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Long-term incidence in hepatocellular carcinoma and intrahepatic bile duct cancer in Denmark, Finland, Norway and Sweden, role of Thorotrast?

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Abstract

We analyzed long-term incidence trends in liver cancer (including hepatocellular carcinoma and intrahepatic cholangiocarcinoma) with an aim to interpret the changes in terms of known risk factors and hypothesize that historical exposure to Thorotrast, a radiographic contrast medium emitting alpha particles, has changed population rates. The NORDCAN database was used to collect cancer registry data from Denmark (DK), Finland (FI), Norway (NO) and Sweden (SE), which we used from 1953 (DK, FI and NO) and 1960 (SE) through 2019. Thorotrast, which caused a 100-fold risk of liver cancer was used in DK and SE, and probably also in FI between 1930 and 1950, but not in NO. The incidence trend for liver cancer showed a broad maximum at around 1980, most prominent and statistically significant in SE and DK men and women, and in all countries, a steadily increasing trend towards the end of follow-up. Incidence for NO was lower than for the other countries and the rates showed no peaking at around 1980. Birth cohort analysis identified a transient risk which could be dated to a period between 1930 and 1950 in countries other than NO. Considering a lag time between Thorotrast use and liver cancer appearance, the large incidence peak around 1980 in DK and DE was probably contributed by

Abbreviations: aapc, average annual percentage changes; BIC, Bayesian Information Criterion; CI, confidence interval; DK, Denmark; FI, Finland; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; HCV, hepatitis C virus; IARC, International Agency for Research on Cancer; ICD, International Classification of Diseases; NO, Norway; SE, Sweden.

Thorotrast but considering the ecological nature of the findings, the association should be considered cautiously as hypothesis generating. The late increase in liver cancer risk is most likely lifestyle related and largely preventable.

KEYWORDS

alcohol, hepatitis virus, hepatocellular carcinoma, risk factors

What's new?

The radiographic contrast medium Thorotrast, which was later found to cause a 100-fold increased risk of liver cancer, was widely used in Denmark and Sweden between the 1930s and the 1950s, but not in Norway. A large transient liver cancer incidence peak was observed in both sexes around 1980 in Sweden and Denmark, but not Norway. Comparison of incidence rates between Norway and Sweden/Denmark suggests that Thorotrast could have contributed to half the liver cancers in Sweden/Denmark over a 30-year period. The more recent increasing trend in liver cancer in all Nordic countries may be due to lifestyle-related, preventable causes.

1 | INTRODUCTION

In the Nordic and other western countries, hepatocellular carcinoma (HCC) and intrahepatic cholangiocarcinoma are relatively rare cancers but their incidence shows large international variation correlating with known risk factors.[1,2] Focusing on northern European risk factors of HCC, they include alcohol-related liver cirrhosis, chronic infection by hepatitis B (HBV) or C virus (HCV), obesity, low physical activity, type 2 diabetes, nonalcoholic metabolic liver disease, smoking, autoimmune diseases and family history.[1-7] According to the Swedish national HCC register, covering years 2009 to 2016 and 3376 patients, the underlying liver disease was caused by HCV in 30%, alcohol in 25% and HBV in 6% of the patients.[8] Diabetes and nonalcohol-induced steatohepatitis have been reported since 2013, and then each accounted for close to 4% of HCC. Cholangiocarcinoma shares many risk factors with HCC but associations with HBV and HCV and alcohol are weaker.[1,9-11] All hepatobiliary tract cancers were increased after exposure to Thorotrast, an alpha particle emitting radiographic contrast agent, used widely between the 1930s and the 1950s.[9,12] Around 60% of the dose was retained in the liver, and the risk was increased 100-fold.[9,12] According to the International Agency for Research on Cancer (IARC) working group, tumors were approximately two-thirds carcinomas (predominantly cholangiocarcinomas) and one-third hemangiosarcomas.[12] A standard dose of 20 mL of Thorotrast caused cancer in almost all exposed individuals, and the risk was observed up to 50 years postexposure.[13]

We use the NORDCAN database to identify "liver cancer," which includes HCC and intrahepatic cholangiocarcinoma.[14,15] The latter is a small part of male liver cancer but it may account for 1/3 for women; we call these cancers here "liver cancer."[10,16,17] Our interest in the Thorotrast hypothesis was kindled by our recent findings on gallbladder cancer trends in the Nordic countries which supported the hypothesis of Thorotrast contribution: incidence peaked at around 1980 when Thorotrast-associated cancers were diagnosed in Denmark (DK) and Sweden (SE) but no peak was noted for Norway (NO) with no documented Thorotrast use.[18] We will analyze the incidence tends in liver cancer (including intrahepatic bile ducts) based on cancer registry data from DK, Finland (FI), NO and SE. The unique aspects of the Nordic cancer registries are that they were the first national cancer registries in the world allowing a long observation time.

2 | MATERIALS AND METHODS

We use the NORDCAN database, which is a compilation of data from the high-level Nordic cancer registries, as described[14] (https://NORDCAN.iarc.fr/en/database#bloc2). The ICD-10 code used for liver cancer was C22, that is, HCC, intrahepatic cholangiocarcinoma and some very rate entities. Incidence data were available from 1943 in DK, 1953 in FI and NO and 1960 in SE to the end of the year 2019 or 2016. However, analysis of the early DK liver cancer data has shown the inclusion of metastatic liver cancers in the early years and we thus started DK incidence follow-up from 1953.[19] NORDCAN contains no histology data but we had a possibility to check liver cancer histology records in the SE cancer registry.

Age-specific incidence trends were analyzed using joinpoint (segmented) lognormal regression models (using log2-transformation of the incidence rate), fitted separately for different countries and both sexes. The joinpoint models were fitted via a "segmented" package for "R" statistical software.[20,21] The numbers of breaking points (maximally 5) were determined using a Bayesian Information Criterion (BIC; model with the lowest BIC was selected) whereas their exact positions were obtained automatically via "segmented" function (with bootstrapping) of the "segmented" R package.[20,22] Starting points for the iterative process were chosen arbitrary according to visually apparent changing trends. The joinpoint models were used to estimate annual percentage changes (apc) and their 95% confidence intervals (95% CIs). Next, we fitted the same joinpoint models using "lm" function (using the previously detected breaking points), implemented in the R software, and performed nonparametric bias-corrected and

accelerated bootstrap simulations (5000 resamplings) to get CIs for the segment-specific apc in the incidence rates (Table S1).[23] Figures were created using basic graphic tools implemented in the "R" statistical software.[21]

The Nordic Cancer registries are generally considered of high quality but we and others have shown by comparing hospital discharge and death registers that liver cancer reporting is lower than that for many other cancers, and in the past quality could have been lower.[24] NORDCAN provides data on quality indicators, the proportion of microscopically verified cases (>80% for DK and NO men, >90% for FI and SE men, 75% for DK and NO women, 85% for FI women and >90% for SE women), cases included only from death certificates (low for all countries) and mortality-to-incidence ratio as a measure for coverage (80%-100%). These are internationally respectable levels of quality.[25]

3 | RESULTS

Patient numbers, median diagnostic ages and incidence rates of liver cancer (HCC and cholangiocarcinoma) are shown in Table 1 in two periods, 1980-1984 and 2015-2019. In the first period, incidence rates were highest for SE men and women, and the rates in NO were less than half of those in SE. In the last period, NO rates were still the lowest but the difference with the other countries had narrowed. Male rates are over two times higher than the female ones. Median diagnostic ages were somewhat higher for women compared to men.

3.1 | Incidence

Age-standardized incidence trends were analyzed for the Nordic populations, starting from 1953 (SE 1960). Points in Figure 1A-D show annual incidence rates and lines were fitted with joinpoint segmented models. In all countries, male rates were about two times higher than female rates. NO incidence is below that in the other countries. SE curves show a prominent maximum in the 1980s, and this is also visible in the DK data. In all countries, incidence increased toward the end of follow-up, and in FI men the increase started already in the 1970s. On top of each panel, annual percentages changes (apc) are shown; these are all showing a significant increase, except for DK female data. The bars on the x-axis show the breaking points detected by the joinpoint model.

In Figure 1E, apc changes are shown for segments separated by joinpoint breaking points. The underlying data are shown in Table S1. The data for DK and SE men and women show a significant increase in apc toward 1980 and a significant decline before 2000. FI data are inconsistent, but NO data show apc segments with consistent upward trends for females and generally upward trend also for males, interrupted with only a modest and statistically insignificant decrease around 1990. Notably, the upward incidence curves towards the end of follow-up were significant in all countries and both sexes.

Analysis by birth cohort was done for SE and NO men for age groups 50 to 84 years (Figure 2). The data for SE showed a very strong influence on the birth cohort with a maximal incidence at age 80 to 84 in the birth cohort of 1900 (Figure 2A). In subsequent birth cohorts, the diminishing peaks shifted to younger ages. A new increase in risk started to emerge from birth cohorts from 1930 onwards. For NO men, there was a small indication of incidence shifts in birth cohorts around 1900 but these were overshadowed by generally higher incidence in later birth cohorts (Figure 2B).

Female SE birth cohort data agreed with the male data with a strong influence on birth cohort and maximal incidence at age 80 to 84 in the birth cohort of 1895. However, there was only a modest increase in incidence in the youngest birth cohorts (Figure 3A). Birth cohort data for NO women showed birth cohort-related increases in incidence over time (Figure 3B).

Birth cohorts for DK and FI are shown in Figures S1 and S2. The NORDCAN cohort analysis tool does not allow the definition of the birth periods. Thus, it was not possible to exclude the unspecific liver

TABLE 1 Numbers of liver cancer patients, their median diagnostic ages and incidence rates (world) in the Nordic countries, 1980-1984 and 2015-2019

	Liver cancer (HCC and intrahepatic cholangiocarcinoma)					
	Men			Women		
Country period	N	Age at diagnosis	Rate/10^5	N	Age at diagnosis	Rate/10^5
1980-1984						
Denmark	743	69	3.8	543	72	2.0
Finland	558	69	4.0	462	73	1.9
Norway	304	68	1.9	188	70	1.0
Sweden	1859	67	4.8	1285	75	2.6
2015-2019						
Denmark	1709	71	5.6	705	72	2.1
Finland	1876	72	5.9	865	75	2.2
Norway	1028	70	4.1	581	73	2.0
Sweden	2766	70	5.4	1299	72	2.3

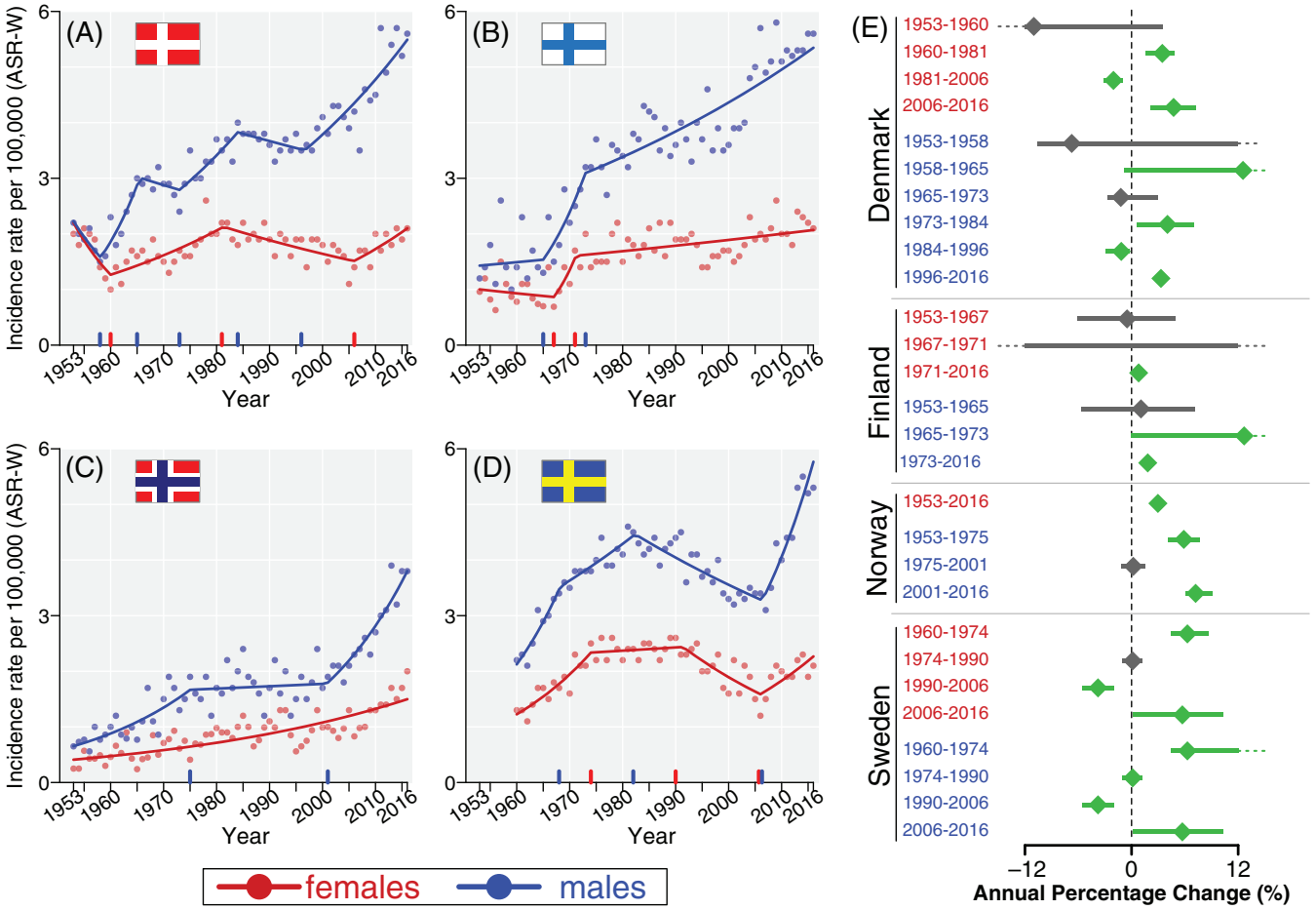

FIGURE 1 Time course of age-standardized (by the world standard population) incidence of liver cancer between 1953 and 2016 (A-D), separately for males (top curves) and females, across four Nordic countries: (A) Denmark, (B) Finland, (C) Norway and (D) Sweden. Points represent year-specific incidence rates whereas lines show predictions from joinpoint (segmented) lognormal regression models. Estimated Annual Percentage Changes (apc) and their 95% confidence intervals (95% CI) were estimated via the joinpoint models. The joinpoint models automatically identified 0-5 breaking points per population; all breaking points are marked as vertical lines at the bottom X-axis of the plots A-D. The average apc for Denmark was −0.1% (95% CI: −0.6 to 0.4) for females and 2.1% (1.8 to 2.4) for males; Finland: 1.7% (1.2 to 2.2) for females and 3.1% (2.6 to 3.6) for males; Norway: 3% (2.4 to 3.5) for females and 4.1% (3.6 to 4.7) for males; Sweden: 1.6% (1.2 to 2) for females and 2.6% (2.3 to 2.9) for males. (E) apc in the incidence rates (marked as diamond), estimated specifically for different time segments divided by the breaking points. 95% confidence intervals of the segment-specific apc estimates were constructed via non-parametric bias-corrected and accelerated bootstrap simulations (horizontal lines). The green color in (E) indicates that the *P*-value (based on percentile bootstrap) for the trend in a given time segment is <.05 (for black diamonds *P*-value is higher). Dotted lines imply that the limits of the confidence intervals fell out of the visualized range (from −12 to 12%). See Section 2 and Table S1 for details [Color figure can be viewed at wileyonlinelibrary.com]

cancers in the early DK birth cohorts; one could still see the peaks at age 75 to 79 in the birth cohorts of 1900-1920 in Figure S1.[19] The FI birth cohort analysis was masked by the continuously increasing incidence from 1965 onwards (Figure 1). Yet in birth cohorts of 1910-1920, an incidence peak was noted for men and women at age 70 to 74 years in Figure S2.

3.2 | Estimation of Thorotrast associated cases in Sweden

Is it plausible that an agent, such as Thorotrast, applied in a defined patient population would influence epidemiology at the population level? For the answer, we compared SE and NO liver cancer rates, assuming that the NO liver incidence rate was unaffected by the extra risk (suggested to be Thorotrast), and the excess risk in SE was due to this factor. The estimation is hampered by the universally lacking data on the exposed population. We used the IARC cited (minimal global) figure of 2.5 million which was extrapolated from the production figures (IARC cited probable exposed population was 10 million).[9] Thorotrast was used in many industrialized countries with a population of 800 million (Europe 550 million, USA 150 million and Japan 85 million) in 1950, when the Swedish population was 7.0 million. The combined global Thorotrast-exposed epidemiological cohorts account for somewhat more than 10 000 individuals, and, per population, the SE cohort (N = 1117, men to women ratio 1.3) was the largest after Denmark, which combined with the advanced health care system to the population at large may implicate a relatively intense application of

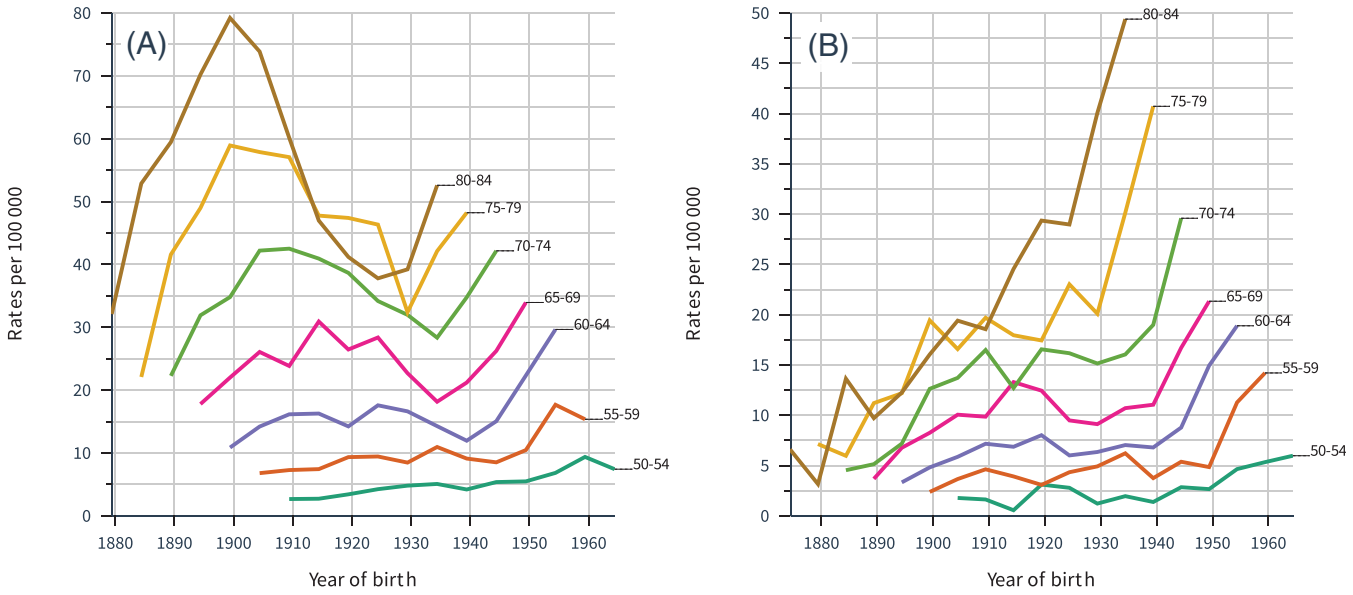

FIGURE 2 Birth cohort analysis of liver cancer in Swedish (A) and in Norwegian (B) men [Color figure can be viewed at wileyonlinelibrary.com]

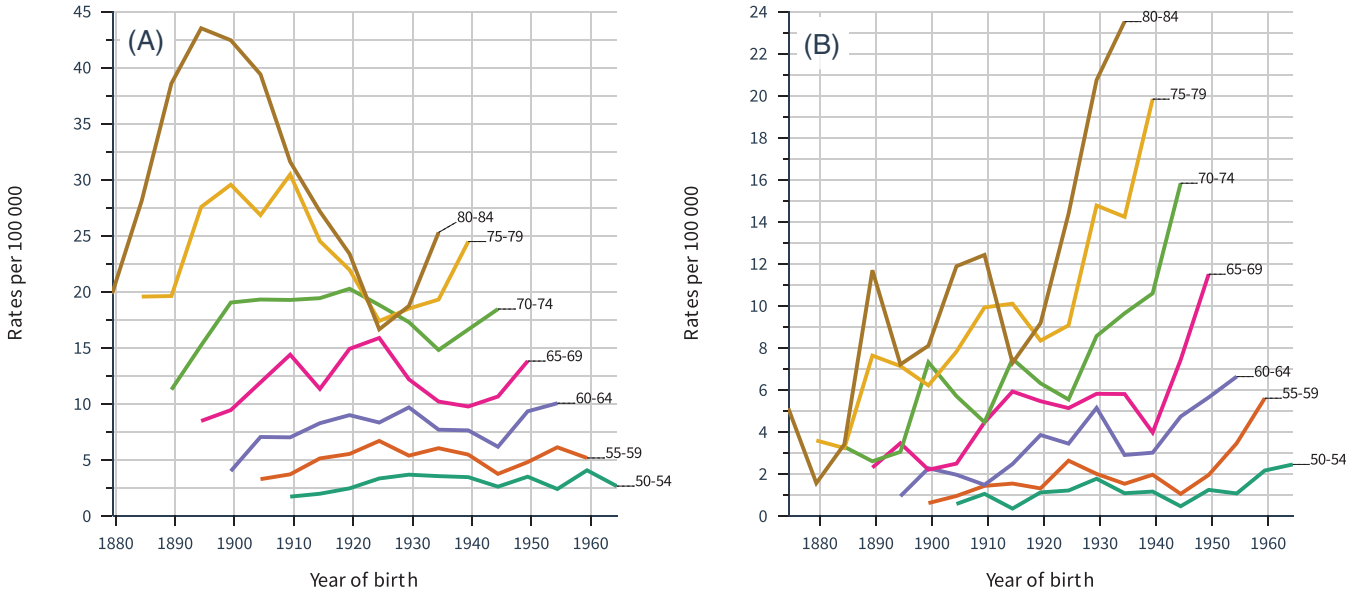

FIGURE 3 Birth cohort analysis of liver cancer in Swedish (A) and in Norwegian (B) women [Color figure can be viewed at wileyonlinelibrary.com]

Thorotrast. The SE population accounted for only 0.9% (7 million of 800 million) of the population in industrialized world in 1950, but we assume that Thorotrast use was more common in SE than in the average country in the total industrialized world (considering the free high-level health care and countries, such as Norway and probably others, which did not use this contrast medium). We thus assume (most likely underestimation) that the SE exposed population would account for 2.0% (and not 0.9%, ie, 2.2 times the global average) of the estimated 2.5 million, that is, 50 000 (0.02 × 2.5 million) exposed individuals, of which more than half (30 000) were men. The population cumulative liver cancer incidence from NORDCAN is available up to age 74 years. Between 1960 and 1999 the incidence of liver cancer was 3.0/100 000 (N = 7264) in SE men and it was 1.4/100 000 (N = 1411) in NO men (relative risk 2.7) with respective cumulative incidences of 0.47% and 0.19%. We consider then the extra (possibly Thorotrast) risk, taking the NO cumulative incidence of liver cancer (0.19%) as the background rate. The estimated relative risk of liver cancer in the exposed population was 100-fold (the IARC cited relative risk in Denmark was 121 for liver cancer; in Germany, the risk was 129; in Portugal, it was 71).[12] Thus, the cumulative risk in Thorotrast exposed men (30 000) should be 19% (100 × 0.19%), which would result in 5700 cases of liver cancer (30 000 × 19%). Thus, the calculated excess of 5700 is a large proportion of the observed 7264 cases. There are many uncertainties in the above calculation, and Thorotrast caused liver cancers up to any age not only up to age 74 years that we used because cumulative risks were available to that age (for higher ages competing risks make the interpretation complicated).

4 | DISCUSSION

In analyzing Nordic gallbladder cancer incidence trends, we observed a broad maximum at around 1980 in men and women; this was the only broad peak for gallbladder cancer in DK, FI and SE and no peak was observed for NO.[18] Use patterns and coincident timing lead us to speculate that Thorotrast could have contributed to these findings.[18] On further analysis of liver cancer incidence, we paid attention to the curious co-variation of incidence trends between liver and gallbladder cancers. As HCC and gallbladder cancer do not share many risk factors, we reasoned that the remarkably uniform incidence patterns may not be a coincidence.[1,2,9,10] Further, the covariation of liver cancer with gallbladder cancer was limited to the main peak at around 1980, and the increasing incidence in liver cancer after the year 2000 was unique to liver cancer, suggesting a different etiology.

Thorotrast contains thorium 232 which is an alpha particle emitter. The IARC working group estimated the number of exposed individuals ranging from more than 2.5 million probably to 10 million persons.[9,12] It is a remarkably potent liver carcinogen, with a 100-fold relative risk, and it caused also gallbladder cancers.[9,12] Thorotrast could be the common denominator explaining the broad peaks at around 1980, some 30 to 50 years after its use in the Nordic countries.[13] The birth cohort analysis showed that the risk of liver cancer was highest at age 80 to 84 in birth cohorts of 1900, thus these cancers were diagnosed between 1980 and 1984 matched the 20- to 50-year latency from treatment, which for some 80% of individuals took place at ages 30 to 59 years.[13] Much of the epidemiological analysis on the global carcinogenic effects of Thorotrast has been performed in DK and SE.[26-28] However, the exceptions are FI and NO lacking documentation about Thorotrast use but in FI, there is anecdotal data on its use. We have been in contact with a retired NO radiochemistry professor who confirmed that there has been no documented Thorotrast use in NO. This is further evidence that Thorotrast was associated with the liver cancer epidemic around the 1980s in DK and SE but not in NO (Figure 1). We show a calculation with assumed exposed population and Thorotrast-related relative risks that the influence is strong enough to increase population-level epidemiological trends and could have caused the excess risk in SE between the years 1960 and 1999. The likelihood of finding population-level epidemiological changes for other Thorotrast associated cancers (such as leukemia, bone and connective tissue cancers) is relatively meager, due to low risks in rare cancers.[9] Replication of the findings in other settings would require long-term, high-level cancer registration and prevalent historical exposure.

Thorotrast has not been implicated in previous studies considering population-level epidemiology. Klint and co-workers used the same Nordic data on liver and gallbladder cancers from the years 1964 to 2004.[15] They observed the peaks at around 1980 but did not comment. Jepsen and coworkers studied incidence in bile duct cholangiocarcinomas in DK from 1978 through 2002.[29] They reported a decrease in incidence over the observation time but could not explain it by known risk factors for which they included Thorotrast.[29] The reported incidence of intrahepatic cholangiocarcinoma peaked in age group over 79 years in 1983-1987 at 9.87/100 000 compared to 2.60/100 000 from 1998 to 2002. A large difference was seen also in the age group 60 to 79 years, 4.67/100 000 compared to 2.59/100 000.[29] For both comparisons, the 95% CIs were non-overlapping. A similar difference was also seen for extrahepatic cholangiocarcinoma. These data are very relevant to the Thorotrast hypothesis because cholangiocarcinoma was one of the main target cancers of Thorotrast and because of the matching timing.[9]

The evidence implicating Thorotrast, although not based on individual exposure assessment, is more than circumstantial: the incidence of liver cancer increased in DK and SE to about 1980 and then declined, matching the use period between 1930 and 1950, considering known latency times and relatively young target population; birth-cohort analyses matched the known exposure period; the timing of incidence changes agreed between men and women; the additional risk at around 1980 was approximately equally high in men and women but the higher incidence in men was related to historically higher rates of liver cancer, as known for DK and USA in the 1940s (probably alcohol-related).[19,30] Most importantly, all these changes were lacking or were much less noticeable in NO, where Thorotrast was not used. Considering any alternative explanations, alcohol consumption increased in all Nordic countries between 1960 and 1975 but the effects are seen in the increases at around 2000 (see below).[31] HBV and HCV infections were rare in the Nordic countries before 1970 (see below), and the weaker risk factor for liver cancer, smoking, decreased in all countries since the 1960s.[31] An extensive study on occupational risks in cancer found uniform patterns for liver cancer between the Nordic countries[16]; the NO rates did not differ from the other Nordic rates for chemical process workers (potential exposure to vinyl chloride) nor for gardeners (potential exposure to pesticides). IARC has stated that positive associations have been reported between arsenic exposure and liver cancer, in contrast to "sufficient evidence" for arsenic and urinary bladder cancer.[32] While the historical population exposure to arsenic is not known in the Nordic countries, the NORDCAN database enables analysis of past bladder cancer incidence rates.[33] For men, the NO rates were at the level of FI and SE, and below the DK rates since 1960. For women, the NO and SE rates were almost superimposable and they were between the highest rates in DK and lowest in FI.[33] If bladder cancer rates could serve as proxies for arsenic exposure, NO data did not deviate from the other countries. None of the alternative risk factors would explain the peak incidence at around 1980 and the deviant experience of NO.

Thorotrast was a sad episode in medical applications of novel technology in which improvements in imaging were so large that considerations of prior safety assessment were bypassed. Animal experiments showed post hoc the carcinogenic potency of Thorotrast, as cited by IARC.[12] Such experiments were completed in a few years in the 1980s coincident with the peak of human epidemy.

There is a major increase in liver cancer incidence starting around 2000 and shared between the sexes in the Nordic countries. For primary liver cancer, alcohol is the main risk factor in the Nordic countries where the past consumption of alcohol (until 1970) was highest in DK and SE and much lower in FI and NO.[16] At around 1970 alcohol

consumption increased in DK and FI and these were the leading countries from 1980 onwards when the Nordic consumption stabilized (http://norden.diva-portal.org/smash/get/diva2:968444/FULLTEXT01.pdf).[16] More recently, deaths due to alcoholic liver disease were highest in FI men and women in 2015 (25.8 and 8.6, all age-standardized rates are per 100 000 population), followed by DK men and women (14.7 and 5.8).[34] For deaths in HCC, the order was the same as above but the differences were smaller, at most 3-fold. Other lifestyle related risks factors of liver cancer, including obesity, physical inactivity and diabetes have increased in all Nordic countries (https://journals.uio.no/NJHE/article/view/2717/2487). Moreover, it has been suggested that improved imaging techniques may have contributed to increased incidence and earlier diagnoses, and thus reducing undiagnosed cases.[35]

HBV diagnostics has been possible since 1969 in Sweden, and the association of blood transmitted infections to HBV was confirmed among rare cases of infected sportsmen and health care personnel.[36,37] A survey of first-time blood donors around 2010 reported positivity for the hepatitis B surface antigen in DK 0.016%, FI 0.000%, NO 0.028% and SE 0.043%; for the antihepatitis C virus antibody the percentages were 0.016, 0.025, 0.033 and 0.059.[38] SE men and women had the highest death rates for viral hepatitis in 2015, exceeding FI men 11-fold and FI women 6-fold; the difference between SE rates with DK and NO viral deaths was about 3-fold.[34] Diagnostics of HCV have been possible only since 1989, and the first SE prevalence estimates HCV infection gave a population prevalence of about 0.5% at the beginning of the 1990s.[39] Infections and HCC in infected persons have increased with time but there is no indication that HCV infection would have been prevalent at the time before 1989.[40] In DK chronic hepatitis C infection was found in 0.2% of the adult population with a decreasing trend.[41]

The study has limitations, first, it is ecological and all inferences about underlying causes are indirect. This applies also to the use of Thorotrast in NO where we relied on lacking publications and expert testimony. No estimates on the size of the exposed populations are available. Second, the reliability of liver cancer diagnostics may be lower than for many other cancers, particularly among old patients.[24,42] Birth cohort analysis showed that increased risks in SE were not limited to old ages. Because early data from DK was reported to include metastatic liver cancers, DK follow-up was started in 1953.[19] The cited quality indicators (in Section 2) were overall reassuring.

In summary, the analysis concludes that while the differences in liver cancer incidence between the countries were earlier large, they have diminished and the NO rates are approaching those of the other countries. We show evidence that the Thorotrast episode coincided with an epidemic of liver cancer that lasted for some 30 years. To the best of our knowledge, Thorotrast has never been associated with population trends in liver cancer in spite of being a potent liver carcinogen. Thanks to the Nordic tradition of high-quality cancer registration this association appears now plausible. Whether it is also related to a relatively large population exposure in DK and SE remains probably unanswered forever. The current concern is the recent increase in HCC incidence, for which prevention should be of critical importance. We assume that the drivers of the recent increase in liver cancer incidence are complex lifestyle factors, increasing obesity, physical inactivity and type 2 diabetes, which predisposes to non-alcoholic fatty liver disease, and alcohol at least in DK and FI.

Risk factors of HCC are known and should be intervened by moderation in alcohol consumption, avoidance of intravenous drug use with dirty needles, increased physical activity and avoidance of obesity. HBV vaccines work well as do antiviral therapies for chronic HBV and HCV infections. Infected persons should be encouraged to seek and keep medical contacts.[35]

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CONFLICT OF INTEREST

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

AUTHOR CONTRIBUTIONS

Kari Hemminki: Design. **Kari Hemminki:** Acquisition of data. **Kari Hemminki, Filip Tichanek, Akseli Hemminki, Asta Försti, Otto Hemminki:** Statistical analysis and interpretation. **Kari Hemminki and Akseli Hemminki:** Manuscript writing. **All authors:** Approval of the final text. The work reported in the study has been performed by the authors unless clearly specified in the text.

ETHICS STATEMENT

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

DATA AVAILABILITY STATEMENT

Publically available NORDCAN data can be accessed at (https://NORDCAN.iarc.fr/en/database#bloc2). The data that support the findings of our study are available from the corresponding author upon reasonable request.

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REFERENCES

1. Valle JW, Kelley RK, Nervi B, Oh DY, Zhu AX. Biliary tract cancer. *Lancet (London, England)*. 2021;397(10272):428-444.
2. Villanueva A. Hepatocellular Carcinoma. *N Engl J Med*. 2019;380(15):1450-1462.
3. Baumeister SE, Leitzmann MF, Linseisen J, Schlesinger S. Physical activity and the risk of liver cancer: a systematic review and meta-analysis of prospective studies and a bias analysis. *J Natl Cancer Inst*. 2019;111(11):1142-1151.
4. Hemminki K, Li X. Familial liver and gall bladder cancer: a nationwide epidemiological study from Sweden. *Gut*. 2003;52:592-596.
5. Liu X, Hemminki K, Försti A, Sundquist K, Sundquist J, Ji J. Cancer risk in patients with type 2 diabetes mellitus and their relatives. *Int J Cancer*. 2015;137(4):903-910.

6. Castro FA, Liu X, Försti A, et al. Increased risk of hepatobiliary cancers after hospitalization for autoimmune disease. *Clin Gastroenterol Hepatol*. 2014;12(6):1038-45.e7.
7. McGee EE, Castro FA, Engels EA, et al. Associations between autoimmune conditions and hepatobiliary cancer risk among elderly US adults. *Int J Cancer*. 2019;144(4):707-717.
8. Henriksson M, Björnsson B, Sternby Eilard M, et al. Treatment patterns and survival in patients with hepatocellular carcinoma in the Swedish national registry SweLiv. *BJS Open*. 2020;4(1):109-117.
9. IARC. Radiation. *IARC Monogr Eval Carcinog Risks Hum*. 2012;100(Pt D):1-441.
10. McGee EE, Jackson SS, Petrick JL, et al. Smoking, alcohol, and biliary tract cancer risk: a pooling project of 26 prospective studies. *J Natl Cancer Inst*. 2019;111(12):1263-1278.
11. IARC. IARC monographs on the evaluation of carcinogenic risks to humans. *Biol Agents Rev Hum Carcinogens*. 2012;100 (Pt B): 1-441.
12. IARC. Ionizing radiation, part 2: some internally deposited radionuclides. Views and expert opinions of an IARC working group on the evaluation of carcinogenic risks to humans. Lyon, 14–21 June 2000. *IARC Monogr Eval Carcinog Risks Hum*. 2001;78(Pt 2):1-559.
13. Travis LB, Hauptmann M, Gaul LK, et al. Site-specific cancer incidence and mortality after cerebral angiography with radioactive thorotrast. *Radiat Res*. 2003;160(6):691-706.
14. Engholm G, Ferlay J, Christensen N, et al. NORDCAN—a Nordic tool for cancer information, planning, quality control and research. *Acta Oncol*. 2010;49(5):725-736.
15. Klint A, Engholm G, Storm HH, et al. Trends in survival of patients diagnosed with cancer of the digestive organs in the Nordic countries 1964-2003 followed up to the end of 2006. *Acta Oncol*. 2010;49(5): 578-607.
16. Pukkala E, Martinsen JI, Lynge E, et al. Occupation and cancer - follow-up of 15 million people in five Nordic countries. *Acta Oncol*. 2009;48:646-790.
17. Zheng G, Sundquist K, Sundquist J, et al. Second primary cancers after liver, gallbladder and bile duct cancers, and these cancers as second primary cancers. *Clin Epidemiol*. 2021;13:683-691.
18. Hemminki K, Försti A, Hemminki O, Liska V, Hemminki A. 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. *Int J Cancer*. 2022;151:200-208.
19. Anderson IB, Sørensen TI, Prener A. Increase in incidence of disease due to diagnostic drift: primary liver cancer in Denmark, 1943-85. *BMJ*. 1991;302(6774):437-440.
20. Muggeo VMR. Segmented: an R package to fit regression models with broken-line relationships. *R News*. 2008;8:20-25.
21. RDC Team. A Language and Environment for Statistical Computing; 2022.
22. Burnham KP, Anderson DR. *Model Selection and Inference*. New York, NY: Springer; 1998.
23. Diciccio TJ, Efron B. Bootstrap confidence intervals. *Stat Sci*. 1996; 11:189-212.
24. Ji J, Sundquist K, Sundquist J, Hemminki K. Comparability of cancer identification among death registry, cancer registry and hospital discharge registry. *Int J Cancer*. 2012;131:2085-2093.
25. Bray F, Parkin DM. Evaluation of data quality in the cancer registry: principles and methods. Part I: comparability, validity and timeliness. *Eur J Cancer*. 2009;45(5):747-755.
26. Andersson M, Storm HH. Cancer incidence among Danish Thorotrast-exposed patients. *J Natl Cancer Inst*. 1992;84(17):1318-1325.
27. Andersson M, Vyberg M, Visfeldt J, Carstensen B, Storm HH. Primary liver tumors among Danish patients exposed to Thorotrast. *Radiat Res*. 1994;137(2):262-273.
28. Nyberg U, Nilsson B, Travis LB, Holm LE, Hall P. Cancer incidence among Swedish patients exposed to radioactive thorotrast: a forty-year follow-up survey. *Radiat Res*. 2002;157(4):419-425.
29. Jepsen P, Vilstrup H, Tarone RE, Friis S, Sørensen HT. Incidence rates of intra- and extrahepatic cholangiocarcinomas in Denmark from 1978 through 2002. *J Natl Cancer Inst*. 2007;99(11):895-897.
30. Polednak A. Trends in cancer incidence in Connecticut, 1935-1991. *Cancer*. 1994;74:2863-2872.
31. Storm HH, Engholm G, Hakulinen T, et al. Survival of patients diagnosed with cancer in the Nordic countries up to 1999-2003 followed to the end of 2006. A critical overview of the results. *Acta Oncol*. 2010;49(5):532-544.
32. IARC. *Monographs on the Evaluation of Carcinogenic Risks to Humans*. 100C ed. Lyon: IARC Press; 2012.
33. Hemminki K, Försti A, Hemminki A, Ljungberg B, Hemminki O. Incidence trends in lung and bladder cancers in the Nordic countries before and after the smoking epidemic. *Eur J Cancer Prev*. 2021;31:228-234.
34. Mårdh O, Quinten C, Amato-Gauci AJ, Duffell E. Mortality from liver diseases attributable to hepatitis B and C in the EU/EEA—Descriptive analysis and estimation of 2015 baseline. *Infect Dis*. 2020;52(9):625-637.
35. Jepsen P, Andersen MW, Villadsen GE, Ott P, Vilstrup H. Time-trends in incidence and prognosis of hepatocellular carcinoma in Denmark: a nationwide register-based cohort study. *Liver Int*. 2017;37(6):871-878.
36. Ringertz O. Some aspects of the epidemiology of hepatitis in Sweden. *Postgrad Med J*. 1971;47(549):465-472.
37. Christenson B. Epidemiology of hepatitis B in Sweden. *J Infect*. 1987; 15(3):269-277.
38. Hofstraat SHI, Falla AM, Duffell EF, et al. Current prevalence of chronic hepatitis B and C virus infection in the general population, blood donors and pregnant women in the EU/EEA: a systematic review. *Epidemiol Infect*. 2017;145(14):2873-2885.
39. Strauss R, Törner A, Duberg AS, Hultcrantz R, Ekdahl K. Hepatocellular carcinoma and other primary liver cancers in hepatitis C patients in Sweden—a low endemic country. *J Viral Hepat*. 2008;15(7):531-537.
40. Batyrbekova N, Aleman S, Lybeck C, Montgomery S, Duberg AS. Hepatitis C virus infection and the temporal trends in the risk of liver cancer: a National Register-Based Cohort Study in Sweden. *Cancer Epidemiol Biomarkers Prev*. 2020;29(1):63-70.
41. Nielsen S, Hansen JF, Hay G, et al. Hepatitis C prevalence in Denmark in 2016-an updated estimate using multiple national registers. *PLoS One*. 2020;15(9):e0238203.
42. Pukkala E, Engholm G, Hojsgaard Schmidt LK, et al. Nordic cancer registries—an overview of their procedures and data comparability. *Acta Oncol*. 2018;57:440-455.

SUPPORTING INFORMATION

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

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