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Original Research

Survival in melanoma in the nordic countries into the era of targeted and immunological therapies

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Abstract ***Objectives:*** Survival in melanoma has been increasing and the most recent interest is to observe the population-level impact of novel targeted therapies and immunotherapy. We analysed survival in melanoma from Denmark (DK), Finland (FI), Norway (NO) and Sweden (SE) over a 50-years period (1971–2020).

Methods: Relative 1–5/1- and 5-year survival data were obtained from the NORDCAN database for the years 1971–2020. We estimated annual changes in survival rates and determined significant breaking points for trends.

Results: Survival in melanoma has reached the point where 1-year survival is approaching 100% (men 97.5–98.6%, women 98.4–99.3%, depending on the country) and 5-year survival is 93% for men (91.5–95.2%) and 96% for women (95.3–97.2%). The highest survival figures were for DK. Significant increases in both 1- and 5-year survival were observed in most countries even towards the end of the follow-up (from 2006 to 2010–2011–2015 and further to 2016–2020).

Conclusions: The main increase in melanoma survival took place up to year 1990, which was probably largely achieved through successful population campaigns for sun protection and programmes for early detection of lesions. Survival increased again after year 2000 up to the

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last period 2016–2020. This late development coincided with the introduction of targeted therapies using BRAF and BRAF/MEK inhibitors, and towards the end of the time period availability of checkpoint inhibitors. The success of melanoma treatment in DK was mostly likely due to the efficient use of modern therapies and to the centralised treatment for metastatic disease.

1. Introduction

Global survival rates in malignant cutaneous melanoma (subsequently 'melanoma') have improved at the same time when there has been an increase in incidence in many countries [1,2]. In the Nordic countries, 5-year relative survival for melanoma patients is currently around 95% [2]. The consequence of good survival is that second primary cancers are increasingly diagnosed in melanoma patients, and these have a negative impact on survival [3]. An earlier Swedish study covering years from 2003 to 2015 analysed the role of tumour characteristics on survival [4]. The study used the TNM data from the cancer registry in multivariable regression analysis and showed a strong age-dependence of mortality; the hazard ratio was 8.46 for the 80–90-year-old persons compared to those diagnosed before age 50 years. Other but much weaker risk factors were ulceration of the tumours, and local and distant metastases [4]. Pioneering work of Clark and Breslow in the 1970s helped to stratify patients for prophylactic lymph node dissection depending mainly on the thickness of the tumour [5]. Also surgical techniques including evaluation of optimal surgical margins, elective lymph node dissection and sentinel lymph node mapping have lessened morbidity and improved outcomes for early-stage and locally advanced melanoma [5].

The main histological type is superficially spreading melanoma which showed marginally better survival than nodular and lentigo maligna melanoma [4]. In the global context, histological specification is often overlooked and a study covering 59 countries reported that the most common melanoma type (42%) was melanoma not otherwise specified [1]. Lacking of histological specification was common even in developed countries, including North America (51%) and Northern Europe (32%).

The dominant environmental risk factor of melanoma is solar UV radiation and the related host factors of fair skin and propensity to sun burns [6]. Also in-house tanning is associated with risk which may be relevant for people of the Nordic countries [6]. Family history of melanoma is a risk factor and the risk is higher when family members present with multiple melanomas [3,7–10]. The most common high-risk gene predisposing to melanoma is cyclin-dependent kinase inhibitor 2A (CDKN2A) [11]. The gene is unique in encoding two structurally and functionally unrelated proteins, $p16^{INK4a}$ and ARF [12].

In Denmark somewhat more than 10% of melanoma patients were diagnosed with metastasis in the course of their disease [13]. Without treatment most metastatic patients died in less than a year, and earlier interleukin 2 was the only medication which helped some metastatic patients [13,14]. Two decades ago it was discovered that about half of metastatic melanoma patients harbour a mutation in the BRAF gene, and targeted therapies were developed to inhibit BRAF alone and later (2014) the BRAF and MEK pathways [13,15,16]. These improved survival in many patients but resistance developed in about a half year [16]. The first successful immune checkpoint inhibitors (ICIs) were developed for metastatic melanoma using anti-CTLA4 antibody (ipilimumab, from 2011), followed by anti-PD-1 antibodies (pembrolizumab from 2014 and nivolumab from 2016) [17]. The listed years were the approximate introductory times for these immunotherapies for metastatic melanoma in the Nordic countries [13,15,18–20]. Later it was observed that combining BRAF/MEK inhibitors with ICI and using ICI combination of ipilimumab and nivolumab achieved a survival advantage [17]. It is reported that long-term durable control in advanced melanoma is now possible in nearly 50% of patients, compared with less than 10% historically [21]. Viral therapy using T-Vec (Imlygic) has been another therapeutic modality for local treatment of metastatic melanoma for some years, and adoptive cell therapy with tumour-infiltrating lymphocytes has achieved promising survival improvements [22].

We assess relative survival in melanoma in Denmark (DK), Finland (FI), Norway (NO) and Sweden (SE) for a 50-year period from 1971 to 2020 with focus on changes in survival times and their possible causes, particularly in reference to application of ICI. In addition to 1- and 5-year survival, we also report estimation of conditional 5/1-year survival and annual changes in survival.

2. Methods

The data were obtained from the NORDCAN database 2.0 [23,24]. The database was accessed at the International Agency for Cancer (IARC) website (https://nordcan.iarc.fr/en) [25], and the available tools were used to extract data on incidence, mortality and 1-year and 5-year survival. NORDCAN uses International Classification of Diseases (ICD) version 10 codes for invasive melanoma (excluding in situ disease).

Using the NORDCAN, we extracted data on 1- and 5-year relative survival, and the follow-up was extended until death, emigration or loss of follow-up or to the end of 2020. Survival data for relative survival were available from 1971 onwards and the analysis was based on the cohort survival method for the first nine 5-year periods, and a hybrid analysis combining period and cohort survival in the last period 2016–2020, as detailed [23]. Age-standardised relative survival was estimated using the Pohar Perme estimator [26]. Age standardisation was performed by weighting individual observations using external weights as defined on the IARC website. Age groups 0–89 years were considered. The national life tables were used to calculate the expected survival.

For the 5/1-year survival ratio estimation, we divided the posterior draws from the 5-year survival model by the posterior draws from the 1-year model to get the posterior distribution of the conditional survival and its estimated annual changes over time [27].

For all survival measures (relative 1- and 5-year survival and 5/1-year ratio), we evaluated when the survival was changing over time with at least 95% plausibility (95% credible interval [Ci] of the 1st derivation of given survival measure did not cross zero for at least 5 years). We also aimed to identify 'breaking points', i.e. times when the annual change of survival changed with at least 95% plausibility. This was assessed by calculation of the 2nd derivation of the given survival measure and its 95% Ci; the 'breakpoint' was defined as a peak value within at least a 3-year interval where 95% Ci for the 2nd derivation did not cross zero [27].

Comparisons with the US Surveillance, Epidemiology and End Results (SEER) data for years 2012–2018 on Non-Hispanic Whites were done through (https://seer.cancer.gov/statistics-network/explorer/application.html?site=1&data_type=1&graph_type=2&compareBy=sex&chk_sex_3=3&chk_sex_2=2&rate_type=2&race=1&age_range=1&hdn_stage=101&advopt_precision=1&advopt_show_ci=on&hdn_view=0&advopt_display=2#graphArea).

3. Results

Incidence and mortality trends for melanoma in the Nordic countries between 1960 and 2020 are shown in Fig. 1. The shapes of the incidence curves between men and women were identical (but high female incidence in DK) with peaks around 1990 and towards the end of the follow-up (peak for FI men, for other men slopes declined). For mortality the peak in 2010 was followed by a steep decline, particularly for NO.

Fig. 2 shows relative 1-, 5/1- and 5-year survival for melanoma in DK men (a) and women (e), in FI men (b) and women (f), in NO men (c) and women (g) and in SE men (d) and women (h). The major differences in the survival plots between the countries were for the FI 5/1- and 5-year curves which started at a lower level compared to the other countries. However, the FI 5/1- and 5-year survival developed very fast until 1990. The DK curves were almost linear but for NO and SE a slow period of improvement occurred around year 2000. In all countries, 5/1- and 5-year survival developed well after year 2010 and for DK men and all women these plots almost met the 1-year survival plots.

Table 1 lists 1- and 5-year survival rates in 5-year periods to allow comparison of the country-specific rates. In 2016–2020, 1-year survival was approaching 100%, and was very close at 99.3% for DK women. In the last period, 5-year survival was best for DK men (95.2%), significantly better than the survival in the other countries. For women, DK was also on top (97.2%) and FI in the bottom (95.3%). Of note, 5-year survival increased significantly between the last three 5-year periods in men and women with a few exceptions (particularly for FI women).

Data from Table 2 enable estimation of the magnitude of survival improvements over the 50-year period. Improvement in 5-year survival in male and female melanoma was highest in FI, 42.8% and 28.2% units. Improvement in NO and SE were over 10% units below FI.

In Table 2 5/1-year survival is reported in 5-year periods. The figure is 96.6% for DK men, while the figure for 1-year survival was 98.6% (in Table 1). Thus 1.4% of the patients died in year 1% and 3.4% died in the four subsequent years. The comparisons for the other countries agreed that the proportion of deaths between year 1 and 4 subsequent years was about 1–2.5.

4. Discussion

Survival in melanoma in the Nordic countries has reached the point where 1-year survival is approaching 100% (men 97.5–98.6%, women 98.4–99.3%) and 5/1-year survival is 95% for men (93.8–96.6%) and 97% for women (96.8–97.9%). DK achieved the highest male and female 1- and 5-year survival rates. The 50-year improvement in 5-year survival was highest in FI (42.8% units in men and 28.2% units in women) and improvement was also high in DK, which meant that the starting levels in survival in FI and DK were well below those in NO and SE in 1971–1975. Considering 5-year survival in the last period, in the best country DK, 5/100 men and 3/100 women died of melanoma. These are impressive figures, considering that over 10% of melanoma patients are diagnosed with metastasis in DK, and less than 20 years ago most of the metastatic patients were dead within 6 months [13]. We should however keep in mind that the largest improvements in melanoma survival took place in the first 20 years of the study. Parts of this gain might be due to better surgical and oncological treatments [5]. In the Stockholm area a clinical

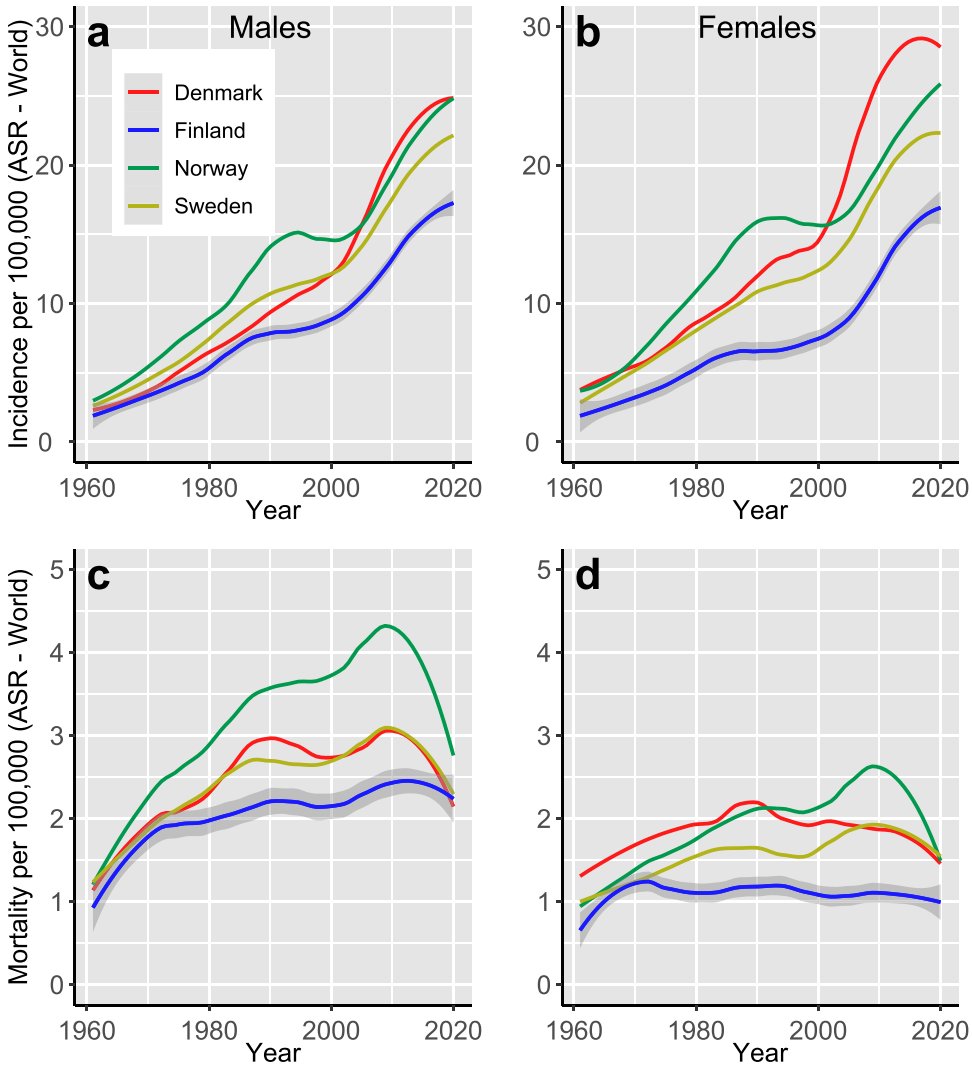

Fig. 1. Age-standardised rates (ASR, world) for invasive cutaneous melanoma in the Nordic countries, (a) male and (b) female incidence, and (c) male and (d) female mortality, based on the NORDCAN database. 95% CIs are shown for FI data with the smallest case numbers; for the other countries with more cases the 95% CI would be narrower. The figure was created in R using data from NORDCAN. Lines were smoothed via cubic smoothing spline.

collaboration was started in 1976 regarding guidelines for diagnosis and treatment of pigmented skin lesions, which were implemented in the other parts of the country later [28]. During the ensuing 18 years melanoma incidence doubled but this was largely contributed by tumours thinner than 0.9 mm and no increase was observed in tumours thicker than 4 mm [28]. Additionally, it is likely that the initial positive development was contributed by early detection which was brought about by population campaigns for skin screening programmes [29]. However many large-scale educational campaigns for sun protection were initiated in Sweden and other Nordic countries in the mid-1980s or later which was past the most favourable phase of the early survival improvement shown in Fig. 1 [28,30–32].

The incidence in melanoma increased in the Nordic countries in two waves, one culminating around 1990 and the other culminating in some countries after 2015 and in the other countries the increasing tempo declined (Fig. 1). Mortality culminated in all countries in 2010. In SE the increasing trend from 1997 to 2018 was mainly contributed by thin tumours (< 0.9 mm) but later an increase was reported also for thicker tumours (> 4 mm) [33]. The increase in predominantly thin and low-stage tumours was reported also in the other Nordic countries, most likely contributing to favourable survival [31,32].

The present survival data are the most up-to-date that national cancer registries can deliver. Such data are keenly awaited because there is a great interest to verify the success of novel immunotherapy beyond clinical trials, and nationwide results would be a 'real-world' proof. When interpreting the survival results we need to keep in mind that the final 5-year period of 2016–2020 is not independent because the NORDCAN hybrid method (see methods) combines data from the last and the penultimate 5-year periods. Thus the last period of

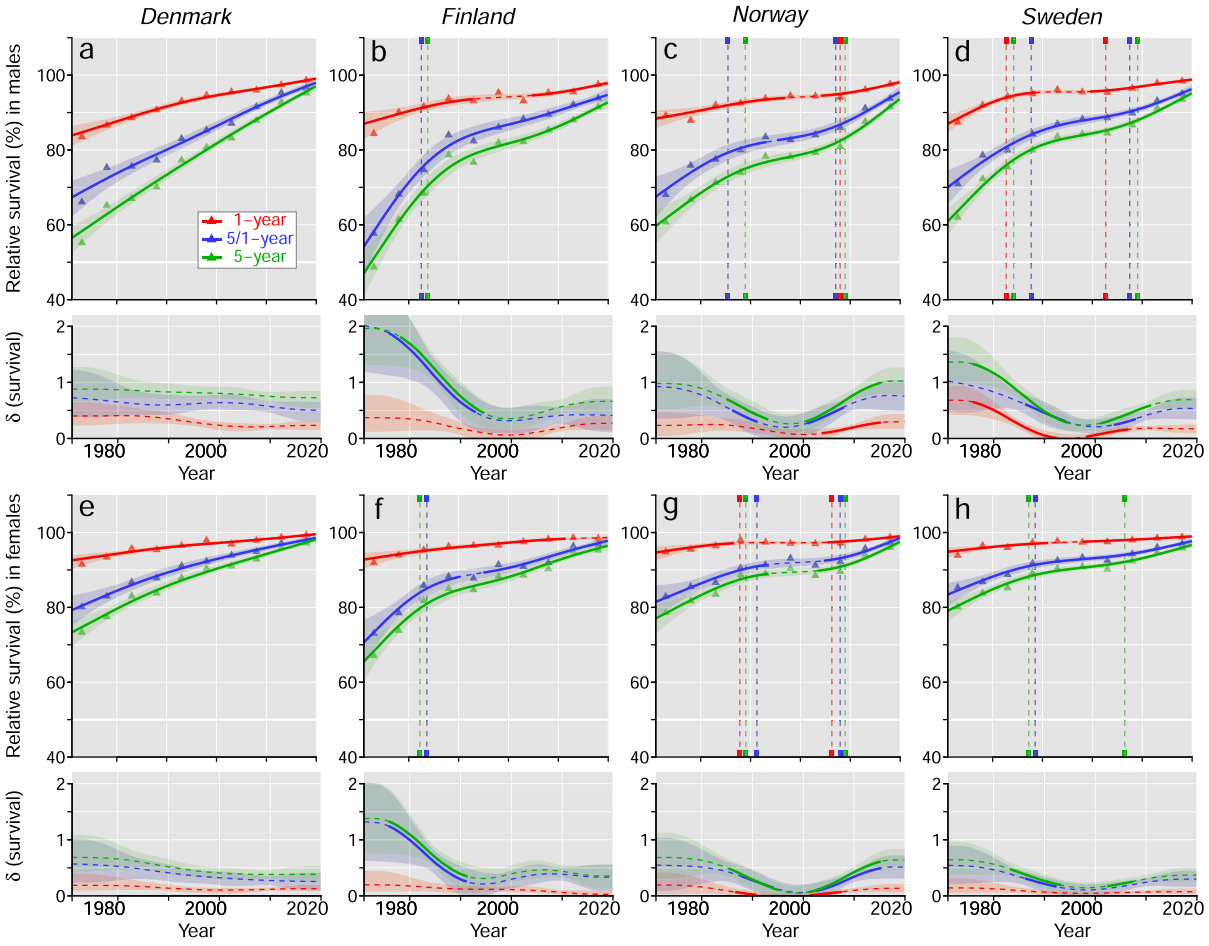

Fig. 2. Relative 1-, 5/1- and 5-year survival in melanoma in Denmark (a,e), Finland (b,f), Norway (c,g) and Sweden (d,h), separately for males (a–d) and females (e–h). The vertical lines mark a detectable change in the survival trends ('breakpoints') and the bottom curves show estimated annual changes in survival. The curves are solid if there is > 95% plausibility that the curve grows or declines. Shadow areas indicate 95% credible intervals. All curves are colour coded (see the insert).

independent cohort survival analysis was 2011–2015, which was followed by a partially dependent last period, 2016–2020. A further point of consideration is that few melanoma patients are metastatic at diagnosis, in SE 0.9% of all diagnosed patients [4]. This figure is derived from the Swedish Cancer Registry, which records metastasis only at the time of diagnosis, as do cancer registries in general [34]. This deficit of lacking metastatic data was featured in Nature Medicine in 2019; CancerRegistration19natureMedMetastases.pdf. The SE figure of 0.9% is less than 10% of melanoma patients who develop metastasis in the course of their disease; metastasis appears most commonly 2–4 years after the initial diagnosis [14,35,36]. Finding the true proportion of metastatic melanoma patients requires *ad hoc* studies or access to the DK national database on metastatic melanoma (DAMMED) where the proportion is about 10% [13,34]. Thus if we consider a patient diagnosed with melanoma in 2014, his metastases were detected between 2016 and 2018, which is the period when the most effective monotherapies with PD-1 antibodies were available. In our study, 5-year survival in patients diagnosed in 2014 or later should be covered by effective PD-1 monotherapies or BRAF/MEK inhibitor combinations. The DK DAMMED database has reported encouraging 'real-world' survival figures on patients treated with ICI [13,15]. From SE, similarly encouraging data have been published from single regional centres [18,19].

There was a lag phase in survival development in NO and SE around year 2000 but systematic improvements were seen in all countries after that with unbroken tempo also into the recent periods, probably contributed by BRAF/MEK inhibitors and ICI [13,15,18,19]. We observed significant increases in 5-year survival in most countries towards the end of the follow-up (from 2006 to 2010–2011–2015 and further to 2016–2020). These periods cover the era of targeted therapies and the last two periods, in part, the era of ICI. It is not known to what extent ICI is used in the Nordic countries but a report in FI gave estimates of the numbers of patients treated with PD-1 or PD-L1 ICIs in any cancer in some countries (https://cancerio.org/wp-content/uploads/2022/03/Cancer-Immunotherapies-in-Finland.pdf). The

Table 1
1-year (a) and 5-year (b) relative survival [95% CI] in melanoma skin cancer from 1971 to 2020, separately for males (left) and females (right). *Significant increase between the marked and the next period (non-overlapping 95% CIs).

Males					Females			
(a) 1-year	Denmark	Finland	Norway	Sweden	Denmark	Finland	Norway	Sweden
1971–1975	83.5 [80.3–86.8]	84.4 [80.5–88.4]	89.2 [86.6–91.8]	87.4 [85.4–89.5]*	91.5 [89.4–93.7]	91.9 [89.4–94.5]	94.8 [92.8–96.8]	93.9 [92.6–95.3]*
1976–1980	86.6 [84.2–89.2]	90.1 [87.3–93.0]	87.9 [85.4–90.4]	92.0 [90.5–93.5]	93.4 [91.8–95.0]	94.0 [92.1–96.0]	95.5 [94.1–96.9]	96.5 [95.6–97.5]
1981–1985	88.6 [86.5–90.8]	91.6 [89.3–94.0]	92.0 [90.2–93.8]	94.3 [93.2–95.4]	95.7 [94.5–96.9]	95.3 [93.9–96.8]	96.4 [95.3–97.5]	96.0 [95.1–96.8]
1986–1990	90.7 [89.0–92.5]	93.7 [91.9–95.4]	92.5 [91.0–93.9]	95.0 [94.1–96.0]	95.4 [94.3–96.5]	96.3 [95.1–97.6]	98.0 [97.2–98.8]	97.3 [96.6–97.9]
1991–1995	93.1 [91.7–94.5]	93.1 [91.5–94.8]	93.8 [92.7–95.0]	96.1 [95.3–96.9]	96.5 [95.6–97.5]	96.5 [95.3–97.7]	97.4 [96.6–98.2]	97.7 [97.1–98.3]
1996–2000	94.6 [93.4–95.7]	95.3 [94.0–96.7]	94.5 [93.4–95.6]	95.5 [94.7–96.2]	97.9 [97.1–98.7]	96.6 [95.5–97.6]	97.1 [96.3–97.9]	97.4 [96.8–98.0]
2001–2005	95.5 [94.6–96.5]	93.1 [91.8–94.4]	94.4 [93.4–95.4]	95.4 [94.7–96.1]	96.9 [96.2–97.6]	97.5 [96.7–98.3]	97.0 [96.3–97.8]	97.5 [96.9–98.0]
2006–2010	96.0 [95.3–96.8]*	95.3 [94.3–96.2]	94.1 [93.2–95.0]*	96.5 [96.0–97.1]*	97.9 [97.4–98.5]	98.2 [97.6–98.8]	97.2 [96.5–97.8]	98.0 [97.6–98.4]
2011–2015	97.4 [96.9–98.0]*	95.5 [94.7–96.3]*	96.1 [95.5–96.8]*	97.9 [97.5–98.2]	98.7 [98.3–99.1]	98.6 [98.2–99.1]	98.2 [97.8–98.7]	98.5 [98.2–98.8]
2016–2020	98.6 [98.2–99.0]	97.5 [97.0–98.1]	97.6 [97.1–98.1]	98.4 [98.1–98.7]	99.3 [99.0–99.6]	98.4 [98.0–98.9]	98.7 [98.4–99.1]	98.8 [98.5–99.0]
(b) 5-year								
1971–1975	55.2 [50.6–60.3]*	48.7 [43.2–54.8]*	60.7 [56.3–65.3]	62.0 [58.7–65.5]*	73.3 [69.7–77.1]	67.1 [62.8–71.8]	78.6 [74.6–82.8]	80.1 [77.6–82.7]
1976–1980	65.2 [61.3–69.3]	61.4 [56.6–66.7]	66.7 [62.8–70.7]	72.3 [69.5–75.2]	77.5 [74.6–80.5]	73.8 [70.2–77.6]*	81.7 [78.9–84.6]	83.8 [81.7–85.9]
1981–1985	67.0 [63.4–70.7]	68.4 [64.2–72.8]*	71.3 [68.0–74.8]	75.4 [73.1–77.7]*	83.0 [80.5–85.5]	81.8 [78.9–84.8]	83.5 [81.1–85.9]*	85.2 [83.4–87.0]*
1986–1990	70.1 [67.1–73.3]*	78.7 [75.3–82.2]	74.0 [71.3–76.8]	80.0 [78.2–82.0]	83.8 [81.6–86.0]	85.0 [82.3–87.7]	88.7 [86.8–90.7]	89.3 [87.9–90.8]
1991–1995	77.3 [74.7–80.0]	76.7 [73.6–79.8]	78.3 [76.0–80.7]	83.6 [82.0–85.3]	87.9 [86.0–89.8]	84.7 [82.2–87.2]	89.0 [87.3–90.8]	90.4 [89.1–91.7]
1996–2000	80.7 [78.3–83.2]	82.0 [79.4–84.7]	78.2 [76.1–80.4]	84.3 [82.8–85.8]	90.4 [88.6–92.2]	88.3 [86.3–90.5]	90.4 [88.8–92.0]	90.9 [89.7–92.1]
2001–2005	83.2 [81.2–85.2]*	82.2 [79.9–84.5]	79.3 [77.4–81.3]	84.5 [83.2–85.8]	91.0 [89.5–92.4]	88.6 [86.8–90.5]	88.5 [86.9–90.0]	90.2 [89.1–91.3]*
2006–2010	87.9 [86.4–89.3]*	85.3 [83.5–87.1]	80.9 [79.2–82.6]*	86.7 [85.6–87.8]*	92.9 [91.7–94.1]*	90.3 [88.8–91.7]*	89.6 [88.3–90.9]*	92.4 [91.5–93.3]*
2011–2015	92.8 [91.7–94.0]*	88.0 [86.6–89.5]*	87.6 [86.3–88.8]*	91.2 [90.3–92.1]*	95.9 [95.0–96.7]	95.0 [94.0–96.1]	94.0 [93.1–95.0]*	94.6 [93.9–95.3]
2016–2020	95.2 [94.3–96.2]	91.5 [90.3–92.8]	91.5 [90.5–92.6]	93.5 [92.7–94.2]	97.2 [96.4–98.0]	95.3 [94.3–96.3]	96.0 [95.2–96.8]	95.8 [95.2–96.4]

Table 2
5/1-year (4-years conditional) survival in melanoma skin cancer from 1971 to 2020, separately for males (left) and females (right).

	Male cancers				Female cancers			
Year period	Denmark	Finland	Norway	Sweden	Denmark	Finland	Norway	Sweden
1971–1975	66.1	57.7	68.0	70.9	80.1	73.0	82.9	85.3
1976–1980	75.3	68.1	75.9	78.6	83.0	78.5	85.5	86.8
1981–1985	75.6	74.7	77.5	80.0	86.7	85.8	86.6	88.8
1986–1990	77.3	84.0	80.0	84.2	87.8	88.3	90.5	91.8
1991–1995	83.0	82.4	83.5	87.0	91.1	87.8	91.4	92.5
1996–2000	85.3	86.0	82.8	88.3	92.3	91.4	93.1	93.3
2001–2005	87.1	88.3	84.0	88.6	93.9	90.9	91.2	92.5
2006–2010	91.6	89.5	86.0	89.8	94.9	92.0	92.2	94.3
2011–2015	95.3	92.1	91.2	93.2	97.2	96.3	95.7	96.0
2016–2020	96.6	93.8	93.8	95.0	97.9	96.8	97.3	97.0

frequency order was NO, DK, SE and a large gap to FI. We do not know how reliable these data are but they could be an explanation for the lagging recent survival figures for FI. The report also pointed out that DK is not requiring formal cost-effectiveness or cost-utility assessments for the ordering of ICI, in contrast to the other Nordic countries. In DK cancer medication is dispensed and financed through hospitals whereas in other countries more centralised decision-making is in place. A likely contributing factor to the DK success in melanoma is the centralisation of treatment for metastatic disease in four large hospitals [13].

In a large international study on cancer survival for years 2010–2014 from 59 countries, melanoma 5-year survival was in the range 60–90% in most countries, and in 11 of those it exceeded 90%, including DK and SE [37]. Best survival was in Switzerland at 93.6%, followed by Germany, 93.1%. The 5-year survival in the US SEER database for Non-Hispanic whites in 2012–2018 was 92.1% for men and 95.4% for women, thus at the level of the Nordic survival but below the DK level.

The limitations in the present study are lacking pathological information of melanoma and any treatment information. According to a previous study from SE, melanoma survival was poor in the old population and the NORDCAN data do not allow age-specific analyses [4]. However, the NORDCAN data are uniquely long in follow-up time, and of particular interest in melanoma, they do allow estimation of the most recent survival figures.

In conclusion, we could document a positive early development in melanoma survival up to year 1990 and a renewed boost for survival increase up to the final period of 2016–2020. We suggest that the early improvement was contributed by population campaigns for early detection of lesions followed by high-quality surgical treatments. The late survival increase was probably at least in part contributed by the introduction of targeted therapies for BRAF/MEK inhibition, and the most recent increase was perhaps achieved using ICIs. Melanoma was the first major cancer for which immunotherapy changed clinical practice. The next few years will be the window to establish the population-level impact of ICI for melanoma. While these developments are encouraging, there are still many patients with metastatic melanoma for whom current therapies fail to provide a cure. Nevertheless, the success of ICI provides proof of concept that immunotherapy can be used for curative intent, providing hope in the treatment of also many other tumour types. Future developments include combination immunotherapies and concurrent use of ICI with radiation and chemotherapies, approaches which appear to provide synergistic efficacy in many situations [17].

Ethics

Anonymous data from a publically available database were used posing no ethical issues.

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Data and code availability

Aggregated data from a publically accessible database were used, posing no ethical issues. Full statistical R code is available at https://github.com/filip-tichanek/nord_melanoma.

CRediT authorship contribution statement

Design: KH, Acquisition of data: FT, KH, Statistical analysis: KH, FT, Interpretation: KH, FT, AF, VL, AH, Manuscript writing: KH, FT and all other authors, Approval of the final text: All authors.

Conflict of interest statement

The authors declare the following financial interests/personal relationships which may be considered as potential competing interests: A.H. is shareholder in Targovax ASA. A.H. is employee and shareholder in TILT Biotherapeutics Ltd. Other authors declared no conflict of interest.

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