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Brief Report

Major improvement in thyroid cancer survival of elderly patients in the Nordic countries

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Abstract

Objectives: We describe age-specific survival in thyroid cancer (TC) from Denmark, Finland, Norway, and Sweden over a 50-year period.

Design: Population-based survival study.

Methods: Relative 5-year survival data were obtained from the NORDCAN database for the years 1972-2021.

Results: In the first period 1972-1976, 5-year survival in TC in Finland, Norway, and Sweden was 90% or higher, but a strong negative step-wise age gradient was observed, which was worse for men than women. Over time, survival increased, and in the final period, 2017-2021, survival for all women and Danish men up to age 69 years was about 90% or higher and, for men from the other countries, only marginally lower. Even for older women survival reached 80%, for older men somewhat less.

Conclusions: Age disadvantage in TC survival was for the most part corrected over the 50-year period, and the remaining task is to boost survival for the oldest patients.

Keywords: prognosis, relative survival, anaplastic cancer, metastasis, trends

Significance

Survival in thyroid cancer has been highly disadvantaged for the old patients, probably because of diagnostic delays. It is known that survival is poor in anaplastic cancer that is mainly diagnosed at high age. Survival in anaplastic cancer has hardly improved and it probably now remains the main cause of mortality in the old patients. Understanding the pathobiology of anaplastic cancer may help to tackle it.

Introduction

Thyroid cancer (TC) is a heterogeneous disease that differs in clinical presentation and outcome. It may be classified into common well-differentiated and rare poorly differentiated types. Papillary histology is by far the most common type accounting for some 3/4 of all TC with an increasing incidence of particularly small tumours, which has been ascribed to screening and diagnostics with sensitive imaging tools.[1-3] According to a recent analysis, survival in TC is among the best of all solid cancers, 5-year relative survival reaching over 90% for women and close to 90% for men in the Nordic countries.[4] Patient characteristics that influence survival in many cancers, including TC, are stage and age at diagnosis.[5-7] While the influence of stage can be rationalized in terms of correlation with tumour spread, the association with age is less clear when stage has been adjusted for and it may be related to comorbidities and frailty that limit treatment.

We published recently a study on relative survival in TC in the Nordic countries Denmark (DK), Finland (FI), Norway (NO), and Sweden (SE) based on the NORDCAN database, but age-specific survival could not be analysed because this tool was lacking in the database.[8] However, this feature was recently added to the database allowing a 50-year analysis of

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age-specific relative survival that we hope will shed light on mortality in TC.

Methods

The data were obtained from the NORDCAN database 2.0, which has been created through collaboration between the Nordic cancer registries containing anonymous data on groups of patients.[9-11] The database was accessed at the International Agency for Cancer website (https://nordcan.iarc.fr/en) in the fall of 2023.[11] We extracted data on case numbers, age-specific incidence, and 5-year relative survival from 1972 until the end of 2021. Statistical analysis was performed using R statistical software (https://www.r-project.org) in the R studio environment (https://posit.co/). The trends in relative survival were modelled using Bayesian generalized additive models, as described previously,[12] using an adopted version of the code (https://github.com/filip-tichanek/nord_intestine). We fitted separate models for each country, including the main effect of the group (combination of age-specific groups and sex) and non-linear effect of time, modelled with thin plate regression splines (*mgcv* package). The female 60-69 year group was modelled as a reference level (intercept) with effects of the other groups having Gaussian prior (mean = 0, sigma = 50). For the purpose of modelling of temporal trends, the relative survival estimates for 5-year period time points were assigned to the middle of the periods. To model uncertainty associated with individual estimates, we used the lower bounds of confidence intervals provided by NORDCAN to calculate standard error under normality approximation.

Thyroid cancer statistics for SE were obtained from the website of the National Board of Health and Welfare (https://sdb.socialstyrelsen.se/if_can/val.aspx).

Results

Case numbers for TC in the 50-year period were (female/male) in DK 6692/2769, FI 12,745/4093, NO 8619/3257, and SE 14,122/5484. We analysed age-specific incidence for the Nordic countries at 2 different time points (Figure 1). In 1972, female and male incidence increased by age reaching 18/100 000 for women and 10/100 000 for men. In 2021, the female curve had shifted towards younger ages, and incidence 18/100 000 was reached already by age 40 years and it plateaued towards higher ages. Also, for men, the incidence had shifted towards younger ages, and the peak of 14/100 000 was reached before age 80 years. The proportion of 80-89-year-old women of all TC patients was about 6% in FI, NO, and SE (13% in DK) in 1972-1981 and it decreased to about 4% in 2012-2021 in all countries; for men, the decrease was from 15% (SE 9%) to 6% in all countries.

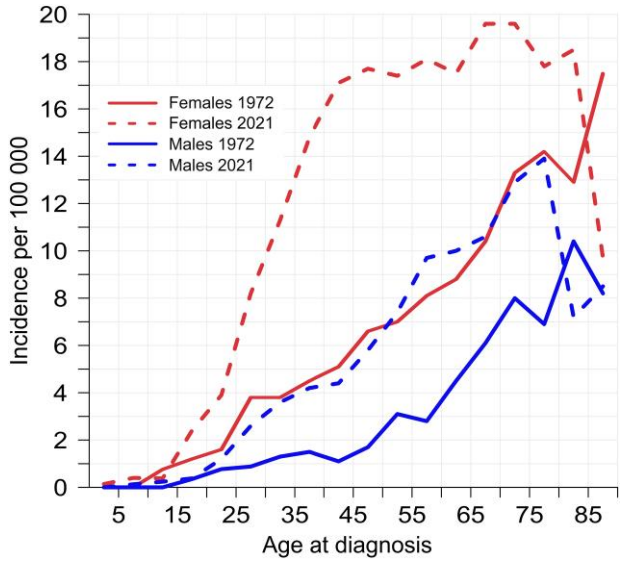

Figure 1. Age-specific incidence of thyroid cancer in Nordic countries (DK, FI, NO, and SE combined estimates) in 1972 and 2021 for female and male population. Data were obtained from the NORDCAN database.

In the period 2012-2021, the SE incidence (world standard) of female TC was 8.6/100 000 and male incidence 2.7/100 000. Anaplastic cancer was 2.2% of all for women and 7.0% for men.

Differences between age groups in female 5-year relative survival were strikingly large in all Nordic countries (Figure 2). In the first period, 1972-1976, survival for women in the age group below 50 years was already high, over 95% in all countries but DK. In the oldest patients (80-89 years), the starting level was barely over 10% in DK and below 40% in NO. Survival improved fast and most among the oldest. Finland and NO were able to show a survival of over 80% for all age groups but the oldest by 2007-2011. Remarkably, the oldest patients were part of the positive development and their survival reached about 80%.

Male age-specific survival data showed similar overall trends to the female data (observations for some older age groups were missing in the early period because of low number of cases) (Figure 3). Male survival was generally below female survival and the difference was largest among older patients. However, the gender gap narrowed over time.

In the final 5-year period in 2017-2021, the DK sex difference (all ages combined) was only 0.7% units; female survival for all TC was 92.4% (95% CI, 90.2%-94.7%), and male survival was 91.7% (88.3%-95.3%). The sex difference in the final period was largest in FI, 9.7% units, female survival 95.2% (93.7%-96.8%), and male survival 85.5% (82.3%-88.7%). The FI sex difference was the only statistically significant one among these countries (95% CIs did not overlap), and TC survival in FI women was the best and, in FI men, it was the worst of the Nordic countries. However, none of the female survival figures of 2017-2021 differed significantly between the countries nor did the male figures.

Relative survival by definition compares overall survival between the groups and elderly cancer patients may die of other causes more often than the reference population. We, therefore, analysed TC-specific mortality from NORDCAN (Figure S1). Mortality in TC was about 7-fold higher in 75- to 84-year-old patients compared with those diagnosed at age 50-59 years.

Discussion

The present NORDCAN data show an impressive improvement in relative 5-year survival for TC in the elderly population. The increase in survival for the 80- to 89-year-old population was from 10%-30% in 1972-76 to 80% in women and DK men 50 years later. SE men also approached the 80% level, but FI and NO men remained at around 60%. In the 1970s, survival in TC in FI, NO, and SE women below age 50 was over 95% and male survival was only slightly lower

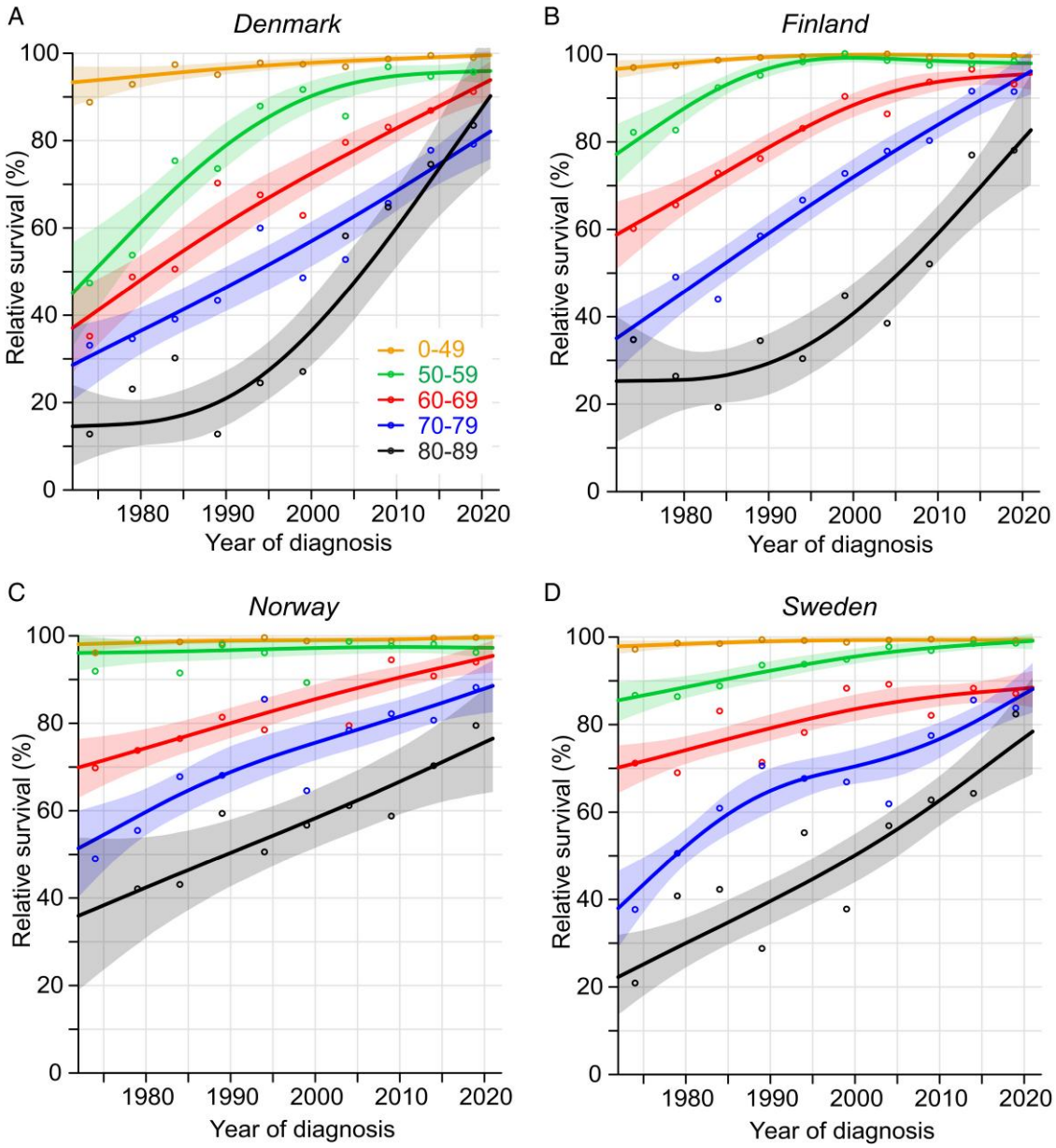

Figure 2. Relative 5-year survival trends in 5-year periods for female thyroid cancer in DK (A), FI (B), NO (C), and SE (D) from 1972-1976 to 2017-2021. Data were obtained from the NORDCAN database.

but survival decreased stepwise in successive older age groups. The positive time-dependent survival increase was shared by all age groups, and, in the end, survival for all women and DK men up to age 69 years was about 90% or higher and, for men from the other countries, survival was only marginally lower. The analysis shows the importance of age group–specific survival data, which helps pinpoint the underserved patient groups.

Thyroid cancer survival data were published in the first version of NORDCAN in 2010.[13] A steep negative age gradient in survival was reported but not commented on. In the EUROCARE II publication on TC (diagnosed in 1985-1989), age differences in 5-year relative survival were also noted and explained in terms of early-age papillary cancer with good survival and late-age anaplastic cancer with poor survival.[14] This explanation is probably more correct now (with a small survival disadvantage for 80+ year old) than then (with a large survival disadvantage for all elderly patients). Survival in anaplastic cancer has not improved in the United States of America and the median survival has remained at 3 months through 30 years up to 2015.[15] Poorly differentiated cancer is another type of fatal TC, but, in SE, its incidence is only about 40% of that of anaplastic cancer and survival is better compared with anaplastic cancer, leaving anaplastic cancer as the main candidate accounting for poor survival (https://cancercentrum.se/globalassets/cancerdiagnoser/skoldkortel/kvalitetsregister/arsrapport_2021_tyreoidea.pdf).

Which factors contributed to the negative age gradients in TC survival, apparently shared in the Nordic countries? Survival is critically dependent on early diagnosis and treatment. Ultrasonographic diagnostics is considered an excellent diagnostic tool but the traditional diagnostic method for TC has been palpation, and according to a SE study, the largest proportion of TC was diagnosed by palpation until 2014.[16]

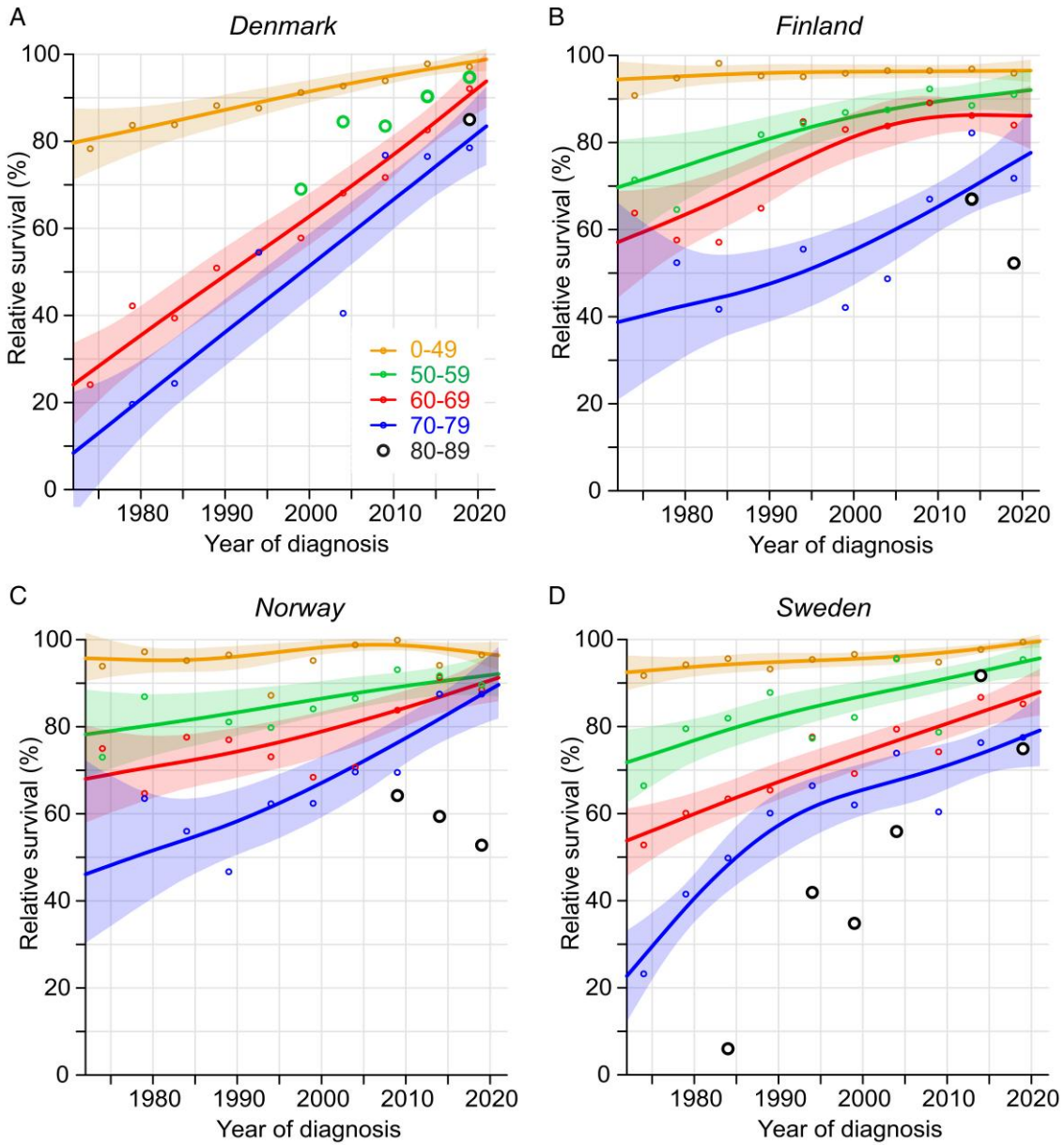

Figure 3. Relative 5-year survival trends in 5-year periods for male thyroid cancer in DK (A), FI (B), NO (C), and SE (D) from 1972-1976 to 2017-2021. For the groups with insufficient data for modelling the trends, only original point estimates are shown. Data were obtained from the NORDCAN database.

Population screening by ultrasonography has not been conducted in the Nordic countries.[16] Palpable thyroid nodules are detected in some 5% of unselected individuals, and in persons over 50 years of age, the frequency is higher, 30-40%.[17] Few of the nodules (1%) actually result in a clinically diagnosed TC and the rate of transformation appears to be higher at a young age.[18] This perception of incidental nodules may have been the reason why old patients with nodules have not been followed up resulting in advanced cancers at diagnosis. The availability of ultrasonography and other imaging modalities has been introduced in the 1970s in SE, and it is likely that palpation findings were increasingly followed by accurate imaging methods.[19] Denmark established a national cancer programme in response to poor survival figure at around the year 2000, and it has been suggested that the established fast-track programme has increased survival in anaplastic cancer nearly 2-fold.[20] Similar national cancer programmes were instituted also in NO and SE. Treatment of frail patients is generally more conservative than that of healthy patients but as adverse survival was observed already in patients older than 50 years, most of them were probably in good health and able to tolerate surgery and radioiodine therapy.

In summary, the NORDCAN age-specific survival data revealed very positive developments in equalizing population survival in TC. We speculate that the negative age gradient was largely due to diagnostic delays in the old. The challenge for the final correction of age disadvantages is to manage anaplastic cancer.

Supplementary material

Supplementary material is available at *European Journal of Endocrinology* online.

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Authors' contributions

František Zitrický (Data curation [equal], Formal analysis [lead], Writing—original draft [supporting], Writing—review & editing [equal]), Anni Koskinen (Conceptualization [equal], Writing—original draft [supporting], Writing—review & editing [equal]), Vaclav Liska (Validation [equal], Writing—original draft [supporting], Writing—review & editing [supporting]), Asta Försti (Formal analysis [supporting], Writing—original draft [supporting], Writing—review & editing [equal]), Akseli Hemminki (Conceptualization [supporting], Writing—original draft [equal], Writing—review & editing [supporting]), and Kari Hemminki (Conceptualization [equal], Data curation [equal], Formal analysis [supporting], Funding acquisition [lead], Supervision [lead], Writing—original draft [lead], Writing—review & editing [Lead])

Conflict of interest: A.H. is a shareholder in Circio holdings ASA. A.H. is an employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

Ethical approval

The guidelines of the Declaration of Helsinki were followed throughout. NORDCAN is a publically accessible database at the International Agency for Research on Cancer containing anonymous groups of individuals delivered by the Nordic cancer registries. No ethical approval for such anonymous data is needed.

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