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Long-term incidence and survival trends in cancer of the gallbladder and extrahepatic bile ducts in Denmark, Finland, Norway and Sweden with etiological implications related to Thorotrast

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Abstract

Cancers of the gallbladder and extrahepatic bile ducts (called here "GBC" because gallbladder cancer is the main component) are rare in Europe, including the Nordic countries. Their incidence has varied for unknown reasons and we hypothesize that Thorotrast, a previously used carcinogenic radiographic contrast medium, has contributed to the incidence trends. We obtained incidence and survival data from the NORDCAN database, which includes cancer registry data from Denmark (DK), Finland (FI), Norway (NO) and Sweden (SE), which are globally the oldest national cancer databases, starting from 1943 in DK, 1953 in FI and NO and 1960 in SE, and extending to 2016. The incidence trend for GBC showed a broad maximum around 1980 in men (close to 3/100 000) and women (4/100 000), except for NO, where this phenomenon was not seen. In 1955, FI and NO incidence rates were equal but FI rates peaked and later declined similar to DK and SE rates. By 2010, the incidence was similar in all Nordic countries, for both men and women, at close to 2.0/100 000. Birth cohort analysis showed strong effects for countries other than NO. Relative 1-year survival increased for men from 20% to about 50% and similarly for women although at a 5 percentage points lower level.

Abbreviations: DK, Denmark; FI, Finland; GBC, gallbladder cancer; HBV, hepatitis B virus; HCV, hepatitis C virus; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; NO, Norway; SE, Sweden.

Survival in NO was better than in other countries in the 1980s. Thorotrast, causing a high risk of GBC, was extensively used in the Nordic countries between 1930 and end of 1940s, with the exception of NO, where these was no documented use. These data suggest that Thorotrast influenced GBC epidemiology and probably worsened survival in certain periods.

KEYWORDS
gallbladder cancer, hepatobiliary carcinoma, incidence trend, relative survival, risk factors

What's new?

While gallbladder cancer (GBC) is a relatively rare malignancy, incidence rates vary across countries for reasons that remain unknown. Here, focusing on Nordic countries, the authors investigated associations between incidence of gallbladder and extrahepatic bile duct cancer and exposure to Thorotrast, a carcinogenic radiographic contrast medium used extensively in Nordic countries, with the exception of Norway, between 1930 and 1950. GBC incidence in Norway was found to be significantly lower than in other Nordic countries, with excess risk in the other countries persisting for three decades. Thorotrast exposure further impacted GBC survival, potentially lowering survival rates in certain periods.

1 | INTRODUCTION

Primary biliary cancers include gallbladder cancer (GBC), cancers of the biliary tract (extrahepatic and intrahepatic bile ducts, also called cholangiocarcinoma) and of the ampulla of Vater.[1] In western countries these are relatively rare cancers but their incidence shows large international variation correlating with known risk factors.[1] In many European countries and United States, GBC incidence has decreased from about 1980 onwards.[2,3] Declining trends have been reported also in extrahepatic bile duct cancer in US whites and Danes from the 1970s.[4,5] The declining rates for GBC have been extensively discussed, and it has been suggested for example that increasing cholecystectomy rates would have led to reduction of GBCs.[5] The weakness of this reasoning is that the decrease in GBC incidence has been much larger than the increase in cholecystectomy rates in United States and in the Nordic countries, where cholecystectomy rates have generally not increased in the last decades.[5,6] Another problem with this hypothesis is that GBCs are being diagnosed in about 1% of incidental cholecystectomy specimens, which would imply that more incidental cancers are found when more cholecystectomy is performed.[7-9]

For GBC, gallstones are an important risk factor, as most patients have a history of cholelithiasis but yet only 0.5% to 3% are diagnosed with GBC.[1] Other risk factors include Salmonella typhi and Helicobacter bilis infection, family history and biliary cysts and other structural abnormalities.[1,10] For female gallbladder cancer, obesity is a strong risk factor, which is also associated with gallstones.[11] Also for biliary tract cancers cholelithiasis is a risk factor but infections with hepatitis B and C virus (HBC and HCV) and alcohol use are additional risks factors although weaker than for hepatocellular cancer.[1,12] GBC and biliary tract cancer are also increased in patients diagnosed with some autoimmune diseases.[5,13]

Of note, hepatobiliary tract cancers (liver, GBC and bile ducts) were vastly increased after exposure to Thorotrast, a widely used radiographic contrast agent which was injected into more than 2.5 million and probably 10 million persons in industrialized countries between the 1930s and the 1950s.[14,15] The epidemic is largely forgotten even though the epidemiological evidence is exquisitely strong: after injection with ≥20 mL Thorotrast (approximate standard dose), the cumulative excess risk of cancer incidence remained elevated for up to 50 years and approached 97%.[14-16]

Surgery is the primary treatment option for these cancers and it can be curative in those rare cases where diagnosis occurs early, but generally survival in these cancers is poor.[1] Surgery techniques have developed over the years for stage T1b and higher, to include resection of segments of liver near the gallbladder and lymph nodes, with improving survival.[17] According to a Swedish study covering years 2000 to 2014 a third of GBC patients were treated with curative intent and their survival improved over the period.[18] Liver bed resections increased as the surgical procedure during the period. For GBC and bile duct cancers, treatment options include chemotherapies and ipilimumab plus nivolumab immunotherapy.[1] Many of these therapies are effective in a meaningful proportion of patients.

We use here the NORDCAN database which is a compilation of cancer registry data from Denmark (DK), Finland (FI), Norway (NO) and Sweden (SE).[19] Our aim was to carry out a descriptive study in the Nordic countries in order to find possible clues about the causes of GBC and to compare survival between the countries. The unique aspect of the Nordic cancer registries is that they were the first national cancer registries in the world, allowing a long observation time for high-quality cancer data. Incidence data were available from 1943 in DK, 1953 in FI and NO and 1960 in

SE. Survival data were available from 1967 onwards, and importantly, as medical care has been essentially free-of-charge to the Nordic population at large, the survival data is truly population-based. The database combines GBC with cancer of the extrahepatic bile ducts, which has been almost equally common as GBC for men but about 1/3 of female GBC. We call these cancers jointly "GBC" to mark the largest constituent.[20] Much of the global Thorotrast cancer epidemiological data was generated in the Nordic countries, with the exception of NO from where no studies have been published, suggesting that Thorotrast was not used.[14,15] Even though many Thorotrast related publications originates from DK and SE, no data are available on the total exposed population. We extrapolated the number of exposed subjects for DK based on the global Thorotrast production figures.

2 | MATERIALS AND METHODS

We use the NORDCAN database in the analysis[19] (https://NORDCAN.iarc.fr/en/database#bloc2). ICD-10 codes were used for GBC, C23, that is, GBC together with C24, that is, cancers of extrahepatic bile ducts with ampulla of Vater and other, unspecified malignancies of bile ducts. Incidence and survival data were collected for each country from the available years through 2016. For incidence analysis, the world standard population was used in age adjustment. NORDCAN provides data on quality indicators: proportion of microscopically verified cases (generally >80% for DK, FI and NO and >90% for SE), cases included only from death certificates (low for all countries) and mortality-to-incidence ratio as a measure for coverage (70%-100%).

All analyses were generated on the NORDCAN web site into which each national cancer registry had supplied cancer and population numbers by age-group, and age-specific incidence and survival data (NORDCAN (iarc.fr]). For age-standardization "world standard population was used" as defined in NORDCAN under "Glossary of statistical terms". The tool for incidence analysis by period ("Time trends (Incidence/Mortality") was selected for analysis. For birth cohort analysis the tool was "Trends by birth cohort." For survival the tools were "Time trends" and "Age-specific survival". In incidence diagrams, lines were smoothed by the LOESS regression algorithm (bandwidth: 0.1, indicating the proportion of all datapoints contributing to each shown value).

For survival analysis, 1- and 5-year relative survival data were available from 1967 onwards and the analysis was based on the cohort survival method for the first nine 5-year periods from 1964 to 2011, and a hybrid analysis combining period and cohort survival in the last period 2012 to 2016, as detailed previously.[21] The hybrid method includes cases from the penultimate 5-year period to allow for 5-year survival analysis.[21] Age groups 0 to 89 were considered, and for age-standardization the International Cancer Survival Standard was used.[20] NORDCAN did not include survival data for persons aged over 89 years, probably because of low case numbers and deficits of cancer notifications.[22] The country-specific life tables were used to calculate the expected survival.

3 | RESULTS

3.1 | Incidence trends

Numbers of GBC patients, median ages at diagnosis and incidence rates of GBC (combining gallbladder, extrahepatic bile ducts and ampulla of Vater) are shown in Table 1. As the incidence rates vary extensively, we show data in Table 1 for the last 5-year period only. For GBC, male and female rates are almost equal in all countries and for women median diagnostic ages are higher than the male ones. Later results show that the female incidence rate for GBC was historically much higher than male incidence.

Age-standardized incidence trends for GBC were analyzed for Nordic populations, starting from the earliest possible date from the respective cancer registries. The trends for men and women were remarkably similar with the absolute level being two times higher in women (Figure 1). The peak was reached in DK by 1970s while in SE and FI it occurred at around 1980s. The maximal incidence levels were highest in SE, 3/100 000 for men and 5/100 000 for women. The peak was missing in the NO curves and the overall incidence rates were below those for the other countries, 1/100 000 for men and 1.5/100 000 for women in 1980. Notably, in 1955 the NO rates matched the FI ones, and by 2010 the NO rates had again reached those for the other countries, while in the intervening period NO rates differed markedly from other Nordic countries.

Age-specific incidence trends were quite uniform for DK, FI and SE men and women with one broad peak, most prominent in the oldest age groups (Figures S1 and S2). However, the maximal incidence rate in DK and for SE women was reached in 1970 while in FI and for SE men the maximum was in the early 1980s. For NO men the trend was increasing in the oldest age groups but trends for the others were stable with fluctuations; for women the rates were stable for all age groups except the oldest (Figure S2A,C).

Analysis by birth cohort was done for SE and NO men for age groups 50 to 84 years (Figure 2). The data for SE suggested very strong influence of birth cohorts with a maximal incidence of 55/100 000 at age 80 to 84 years in the birth cohort of 1900 (Figure 2A). For any later birth cohorts there was still a steep drop in incidence and the peak incidence changed to lower ages; for later birth cohorts the changes became gradually more modest. For NO the modest birth cohort effects defined a gradual increase in incidence over time, except for a steeper increase in the beginning (Figure 2B). The data for DK and FI men agreed with the SE data and are not shown.

Female SE birth cohort data agreed largely with the male data suggesting a strong influence of birth cohorts (Figure 3A). Birth cohort data for NO women showed small decreases in incidence over time (Figure 3B).

Country	Men			Women		
	N	Age at diagnosis	Rate/10^5	N	Age at diagnosis	Rate/10^5
Denmark	466	71	1.6	586	73	1.7
Finland	611	72	2.0	831	77	2.0
Norway	411	70	1.7	461	74	1.6
Sweden	896	71	1.7	1222	73	2.0

TABLE 1 Numbers of gallbladder and extrahepatic bile duct cancers, median ages at diagnosis ages and incidence rates in the Nordic countries, 2012–2016

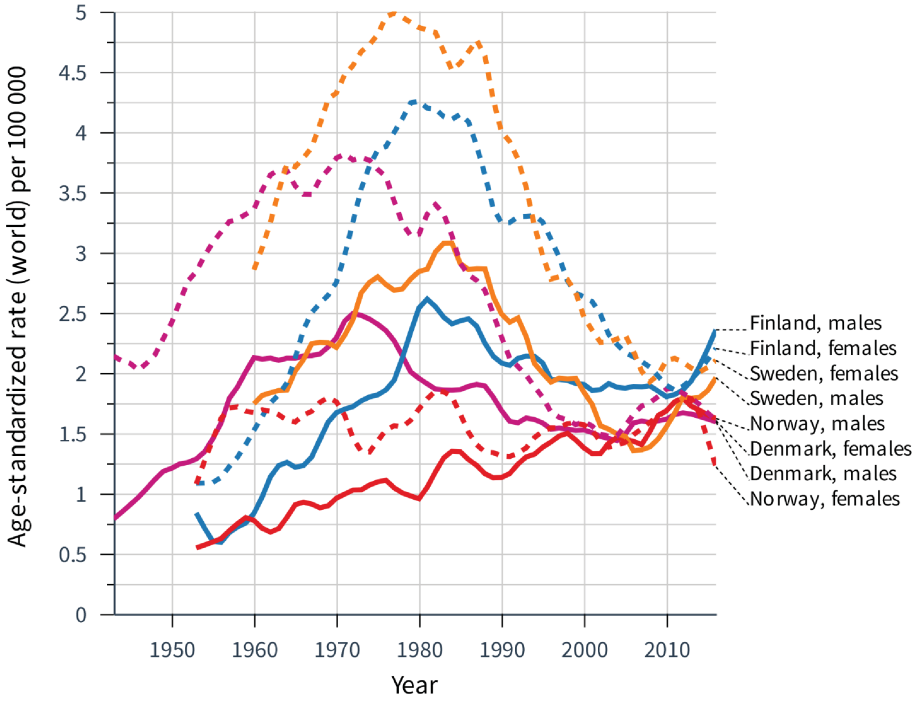

FIGURE 1 Age-standardized incidence trends for male (solid lines) and female (broken lines) in GBC (ie, cancers of the gallbladder and extrahepatic bile ducts) in Denmark, Finland, Norway and Sweden (smoothing with bandwidth 0.1) [Color figure can be viewed at wileyonlinelibrary.com]

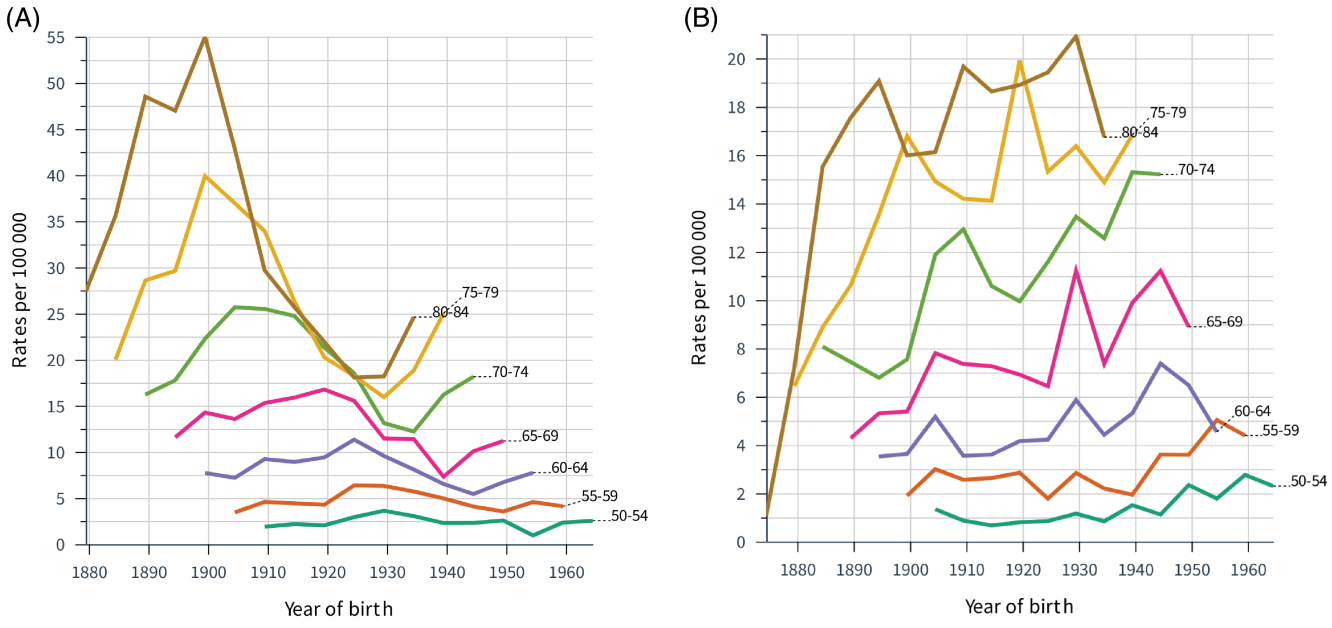

FIGURE 2 Birth cohort analysis of GBC for Swedish (A) and Norwegian (B) men [Color figure can be viewed at wileyonlinelibrary.com]

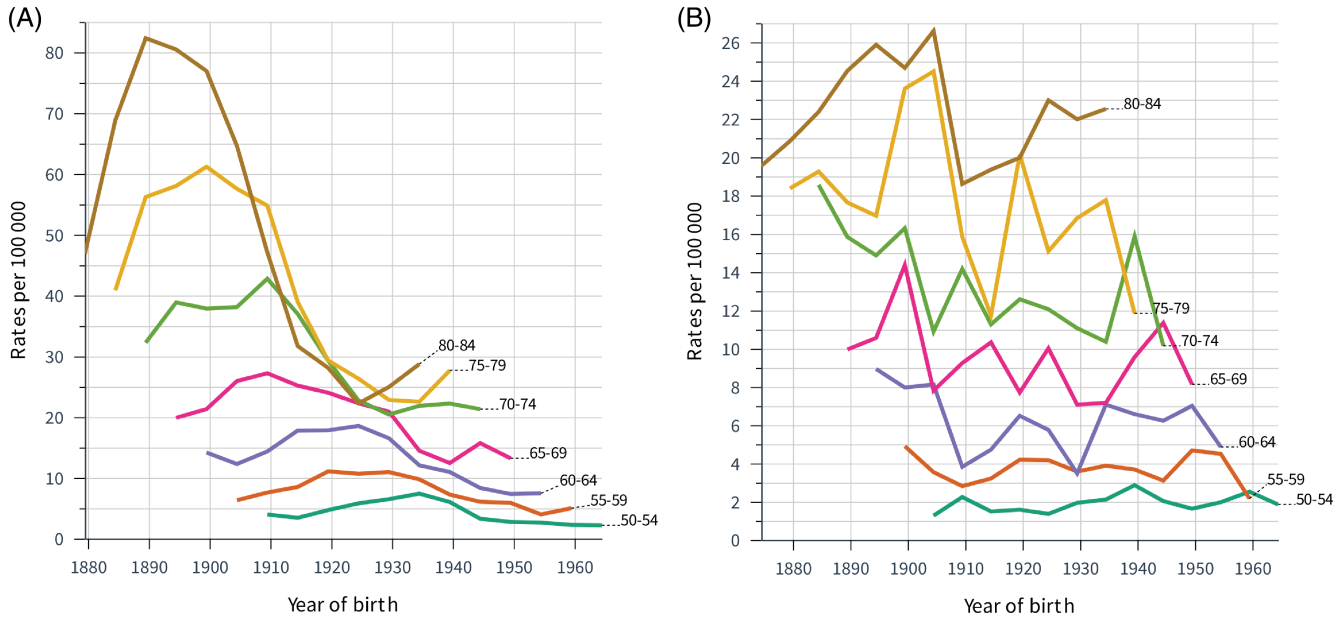

FIGURE 3 Birth cohort analysis of GBC for Swedish (A) and Norwegian (B) women [Color figure can be viewed at wileyonlinelibrary.com]

3.2 | Estimation of the number of cases due to Thorotrast

We tested the feasibility of the assumption that Thorotrast would influence population level incidence change using available data from DK and NO. For this purpose, we assume that the NO GBC rate was unaffected by the extra risk factor (suggested to be Thorotrast), and the excess risk in DK was due to this factor. The difficult in doing this kind of estimation relates to the fact that the number of individuals exposed to Thorotrast globally or in any country are not known precisely. We used the International Agency for Research on Cancer (IARC) cited figure of 10 million which was extrapolated from production figures.[15,23] Thorotrast was widely used in several industrialized countries which had an overall population of 800 million in 1950 (Europe 550 million, United States 150 million and Japan 85 million), when the DK population was 4.3 million.

The combined global Thorotrast-exposed cohort is circa 10 000 individuals, and, per population, the DK cohort (N = 1095, somewhat more men than women) was the largest (about 10% of IARC evaluated exposed persons).[23] The size of the DK cohort, the advanced nature of the DK health care system, and its availability to basically the entire population, may implicate a relatively intense application of Thorotrast in DK. Furthermore, Thorotrast was "virtually the sole contrast medium used in DK prior to 1945".[16] The DK population accounted for only 0.5% of the population in the industrialized world in 1950, but we assume that Thorotrast use was 5-times more common than average in the industrialized world overall (considering that there were countries, such as NO and probably others, which did not use this contrast medium). If this was true, the DK exposed population would account to 2.5% of the estimated 10 million, that is, 250 000 exposed individuals, of which more than half (140 000) were men.

Population cumulative incidence is available up to 75 years in NORDCAN. Between 1955 and 1994 male incidence of GBC was 1.5/100 000 (N = 1923) in DK men and 0.8/100 000 (N = 850) in NO men, with respective cumulative incidences of 0.23% and 0.13%. We consider the NO incidence of 0.13% as the background rate and a 10-fold excess risk for Thorotrast in the exposed population (the IARC cited relative risk in DK was 17 for GBC but in Germany the risk was only 2.7; in a joint DK, SE, US study the risk was 11).[15,16] Thus the cumulative risk in Thorotrast exposed persons (140 000) should be 1.3% (10 × 0.13%), which would result in 1820 cases of GBC (140 000 × 0.013 = 1820). The total number of diagnosed GBCs in DK men in that period was 1923.

3.3 | Survival trends

Relative 1-year survival in GBC in men and women showed a steady increase from about 20% (1967-1971) to about 50% (2012-2016) (Figure 4A). For women the trend was similar but the survival was 5 percentage units below the male survival throughout (Figure 4B). Rates for NO were somewhat better than for the other populations, particularly in the 1980s when some male and many female periodic rates were significantly better than those for some other countries. For example, for period 1982 to 1986 relative survival for NO women was 33% (95% confidence intervals 27%-39%), compared to DK 18% (15%-21%), FI 20% (17%-23%) and SE 17% (15%-19%). This NO advantage was also evidenced in 5-year survival: NO 18% (14%-24%), DK 6% (4%-8%), FI 7% (5%-9%) and SE 6% (4%-7%) (Figure S3). Overall, relative 5-year survival for GBC increased modestly over the 50-year period, but even in the final period it was at 20% or less in all Nordic countries.

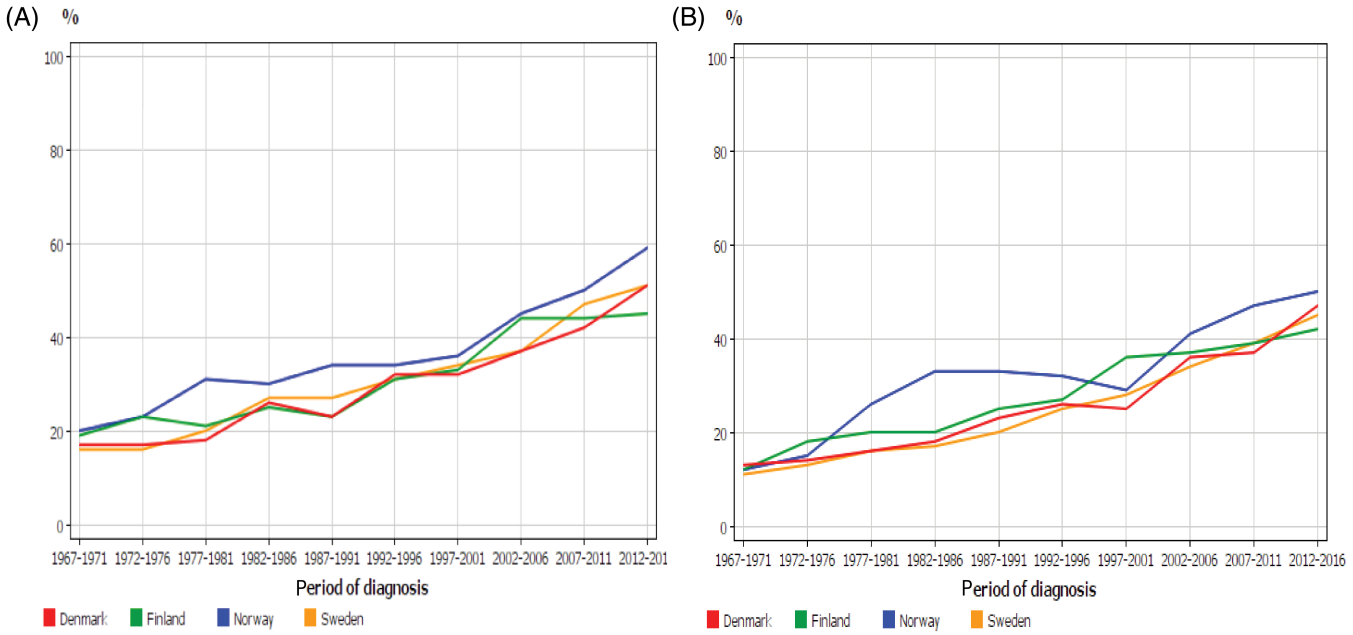

FIGURE 4 Relative 1-year survival trends in GBC in Nordic men (A) and women (B) [Color figure can be viewed at wileyonlinelibrary.com]

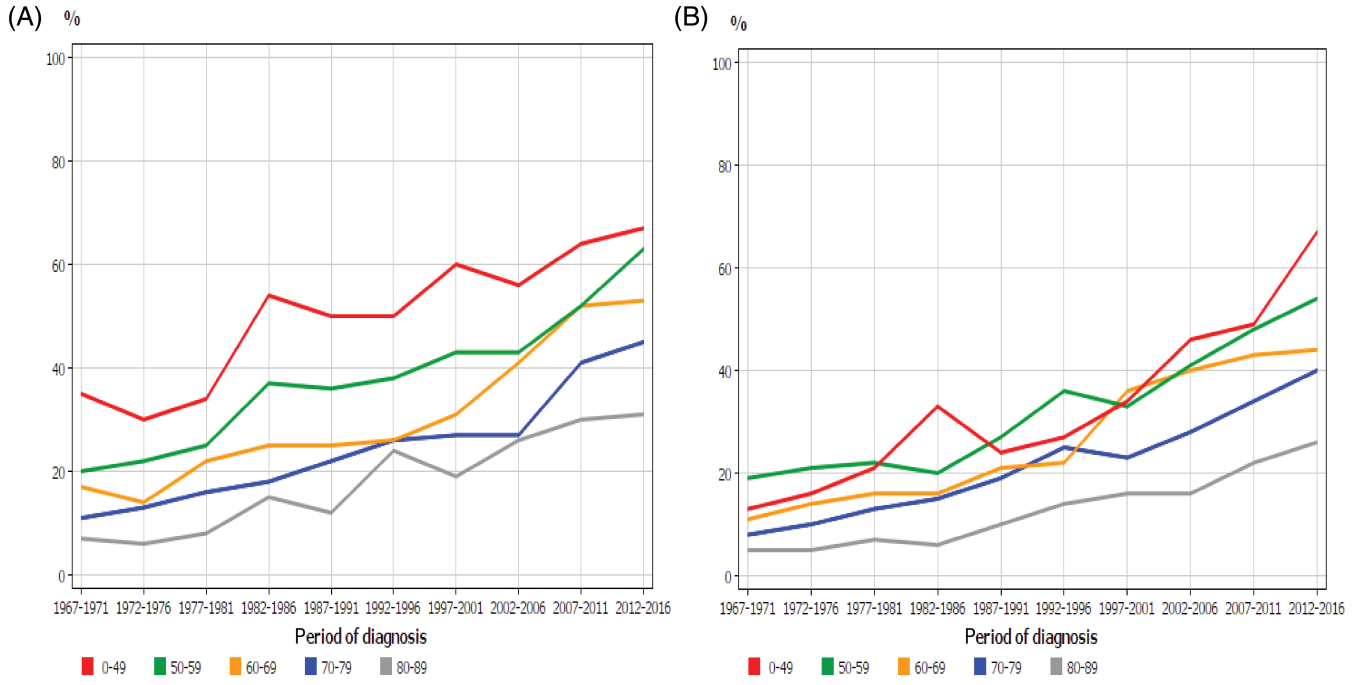

FIGURE 5 Age-specific relative 1-year survival in GBC among Swedish men (A) and women (B) [Color figure can be viewed at wileyonlinelibrary.com]

Figure 5 shows age-specific relative 1-year survival in GBC for SE men and women (with the largest patient numbers, and well representing the similar data for the other Nordic counties which are not shown). Relative survival decreased with chronological age; particularly those diagnosed before age 50 survived better than older patients. The survival age gap was largest for male GBCs.

4 | DISCUSSION

The declining incidence in GBC in industrialized countries since about 1980 has remained unexplained heretofore.[2,5] These trends have not correlated with disappearance of known risk factors, and the increasing prevalence of obesity would be expected to counteract the declining trend.[11] We paid attention to the curious covariation of incidence trends of GBC

in men and women in the Nordic countries with a prominent incidence peak at around 1980, and the lacking of this peak in NO. However, NO incidence matched FI incidence in the 1950s, and at around 2010 NO rates had caught up with the other Nordic rates in both men and women. This suggested the presence of a risk factor influencing GBC rates, with maximum effect around 1980, which was seen in other Nordic countries but not in NO. This appeared to be confirmed in birth cohort analysis, which showed that this factor increased GBC risk at age over 75 years in those born before year 1910 and then showed a declining influence. People who were born in 1910 reached age 75 in 1985, coinciding with the maximal incidence in DK, FI and SE. In NO, no birth cohort effect was observed. In later birth cohorts the maximal incidence also marked the period around 1980.

We tried to understand these differences with the hypothesis about associations of GBC rates with cholecystectomy rates. This explanation did not match long-term DK regional autopsy or SE hospital data, both setting the peak for cholecystectomy prevalence to the late 1950s.[23-26] This hypothesis was also refuted in a 16-year Swedish study comparing regional cholecystectomy and GBC rates; the results showed nonsignificant positive correlation between the rates, suggesting that cholecystectomy might actually increase the rate of GBC due to fortuitous diagnosis of incidental tumors.[7]

Of note, our literature review (and contacts with the authors) revealed that Thorotrast had been used in radiology in DK, SE and probably in FI from the 1930s until about 1950.[14-16] Thorotrast is known to increase hepatobiliary cancer risk, including GBC and biliary tract cancer, for up to 50 years after exposure.[16,27,28] The shapes of the incidence curves matched well the assumed effects of Thorotrast and birth cohort data. But what about NO? We found no publications on Thorotrast from NO, and when we contacted a retired NO radiochemistry professor, he confirmed that there has been no documented Thorotrast use in NO. This appeared to strengthen our suspicion regarding the role of Thorotrast, which may not be unique to the Nordic countries, as Thorotrast-related cancer data have been published from many industrialized countries, including United States, Canada, Germany, Japan, United Kingdom and Portugal.[15,29] Thorotrast has been tested in many animal species which were able to show its carcinogenic potency in the course of the test period of a few years.[14] Unfortunately these studies were carried out in the 1980s, and not 50 years earlier when they would have informed about risk to patients.

We addressed the question if it is plausible that an agent used for specific medical purposes (such as Thorotrast) could influence the macroepidemiology of GBC, for which many other possible risk factors exist. It was assumed that 140 000 DK men were exposed to Thorotrast causing a 10-fold risk of gallbladder cancer. As a consequence, 1420 attributable cases of GBC were assigned to Thorotrast when at the same period 1923 were diagnosed. If the assumptions were correct, it appeared indeed feasible that Thorotrast was a possible cause for the incidence peak at around 1980 in Nordic countries other than NO. The excess risk in the other countries lasted about 30 years, during which approximately half of GBCs were associated with this exposure.

The systematic incidence profiles for GBC between the Nordic countries prompt further questions, such as why DK incidence increased earlier than that for SE or FI, and why was the SE incidence maximum higher than that of DK or FI? In theory, part of the answer could be that Thorotrast use started earlier in DK than in SE and FI, and that the injected doses were higher in SE than in DK and FI. However, no documentation is available.

Among other factors that may influence risk of GBC between the Nordic countries, fish consumption has been clearly highest in NO (https://landgeist.com/2021/01/14/seafood-consumption-in-europe/). In Japan, high consumption of fish has been reported to be protective for bile duct cancer and GBC.[30] Furthermore, data have been provided on benefits of n-3 polyunsaturated fatty acids as dietary compounds offering protection against radiation effects on cancer cells and cancer progression.[31] We thus wondered if the low rates for GBC in NO could be in part due to diet. However, this hypothesis did not seem to allow for the early equal GBC rates between NO and FI nor "catching up" of the NO GBC rate with the rates of the other Nordic countries. Nevertheless, fish consumption has increased in SE, FI and DK and therefore it is not impossible that fish and its omega-3 fatty acids play some role in a multifactorial situation.[31] Finally, international rates for GBC differ and as the immigrant population is relatively large in the Nordic countries we were able to exclude the contribution by immigrant populations from published SE data.[1] Chilean immigrants had a significantly higher GBC incidence (N = 8) than native Swedes (N = 8000) but the case numbers even for all immigrants accounted for only 5% of all cases in SE.[32]

Survival in GBC has been poor, but over the 50-year period covered here it has improved, 1-year survival reaching over 40% for women and around 50% for men. Age-group specific survival showed large differences in favor of younger patients. Improvement was also seen in 5-year survival but it remained at or below 20%, probably marking those patients whose tumors were diagnosed early and successfully operated radically. Most likely both early detection and improved treatment have contributed to the advances in survival. Relative survival was somewhat better in NO compared to the other countries, particularly around the 1980s, suggesting that the excess GBC (probably Thorotrast associated) resulted in worse survival than that of NO tumors. This could be explained by alpha radiation causing particularly aggressive tumors. However, as we lack stage data for GBC, the results are not conclusive.

The study has several limitations, first, it is descriptive and allows no causal conclusions. Most importantly, documentation of the use (or nonuse) of Thorotrast in NO is based on expert testimony. Second, the reliability of GBC diagnostics and coverage of cancer registration, particularly in the early period, may be suboptimal. However, the quality indicators for the included cancers, cited in Section 2, attested for a reasonable quality, and by no means singled out NO. Third, we were limited to the diagnostic classification used by NORDCAN which did not allow identification of the defined cancer entities (gallbladder and extrahepatic bile ducts) but for women GBC was the main type. Thorotrast is, however, a risk factor for both of these cancers.[16] Whether histology or genetic basis of GBC may differ between

various populations is not known but Thorotrast related cancers were largely similar between European and Japanese populations.[15,33]

Large international variations in the incidence of hepatobiliary cancer are known but large historical differences between the Nordic countries are almost unique to cancers other than those related to smoking.[34,35] Our analysis showed that NO GBC rates were at the level of FI rates in the 1950s, and they caught up with the other Nordic rates in 2010, demarcating a half century when the rates for other Nordic countries rapidly increased from the background rate, and then returned to levels seen in NO. The uniformity of this increase and its return implicated a defined cause, also supported by birth cohort analysis.

In view of the well documented carcinogenic effects of Thorotrast on GBC and biliary tract cancer it is surprising that the there are no previous studies suggesting links between Thorotrast and macroepidemiology of GBC. Outside the Nordic countries, the reason may be lower population exposure to Thorotrast, lack of reliable historical epidemiological data on GBC, or both. Survival in GBC has improved in all countries, and interestingly, there appeared to be a small NO advantage in the period of the peak incidence for the other Nordic countries. By all accounts, the Thorotrast cancer epidemic is over by now, but the present data suggest that it was a true epidemic that influenced cancer risks and shook the foundations of medical ethics. The Thorotrast story provides a cautionary example on the risks of diagnostic tools. On the other hand, it demonstrates the utility of epidemiological studies in identifying risks to society and individuals.

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CONFLICT OF INTEREST

Akseli Hemminki is shareholder in Targovax ASA. Akseli Hemminki is employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

AUTHOR CONTRIBUTIONS

Design: Kari Hemminki, Akseli Hemminki. *Acquisition of data*: Kari Hemminki. *Statistical analysis and interpretation*: Kari Hemminki, Akseli Hemminki, Asta Försti, Otto Hemminki. *Manuscript writing*: Kari Hemminki and Akseli Hemminki. *Approval of the final text*: All authors.

DATA AVAILABILITY STATEMENT

Publically available NORDCAN data can be accessed at (https://NORDCAN.iarc.fr/en/database#bloc2). Further information is available from the corresponding author upon request.

ETHICS STATEMENT

Aggregated data from a publically accessible database were used posing no ethical issues.

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SUPPORTING INFORMATION

Additional supporting information may be found in the online version of the article at the publisher's website.

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