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Original research

# Survival trends for patients diagnosed with cutaneous malignant melanoma in the Nordic countries 1990-2016: The NORDCAN survival studies

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ABSTRACT

*Background:* The survival in patients diagnosed with cutaneous malignant melanoma (CMM) has improved in the Nordic countries in the last decades. It is of interest to know if these improvements are observed in all ages and for both women and men.

*Methods:* Patients diagnosed with CMM in the Nordic countries in 1990–2016 were identified in the NORDCAN database. Flexible parametric relative survival models were fitted, except for Iceland where a non-parametric Pohar-Perme approach was used. A range of survival metrics were estimated by sex, both age-standardised and age-specific.

*Results:* The 5-year relative survival improved in all countries, in both women and men and across age. While the improvement was more pronounced in men, women still had a higher survival at the end of the study period. The survival was generally high, with age-standardised estimates of 5-year relative survival towards the end of the study period ranging from 85% in Icelandic men to 95% in Danish women. The age-standardised and reference-adjusted 5-year crude probability of death due to CMM ranged from 5% in Danish and Swedish women to 13% in Icelandic men.

*Conclusion:* Although survival following CMM was relatively high in the Nordic countries in 1990, continued improvements in survival were observed throughout the study period in both women and men and across age.

## 1. Introduction

The incidence of cutaneous malignant melanoma (CMM) has increased dramatically in the Nordic countries (Denmark, Finland, Iceland, Norway, Sweden) over the past decades [1–3]. CMM is not uncommon in younger individuals and is the second most common cancer in men and women aged 20–49 [4]. The prognosis of CMM is highly dependent on the stage at diagnosis, where those diagnosed with a thin melanoma have a 5-year melanoma-specific survival over 95% with much poorer survival in late stage disease [5]. The prognosis of CMM also differs by sex [6], with men having worse prognosis. The reasons for this discrepancy are not fully known, but can partly be explained by the stage distribution at diagnosis [6]. Given the high incidence at younger ages and the sex differences in prognosis, it is of interest to investigate if

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**Table 1**
Numbers of cutaneous malignant melanoma cases in the Nordic countries 1990–2016, by age at diagnosis.

| Women | Denmark | | Finland | | Iceland | | Norway | | Sweden | |
|---|---|---|---|---|---|---|---|---|---|---|
| Cases 1990-2016, n | 21,133 | | 11,652 | | 656 | | 17,226 | | 29,267 | |
| Years of follow-up[a] | | | | | | | | | | |
| **Total, years** | 166,700 | | 79,169 | | 6261 | | 137,065 | | 232,172 | |
| **Mean (SD)** | 7.9 | (5.0) | 6.8 | (5.2) | 9.5 | (5.1) | 8.0 | (5.2) | 7.9 | (5.1) |
| By age group, n % | | | | | | | | | | |
| **18-29 years** | 1559 | 7.4% | 486 | 4.2% | 104 | 15.9% | 854 | 5.0% | 1372 | 4.7% |
| **30-39 years** | 2733 | 12.9% | 979 | 8.4% | 123 | 18.8% | 1705 | 9.9% | 2829 | 9.7% |
| **40-49 years** | 3864 | 18.3% | 1616 | 13.9% | 112 | 17.1% | 2748 | 16.0% | 4564 | 15.6% |
| **50-59 years** | 3766 | 17.8% | 1974 | 16.9% | 118 | 18.0% | 3071 | 17.8% | 5080 | 17.4% |
| **60-69 years** | 3842 | 18.2% | 2361 | 20.3% | 83 | 12.7% | 3307 | 19.2% | 5651 | 19.3% |
| **70-79 years** | 3059 | 14.5% | 2318 | 19.9% | 62 | 9.5% | 3022 | 17.5% | 5325 | 18.2% |
| **80-89 years** | 1913 | 9.1% | 1546 | 13.3% | 44 | 6.7% | 2057 | 11.9% | 3641 | 12.4% |
| **≥ 90 years** | 397 | 1.9% | 372 | 3.2% | 10 | 1.5% | 462 | 2.7% | 805 | 2.8% |
| Age, mean (SD) | 56.0 | (17.8) | 61.4 | (17.4) | 50.0 | (18.6) | 59.5 | (17.6) | 60.0 | (17.6) |
| Age, median (IQR) | 56 | (42–70) | 63 | (49–75) | 49 | (35–63) | 60 | (46–73) | 61 | (47–74) |
| **Men** | **Denmark** | | **Finland** | | **Iceland** | | **Norway** | | **Sweden** | |
| Cases 1990-2016, n | 17,450 | | 12,147 | | 438 | | 16,282 | | 28,994 | |
| Years of follow-up[a] | | | | | | | | | | |
| **Total, years** | 118,687 | | 73,758 | | 3261 | | 108,595 | | 203,301 | |
| **Mean (SD)** | 6.8 | (4.9) | 6.1 | (5.0) | 7.4 | (5.2) | 6.7 | (5.1) | 7.0 | (5.0) |
| By age group, n % | | | | | | | | | | |
| **18-29 years** | 650 | 3.7% | 243 | 2.0% | 31 | 7.1% | 377 | 2.3% | 672 | 2.3% |
| **30-39 years** | 1369 | 7.8% | 658 | 5.4% | 34 | 7.8% | 985 | 6.0% | 1759 | 6.1% |
| **40-49 years** | 2413 | 13.8% | 1391 | 11.5% | 79 | 18.0% | 2134 | 13.1% | 3247 | 11.2% |
| **50-59 years** | 3290 | 18.9% | 2304 | 19.0% | 69 | 15.8% | 3070 | 18.9% | 4875 | 16.8% |
| **60-69 years** | 4302 | 24.7% | 3130 | 25.8% | 84 | 19.2% | 3918 | 24.1% | 7115 | 24.5% |
| **70-79 years** | 3625 | 20.8% | 2827 | 23.3% | 92 | 21.0% | 3611 | 22.2% | 7060 | 24.3% |
| **80-89 years** | 1589 | 9.1% | 1427 | 11.7% | 45 | 10.3% | 1930 | 11.9% | 3742 | 12.9% |
| **≥ 90 years** | 212 | 1.2% | 167 | 1.4% | 4 | 0.9% | 257 | 1.6% | 524 | 1.8% |
| Age, mean (SD) | 60.2 | (15.8) | 62.9 | (14.8) | 58.7 | (17.4) | 62.2 | (15.3) | 63.4 | (15.4) |
| Age, median (IQR) | 62 | (49–72) | 64 | (53–74) | 60 | (47–73) | 64 | (52–74) | 65 | (53–75) |

[a] Follow-up included in analyses, up to 15 years per patient. SD = standard deviation.

the survival improvement observed for CMM patients in the Nordic countries [2] are similar across age at diagnosis and sex.

The aim of this study was to investigate temporal survival trends in patients diagnosed with CMM in the Nordic countries by taking advantage of the high-quality population-based standardised cancer registration within the countries. We present a range of survival measures to provide a comprehensive picture of the prognosis of CMM patients.

## 2. Material and methods

### 2.1. Data

The NORDCAN database was used to obtain Individual-level data on patients diagnosed with CMM (International Classification of Diseases version 10 [ICD10]: C43) in Denmark, Finland, Iceland, Norway and Sweden in the years 1990–2016. The NORDCAN database includes information from the national cancer registries in the Nordic countries, with a population of around 27 million inhabitants [7]. Individuals were followed until date of emigration (except for Iceland where emigration information was not available), date of death or 31st of December 2017 (2016 for Finland), whichever occurred first. Only adult individuals (aged 18 years and above at diagnosis) were included in analysis of survival. Death certificate only cases, incidental autopsy findings and subsequent primary tumours at the same site in the same patient (Appendix A.1) were excluded in the survival analysis. Population-based mortality rates stratified by age, sex and calendar year were obtained from each country's national statistics office and used as expected mortality rates for the cancer patients.

### 2.2. Statistical analysis

Incidence and mortality rates were estimated in each country by sex, 10-year age groups and five-year period diagnosis windows. Age-standardized rates were also estimated with three-year diagnosis windows using the Nordic population distribution in the year 2000 for standardization (Appendix A.2).

Flexible parametric relative survival models [8–10] were fitted separately to the data from each country. This type of modelling approach has been widely used for estimation of cancer patient survival [2,11,12]. All models included age at diagnosis (using restricted cubic splines with 3 degrees of freedom), calendar year at diagnosis (using restricted cubic splines with 3 degrees of freedom) and sex. The models included two-way interactions between each of the three covariates (age, year and sex), and non-proportional excess hazards were allowed by including interactions between the time-scale (time since diagnosis) and each of the covariates. The log cumulative baseline excess hazard was modelled with restricted cubic splines with 5 degrees of freedom (df), and the time-varying effects with 3 df. Winsorizing was used to improve model stability, where 96% of the age distribution was modelled continuously while individuals outside the 2nd and 98th percentile of age had their age reassigned to those percentile limits and were assumed to have the same relative survival [13]. Due to the small population size, leading to few deaths, a modelling approach was not used for Iceland, instead Pohar Perme estimates [14] were calculated by two age groups (18–69, ≥70 years), three calendar periods (1990–99, 2000–09, 2010–12) and sex. For comparison, non-parametric estimates were obtained in the same way for the other countries.

Based on the models described, 5-year relative survival [15] was estimated by sex for each calendar year and selected ages at diagnosis [35, 45, 55, 65, 75, 85]. Age-standardised estimates of relative survival were also obtained from the models, using regression standardization by sex and calendar year of diagnosis [7], with an adapted version of the International Cancer Survival Standard 2 (ICSS2) [16] weights (Appendix A.2). Similarly, age-standardised Pohar Perme estimates were obtained for Iceland, using pre-weighting [17] in five calendar periods

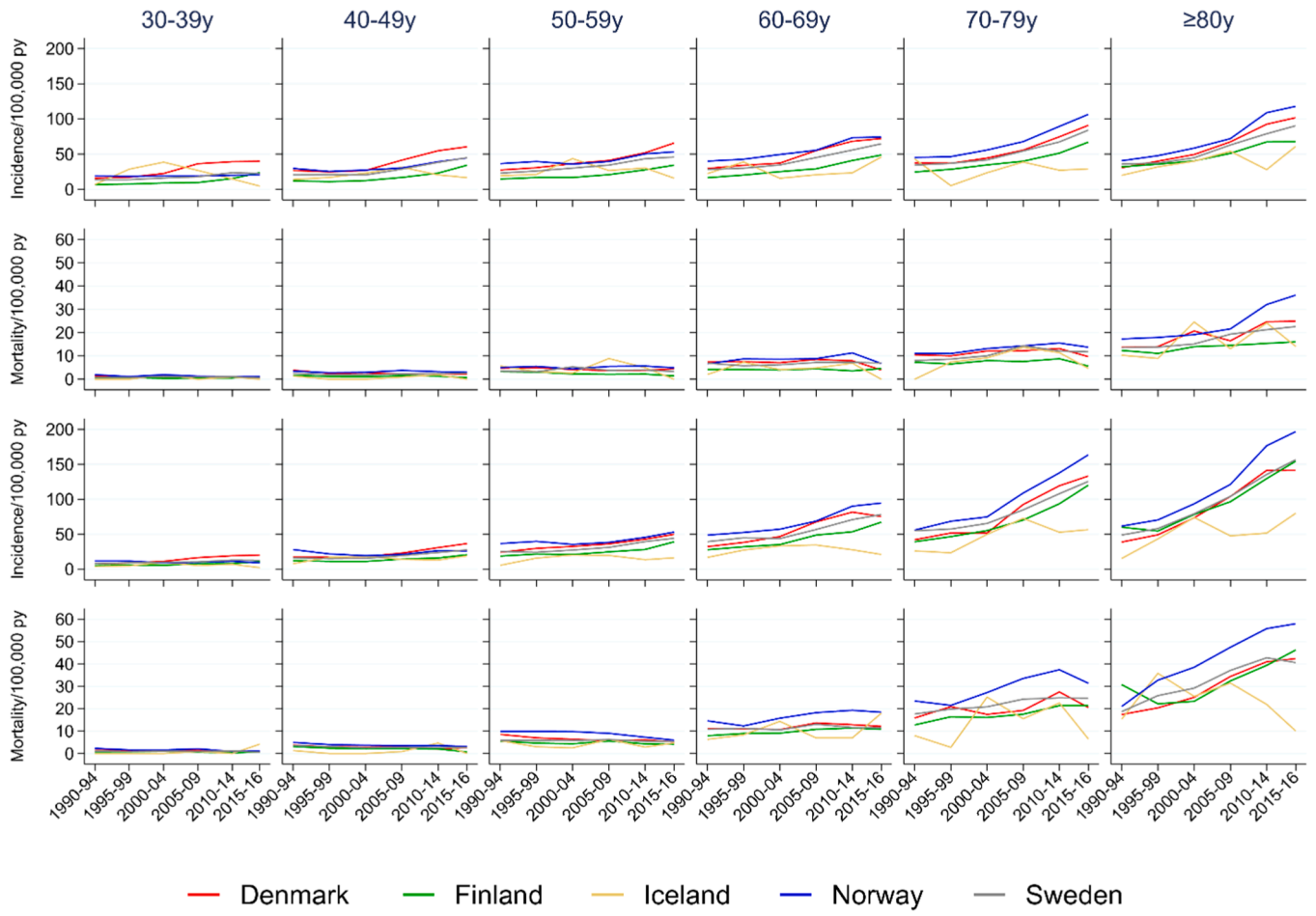


**Fig. 1.** The incidence and mortality of cutaneous malignant melanoma per 100,000 inhabitants, the figures reveal the differences between the Nordic countries for women (two top rows) and men (two bottom rows) and by time periods and age groups.

and by sex.

A period approach was used to obtain estimates for the latest calendar years where long-term follow-up was not available [18]. For Denmark, Norway and Sweden the period window was 2013–2017, for Iceland 2012–2017 and for Finland 2013–2016. Flexible parametric models as described above were fitted to the data in each country, with the only difference being that calendar year of diagnosis was not included in these models. Again, the Pohar Perme method was used for Iceland.

From the models using a period approach, the crude probabilities of all-cause death and death due to cancer at 5 years after diagnosis [19] were estimated, along with the average loss in life expectancy (or life-years lost) [20]. The number of life-years lost is an average based on the full cohort. These measures were age-standardised and reference-adjusted [21–23] (the average background mortality in the Nordic countries was used rather than country-specific mortality rates), to make the estimates comparable across countries. The crude probabilities of death and the loss in life expectancy depend not only on the excess mortality, but also the background mortality, which means that any differences could be due to differences in excess mortality, background mortality or both. By the use of a reference background mortality, i.e., reference-adjustment, differences observed are only due to differences in excess mortality. Marginal estimates that are not reference-adjusted, and not age-standardised were also obtained to get observed values for each country. Age-specific estimates of life-years lost were also estimated using the average background mortality in the Nordic countries (reference-adjusted).

The analyses performed, and measures presented, are similar to previous publications from the NORDCAN survival studies, and a more detailed description of the interpretation of each measure can be found there [2,24,25]. The analyses were performed in Stata (Stata Statistical Software: Release 17. College Station, Texas: Stata Corp LLC), using the commands stpp [26], stpm2 [8] and standsurv [27].

The study was approved by the Swedish Ethical Review Authority (approval 2017/641–31/1, amendment 2019–01913) and the National Institute of Health and Welfare in Finland (approval THL/870/5.05.00/2014, amendment 2019).

## 3. Results

The study included more than 78,000 individuals diagnosed with CMM in the Nordic countries during the years 1990–2016, descriptive statistics of the cohort is presented in Table 1. There were more women than men diagnosed with CMM in all countries (Denmark 54.8%, Iceland 60.0%, Norway 51.4%, Sweden 50.2%) except Finland (49.0%). The mean age at diagnosis was lower in women than in men, ranging from 50.0 (Iceland) to 61.4 (Finland) among women, and 58.7 (Iceland) to 63.4 (Sweden) among men.

The incidence of CMM has increased in both women and men in all age groups and all countries, with the possible exception of Iceland where the interpretation of trends is hampered due to small numbers (Figure 1). The mortality has not increased to the same extent, although an increase can be observed in older age groups, especially among men. Age-standardised incidence and mortality rates are presented in the supplementary material (Figure A.1).

Since 1990, the 5-year relative survival has improved continuously

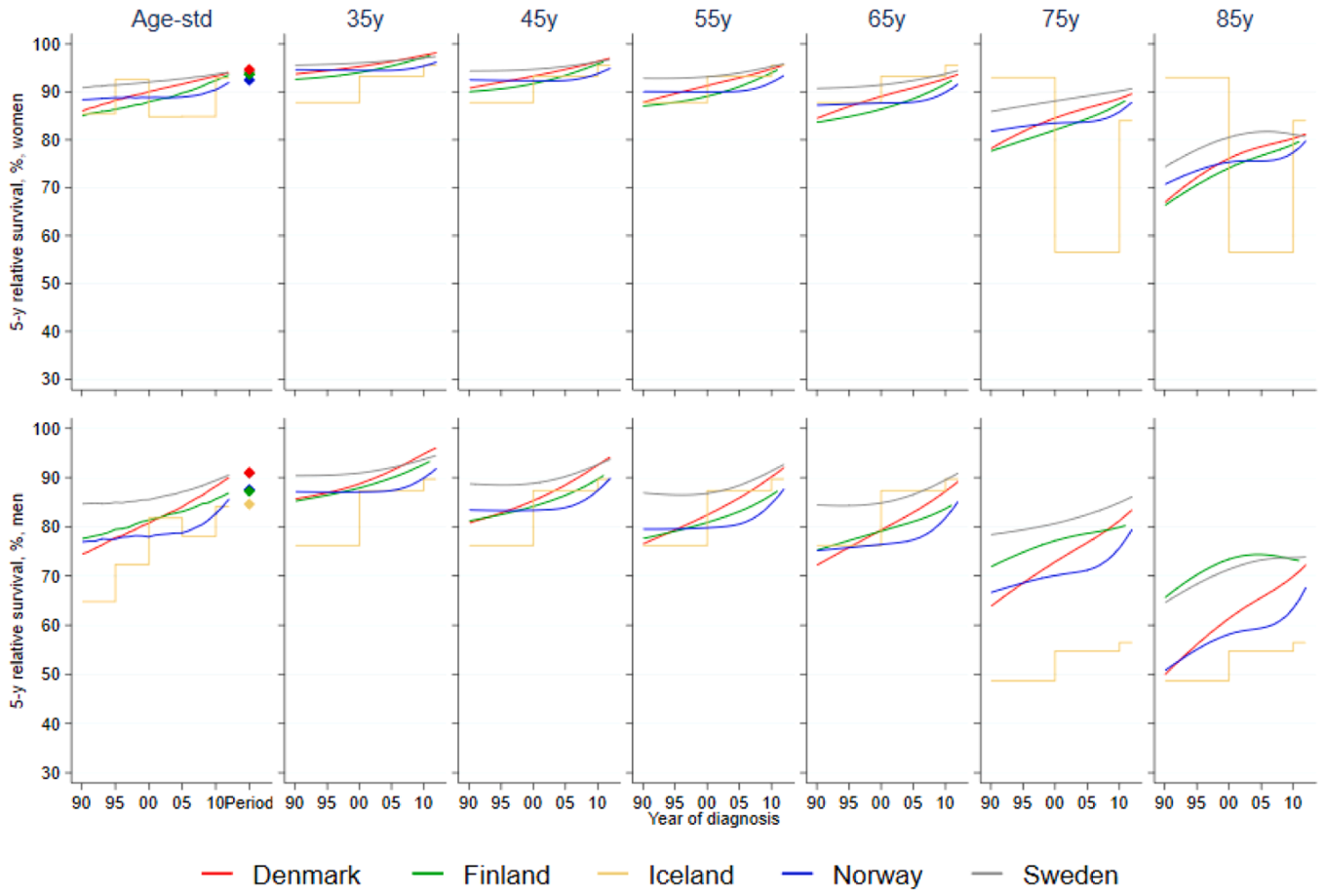


**Fig. 2.** Trends in 5-year relative survival over time for women (top row) and men (bottom row) diagnosed with cutaneous malignant melanoma in the Nordic countries, age-standardised and by age at diagnosis.

in all countries with a similar pattern across age groups (Figure 2, Table A.3, Table A.4, Table A.5). For Iceland, the increase observed in the non-parametric age-standardised 5-year relative survival was not statistically significant (Table A.3). Survival improvements were observed inboth women and men and across age, however with largest improvement among men and for those diagnosed at older ages, where the survival was lower in 1990 (Figure 2, Table A.5, Table A.6). The non-parametric estimates by age groups for Iceland are presented in Table A.6. To enable comparison, non-parametric estimates using the same age groups and calendar years are included for the other countries as well.

The period analysis gave age-standardised estimates of 5-year net probability of death (1 minus 5-year relative survival) ranging from 5.3% (95% CI 4.4–6.1) in Norway to 7.3 (95% CI 6.3–8.2) in Denmark for women, and for men from 9.1 in Sweden (95% CI 8.3–9.9) and Denmark (95% CI 8.1–10.1) to 14.3 (95% CI 6.4–21.5) in Iceland (Table 2). The age-standardised and reference adjusted 5-year crude probability of death due to CMM ranged from 5.0% (95% CI 4.3–5.8) in Denmark to 6.8% (95% CI 6.0–7.8) in women in Norway, and from 8.3% (95% CI 7.6–9.1) in Sweden to 13.2% (95% CI 7.1–21.3) in Icelandic men (Table 2). The loss in life expectancy among women was 2.0 years (95% CI 1.5–2.5) in Denmark, 2.8 (95% CI 1.4–4.1) in Finland, 4.0 (95% CI 2.8–5.1) in Norway and 2.3 (95% CI 1.8–2.8) in Sweden. Inmen the loss in life expectancy was 3.3 years (95% CI 2.5–4.0) in Denmark, 3.6 (95% CI 2.3–4.7) in Finland, 4.6 (95% CI 3.5–5.6) in Norway and 3.1 (95% CI 2.5–3.7) in Sweden. Table A.7 shows marginal estimates for each country that are not age-standardised and not reference-adjusted.

Figure 3 shows the 5-year relative survival and the loss in life expectancy in women and men across age at diagnosis, based on the period analysis. The 5-year relative survival was above 95% in all countries in women diagnosed before age 50, and the loss in life expectancy was less than 5 years for all ages. In men the 5-year relative survival was slightly lower than for women, and the difference increased with age at diagnosis. Norway and Finland had lower survival than the other countries, especially among men. The loss in life expectancy was higher for younger ages, since they have more years to lose. Both women and men diagnosed at age 75–85 lost on average 1–2 years.

## 4. Discussion

In this population-based study we showed continuous improvements in survival following CMM between 1990 and 2016, and improvements were observed in both women and men and across age. The largest improvements were observed in Denmark, where survival was initally among the lowest in the Nordic countries. Similarly, larger improvements were seen among men and in patients diagnosed at older ages, groups with lower survival at the start of the study period and therefore with most potential for improvement. A large improvement was also seen in Norwegian men, attenuating but not eliminating the previous survival disadvantage. At the end of the study period, the survival among women was fairly constant up until age 65 at diagnosis, after which it decreased with increasing age. A similar pattern was seen among men, although declining survival was observed from an earlier age.

A similar improvement has been observed in many European countries [28], and the 5-year net survival in melanoma diagnosed 2010–2014 exceeded 90% in 8 European countries included in the CONCORD-3 study [29]. Improvement in survival can be ascribed to a

**Table 2**
Period estimates of age-standardised and reference adjusted 5-year net and crude probability of death and life-years lost, with 95% confidence intervals, for patients diagnosed with cutaneous malignant melanoma in the Nordic countries.

| Women | Denmark | Finland | Iceland[b] | Norway | Sweden |
|---|---|---|---|---|---|
| 5-year net probability of death, %[c] | 5.3 (4.4-6.1) | 6.3 (5.1-7.4) | 5.7 (−0.1-11.8) | 7.3 (6.3-8.2) | 5.6 (5.0-6.3) |
| 5-year crude probability of death, % | | | | | |
| **Cancer** | 5.0 (4.3-5.8) | 5.8 (4.8-7.0) | 5.8 (1.6-13.9) | 6.8 (6.0-7.8) | 5.2 (4.7-5.9) |
| **Other causes** | 5.4 (5.3-5.5) | 5.6 (5.5-5.8) | 4.1 (3.9-4.2) | 5.4 (5.3-5.6) | 5.6 (5.5-5.7) |
| **All-cause**[d] | 10.4 (9.7-11.1) | 11.4 (10.4-12.5) | *9.9 (5.5-18.1)* | 12.3 (11.4-13.1) | 10.8 (10.3-11.4) |
| Life-years lost[e] | 2.0 (1.5-2.5) | 2.8 (1.4-4.1) | NA | 4.0 (2.8-5.1) | 2.3 (1.8-2.8) |
| **Men** | **Denmark** | **Finland** | **Iceland[b]** | **Norway** | **Sweden** |
| 5-year net probability of death, %[c] | 9.1 (8.1-10.1) | 12.8 (11.2-14.3) | 14.3 (6.4-21.5) | 12.7 (11.4-13.9) | 9.1 (8.3-9.9) |
| 5-year crude probability of death, % | | | | | |
| **Cancer** | 8.4 (7.5-9.4) | 12.1 (10.7-13.7) | 13.2 (7.1-21.3) | 12.0 (10.9-13.2) | 8.3 (7.6-9.1) |
| **Other causes** | 7.1 (7.0-7.3) | 6.9 (6.7-7.1) | 6.5 (6.2-6.8) | 7.2 (7.1-7.3) | 7.5 (7.4-7.6) |
| **All-cause**[d] | 15.5 (14.7-16.4) | 19.0 (17.6-20.4) | *19.7 (13.3-28.1)* | 19.2 (18.1-20.3) | 15.8 (15.1-16.5) |
| Life-years lost[e] | 3.3 (2.5-4.0) | 3.6 (2.3-4.7) | NA | 4.6 (3.5-5.6) | 3.1 (2.5-3.7) |

Period window 2013-2017 (2012-2017 for Iceland, 2013-2016 for Finland). Estimates of crude probability of death and life-years lost based on average background mortality in the Nordic countries (reference-adjusted measures).

[b] Iceland estimates obtained non-parametrically

[c] 5-year net probability of death is estimated as 1 minus 5-year relative survival

[d] All-cause is the sum of the crude probability of death due to cancer and other causes

[e] Average number of life years lost due to cancer

multitude of factors: earlier diagnosis of CMM, likely to reflect increased awareness both in the population and among healthcare providers, improved organizational structure for diagnosis, treatment, and follow-up, development of evidence based guidelines and quality of care monitoring, improved surgical procedures with sentinel node biopsy, cancer pathways with time limits for diagnosis and treatment, and improved oncologic treatment [30,31]. Overdiagnosis can explain some of the dramatic increase in incidence and to some extent also impact the survival measures [32,33]. There have been public health strategies introduced in the Nordic countries to reduce the incidence of melanoma and improve survival. For instance, there are general awareness campaigns in Finland organised by the Radiation and Nuclear Safety Authority, the Cancer Society of Finland and the Finnish Meteorological Institute, in Norway by The Norwegian Cancer Society and the Cancer Registry of Norway, and in Sweden coordinated by the Swedish Safety Authority. A sun protection campaign started in 2007 in Denmark by the Danish Cancer Society and Tryg Fonden, and The Icelandic Cancer Society have had campaigns against sunbed use and for general caution in the sun. Sunbed use legislation have also been introduced, and age restrictions are in place in Finland, Iceland, Norway, and Sweden.

The diagnosis of CMM in the clinical setting is demanding, and the more tumors that are surgically excised for examination, the more patients will be diagnosed with cancer [34]. Another possible reason for the improvements in survival is a shift in the distribution of histological type. CMM includes several histologic subtypes, and the proportion of the superficial spreading type, which in particular is associated with UV exposition, has increased substantially, while the number of nodular melanomas which is associated with faster growth and a dismal prognosis seems more constant [26]. Unfortunately, information on histology was not available for all countries and all calendar years, and we did therefore not include histology in any analyses. Another factor for which data was not available for all countries and calendar years was anatomic site.

The most important tumor prognostic factor is tumor thickness and thin tumors have been shown to account for an increasing proportion over calendar time [35–38]. This stage shift could potentially explain part of the survival improvements observed, however it is unlikely to fully explain the observed improvement [39]. Since stage information was only partly available, we were unable to assess stage-specific survival. No stage information was available for Finland and Iceland, and in the other countries stage data was only partially available since 2004. Future survival comparisons across the Nordic countries would benefit from improved registration of TNM stage, and efforts should be taken to increase the reporting of stage and to harmonize the collection and reporting across the Nordic countries.

The introduction of modern systemic treatment with immunotherapy and targeted therapy for advanced (inoperable) melanoma has improved the prognosis radically [40]. The European Medicines Agency (EMA) approved the CTLA-4 checkpoint inhibitor ipilimumab in 2011, and the PD-1 inhibitors nivolumab and pembrolizumab in 2015. The BRAF inhibitor vemurafenib was approved for BRAF-mutated melanoma in 2012, and additional BRAF and MEK inhibitors and combined therapy have followed since. Approvals in the Nordic countries generally followed shortly after, although Finland seems to have been somewhat slower to implement the treatment [41]. Prior to approvals, some patients had been participating in the multinational clinical trials which the approvals were based upon, with slight improvements in survival noticed in patients treated with interleukin-2 and interferon already in the years before the checkpoint inhibitors became available [42]. The survival impact of modern oncologic melanoma treatment has been prevalent from the latest periods in the current study; and the effect is expected to be more pronounced in the period to follow.

A strength of our study is the use of population-based cancer registry data from the NORDCAN database, covering a population of 27 million inhabitants [7]. All the Nordic countries have cancer registries with a long history and high quality [43], and similar tax-funded health care systems. Using personal identity numbers given to permanent residents in each country, follow-up information on deaths and migration has been individually linked to the cancer registry data. The data are thus generally comparable as demonstrated in previous joint Nordic studies [2,3,24,25]. There are, however, some differences that could bias the comparisons of survival between the countries. All countries except Sweden include death certificate-initiated cancers [44], but the impact on melanoma survival should be low. Other differences were that we only had follow-up information up until 2016 in Finland and that we lack information on migration in Iceland. Also, the small number of cases, and particularly small number of deaths, made the Icelandic data difficult to interpret. A weakness of the present study was the lack of reliable and complete information on stage, precluding assessment of trends in stage specific survival.

Within this study we have presented several survival metrics, that provide different perspectives on the prognosis following a diagnosis of CMM. The age-standardised and reference-adjusted measures are useful for making fair direct comparisons since any differences in age distribution or other-cause mortality rates between the countries have been accounted for. On the other hand, these measures should not be interpreted as the observed average within each country. For completeness, we have also presented the crude estimates for each country in the supplementary material. One of the great advantages of the flexible

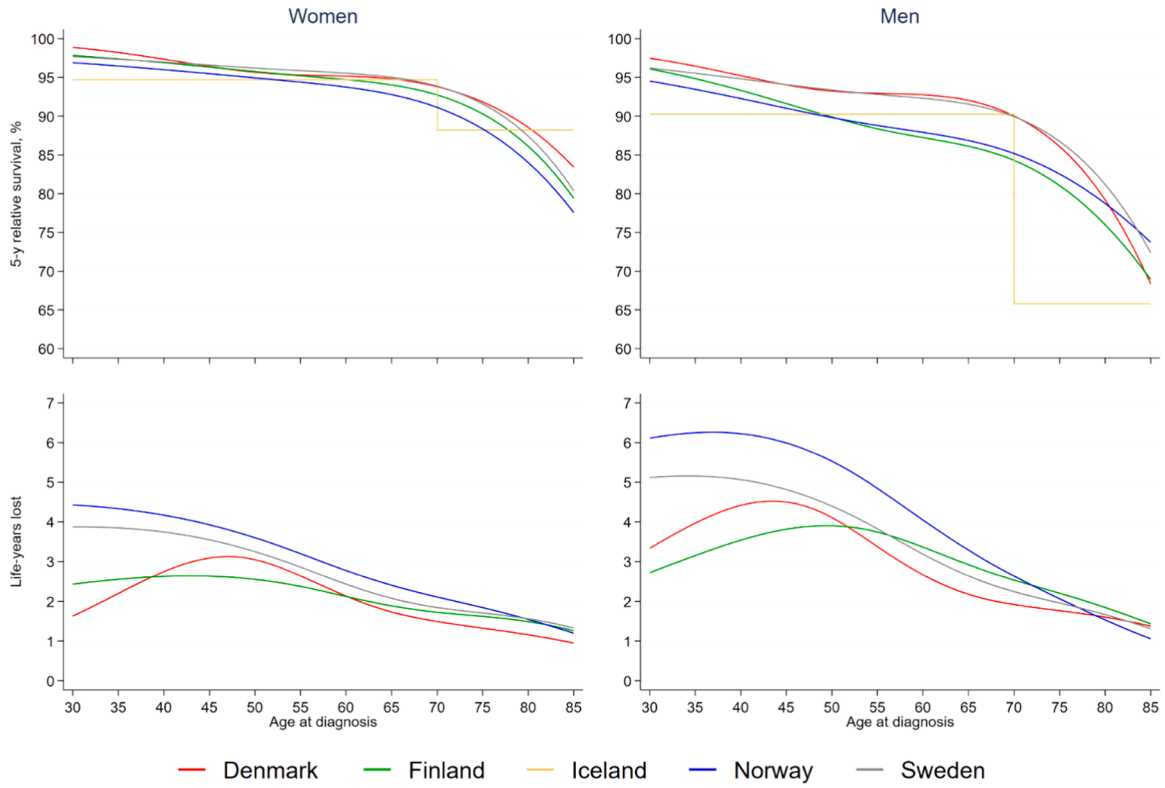


**Fig. 3.** Period estimates of 5-year relative survival (top row) and reference-adjusted loss in life expectancy in years (bottom row) for patients diagnosed with cutaneous malignant melanoma in the Nordic countries. Period window 2013–2017 (2012–2017 for Iceland, 2013–2016 for Finland). Reference-adjustment based on average background mortality in the Nordic countries.

parametric models used in this study is the range of metrics that can be presented. Previous studies have shown that the model is robust to the number of knots used for modelling the baseline [45,46]. A potential limitation is the extrapolation of the survival function that is required to estimate the life-years lost. Although this has also shown to be robust for many cancer sites [20], any measures that requires extrapolation should be interpreted with caution.

## 5. Conclusion

Survival following a diagnosis of CMM has continuously improved in the Nordic countries between 1990 and 2016 with improvements observed both among women and men, and across age. The largest improvements were observed in men in Denmark diagnosed at older age, the group with the lowest survival at the start of the study period.

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## CRediT authorship contribution statement

**Frida E Lundberg:** Conceptualization, Methodology, Formal analysis, Visualization, Writing-Original draft preparation. **Helgi Birgisson:** Writing-Original draft preparation. **Gerda Engholm:** Data curation, Writing-Reviewing and Editing. **Elinborg J Ólafsdóttir:** Writing-Reviewing and Editing. **Lina Steinrud Mørch:** Writing-Reviewing and Editing. **Tom Børge Johannesen:** Writing-Reviewing and Editing. **David Pettersson:** Writing-Reviewing and Editing. **Mats Lambe:** Writing-Reviewing and Editing. **Karri Seppä:** Writing-Reviewing and Editing. **Paul C Lambert:** Conceptualization, Methodology, Funding acquisition, Supervision, Writing-Reviewing and Editing. **Anna LV Johansson:** Conceptualization, Methodology, Writing-Reviewing and Editing. **Lisbet Rosenkrantz Hölmich:** Writing-Reviewing and Editing. **Therese M-L Andersson:** Conceptualization, Methodology, Writing-Original draft preparation.

## Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could appear to influence the work reported in this paper.

## Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.ejca.2024.113980.

## References

[1] Bray F., Ferlay J., Soerjomataram I., et al. Global cancer statistics 2018: Globocan estimates of incidence and mortality worldwide for 36 cancers in 185 countries.
[2] Lundberg FE, Andersson TM, Lambe M, Engholm G, Morch LS, Johannesen TB, et al. Trends in cancer survival in the Nordic countries 1990-2016: the NORDCAN survival studies. Acta Oncol 2020;59(11):1266–74.
[3] Tryggvadóttir L, Gislum M, Hakulinen T, Klint Å, Engholm G, Storm HH, et al. Trends in the survival of patients diagnosed with malignant melanoma of the skin in the Nordic countries 1964–2003 followed up to the end of 2006. Acta Oncol 2010;49(5):665–72.
[4] Larønningen S., Arvidsson G., Bray F., Engholm G., Ervik M., Guðmundsdóttir E.M., Gulbrandsen J., Hansen H.L., Hansen H.M., Johannesen T.B., Kristensen S., Kristiansen M.F., Lam F., Laversanne M., Miettinen J., Mørch L.S., Ólafsdóttir E., Pejicic S., Petterson D., Steig B.Á., Skog A., Tian H., Aagnes B., Storm H.H. NORDCAN: Cancer Incidence, Mortality, Prevalence and Survival in the Nordic Countries, Version 9.3 (02.10.2023). Association of the Nordic Cancer Registries. Cancer Registry of Norway. 2023. https://nordcan.iarc.fr/.

[5] Gershenwald JE, Scolyer RA, Hess KR, Sondak VK, Long GV, Ross MI, et al. Melanoma staging: evidence-based changes in the American Joint Committee on Cancer eighth edition cancer staging manual. CA Cancer J Clin 2017;67(6):472–92.

[6] Schwartz MR, Luo L, Berwick M. Sex differences in melanoma. Curr Epidemiol Rep 2019;6.

[7] Engholm G, Ferlay J, Christensen N, Bray F, Gjerstorff ML, Klint A, et al. NORDCAN - a Nordic tool for cancer information, planning, quality control and research. Acta Oncol 2010;49(5):725–36.

[8] Lambert PC, Royston P. Further development of flexible parametric models for survival analysis. Stata J 2009;9(2):265–90.

[9] Nelson CP, Lambert PC, Squire IB, Jones DR. Flexible parametric models for relative survival, with application in coronary heart disease. Stat Med 2007;26(30):5486–98.

[10] Royston P, Parmar MK. Flexible parametric proportional-hazards and proportional-odds models for censored survival data, with application to prognostic modelling and estimation of treatment effects. Stat Med 2002;21(15):2175–97.

[11] Myklebust TÅ, Aagnes B, Nilssen Y, Rutherford M, Lambert PC, Andersson TML, et al. Improving communication of cancer survival statistics-feasibility of implementing model-based algorithms in routine publications. Br J Cancer 2023;129(5):819–28.

[12] Devasia TP, Howlader N, Dewar RA, Stevens JL, Mittu K, Mariotto AB. Increase in the life expectancy of patients with cancer in the United States. Cancer Epidemiol Biomark Prev 2023. OF1–10.

[13] Syriopoulou E, Mozumder SI, Rutherford MJ, Lambert PC. Robustness of individual and marginal model-based estimates: A sensitivity analysis of flexible parametric models. Cancer Epidemiol 2019;58:17–24.

[14] Perme MP, Stare J, Esteve J. On estimation in relative survival. Biometrics 2012;68(1):113–20.

[15] Dickman PW, Adami HO. Interpreting trends in cancer patient survival. J Intern Med 2006;260(2):103–17.

[16] Corazziari I, Quinn M, Capocaccia R. Standard cancer patient population for age standardising survival ratios. Eur J Cancer Oxf Engl 1990 2004 Oct;40(15):2307–16.

[17] Rutherford MJ, Dickman PW, Coviello E, Lambert PC. Estimation of age-standardized net survival, even when age-specific data are sparse. Cancer Epidemiol 2020;67:101745.

[18] Brenner H, Gefeller O. Deriving more up-to-date estimates of long-term patient survival. J Clin Epidemiol 1997;50(2):211–6. /02/01 ed. 1997 Feb.

[19] Lambert PC, Dickman PW, Nelson CP, Royston P. Estimating the crude probability of death due to cancer and other causes using relative survival models. Stat Med 2010;29(7–8):885–95.

[20] Andersson TM, Dickman PW, Eloranta S, Lambe M, Lambert PC. Estimating the loss in expectation of life due to cancer using flexible parametric survival models. Stat Med 2013;32(30):5286–300.

[21] Lambert P.C., Andersson T.M., Rutherford M.J., Myklebust T., Møller B. Reference-adjusted and standardized all-cause and crude probabilities as an alternative to net survival in population-based cancer studies. Int J Epidemiol. 2020/08/24 ed. 2020 Aug 23;

[22] Rutherford MJ, Andersson TML, Myklebust TÅ, Møller B, Lambert PC. Non-parametric estimation of reference adjusted, standardised probabilities of all-cause death and death due to cancer for population group comparisons. BMC Med Res Method 2022;22(1):2.

[23] Andersson TML, Rutherford MJ, Møller B, Lambert PC, Myklebust TÅ. Reference-Adjusted Loss in Life Expectancy for Population-Based Cancer Patient Survival Comparisons-with an Application to Colon Cancer in Sweden. Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol 2022;31(9):1720–6.

[24] Lundberg FE, Birgisson H, Johannesen TB, Engholm G, Virtanen A, Pettersson D, et al. Survival trends in patients diagnosed with colon and rectal cancer in the nordic countries 1990-2016: The NORDCAN survival studies. Eur J Cancer 2022;172:76–84. /06/28 ed. 2022 Sep.

[25] Lundberg FE, Kroman N, Lambe M, Andersson TML, Engholm G, Johannesen TB, et al. Age-specific survival trends and life-years lost in women with breast cancer 1990-2016: the NORDCAN survival studies. Acta Oncol Stock Swed 2022;61(12):1481–9.

[26] Lambert P. STPP: Stata module to compute Pohar-Perme non-parametric estimate of marginal relative (net) survival [Internet]. 2020. Available from: ⟨https://ideas.repec.org/c/boc/bocode/s458743.html⟩.

[27] Lambert P. STANDSURV: Stata module to compute standardized (marginal) survival and related functions [Internet]. 2021. Available from: ⟨https://ideas.repec.org/c/boc/bocode/s458991.html⟩.

[28] Galceran J., Uhry Z., Marcos-Gragera R., Borràs J., GRELL EUROCARE-5 Working Group. Trends in net survival from skin malignant melanoma in six European Latin countries: results from the SUDCAN population-based study. Eur J Cancer Prev Off J Eur Cancer Prev Organ ECP. 2017 Jan;26 Trends in cancer net survival in six European Latin Countries: the SUDCAN study:S77–84.

[29] Allemani C., Matsuda T., Di Carlo V., Harewood R., Matz M., Nikšić M., et al. Global surveillance of trends in cancer survival: analysis of individual records for 37,513,025 patients diagnosed with one of 18 cancers during 2000–2014 from 322 population-based registries in 71 countries (CONCORD-3). Lancet Lond Engl. 2018 Mar 17;391(10125):1023–1075.

[30] Hölmich LR, Klausen S, Spaun E, Schmidt G, Gad D, Svane IM, et al. The Danish melanoma database. Clin Epidemiol 2016;8:543–8.

[31] Ellebaek E, Svane IM, Schmidt H, Haslund CA, Donia M, Hoejberg L, et al. The Danish metastatic melanoma database (DAMMED): a nation-wide platform for quality assurance and research in real-world data on medical therapy in Danish melanoma patients. Cancer Epidemiol 2021;73:101943.

[32] Rubin R. Melanoma diagnoses rise while mortality stays fairly flat, raising concerns about overdiagnosis. JAMA 2020;323(15):1429–30.

[33] Welch HG, Kramer BS, Black WC. Epidemiologic Signatures in Cancer. N Engl J Med 2019;381(14):1378–86.

[34] Kerr KF, Eguchi MM, Piepkorn MW, Radick AC, Reisch LM, Shucard HL, et al. Dermatopathologist Perceptions of Overdiagnosis of Melanocytic Skin Lesions and Association With Diagnostic Behaviors. JAMA Dermatol 2022;158(6):675–9.

[35] Helvind NM, Hölmich LR, Smith S, Glud M, Andersen KK, Dalton SO, et al. Incidence of In Situ and Invasive Melanoma in Denmark From 1985 Through 2012: A National Database Study of 24,059 Melanoma Cases. JAMA Dermatol 2015;151(10):1087–95.

[36] Isaksson K, Mikiver R, Eriksson H, Lapins J, Nielsen K, Ingvar C, et al. Survival in 31 670 patients with thin melanomas: a Swedish population-based study. Br J Dermatol 2021;184(1):60–7.

[37] Eriksson H, Nielsen K, Vassilaki I, Lapins J, Mikiver R, Lyth J, et al. Trend shifts in age-specific incidence for in situ and invasive cutaneous melanoma in Sweden. Cancers 2021;13(11).

[38] Svedman FC, Pillas D, Taylor A, Kaur M, Linder R, Hansson J. Stage-specific survival and recurrence in patients with cutaneous malignant melanoma in Europe – a systematic review of the literature. Clin Epidemiol 2016;8:109–22.

[39] Zamagni F, Bucchi L, Mancini S, Crocetti E, Dal Maso L, Ferretti S, et al. The relative contribution of the decreasing trend in tumour thickness to the 2010s increase in net survival from cutaneous malignant melanoma in Italy: a population-based investigation. Br J Dermatol 2022;187(1):52–63.

[40] Soerensen AV, Ellebaek E, Bastholt L, Schmidt H, Donia M, Svane IM. Improved progression-free long-term survival of a nation-wide patient population with metastatic melanoma. Cancers 2020;12(9).

[41] Cancer immunotherapies in Finland [Internet]. 2022 Mar. Available from: https://cancerio.org/wp-content/uploads/2022/03/Cancer-Immunotherapies-in-Finland.pdf.

[42] Bastholt L, Svane IM, Bjerregaard JK, Herrstedt J, Hróbjartsson A, Schmidt H. High-dose interleukin-2 and interferon as first-line immunotherapy for metastatic melanoma: long-term follow-up in a large unselected Danish patient cohort. Eur J Cancer Oxf Engl 1990 2019;115:61–7.

[43] Pukkala E, Engholm G, Hojsgaard Schmidt LK, Storm H, Khan S, Lambe M, et al. Nordic cancer registries - an overview of their procedures and data comparability. Acta Oncol 2017:1–16.

[44] Lambe M, Wigertz A, Sandin F, Holmberg E, Amsler-Nordin S, Andersson TM, et al. Estimates of lung and pancreatic cancer survival in Sweden with and without inclusion of death certificate initiated (DCI) cases. Acta Oncol 2020;59(11):1322–8.

[45] Rutherford MJ, Crowther MJ, Lambert PC. The use of restricted cubic splines to approximate complex hazard functions in the analysis of time-to-event data: a simulation study. J Stat Comput Simul 2015;85(4):777–93.

[46] Bower H, Crowther MJ, Rutherford MJ, Andersson TML, Clements M, Liu XR, et al. Capturing simple and complex time-dependent effects using flexible parametric survival models: a simulation study. Commun Stat Simul Comput 2021;50(11):3777–93.