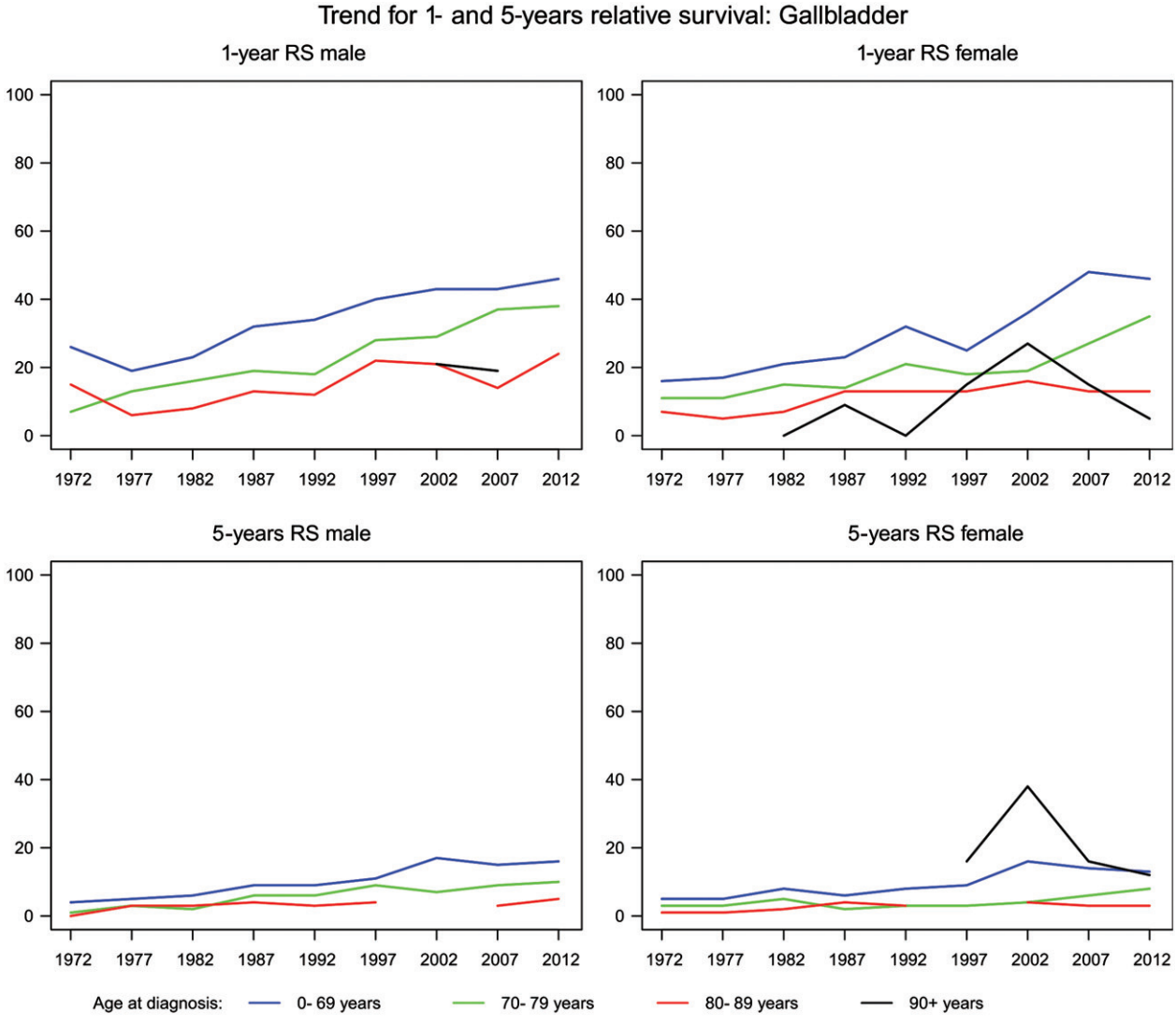

Figure 5. Age-specific relative survival after biliary cancer in Denmark.

program [7,16]. In Denmark, this rate has been more or less constant at 20% [17]. Further, rare histological subtypes of specific cancers associated with either a much worse or better prognosis will reduce generalizability: an example is the pancreatic neuroendocrine tumors which will make up a larger part of the patients who achieve long-term survival, but a very low percentage of diagnosed cases.

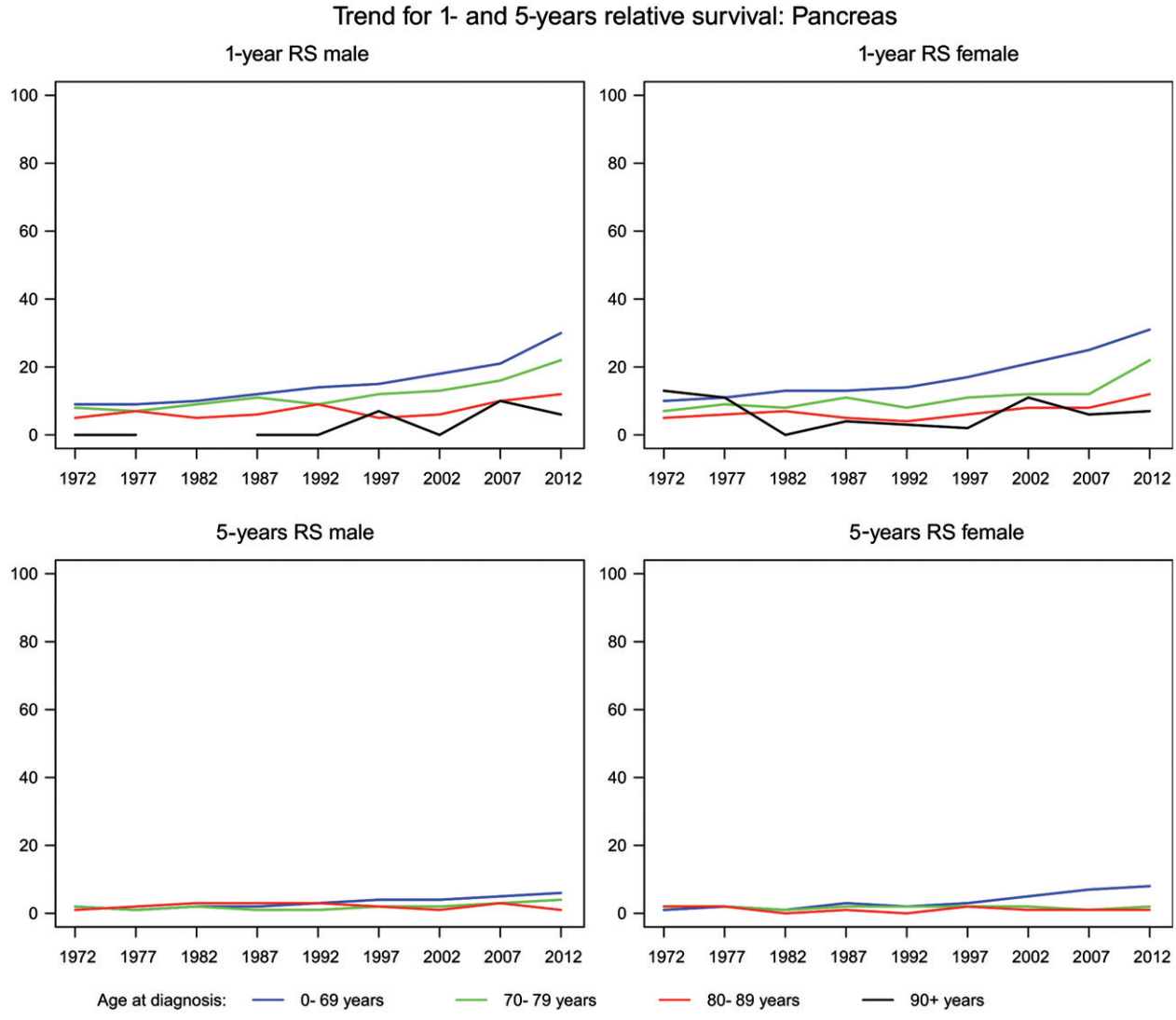

Figure 6. Age-specific relative survival after pancreatic cancer in Denmark.

Despite these shortcomings in population-based registries, they often represent the only way to examine non-trial patients, and especially gain knowledge about patients who never were referred for evaluation in an oncological department.

During the examined period many advances have been made with regards to diagnosis and treatment of HPB cancers. Surgical techniques and postoperative care have improved considerably and this will lead to both increased short-term, but also increased long-term survival. The introduction of dedicated multidisciplinary HPB surgical programs may have contributed to the overall improvement in both the number of referred patients and the surgical outcome [18]. In addition, the trend towards surgery being performed in high volume centers seems to be a potential factor regarding the willingness to perform surgery in the elderly and regarding a more positive postoperative outcome in general [19]. The role of minimal invasive resection techniques regarding the short- and long-term outcome is difficult to assess. Laparoscopic resected HPB cancer is technically feasible and with a better short-time outcome (e.g. reduced pain, lower hospital morbidity rate and hospitalization time), but the long-term prognosis is not necessarily improved as well [20]. The use of robot-assisted surgery may provide such data in the future, and this technique would also be interesting in a more fragile population [21].

A quicker return to preoperative performance status as a consequence of minimally invasive surgery may allow more patients to complete adjuvant chemotherapy, but this effect may not yet be evident due to the relative novelty of this kind of HPB surgery. Data suggest that patients with non-resectable or disseminated disease may also benefit from a diagnostic laparoscopy instead of an open laparotomy to confirm that surgery is not possible [22]. These benefits include shorter time interval to palliative treatment and more patients being able to receive palliative treatment.

Thus, a general change towards a more minimally invasive surgical approach regarding both improved staging of disseminated disease and in radical surgery may explain some of the observed overall improvement in HPB-c outcome over time. However, the potential effect of minimally invasive and fast-track surgery may not have reached its maximum yet.

An earlier diagnosis can potentially lead to improved long-term survival if the patient is able to be offered a curative resection. The improved diagnostic modalities (e.g. MRI, endoscopic ultrasonography) and biopsy evaluation has led

to more patients being diagnosed and treated for premalignant lesions (e.g. IPMN) during the study period. Early diagnosis will also lead to apparent longer short-term survival due to lead time bias. Chemotherapy and radiotherapy for patients with HPB cancers was not routinely introduced in Denmark until the early 2000s. Palliative chemotherapy increased median survival from around 3 months to 6–9 months on average, but only in fit patients included in clinical trials, and this resulted in increases in short-term but not long-term survival. For patients who have had a pancreatic cancer resection, adjuvant therapy doubles long-term survival, however, routine therapy was not introduced until the publication of the CONKO-3 study in 2007 and will only apply to patients fit for therapy following surgery, which can be as low as 50–60% [23].

A large proportion of patients with upper gastro-intestinal cancer do not receive either surgery or chemotherapy/radiation therapy. For patients diagnosed with pancreatic cancer we have previously shown that less than half of the population in a cohort diagnosed from 2007 to 2009 actually receive any therapy [23]. Old age and lack of microscopically verification were important factors in this. Other population-based studies have shown inequity to be a factor for some upper gastrointestinal cancers; however, not for pancreatic cancer [7,9,24,25]. In this respect, Denmark has often been reported to have a lower survival compared to the other Nordic countries, also including upper gastrointestinal cancers [10]. It is unknown whether underutilization of therapy, staging differences or comorbidity explains these differences.

Conclusion

HPB cancers are relatively infrequent in Denmark and with a substantial diagnostic uncertainty. One- and five-year relative survival increased during the study period, largest among the younger and only a small to no increase was seen in persons aged 80 years or more. As the number of persons aged 80 years or more will increase dramatically in the following years, and our results show a gap in relative survival, it is important to continue to study this population in order to improve management and outcome.

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Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of the paper.

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