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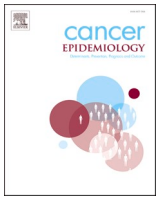

A metric for comparison and visualization of age disparities in cancer survival

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ABSTRACT

Aims: Diagnostic age is an important determinant of cancer survival but the methods generally used to analyze age-group-specific survival are not developed for ready visualization of survival differences. We aim at developing a novel metric for comparing and visualizing age-group-specific survival data over different cancers, sexes, periods and countries.
Methods: The metric describes the mean absolute deviation between age-groups. The metric can be used in two variations, one showing the mean variation and its 95% confidence intervals and the other highlighting individually each age-groups distinguishing positive or negative deviations. We demonstrate the applications with age-group- specific 5-year relative survival data from the NORDCAN database
Results: The mean absolute deviation between age-groups for Swedish colon cancer survival declined from about 5% in 1972–1981–1% in 1992–2001 and to 1.3% in 2012–2021. Patients diagnosed before age 50 years accounted for the largest positive deviation. For acute myeloid leukemia (AML) the mean deviation increased from 4% (female) to 17% and 23%. Patients diagnosed at age below 50 years showed the largest deviations. Comparing colon cancer mean deviations between the Nordic countries, a time-related decline was observed for all, those in Sweden ending at the lowest and in Finland the highest level.
Conclusions: We demonstrated the usefulness of the devised metric for summarizing age-specific survival data between cancers, sexes, periods and countries. The two variations of the metric allow a simple visual presentation of the survival experience as to deviation of the survival data, its 95%CIs and its highlighted individual age-group components.

1. Introduction

Cancer survival is one of the key measures of success in cancer control [1]. It is well known that age at diagnosis is an important determinant of survival in practically all adult cancers but its influence varies between cancers. In cancers of very good survival obviously there cannot be large differences between age-groups. Among common solid cancers, about 10 had a 5-year relative survival of over 80% according to the recent data from the Nordic countries [2]. For these cancers age-group specific survival would be expected to be fairly similar in common age-groups. For the remaining 25 cancers 5-year survival ranged from 70% to 10% which would leave space for large age differences [2]. When evaluating improvement in cancer survival all individual age-groups should be considered. Sometimes diagnostic age has been one of many adjustment variables or it has been completely overlooked. In studies where age-specific survival has been reported the data have been displayed in various ways. In some studies survival or survival trends in age-groups have been shown with confidence intervals (CIs) or just by visual comparison [3–10]. Other studies have used dichotomous age-groups (such as divided at age 75 years) and compared these to each other or a few age-groups and selected the largest age-group for comparison [11–13]. A recent Dutch study on all cancer noted that the incidence in cancer in persons diagnosed at age 80+ years was doubled in the last 30 years [14]. During that period, 5-year overall survival of the 80+-year-old patients increased by 7 percentage points to 26% but for the younger patients the increase was 19 points to 63%; thus, the survival gaps widened. There was a large age-gradient in the application of surgery, radiotherapy and systemic treatment in favor of young patients while pateints aged 80+ years received often no treatment [14]. While these studies describe age-specific survival or

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differences in survival between selected age groups, they do not allow an overall estimate of disparities in survival across the range of all age groups.

We present here a novel metric for comparing and visualizing age-group-specific survival data over different cancers, sexes, periods and countries. The metric describes the mean absolute deviation of relative survival estimates for specific age-groups. The metric can additionally be split into deviations of each age-group helping visualization of the deviant age-groups and their directions. Our framework thus allows to measure overall level of dispersion of survival estimates across age groups with complementary description at specific group level. We will demonstrate the utility of the metric on the recently released age-group specific survival data from the NORDCAN database of the Nordic cancer registries (https://nordcan.iarc.fr/en). For the demonstration we select a common cancer of the colon and a rare malignancy, acute myeloid leukemia (AML) which we test in three 10-year periods (1972–1981, 1992–2001 and 2012–2021).

2. Materials and methods

The NORDCAN database 2.0 was accessed at the IARC website (https://nordcan.iarc.fr/en) in winter of 2024 [15–17]. Most analyses were based on Swedish data, except that for international comparison also Danish, Finnish and Norwegian data were used. The available data are grouped and not based on individual patients. We extracted data on case numbers and 5-year relative age-specific survival with 95%CIs from 1972 until the end of 2021.

Relative survival in NORDCAN is calculated using Pohar Perme method [18,19]. National general population life-tables stratified by sex, year and age were used in the calculation of expected survival. Exclusions included patients with only death certificate data and those 90 years or older. Inclusion criteria were a minimum 30 patients were alive at start and a minimum 3 patients in any one of age-groups used for weights.

Age-specific 5-year relative survival for 10-year periods was calculated as an average of relative survival estimates available at NORDCAN for subsequent 5-year periods for each age-group. The age-specific relative estimates are provided by NORDCAN for following age groups: 0–49, 50–59, 60–69, 70–79, and 80–89 years. Age-standardized (ICSS weights) relative survival estimates for 10-year periods were extracted from NORDCAN.

To measure dispersion of age-specific survival, we first averaged relative survival estimates for subsequent 5-calendar year periods to obtain average age-specific estimates for 10-year periods.

$$S_i = \frac{1}{2}(S_i^A + S_i^B)$$

where S_i^A, S_i^B are relative survival estimates for i-th age group in consecutive 5-year periods.

Then we derived mean absolute deviation corresponding to average absolute deviation of individual age-specific estimates from their mean.

$$D = \frac{1}{n}\sum_{i=1}^{n}|S_i - S_{mean}|$$

Where

$$S_{mean} = \frac{1}{n}\sum_{i=1}^{n}S_i$$

Is the mean of age-specific relative survival estimates S_i. We have additionally calculated differences between age-specific survival estimates and S_{mean}, providing estimates of directional deviation for specific age-groups.

The 95%CIs of the mean absolute deviation estimates were derived from CIs provided by NORDCAN for relative survival data. The asymmetric CIs on the survival scale were transformed to calculate variance on the cumulative hazard scale. We next performed 10,000 Monte Carlo simulations, where cumulative excess hazard was drawn from the normal distribution, with estimated mean and standard deviation:

$$Hr_i^P \sim N(-\ln(S_i^P), sd = (-\ln(ciL(S_i^P)) + \ln(ciU(S_i^P)))/3.92)$$

where Hr_i^P is randomly drawn cumulative excess hazard for i-th age group in period P, ciL and ciU are lower and upper bounds of 95% CI provided by NORDCAN for each age-specific relative survival estimate. These values were transformed to the relative survival scale and used to calculate random distribution for the metric, with 2.5th and 97.5th quantiles corresponding to the bounds of the 95%CIs. The obtained 95% CIs thus reflect uncertainty of the mean absolute deviation estimate based on uncertainty of the original NORDCAN age-specific relative survival estimates under assumption of independence of individual estimates.

The cumulative excess hazard was calculated as cumulative hazard associated with the derived relative survival estimates for individual 10-year periods.

$$H_i = -\ln(S_i)$$

We then calculated the ratios of the age-specific cumulative excess hazard and cumulative excess hazard in the youngest group (reference group). The CIs were derived analogously as for the dispersion metric above.

Differences in the mean absolute deviation were called significant when the 95%CIs were non-overlapping; the relative cumulative excess hazard was considered significant if the corresponding cumulative excess hazard ratio was larger than 1.0.

3. Results

NORDCAN provides age-specific survival data in 5 groups: below 50, 50–59, 60–59, 70–79 and 80–89 years. In Table S1 case numbers are shown in 10-year periods in 1972–1981, 1992–2001 and 2012–2021. During the 50-year period, case number doubled for colon cancer, and increased even more for the 80+-year-old patients. For younger AML patients case numbers remained fairly constant but for the oldest patients they trebled.

Overall and age-specific 5-year relative survival data are shown in Table 1. For colon cancer, female 5-year survival was initially over 3% units better than male survival but the gap narrowed to less than 2% units, but was 5% unit among 80–89-year old. At all periods the age-related negative gradient in survival remained. For AML there was also an age-gradient. Even for the youngest female patients the survival in 1972–1981(male data were incomplete) was less than 14% and overall survival was 5.2%, Survival increased in all age-groups but the oldest.

The differences in survival translate differently to relative excess hazards, depending on the level of survival. In Table 2 we thus show cumulative excess hazard ratios (ceHR) for survival using the youngest age groups as references. For female colon cancer in 1972–1981 ceHRs increased step-wise by age to 1.89, similar to men of 1.75. The age gradient levelled off fast and in 1992–2001 none of the ceHRs were significant (except 1.17 for 50–59-year-old women). By the end of the study, ceHRs increased moderately again. For AML the development was quite opposite. In 1972–1981 there was an age-gradient in women and ceHRs increased to 2.24 (relative cumulative excess hazard for the oldest women was not significant). From 1992–2001 onwards a steep age gradient could be observed and in 2012–2021 ceHRs for the oldest women were 9.89 and for men 11.97.

Fig. 1 shows the mean absolute deviation for 5-year relative survival in age-specific colon cancer in the 5 age-groups. In panel A, women and men are shown side-by-side in the three periods. The mean deviation declined from about 5% in 1972–1981–1% in 1992–2001 and 1.3% in

Table 1
Age-specific relative survival [95% CI] for colon cancer and AML in Sweden in 3 periods.

	Colon cancer					
	Females			Males		
Age group	1972–1981	1992–2001	2012–2021	1972–1981	1992–2001	2012–2021
0–49	60.3 [57.1–63.7]	62.1 [58.6–65.7]	73.4 [70.9–76.0]	54.4 [50.7–58.5]	58.5 [55.0–62.4]	71.7 [69.0–74.3]
50–59	48.3 [45.7–51.0]	57.2 [54.7–59.9]	70.8 [68.7–73.1]	45.0 [42.1–48.0]	56.5 [53.8–59.2]	68.8 [66.7–71.2]
60–69	46.2 [44.3–48.2]	58.7 [56.9–60.6]	69.0 [67.5–70.5]	43.5 [41.5–45.6]	55.7 [53.8–57.7]	68.2 [66.8–69.6]
70–79	44.0 [42.2–45.9]	58.5 [56.9–60.1]	68.7 [67.4–70.0]	41.2 [39.2–43.3]	57.0 [55.2–58.7]	68.3 [67.0–69.7]
80–89	38.5 [35.5–41.7]	59.6 [57.2–62.2]	69.8 [67.8–71.8]	34.5 [30.8–38.7]	54.9 [51.6–58.3]	64.9 [62.5–67.5]
total	46.4 [45.3–47.5]	58.9 [57.9–60.0]	69.9 [69.0–70.8]	43.1 [41.9–44.3]	56.3 [55.2–57.4]	68.3 [67.3–69.3]
	Acute myeloid leukemia					
	Females			Males		
Age group	1972–1981	1992–2001	2012–2021	1972–1981	1992–2001	2012–2021
0–49	13.9 [10.1–19.7]	57.0 [51.6–63.0]	73.0 [68.0–78.4]	8.3 [5.6–13.0]	51.4 [45.9–57.6]	72.5 [67.7–77.8]
50–59	5.8 [3.1–13.8]	30.2 [23.7–39.3]	61.1 [53.3–70.4]	7.2 [3.9–15.2]	28.0 [22.4–35.9]	60.0 [53.3–67.6]
60–69	2.0 [0.7–7.2]	18.6 [14.6–24.1]	40.8 [35.4–47.2]	3.1 [1.5–7.9]	12.3 [9.0–17.4]	37.8 [32.9–43.7]
70–79	1.2 [0.4–6.3]	6.9 [4.7–10.4]	16.4 [13.0–21.0]	1.6 [0.5–8.2]	6.6 [4.5–10.1]	14.7 [11.6–19.2]
80–89	9.9 [3.9–30.8]	1.2 [0.4–7.0]	4.4 [2.5–8.5]	-	2.4 [0.7–11.7]	2.1 [0.9–6.0]
total	5.2 [3.9–7.1]	21.1 [19.2–23.2]	35.8 [33.3–38.5]	3.7 [2.6–5.2]	17.7 [15.8–19.7]	34.0 [31.6–36.5]

Table 2
Age-specific cumulative excess hazard ratios [95% CI] with respect to youngest age-group.

	Colon cancer					
	Females			Males		
Age group	1972–1981	1992–2001	2012–2021	1972–1981	1992–2001	2012–2021
0–49 (ref.)	1.00	1.00	1.00	1.00	1.00	1.00
50–59	1.44 [1.26–1.64]	1.17 [1.02–1.37]	1.11 [0.96–1.29]	1.31 [1.14–1.52]	1.07 [0.93–1.24]	1.12 [0.97–1.29]
60–69	1.53 [1.36–1.73]	1.12 [0.98–1.29]	1.20 [1.06–1.37]	1.37 [1.21–1.57]	1.09 [0.96–1.26]	1.15 [1.02–1.31]
70–79	1.62 [1.45–1.84]	1.13 [0.99–1.29]	1.21 [1.08–1.38]	1.46 [1.29–1.67]	1.05 [0.93–1.21]	1.14 [1.01–1.30]
80–89	1.89 [1.65–2.17]	1.09 [0.94–1.26]	1.16 [1.02–1.34]	1.75 [1.50–2.06]	1.12 [0.96–1.31]	1.30 [1.12–1.50]
	Acute myeloid leukemia					
	Females			Males		
Age group	1972–1981	1992–2001	2012–2021	1972–1981	1992–2001	2012–2021
0–49 (ref.)	1.00	1.00	1.00	1.00	1.00	1.00
50–59	1.44 [0.98–1.91]	2.12 [1.58–2.78]	1.56 [1.06–2.22]	1.06 [0.73–1.42]	1.91 [1.46–2.46]	1.59 [1.14–2.19]
60–69	2.00 [1.30–2.69]	2.99 [2.38–3.78]	2.85 [2.17–3.82]	1.40 [0.99–1.84]	3.14 [2.48–3.98]	3.03 [2.35–3.99]
70–79	2.24 [1.37–3.06]	4.75 [3.77–6.00]	5.74 [4.47–7.58]	1.66 [1.00–2.29]	4.10 [3.23–5.15]	5.97 [4.66–7.82]
80–89	1.17 [0.58–1.73]	7.78 [4.60–10.57]	9.89 [7.21–13.39]		5.60 [3.17–7.80]	11.97 [8.27–16.22]

the last period. Deviations for women and men were equal and the 95% CIs were initially about 3% units and then declined to 2% units. Data in panel B show deviations of age-specific relative survival from their mean. Smallest deviations in all periods were for the 50–59 and 60–69-year-old pateints. In the first period both the youngest (better than the mean) and oldest (worse than the mean) age-groups deviated most and for men these prevailed in the later periods. For women in contrast the below 50-year-old showed the largest and the 80–89-year-old the smallest deviation.

Fig. 2 shows deviation for 5-year relative survival in age-specific AML in the 5 age-groups. In panel A women and men are shown side-by-side in the three periods (male data for the first period were incomplete). The mean deviation increased from 4% (female) to 17% and 23%. In panel B, the deviations were small in the first period when survival was poor. In the later periods the positive deviation for the youngest patients was about 35%. Largest negative deviations were noted for 80–89-year-old ranging from −20 to −35%. Deviations for the 60–69-year-old pateints remained closest to the mean and their last deviation approached 0%. For 50–59-year-old pateints survival increased in the course of time and their positive deviations increased from less than 10% to more than 20%. For the 70–79- year-old pateints the opposite trend was observed and their last deviation was over −20%. It is noteworthy that even if large periodic changes took place female and male data remained almost identical.

In Fig. 3 we applied the same method that was used in Fig. 1 for colon cancer in the four Nordic countries. The Swedish data of Fig. 1 are included as a reference. The Norwegian mean absolute deviations agreed with the Swedish ones, except for the last period for which the deviations were slightly larger than the Swedish ones. The reason was the higher deviation for the youngest men and for youngest and oldest women. In the first period the Danish deviations were the smallest among the Nordic countries, but the subsequent results showed larger deviations than the Swedish data. In the last period mean deviation for males was a half of that for females, as male deviations in the oldest and youngest pateints were curbed. At all periods the Finnish deviations were higher than those in the other countries. This was mainly due to the largest positive deviations for the youngest patients.

4. Discussion

The aim of the present study was to develop a metric for the comparison of age-specific survival between age-groups, sexes, periods and populations in various cancers. We were able to achieve the task by two variations of the metric, one considering the deviation over all age-groups and the other additionally marking the deviations and their directions of each age-groups. The metric readily shows the mean absolute

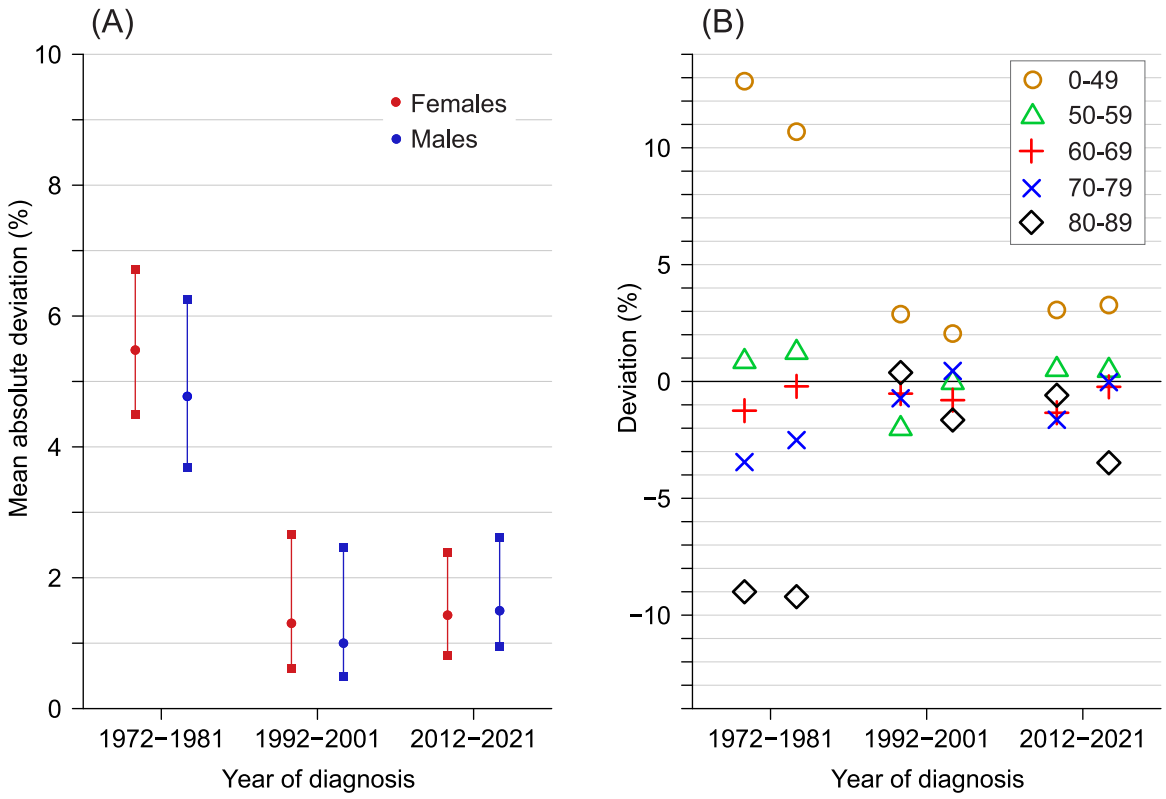

Fig. 1. Mean absolute deviation for age-specific 5-year relative survival in male and female colon cancer in 5 age-groups and three periods (panel A). In panel B deviations for individual age-groups are marked, positive ones showing relative survival better than mean and negative ones worse than the mean (estimates for males on right side to estimates for females).

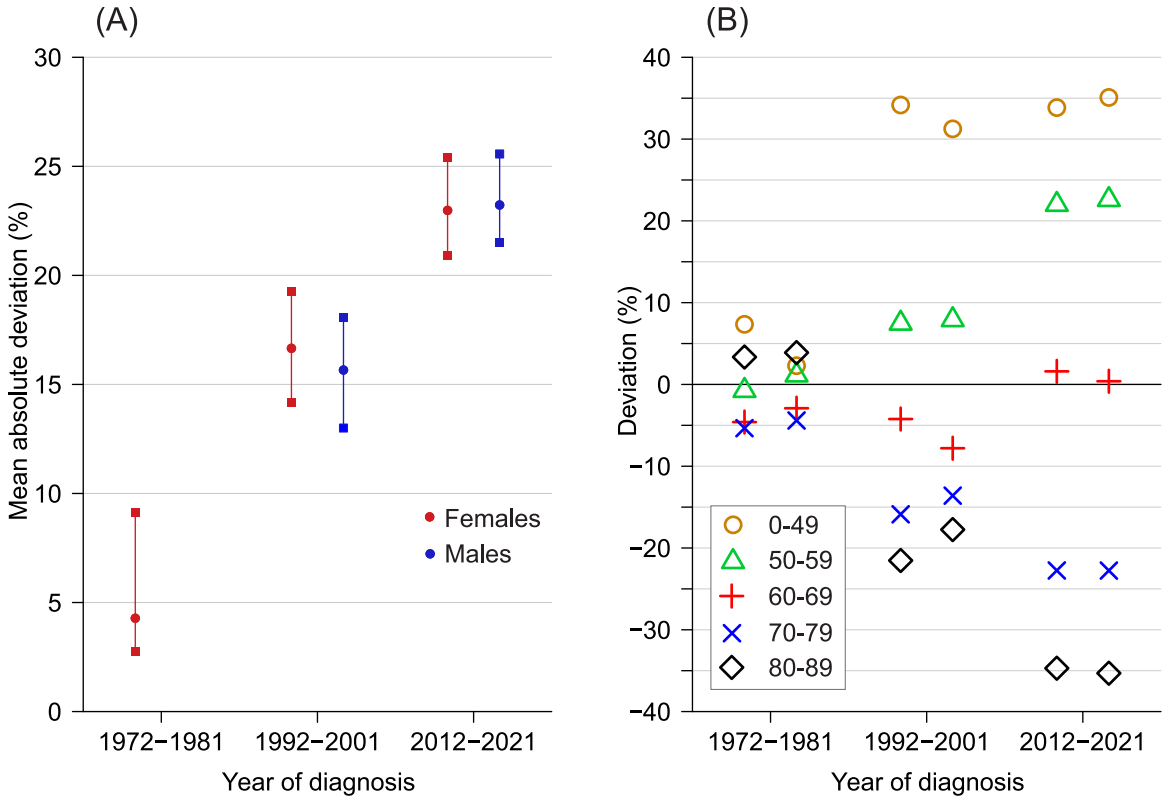

Fig. 2. Mean absolute deviation for age-specific 5-year relative survival in male and female acute myeloid leukemia in 5 age-groups and three periods (panel A). In panel B deviations for individual age-groups are marked, positive ones showing relative survival better than mean and negative ones worse than the mean (estimates for males on right side to estimates for females).

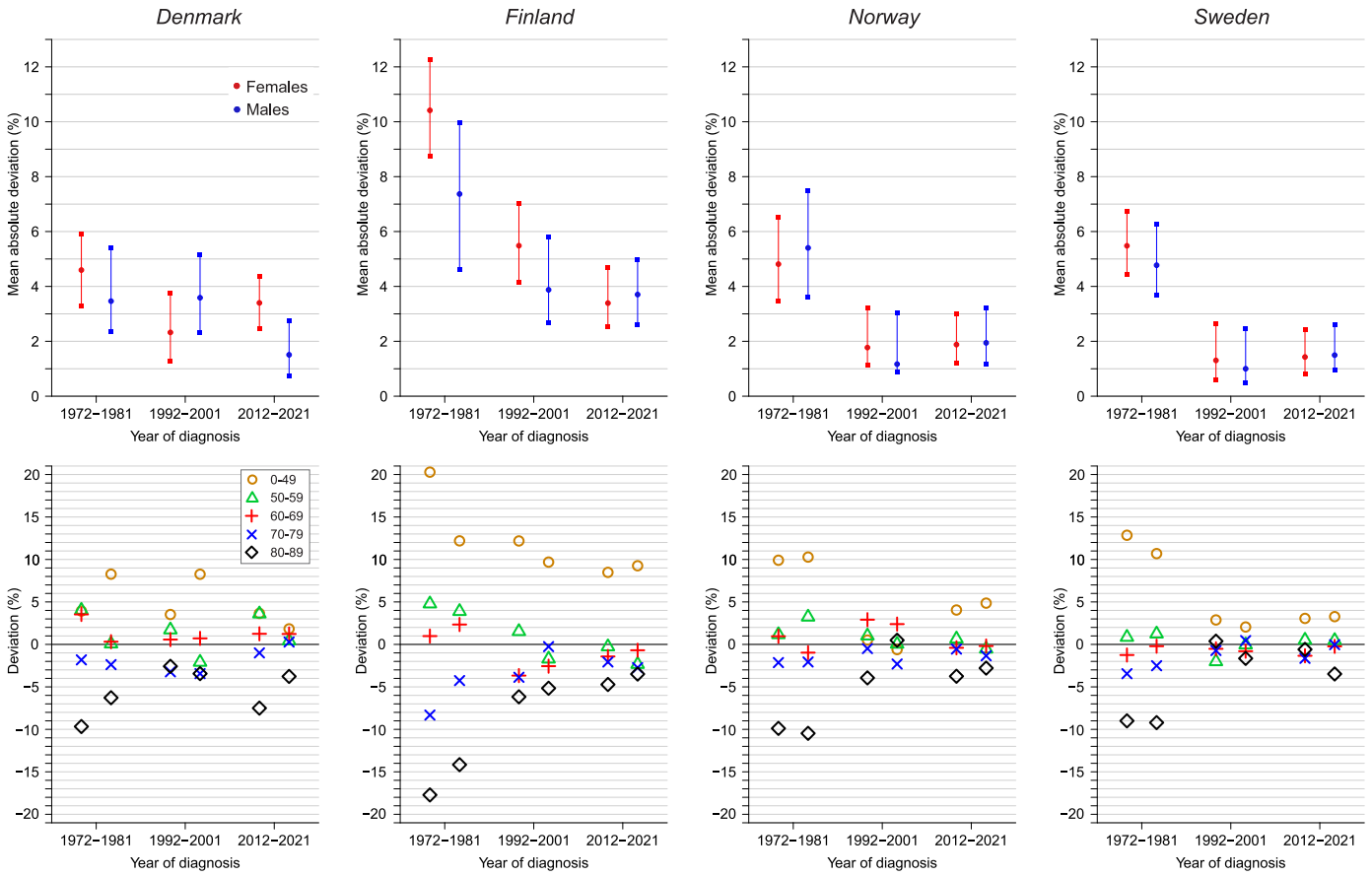

Fig. 3. Mean absolute deviation for age-specific 5-year relative survival in male and female colon cancer in 5 age-groups and three periods for four Nordic countries (top panels). In the bottom panels deviations for individual age-groups are marked for the four Nordic countries (estimates for males on right side to estimates for females).

deviation in survival age-groups and highlights the individual age-groups revealing reasons for the deviations. By developing a framework to measure age-related disparities across whole range of age groups we fill the gap in the existing literature, which has been mostly limited to comparing survival between selected groups. The proposed measure should be useful for the oncologists and health policy planners as a fair goal in policy should be a minimal deviation in survival between the age-groups. It would be advisable to apply the developed framework in combination with survival data because the metric tells about survival deviations between age groups but not about the level of survival.

We demonstrated the usefulness of the novel metric both with the common colon cancer and with the rare AML. In the first application using the Swedish colon cancer and AML data, both with an overall increase in 5-year survival, age-group specific survival nevertheless developed completely differently. For colon cancer deviations between the age-groups were suppressed to 1% by 1992–2001 and marginally increased to 2012–2021, which was due to deviations for the youngest women and oldest and youngest men; apparently, deviations for these small age-groups could not be curbed. However, the remarkable small deviations of slightly over 1% and 95%CIs of 2% units signal functioning health care for patients of all ages [7]. For AML overall survival increased also but the mean absolute deviation increased as well, from less than 5–23% in the last period. In all periods the youngest contributed to largest (positive) difference but in the last period also the oldest patients showed large (negative) deviations.

To further test the applicability of the new metric, we compared survival in colon cancer between the four Nordic countries. In all countries age-group-specific differences declined, Sweden and Norway reaching the smallest differences while in Finland the differences remained some 3 times higher than the Swedish ones. Patients diagnosed before age 50 years accounted for the largest deviation in Finland but in the other countries also the oldest patients showed equally large deviations. Deviations for women and men were equal, except for a small male advantage in Denmark. The overall survival in colon cancer has not developed as well in Finland as in the other Nordic countries, and it was the only country with a sex-difference in survival, with a male disadvantage [20].

The fact that deviations in age-groups were often large for the 80–89-year-old population are consistent with the notion that old patients are frail, suffer from comorbidities and do not tolerate heavy treatment [14]. As the theme of the present paper was the description of the metric, it is outside the scope to try and interpret why these two cancers behaved so differently. Colon cancer has traditionally been treated with surgery, for which methods have been improving and additionally chemotherapy has become a part of the treatment [21]. Physically fit elderly patient tolerate surgery well which may explain the narrow deviations between age-groups. AML is a hematological malignancy which is sometimes diagnosed after another malignancy. Treatment algorithms for AML have been defined by age of the patients and they have been modified periodically which is the likely explanation to the age-group related diversity in survival [22–24]. For younger patients the treatment has been intense chemotherapy and hematopoietic stem cell transplantation [25]. For older patients the treatment has often been palliative, including prevention of infections. However new medications are constantly becoming available and there is hope that survival in the elderly will improve [25].

A limitation of the method is that it is most useful when several discrete age-groups are available for analysis. Application to data with

dichotomous or sparse age-groups would be less instructive. Of course, the method can be applied to any sample sets for which the relevant basic survival figures can be calculated. Individually-based population datasets, such cancer registry data, would allow further modification of the age-groups.

In conclusion, we demonstrated the usefulness of the novel metric for summarizing age-specific survival data between cancers, sexes, periods and countries. The two variations of the metric allow a simple visual presentation of the survival experience as to mean absolute deviation of the age-specific data and its 95%CIs with highlighted individual age-groups. It was an interesting finding that there were no sex differences between any of the mean absolute deviations. The present metric should facilitate efforts to standardize cancer care for patients of various ages.

Ethics

Publically available data without individual identifiers pose no ethical issues.

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CRediT authorship contribution statement

Frantisek Zitricky: Writing – original draft, Methodology, Formal analysis, Data curation. **Kari Hemminki:** Writing – review & editing, Writing – original draft, Project administration, Conceptualization.

Declaration of Competing Interest

None

Data availability

Publically available data at https://nordcan.iarc.fr/en/database#bloc2

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.canep.2024.102586.

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