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Long-term survival trends in solid cancers in the Nordic countries marking timing of improvements

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Abstract

Survival studies are an important indicator of the success of cancer control. We analyzed the 5-year relative survival in 23 solid cancers in Denmark, Finland, Norway and Sweden over a 50-year period (1970-2019) at the NORDCAN database accessed from the International Agency for Research on Cancer website. We plotted survival curves in 5-year periods and showed 5-year periodic survival. The survival results were summarized in four groups: (1) cancers with historically good survival (>50% in 1970-1974) which include melanoma and breast, endometrial and thyroid cancers; (2) cancers which constantly improved survival at least 20% units over the 50 year period, including cancers of the stomach, colon, rectum, kidney, brain and ovary; (3) cancer with increase in survival >20% units with changes taking place in a narrow time window, including oral, oropharyngeal, testicular and prostate cancers; (4) the remaining cancers with <20% unit improvement in survival including lung, esophageal, liver, pancreatic, bladder, soft tissue, penile, cervical and vulvar cancers. For cancers in groups 1 and 2, the constant development implied multiple improvements in therapy, diagnosis and patient care. Cancers in group 3 included testicular cancers with known therapeutic improvements but for the others large incidence changes probably implied that cancer stage (prostate) or etiology (oropharynx) changed into a more tractable form. Group 4 cancers included those with dismal survival 50 years ago but a clear tendency upwards. In 17 cancers 5-year survival reached between 50% and 100% while in only six cancers it remained at below 50%.

KEYWORDS
early diagnosis, periodic survival, prognosis, relative survival, treatment

What's new?

The authors analyzed the 5-year relative survival rates in 23 solid cancers in Denmark, Finland, Norway and Sweden over the 1970 to 2019 period. Cancers in groups 1 and 2

Abbreviations: AJCC, the American Joint Committee on Cancer; CI, confidence interval; CT, computed tomography; DK, Denmark; FI, Finland; IARC, International Agency for Research of Cancer; ICD, International Classification of Diseases; MRI, magnetic resonance imaging; N, number; NO, Norway; PET, positron emission tomography; PSA, prostate specific antigen; SE, Sweden; TNM, tumor-node-metastasis; UICC, the Union for International Cancer Control; US, ultrasound.

(eg, breast and colon cancer) were characterized by constant survival improvements due to multiple developments in therapy, diagnosis and patient care. Cancers in group 3 showed periodic improvements in survival due to novel therapies or changing presentations (testis and prostate cancer). Group 4 included fatal cancers (pancreas cancer) with a historically dismal survival but clear tendency towards improvement. The 5-year survival rate reached above 50% in 17 out of the 23 cancers.

1 | INTRODUCTION

Improving cancer survival without compromising quality of life is the ultimate goal of oncology. Survival depends on many factors relating to the patient, treatment, diagnostics and supportive care. Surgery is the oldest treatment modality which was supplemented in due course with radiotherapy. Also various chemicals such as arsenic were used to treat cancers but a real advent of chemotherapy started in the 1940s when alkylating agent nitrogen mustard and many of its derivatives such as cyclophosphamide were synthesized and found to be effective.[1] Shortly afterwards antimetabolites methotrexate and 5-flurouracil were introduced. In their review from 2008, DeVita and Chu listed 12 solid cancers for which primary chemotherapy was indicated in advanced disease, and another 11 cancers, in which chemotherapy was used in the adjuvant setting. While overall survival in many cancers has improved over the past years the reasons for the favorable development may have many interpretations.[2,3] Among individual cancers for improved survival was achieved during relatively short periods, the success has usually been ascribed to therapy and supportive care. Among solid cancers the prime example is testicular cancer, for which a rational utilization of combination chemotherapy, with integration of medical and surgical specialties enabled the success.[4]

The American Joint Committee on Cancer/the Union for International Cancer Control (AJCC/UICC) tumor-node-metastasis (TNM) staging system is widely used for classifying the extent of spread of cancer at diagnosis with implications for treatment and survival.[5] Tumor stage depends on how early cancer is diagnosed, which is the basis of screening methods aiming at detection of precursor lesions or treatable early-stage cancers.[6] While roentgen radiation was the early method of visualization of internal organs, further imaging modalities have been developed, including x-ray based computed tomography (CT), ultrasound (US), isotope imaging, magnetic resonance imaging (MRI), positron emission tomography (PET) and their various combinations, which have helped, along with refined endoscopic techniques, to find small early lesions and interpret their behavior.[7] Also blood based biomarkers such as prostate specific antigen (PSA) have contributed to the diagnostic arsenal. An example on the increase in imaging capacity is the number of CT instruments in Sweden; the first CT instruments were procured in the early 1970 s and the number of installed units reached 15 by 1979, 85 by 1989, 125 by 1999 and 200 by 2010.[8]

Population-level survival studies describe one of the key elements of cancer control, and detailed periodic analysis may also suggest what the underlying factors might have been, considered against the background of cancer incidence and mortality.[9,10] A gradual increase in survival may indicate step-wise improvements in treatment and/or early diagnosis. An increase in a relatively short time may be the result of an introduction of a new treatment, diagnostic method or change in diagnostic classification. A constant survival rate may indicate that no material improvements have been achieved in treatment or diagnostics. Survival data are often reported for 1- and 5-year survival, and for cancers of excellent survival (eg, breast and prostate cancer) 10-year data may be reported. These survival times have probably been selected as a historical convention reflecting short-term and long-term survival. Nevertheless, they have certain cancer biological and treatment related connotations, as patients with metastatic disease can rarely be treated with curative intent; there are exceptions, such as testicular cancer which responds to cisplatin and breast and prostate cancers for which hormonal treatment can extend survival past 5 years even in many metastatic patients.[10,11] Thus, early diagnosis and well-organized clinical practice with multidisciplinary teams may extend survival even in most fatal cancers past year 1 but, being unable to cure metastatic disease, patients die before reaching year 5.[12-14] Even though many patients who survive 5 years of their cancer may be cured, but for others metastases may appear even after extended periods of time and the times for actual cure (survival equal to the background population) is over 5 years for most cancers.[15]

We assess periodic 5-year relative survival in 23 solid cancers from Denmark (DK), Finland (FI), Norway (NO) and Sweden (SE) from 1970 to 2019. Collaboration between the Nordic countries has a long tradition and they have organized health care largely in a similar way with the principle that the main share of costs is covered by the state and patients are guaranteed access to care with minimal costs. The collaboration in cancer registration is long standing and these counties have the oldest national cancer registries in the world, DK since 1943, FI and NO since 1953 and SE since 1958; the joint population was 26 million around 2015.[16] We focus here on periodic changes in survival rates complementing our previous study which reported on overall improvements over the 50-year period.[17] The present multidisciplinary medical team lays out a synopsis of the essential therapeutic, diagnostic and organizational innovations which enabled survival improvements in these 23 cancers. We show data on 5-year survival as an indicator of sustained development.

2 | METHODS

The data originate from the NORDCAN database which is a compilation of aggregated individual-based data from the Nordic cancer registries as described.[16,18] The database was accessed at the International Agency for Research on Cancer (IARC) website (https://nordcan.iarc.fr/en/database#bloc2). We included only solid cancers in the analysis defined by the International Classification of Diseases (ICD) version 10 as used by NORDCAN. The code list and case numbers for each in the four Nordic countries are found as Tables S1 and S2 of our recent paper.[17] In the text, we use abbreviated names for cancer sites, even though ICD-10 may cover multiple cancers within single codes. For example, liver cancer includes hepatocellular carcinoma and intrahepatic bile duct cancer, penile cancer includes other male genital cancers, vaginal cancer includes vulvar and other female genital cancer, ovarian cancer includes ovarian tube tumors, bladder cancer includes urinary tract cancer, brain cancer includes central nervous system cancers and both malignant and benign tumors are included.

Survival data were available from 1970 through 2019 and the accessible 5-year analysis was based on the cohort survival method for periods from 1970 to 2014, and a hybrid analysis combining period and cohort survival in the last period 2015 to 2019, as detailed.[18,19] For 10-year survival: cohort approach was used for all but the two final 5-year periods: the last 5-year period used period approach, for the second to last 5-year period, observations from the third to last period were left-truncated at the start of the last 5-year period. Age-standardized relative survival was estimated using the Pohar Perme estimator.[20] Age-standardization was performed according to International Cancer Survival Standards by weighting individual observations using external weights as defined at the IARC web site. National general population life-tables stratified by sex, year and age were used in the calculation of expected survival.

Inclusion and exclusion criteria: Groups were analyzed if a minimum 30 patients were alive at start and with a minimum three patients in any one of age-groups used for weights. Only month and year were available for the date of diagnosis and death. In the very rare cases of missing months for diagnosis, they were estimated based on the dates of death.[21] Patients were excluded form analysis if they were identified only by death certificates, or if they were 90 years or older, or if their death data preceded their diagnosis data.

We plotted 50-year 5-year relative survival curves for SE solid cancers (N = 23) and, as background to each figure, we provide the exact survival figures in 5-year periods with 95% confidence intervals (CIs), and list the figures for each Nordic country to allow comparison. We marked by an asterisk significant increases (ie, in this study defined by non-overlapping 95CIs) between the 5-year periods. For prostate and breast cancers NORDCAN enabled analysis of 10-year survival and these data are also shown (data were available from 1971 to 2020).

The survival results were presented in figures grouping cancers at closely related anatomical sites when possible.

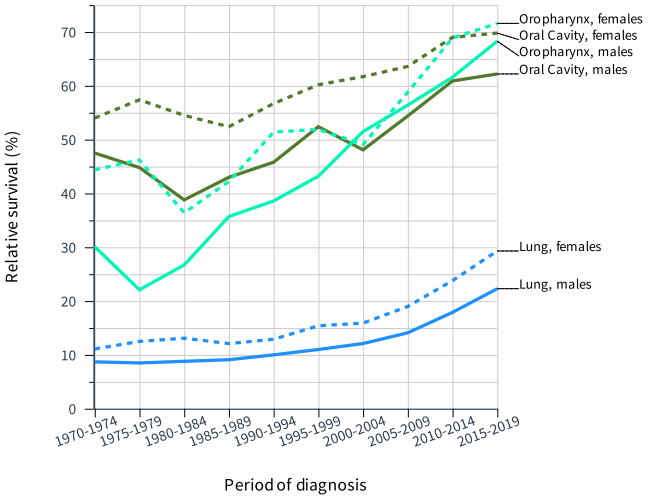

FIGURE 1 Relative 5-year survival in SE men and women in oral, oropharyngeal and lung cancers. The underlying data are shown in Table S1 also for the other Nordic countries. Note that because of the applied survival method data for the last 5-year period is not independent (see Section 2)

3 | RESULTS

Relative 5-year survival in cancers of the oral cavity, oropharynx and lung in SE are shown in Figure 1 and the underlying data are tabulated in Table S1 together with the corresponding data from DK, FI and NO. For oral cancer the positive development for men and women started as late as in year 2000 but the increases between the 5-year periods were not significant. The latest male survival in SE men for oral cancer was some decimals below the best survival which was for NO men at 62.9%. The best female survival at 74.4% was in FI. For oropharyngeal cancer survival increased monotonously after a lag period with female advantage; the SE final survival rates were the best in the Nordic countries. Lung cancer survival increased significantly towards the end of the follow up, NO final rates of 24.4% (men) and 31.8% (women) were significantly higher than those for most other countries.

The next set of cancers included the most fatal cancers of the esophagus, stomach, liver and pancreas (Figure 2 and Table S2). Survival was best for stomach cancer and increases in survival took place through the 50-year period. For the others, strong improvement started around year 2000 and many periodic increases were significant in the past 10 years. The latest rates were highest for NO for esophageal and pancreatic cancer for both sexes, and for male stomach and liver cancers.

Among next cancers, melanoma survival developed positively through the 50 years, and rates for men almost caught up with those of women (Figure 3 and Table S3). For melanoma, DK was the leading country but all male rates were at 90% or higher and female rates around 95% or higher. DK was also the leading country for rectal and male colon cancers; positive development took place for all countries with somewhat higher rate for rectal than

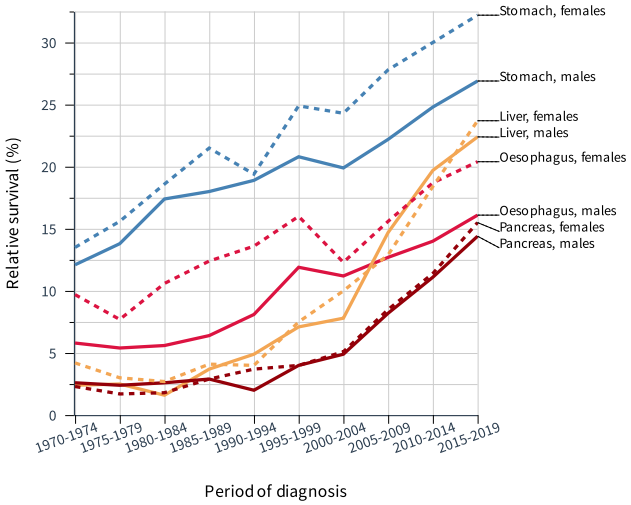

FIGURE 2 Relative 5-year survival in SE men and women in stomach, liver, esophageal and pancreatic cancers. The underlying data are shown in Table S2 also for the other Nordic countries. Note that because of the applied survival method data for the last 5-year period is not independent (see Section 2)

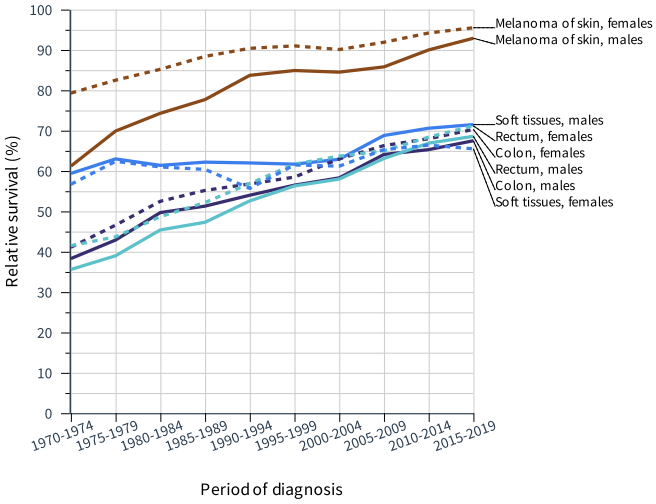

FIGURE 3 Relative 5-year survival in SE men and women in colon, rectal and soft tissue cancers and in melanoma. The underlying data are shown in Table S3 also for the other Nordic countries. Note that because of the applied survival method data for the last 5-year period is not independent (see Section 2)

colon cancer. Survival for soft tissue tumors (eg, sarcoma) improved modestly in SE but more in FI and NO where the starting level was low.

Kidney cancer survival doubled in the 50-year period in SE and it tripled in DK, with the steepest increase in the first decennium into the new millennium (Figure 4 and Table S4). For bladder cancer the initial survival was two times better than for kidney cancer but in 2015 to 2019 the rates had equaled. Brain cancer survival increased from 27% to 50% in men and from 41% to 70% in women. Thyroid cancer survival improved continuously, male rates almost reaching 90% and female even higher.

Male sex-specific cancers included testicular cancers with a 20% unit jump in survival in the 1970s, and prostate cancer with an almost doubling in survival percentage in 50 years (Figure 5 and Table S5). Testicular cancer reached a 100% survival (100.8%) in SE. Survival in SE penile cancer hardly improved, which was also true for NO but not for DK with positive development. Survival in female breast improved already in the 1970s by some 10% units, and increased with slower but significant tempo thereafter, reaching 92.0% in SE. Endometrial (corpus uteri) cancer showed high survival throughout but the increase was stalled at around year 2000 in all countries. Cervical and vulvar cancers showed modest improvement which was worst in FI. Survival in ovarian was well below other female cancers but it reached the 50% mark towards the end (SE 53.5%).

Data on 10-year survival were available on prostate and breast cancers. Survival in prostate cancer showed small improvements until 1990 when a steep increase started in FI, NO and SE (Figure 6A). Survival in DK was 20% units below that in the other countries but the difference narrowed towards the end of the follow-up. For breast cancer, 10-survival was about 20% units below the rate for 5-year survival (Figure 5) but the increase was almost linear reaching over 85% in 2016 to 2020, only some 5% units below 5-year survival (Figure 6B).

We summed up the countries that received rank one in 5-year survival in 2015 to 2019. NO had 10 male and nine female best ranks, DK had five male and four female, SE had three male and five female and FI had two female best ranks. We also considered if survival in any country was significantly lower than that in all other countries in 2015 to 2019. FI scored the lowest rank in male and female lung cancer and in vulvar cancer. DK scored lowest rank in prostate cancer.

4 | DISCUSSION

The use of the NORDCAN database uniquely allows survival analysis for 50 years with the caveat that for the final 5-year period of 2015 to 2019 is not independent because the applied hybrid analysis (see Section 2) combines data from the last and the penultimate 5-year periods. Thus, the last period of independent cohort survival analysis was 2010 to 2014. This has implications for the assessment of the novel therapies including application of immunotherapies using immune checkpoint inhibitors (ICIs) for which the clinical applications started in 2011 in the Nordic countries with melanoma.[22] The level of national use of ICI medication is not available but the registration of ICI use in a Stockholm oncology clinic between January 1, 2010 and February 1, 2017 showed 175 treatments for melanoma, 12 for lung cancer and 14 for diverse other cancers.[23] Thus, metastatic melanoma may be the only indication for which ICI medication may have influenced survival within the scope of this study. We discuss the results in the order of their presentation in Figures 1 to 5, and then summarize them at the end.

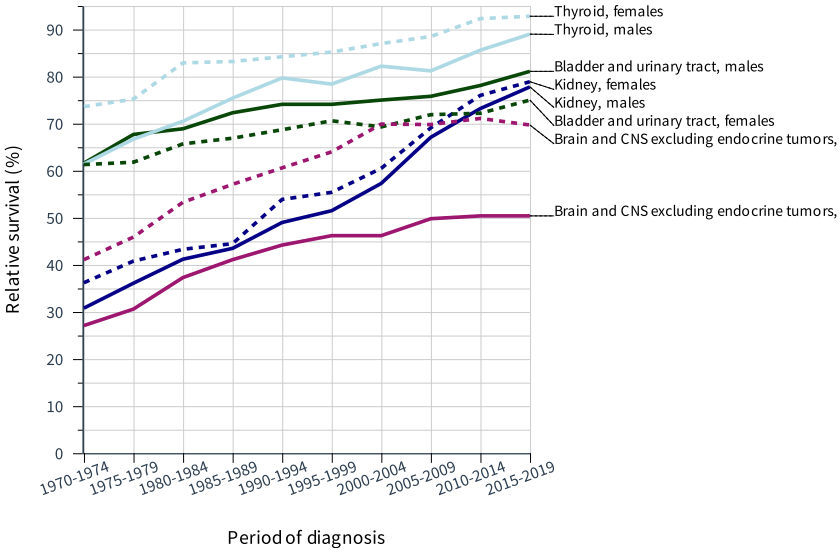

FIGURE 4 Relative 5-year survival in SE men and women in kidney, bladder, thyroid and brain cancers. The underlying data are shown in Table S4 also for the other Nordic countries. Note that because of the applied survival method data for the last 5-year period is not independent (see Section 2)

For oral and oropharyngeal cancers (Figure 1) the positive survival development started after a lag time which may be related to large increases in incidence in these cancers; for oropharyngeal cancer the increase has been suggested to be related to infections by human papilloma virus (HPV).[24] HPV related oropharyngeal cancers are often treatment-responsive contributing to improved survival; other shared factors with oral cancers helped boost survival, including earlier detection because of improved imaging, and more efficient treatment, particularly application of chemoradiotherapy.[25-29] For lung cancer survival started to increase at around year 2000 and doubled by the end. Surgery is the main therapeutic modality for early stage lung cancers which were increasingly detected because of improving sensitivity of thorax CT; radio- and chemotherapy are used in advanced stages.[30] The more common non-small cell lung cancer develops resistance towards chemotherapy and targeting radiation is difficult because of breathing, whereby surgery and immunotherapy are currently the treatments of choice. Small cell carcinoma may initially respond well to chemotherapy and radiation, but has usually metastasized before diagnosis, making surgery ineffective.[30]

Among the most fatal cancers of Figure 2, survival in stomach cancer was most favorable. The incidence in this cancer has markedly decreased and associated with decreasing prevalence of H. pylori infections, which may play a role in survival changes.[31] Survival in female stomach cancer has been better than in male cancer and the difference increased over time. The recent changes in treatment for stomach cancer in SE included increasing minimally invasive surgery, decreasing resection rates (excluding endoscopic resections) and increasing application of preoperative treatment with chemotherapy.[32] Also large organizational improvements were instituted, including facilitated presentation of patients to multidisciplinary teams and centralization of treating hospital.[32] The only curative treatment in liver cancer and pancreatic ductal adenocarcinoma is surgery.[33,34] According SE data on hepatocellular cancer, the treatments included resection, ablation, transarterial chemoembolization and sorafenib, each accounting for 10% to 15% of the patients, and best supportive care was offered to 35% of patients; some 5% were recipients of a liver transplantation.[12] Pancreatic cancer showed the worst survival in the present study; the SE national registry on pancreatic cancer patients showed that about 1/3 of the patients underwent resection.[13] Survival in esophageal cancer was only slightly better than that in pancreatic cancer. Treatment of esophageal cancer has been increasingly centralized to specialist clinics for endoscopic and other surgical techniques; chemotherapy and chemo-radiation is used in advanced disease.[35,36] The positive news from these cancers of worst survival was the strong upward trends in survival curves since about 2000, most likely thanks to treatment and how it is organized, as well as sensitive CT and MRI detection methods.

Surgery has been the main treatment for melanoma (Figure 3); female survival has been better than male survival but male survival was almost catching up in all countries. Campaigns for solar protection have been repeatedly launched in these fair skinned populations. There was a lag phase in survival between 1995 and 2005 but improvements were seen also in the recent periods which may be contributed by MAPKinase (BRAF/MEK) inhibitors and ICI.[22] For colon and rectal cancers the survival curves were moderately curvilinear implying that the improvements in survival were larger in the early as compared with the late periods.[37] Population screening for colorectal cancer was implemented only in FI (since 2004) and DK (2014).[38] Our 5-year survival data show best survival for rectal and male colon cancers for DK and worst survival for male colon and rectal cancers for FI men but all differences were small (Table S3). The survival curves for these cancers crossed in favor of rectal cancer which has been ascribed to improvements in surgical procedures, such as total mesorectal excision and wide use of preoperative chemo-radiotherapy.[39-42] Stool blood testing and especially colonoscopy have become widely available, colonoscopy is offered for abdominal symptoms. An array of new drug regimens have demonstrated improved survival for colorectal cancer with likely influence in future survival trends.[43] For

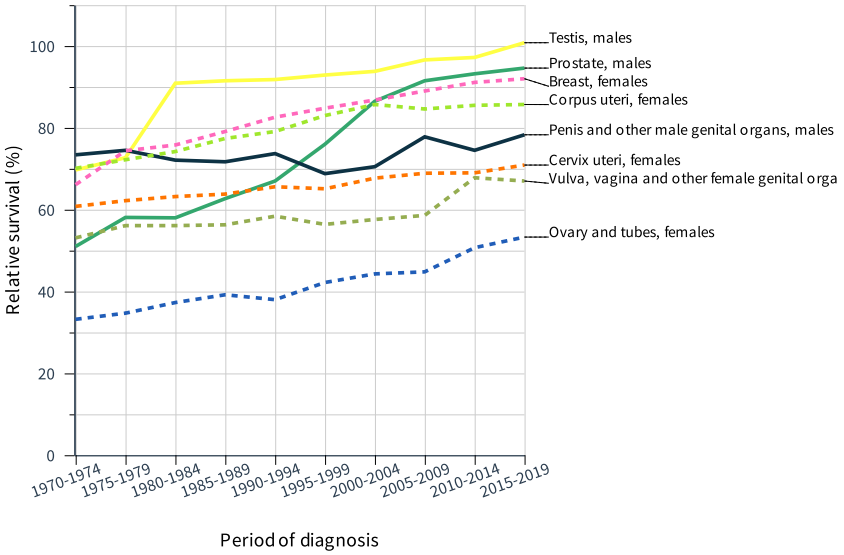

FIGURE 5 Relative 5-year survival in SE sex-specific cancers of the prostate, testis and penis, and the breast, endometrium (corpus uteri), cervix, vulva and ovary. The underlying data are shown in Table S5 also for the other Nordic countries. Note that because of the applied survival method data for the last 5-year period is not independent (see Section 2)

soft tissue tumors improvement in survival was slow in SE and DK allowing FI and NO with low starting level to catch up.

Kidney cancer (Figure 4) showed a superior survival development among all 23 solid cancers studied. Survival increased particularly favorable after year 2000, and it has been shown elsewhere that the improvement in 1-year survival was driving this development, accompanied by earlier detection of tractable tumors plausibly ascribed to the increased CT and US imaging capacity.[44] After 2006, antiangiogenic drugs have largely replaced earlier cytokine treatments for metastatic kidney cancer, however with debated impact and giving way to ICIs.[45,46] For bladder cancer, novel imaging technologies and improvements in treatment have been assumed to contribute to survival.[47] For advanced disease second resections, increased use of intravesical Bacillus Calmette-Guerin or chemotherapy instillations and introduction of neoadjuvant chemotherapies have been used.[47] In the 1980s cisplatin chemotherapy was introduced in advanced bladder cancer and later as neoadjuvant therapy, it has shown small advantage in survival.[48] Thyroid cancer is a female dominated disease; the increasing incidence in the common papillary type has kindled the dispute about overdiagnosis.[49] Treatment has been total thyroidectomy followed by radioactive iodine therapy, depending on risk stratification, but also partial surgeries (lobectomies) have been conducted.[49] More extensive surgery and external radiation is considered for high-risk patients.[49] In view of the very large increase in incidence of thyroid cancer it is not possible to conclude about survival trends.[9,10] Nevertheless, over 90% survival in women and close to 90% in men is favorable. Evaluating survival in brain cancer is complicated by the presence of both benign (eg, meningioma) and aggressive (eg, glioma) tumors. For meningioma the incidence has been increasing and the tumor is more common in women, which may explain the increasing survival and the observed sex difference.[50]

In female breast cancer (Figure 5), the increase in survival has been constant in each country over the 50-year period. Mammographic screening has been offered to women in FI and SE since the 1980 s and in DK and NO since the 1990 s.[51] According to Figure 6B, 10-year survival in SE was best of the Nordic countries through the 50-year period and the role of screening is not obvious. However, the strong improvement in breast cancer survival in FI after 1980 and in DK after 2000 coincided with rolling out of screening mammography. Surgery has been the main therapeutic modality, supported by radiotherapy in the context of breast conservation; imaging technologies have improved.[52] Adjuvant therapies (eg, tamoxifen) have had a major impact on survival, and these have been extended to longer treatment periods and with extended indications and aromatase inhibitors were introduced.[52] Adjuvant chemotherapy has been improved by agents such as anthracyclines and taxanes; antiemetic drugs have increased toleration for medication.[52] Later trastuzumab was introduced around the year 2000 for HER2 positive disease, followed by newer therapies.[52] For metastatic breast cancer, chemotherapy has been used even in recurring cases, and metastatic tumors have been be targeted as feasible.[53] Survival in endometrial cancer was better than that in breast cancer in 1970 to 1974 while the opposite was the case in 2015 to 2019 in each country. Endometrial cancer survival has almost stalled since year 2000. The standard therapy has been hysterectomy with bilateral salpingo-oophorectomy, sentinel node biopsies and lymphadenectomy in higher risk patients.[54] The majority of patients with endometrial cancer have a low risk of recurrence and are managed by surgery alone. Adjuvant brachytherapy is recommended for some intermediate or high-intermediate risk patient to decrease vaginal recurrence, while high-risk patients receive adjuvant external beam radiotherapy. For these patients chemotherapy may improve progression-free survival and cancer specific survival, however obviously improving survival over the 85% mark is difficult.[54] Surgery is the main treatment for ovarian cancer with careful removal of suspicious lymph nodes in early stage disease and radical cytoreductive surgery of potentially tumor containing sections in the peritoneal organs.[55] Adjuvant chemotherapy with paclitaxel and carboplatin

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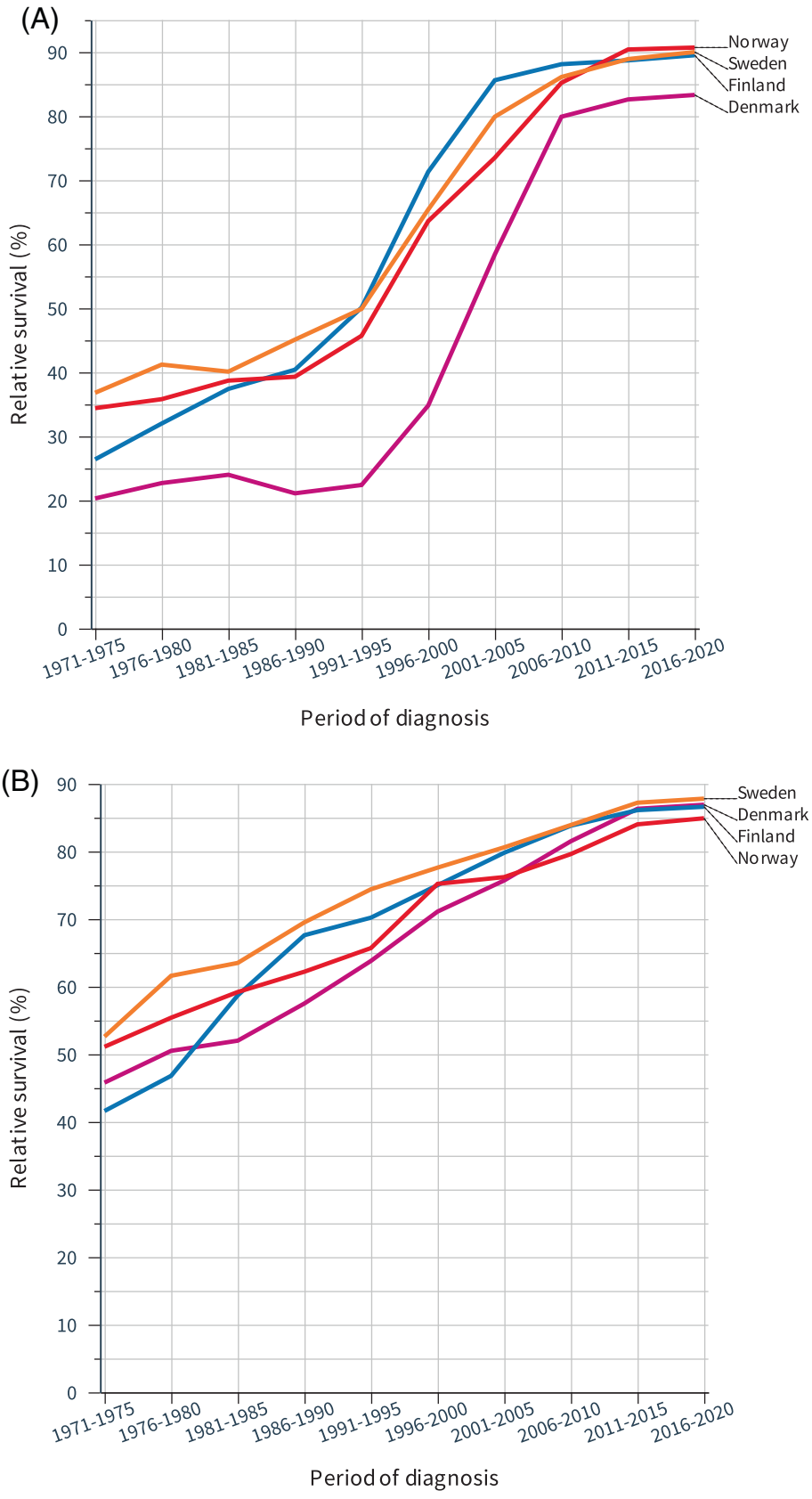

FIGURE 6 Relative 10-year survival in the Nordic countries in prostate (A) and breast (B) cancers. Note that because of the applied survival method data for the last 10-year period is not independent (see Section 2)

may be administered with bevacizumab and more recently with PARP inhibitors.[55] Survival development in cervical and vulvar cancers was <20% units in the 50-year period, and it was significantly worst for FI. Therapy for cervical and vulvar cancers is multimodal definitive chemoradiotherapy or combining surgery and adjuvant chemoradiation. Chemotherapy is used in advanced tumors either as a

neoadjuvant regimen or a palliative treatment.[56,57] Yet the low increase in survival remains a puzzle. Cervical cancer screening was started in FI and SE in the 1970 s and in DK and NO in the 1990 s but a previous study found no time-dependent changes in survival between these countries that could be associated with screening[57]; data in Table S5 is in agreement with this conclusion. Screening was associated with a vast decrease in incidence but not in survival.[57]

Testicular cancer is the classical example of successful treatment of a solid cancer, which we can witness in Figure 5.[4] Treatment and cure have been centralized and optimized to the patient needs, and we could report here relative survival of 100.8% for SE.[58] For prostate cancer, application of PSA testing hugely increased the incidence of this cancer, and although the incidence has decreased from the peak times, the problem of assessing survival remains.[9,10] Nevertheless, the present 10-year survival data at 90% showed excellent results for FI, NO and SE (Figure 6A). There has been large improvements in diagnostics and treatment aiming at risk/stage adaptive therapies, which after active surveillance include brachytherapy or external beam radiotherapy, prostatectomy and possible also chemotherapy.[59] Androgen deprivation therapy is applied in the adjuvant or neoadjuvant setting; chemotherapy or radiotherapy with 223Ra is used in castration-resistant disease, and androgen receptor-axis-targeted therapy as a recent addition.[59] Survival reached almost 95% in NO and SE. For penile cancer surgical techniques have improved and radiotherapy and chemotherapy has additionally been used but survival increased significantly only in DK.[60]

The results from Figures 1-5 and the above discussion could be summarized into four groups: (1) cancers with historically reasonably good survival (>50% in 1970-1974) which include melanoma and breast, endometrial and thyroid cancers; (2) cancers which improved survival by total of at least 20% units, with more or less constant improvement over the 50 year period, including cancers of the stomach, colon, rectum, kidney, brain and ovary; (3) cancers with increase in survival >20% units with changes taking place in a narrow time window (<50 years), including oral, oropharyngeal, testicular and prostate cancers; (4) the remaining cancers with <20% units improvement in survival including lung, esophageal, liver, pancreatic, bladder, soft tissue, penile, cervical and vulvar cancers. For cancers in groups 1 and 2, the constant development implies multiple improvements in therapy and diagnosis. Cancers in group 3 included testicular cancers with known therapeutic improvements but for the others large incidence changes probably implied that cancer stage (prostate) or etiology (oropharynx) changed into a more tractable form. Group 4 cancers included the fatal ones with poor survival 50 years ago but a clear tendency upwards, and others, such as cervical cancer for which survival has not matched the gains that have been achieved in cervical cancer prevention by screening.

A study on 23 solid cancers has limitations in details, including histological and stage characteristics of the tumors, which have important implications for survival. As a related caveat, screening programs were instituted in these countries for cervical and breast cancers during the current study period which has influenced the stage distribution of diagnosed cases, as has opportunistic screening for prostate cancer.[57] Further, our focus on 5-year survival does not allow a closer timing of the survival gains. The preset version of NORDCAN does not allow age-specific survival analysis which for many cancers shows large survival disadvantages for old patients.[61] We show data on the four countries separately to add to the generalizability of the results. While the overall survival differences were small and there were only a few cancers where survival in one country was significantly below the others in 2015 to 2019, NO was able to achieve the best survival outcomes for 18 male and female cancers, DK and SE both for 9, and FI for two cancers. The ranking approximately correlates with the national health care expenditure over the past decades (https://doi.org/10.1787/health_glance-2015-en). In 2004, the purchase power corrected health care expenditure (US$) per capita was 2838 in DK, 2274 in FI, 3862 in NO and 2875 in SE (Overview of the Healthcare Systems in the Nordic Countries—HealthManagement.org).

In conclusion, we used 5-year survival as a landmark of survival success. This landmark was reached in 17 cancers between 50% and 100% of the patients while in six cancers <50% the patients reached the landmark. One positive message emerging from these analyses is that even in the six most fatal cancers survival markedly improved in the last decades. Moreover, in five cancers, including breast and prostate cancers, survival now exceeds 90%. In about half of the cancers survival percentage more than doubled during the 50-year period. Metastatic cancer is still difficult to cure which emphasizes the importance of early diagnosis and prevention, and the need for new therapies with curative potential, such as immunotherapy.

AUTHOR CONTRIBUTIONS

Design: Kari Hemminki. Acquisition of data: Kari Hemminki. Statistical analysis and interpretation: Kari Hemminki, Akseli Hemminki and other authors. Manuscript writing: Kari Hemminki and all other authors. Approval of the final text: All authors. The work reported in the paper has been performed by the authors, unless clearly specified in the text.

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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.

DATA AVAILABILITY STATEMENT

Only publicly available data were used in this study, and data sources and handling of these data are described in the Materials and Methods. Further information is available from the corresponding author upon request.

ETHICS STATEMENT

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

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SUPPORTING INFORMATION

Additional supporting information can be found online in the Supporting Information section at the end of this article.

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