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# Impact of era of diagnosis on cause-specific late mortality among 77,423 five-year European survivors of childhood and adolescent cancer: the PanCareSurFup consortium

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This article has been accepted for publication and undergone full peer review but has not been through the copyediting, typesetting, pagination and proofreading process which may lead to differences between this version and the Version of Record. Please cite this article as doi: 10.1002/ijc.33817

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**Keywords:** survivors of childhood cancer, late mortality, European, causes of death, second malignant neoplasms, cardiovascular

**Novelty and impact**

Long-term survivors of childhood and adolescent cancer experience excess mortality compared to the general population. Little is known of trends in late mortality (more than five years from diagnosis) in European survivors, nor of their mortality risks into later life. To evaluate these issues we assembled the largest cohort of survivors – more than 77,000 who contributed more than 1.2 million-person years for analysis. All-cause mortality fell steeply over the 70 years covered by the study; but survivors experienced 2-fold excess mortality into their sixties, indicating the need for long-term care.

**Abbreviations**

AER: Absolute excess risk

CCSS: Childhood Cancer Survivor Study

CI: Confidence Interval

DP: Data provider

FN: First neoplasm

HMD: Human Mortality Database

ICCC-3: International Classification of Childhood Cancer, 3rd Edition

ICD: International Classification of Diseases

PCSF: PanCareSurFup

SMR: Standardized mortality ratio

SN: Second neoplasm

**ABSTRACT**

Late mortality of European five-year survivors of childhood or adolescent cancer has dropped over the last 60 years, but excess mortality persists. There is little information concerning secular trends in cause-specific mortality among older European survivors.

PanCareSurFup pooled data from 12 cancer registries and clinics in 11 European countries from 77,423 five-year survivors of cancer diagnosed before age 21 between 1940 to 2008 followed for an average age of 21 years and a total of 1.27 million person-years to determine their risk of death using cumulative mortality, standardized mortality ratios (SMR), absolute excess risks (AER), and multivariable proportional hazards regression analyses.

At the end of follow-up 9,166 survivors (11.8%) had died compared to 927 expected (SMR 9.89, 95% confidence interval (95%CI) 9.69-10.09), AER 6.47 per 1000 person-years, (95%CI 6.32- 6.62). At 60-68 years of attained age all-cause mortality was still higher than expected (SMR=2.41, 95%CI 1.90-3.02). Overall cumulative mortality at 25 years from diagnosis dropped from 18.4% (95%CI 16.5 – 20.4) to 7.3% (95%CI 6.7 – 8.0) over the observation period. Compared to the diagnosis period 1960-69, the mortality hazard ratio declined for first neoplasms (p for trend <0.0001) and for infections (p<0.0001); declines in relative mortality from second neoplasms and cardiovascular causes were less pronounced (p=0.1105 and p=0.0829, respectively).

PanCareSurFup is the largest study with the longest follow-up of late mortality among European childhood and adolescent cancer five-year survivors, and documents significant mortality declines among European survivors into modern eras. However, continuing excess mortality highlights survivors' long-term care needs.

## INTRODUCTION

Decades of clinical research have improved survival after childhood and adolescent cancer in Europe, the United States and Canada (1-16) resulting in a growing population of childhood cancer survivors. Nevertheless, despite declining mortality, the overall mortality of adult survivors continues to exceed rates expected from the general population (7, 8, 11, 15, 17). Studies of cause-specific mortality have shown that cumulative mortality attributed to the first neoplasm tapers off with time since diagnosis and drops considerably with each successive era of diagnosis (2, 3, 5, 7, 8, 11, 15, 17). Although deaths from recurrence account for the majority of deaths overall (5), deaths from second neoplasms and cardiovascular disease cause most deaths after age 25 (9). The era-specific risk for second neoplasms drops in some studies (5, 18), but not in the majority (2-4, 6, 7, 11, 17). Studies disagree on the changes over time for cardiovascular disease deaths (5, 6, 14). The impact of these trends on older survivors and into more recent diagnosis eras remains largely unstudied (9). PanCareSurFup is a mainly population-based pan-European study of late effects after childhood and adolescent cancer. We investigated causes of and changes in late mortality focussing on era of diagnosis in survivors of cancer diagnosed before age 21 from 1940 to 2008 and followed into older ages.

## METHODS

### The PanCareSurFup cohort

Twelve European cancer registries, studies and clinics participated in PanCareSurFup (PCSF, www.pancaresurfup.eu) (20). Data providers pooled cases from their population-based registries (Denmark, Finland, Iceland, Sweden, Switzerland, Slovenia, Italy and Hungary) and clinics (France (solid tumours only), Netherlands and Italy); about 75% of cases come from population-based registries (20). Data from cited European reports (3, 7, 9, 10, 15-17) is included in PCSF. The first and subsequent neoplasms were classified according to the World Health Organisation International Classification of Diseases for Oncology (21).

### The Late Mortality Study

Data for the late mortality study was derived from the total PanCareSurFup study (20, 22) of 115,596 survivors. Data providers (DPs) used different methods to identify new cases of cancer, including active collection by registry staff, mandatory reporting by physicians and pathologists, and transfer of cases from a national cancer registry to a childhood cancer registry. Some DPs used multiple methods and their methods may have changed over the time covered by PCSF. The estimated coverage (%) of incident reportable cases was between 95 and 100% for the population-based registries and for children aged less than 15 at diagnosis. For the non-population-based registries the completeness of coverage was estimated at 80%. The date of last contact with cohort members (cohort exit date) ranged from 1 December 2006 (Britain) to 1 March 2015 (France) with 5 DPs ending their observation period in 2014 (20). The proportion of cohort members whose last contact date was before the exit date was 46.8%; of these 58.2%, or 19.6% of the total, had a last contact date more than 24 months before the cohort exit date. As many cancer registries update only annually or biennially, and the DPs themselves estimate their LTFU percentage at 2% (range 0% to <5.6%), this figure of 19.6% may not be an accurate estimate of the lost-to-follow-up percentage. Ascertainment of vital status was by linkage to national/regional population registers for all DPs, except Hungary, where national laws prohibited linkage. Hungary obtained this information manually. Three other DPs also supplemented their ascertainment of vital status by manual

means. Almost all cancer cases (range 91 - 100%, median 96%) registered by each data provider were microscopically confirmed.

The inclusion criteria for the late mortality analysis were 1) survival for at least five years from diagnosis, 2) diagnosis from 1940 to 2008 and 3) before age 21 years, and 4) assignment of the first neoplasm initially to an ICD code (ICD6 to ICD10; International Classification of Diseases (23), and then into the 12 categories of ICCC-3 (International Classification of Childhood Cancer) (24). This resulted in 38,173 persons being ineligible, leaving for analysis 77,423 five-year survivors (Figure 1).

Because of the large numbers of survivors, we subdivided first neoplasms as follows: leukemias into lymphoid leukemia and other (non-lymphoid) leukemias; lymphomas into Hodgkin's lymphoma and other lymphomas, according to the ICCC-3 diagnostic subgroups (24). Causes of death were assigned to ICD codes by each data provider (20), and subsequently aggregated as follows: 1) first neoplasm, 2) second or subsequent neoplasm, 3) cardiovascular disease, 4) infection, 5) external causes (including suicide, homicide and accidents), 6) other known causes and 7) unknown causes. The causes of death were classified into their appropriate ICD categories, according to the relevant chapter in the ICD manuals. Thus 'infection" and "circulation" (here labelled as cardiovascular) are categories within the ICD manual. "External" includes only suicide, homicide, and accidents. "Other known causes" include groups like "respiratory", "endocrine", "digestive" and "skin", that are not otherwise categorized for this report.

The first treatment era comprised the two decades of the 1940s and 1950s; otherwise, treatment eras are in decades with an incomplete decade in the 2000s. Data providers supplied treatment information (where available) in broad categories: chemotherapy only with/without surgery, radiotherapy only with/without surgery, chemotherapy & radiotherapy with/without surgery.

**Statistical methods**

Follow-up started five years after diagnosis and ended at the date of death, date of last contact, or cohort exit date, defined above, whichever occurred first. Standardized mortality ratios (SMR) and absolute excess risks (AER) were used to compare overall observed mortality in survivors with expected mortality in one-year intervals, averaged over five years. The SMR was defined as the number of observed deaths divided by the number of expected deaths. The AER was

defined as the difference between the number of observed and expected deaths divided by the person-years at risk multiplied by 1000. The mortality rate was calculated as the number of deaths divided by person-years at risk.

Data on expected mortality was extracted from the Human Mortality Database (HMD) (25). Data for Slovenia, which contributed 1,258 participants of whom 179 had died, was only available in HMD for the period 1983 onwards. For Slovenian cases diagnosed between 1965 and 1977 there were some periods without matching expected deaths. A linear regression model with the terms age, age$^2$, year and age*year as covariates was generated to extrapolate the missing data from 1965 to 1982. To obtain the expected number of deaths for all individuals in the study population for each year they were under observation, the probability of death in this calendar year of a same-sex person from the general population in the same country and born in the same year was extracted from the HMD life tables. The expected number was computed by adding all probabilities pertaining to the relevant person-years. SMRs and AERs were compared using chi-square tests for heterogeneity and trend tests for ordered levels. HMD does not currently include cause of death for the years and countries covered by PCSF. For this reason we could not compute cause-specific SMRs and AERs.

Overall and cause-specific cumulative mortality, that is, the probability of being dead by a specific time from a specific cause, was estimated as a function of time starting when each survivor reached five years from diagnosis. Different causes of death were considered as competing risks. An adjusted multivariable regression model that included terms for sex, attained age, treatment era and type of first neoplasm was constructed to evaluate the independent effects of each factor on cumulative mortality among survivors, using Cox regression for all-cause mortality and the Fine and Gray methodology for competing causes of death (26). Hazard ratios and sub-distribution hazard ratios were based on the diagnosis era 1960-69 as comparison since the majority of data providers had started to enroll survivors by that time (20). The analysis was done using SAS version 9.4, including macros, and Dickman's (27) routine SURVIVAL_PERIOD. The point estimates of survivor functions and cumulative mortality functions are shown in figures only if the limits of the 95% CIs do not differ by more than 3% from the point estimate to minimise over-interpretation of the data. However, the tables include all the data. Cumulative mortality between eras was compared using Gray's test.

**RESULTS**

The 77,423 eligible survivors contributed 1,273,414 person-years, were diagnosed on average at 7.6 years, and followed up for an average of 21 years from diagnosis; 54.6% were male. At the end of the study survivors were aged from 5 to 68 years. Leukemia was the most frequent first neoplasm at 26.7%, followed by central nervous system tumours at 18.6% and lymphomas at 16.3% (Table 1). By the end of follow-up 9,166 (11.8%) of 77,423 five-year survivors had died, yielding an overall SMR of 9.89 (95% confidence interval (95%CI) 9.69–10.09) and an AER of 6.47 per 1000 person-years (95%CI 6.32-6.62). The SMR for females was higher than that for males (13.89 vs 8.18, P<0.0001). Overall, both SMR and AER dropped with increasing age at diagnosis (p<0.0001). With each era of diagnosis the unadjusted SMR increased from 5.20 (95%CI 4.69–5.53) to 27.08 (95%CI 23.96–30.50), while the AER declined. The SMR declined steadily with attained age but was still higher than expected at the oldest age, 60-68 (SMR 2.41, 95%CI 1.9–3.02); the AER was U-shaped, declining initially, then increasing to reach 14.04 (95%CI 8.95-20.07). The highest SMRs were among survivors treated for leukemia other than lymphoid (20.86; 95%CI 18.74–23.15), lymphoid leukemia (15.73; 95%CI 15.04–16.44), and central nervous system neoplasms (13.96; 95%CI 13.44–14.50). Survivors who were treated with both chemotherapy and radiotherapy had the highest SMR among treatment types (14.96; 95%CI 14.43–15.51), but treatment information was either incomplete or missing for 45.3% of survivors. With the passage of time since diagnosis the SMR fell steadily (p for trend <0.0001), while the AER was again U-shaped.

The first neoplasm (FN) was the most frequent cause of death with 5,138 deaths or 56.1% of the total, followed by deaths from second neoplasms (SN) with 1,355 (14.8%) deaths. Deaths from causes attributed to cardiovascular, infections and external accounted for 5.3%, 4.1% and 5.0% respectively (Table 2).

Overall cumulative late mortality fell steeply with each era of diagnosis (Figure 2). At 25 years post-diagnosis it had dropped from 18.4% in five-year survivors diagnosed before 1960 to 7.3% for survivors diagnosed during the decade 1990-99. Cumulative mortality reached 43.1% (CI 40.0–46.2) at 55 years post-diagnosis for survivors diagnosed from 1940-1959.

Cumulative mortality showed different patterns by cause (Figure 3). Deaths from the first neoplasm increased rapidly from 5 to 10 years after diagnosis, then slowed. Cumulative mortality from the first neoplasm reached 10.6% (CI 9.8 –

11.5) at 55 years from diagnosis. In contrast mortality from second neoplasms, cardiovascular disease and external causes was low during the first decades after diagnosis but increased thereafter. At 55 years from diagnosis cumulative mortality from second neoplasms exceeded deaths from the primary neoplasm to become the leading cause of cumulative mortality at older ages (11.1%, 95%CI 9.5 – 12.7). By this time point cumulative mortality from cardiovascular diseases reached 5.5% (95%CI 4.3 – 6.8), from infections reached 1.0% (95%CI 0.7-1.3), and from external causes reached 2.5% (95%CI 1.9 – 3.3).

Cumulative mortality from the first neoplasm at 25 years from diagnosis dropped steadily with each era to reach 4.4% (CI 4.1 – 4.7; p<0.0001, Figure 4). Cumulative mortality at 25 years from second neoplasms and from cardiovascular disease was little changed until the 1990s when both dropped steeply (Figures 5A and 5B, p=0.0034 and p=0.0008, respectively). Deaths from infections dropped steadily over the observation period (Supplementary Figure 1A, p<0.0001); the low mortality from infections before 1960 may reflect poorer survival, or varying diagnostic practices. Deaths from external causes were little changed until the most recent era (Supplementary Figure 1B, p=0.2463).

We adjusted for the effects of each variable (sex, primary neoplasm, era of diagnosis and attained age), whose unadjusted effects on late mortality were shown in Table 1, with Cox multivariable regression analyses for all-cause mortality and applying the Fine and Gray method for competing causes of death (Table 3).

To evaluate the independent effect of era of diagnosis we compared mortality among individuals diagnosed in later eras to that from 1960-69. The model showed the steep drop in relative mortality (p<0.0001) driven largely by declines in mortality from the primary neoplasm (p<0.0001). However, declines in mortality by era from a second neoplasm and from cardiovascular disease seen in cumulative mortality curves, while apparent in the multivariable analysis, did not reach statistical significance when the influence of other factors was considered. In the era 2000-2008 relative mortality from a second neoplasm had dropped to 0.84 (95%CI 0.53-1.34), and from cardiovascular causes was 0.50 (95%CI 0.16-1.58), probably due to the small number of deaths and shorter follow-up period. Compared to mortality among survivors of a primary leukemia, overall relative mortality was less for survivors of eight other primary neoplasms. Higher HRs were observed among survivors whose FN was other leukemias (HR=1.50, CI 1.34 – 1.68) or a central nervous system tumour (HR=1.34, 95%CI 1.26-1.43). Trends by attained age (Table 3) suggested that relative mortality increased for all

causes of death (p for trend <0.0019). Secular trends by type of treatment were not included in the models, due to the large proportion of missing data. The distribution of types of treatment changed markedly over the time period covered by our study (Supplementary Figure 2): radiotherapy was the most common treatment up to 1969; treatment with chemotherapy only was most common in more recent eras.

**DISCUSSION**

The PanCareSurFup consortium presents results from the largest study with the longest follow-up that describes late mortality among five-year survivors diagnosed and treated for childhood or adolescent cancer between 1940 and 2008. For this study 12 cancer registries and clinics in 11 European countries pooled their data on more than 77,000 five-year survivors who contributed over 1.2 million person-years of observation. Most survivors came from population-based cancer registries; thus our results are of relevance to most European survivors.

We found significant declines in cumulative late mortality over treatment eras, with an overall drop of about 2.5-fold measured at 25 years from diagnosis. Recurrence or progression of the primary neoplasm accounted for most of the decline, dropping by 40% from its highest value, followed by deaths from external causes that dropped by one-third. Trends in the decline in deaths from cardiovascular diseases and infections were not statistically significant.

However, in our study late mortality continued to occur to excess even in the oldest survivors. Survivors followed up to ages 60-68 experienced 2.4-fold excess mortality compared to the general population (95%CI 1.90 – 3.02). PCSF's extension of observation into older life shows the continuing burden of excess mortality on survivors and the continuing risk of mortality from second malignancies and cardiovascular disease as survivors age.

We confirm the striking reduction in mortality from the primary neoplasm and from infections since the first years of curative therapy that have been reported earlier (4-8, 10-12, 14, 15, 17, 28), evidence of the success of front-line therapies developed over the last 60 years, and their lasting benefits. However, the small number of deaths from the primary neoplasm into old age (Supplementary Table 1) deserve further scrutiny.

Interactions between genetic predisposition, treatment, type of first malignancy (18) and aging (29) contribute to the increased risk for a second malignancy. In common with other studies we show a substantial increase in second

malignancies as survivors age. In multivariable analyses that adjusted for the effect of attained age we observed a decline that did not achieve statistical significance in late relative mortality from second neoplasms in European survivors; this is consistent with other European studies (7, 11, 15, 30, 31) that did not document a mortality drop. In the United States, mortality from second neoplasms has declined in recent years (32) in data from pediatric tertiary care hospitals participating in the Childhood Cancer Survivor Study (CCSS). Reasons for these differences may lie in the differing nature of each underlying population: PanCareSurFup aims to reflect the population of Europe, while the CCSS assembles data from some of the leading pediatric institutions in the US.

Cardiac disease in childhood cancer survivors has been attributed variously to heart and vascular damage from thoracic radiotherapy as well as from chemotherapy with anthracyclines, also with alkylating agents, vinca alkaloids, antimetabolites, and biological agents (33, 34). Anthracyclines, introduced in the late 1970s, are effective chemotherapeutic agents now widely used, but carrying significant risk for heart disease (34). An analysis of late mortality from cardiac disease from the British Childhood Cancer Survivor Study shows a significant fit for a quadratic model by era of treatment (14) with a peak of mortality in the 1980s. These authors speculate that the peak and decline in cardiac mortality may be associated with the introduction of anthracycline chemotherapy in the 1980s (14), followed by efforts to reduce cumulative and improve monitoring and treatment. In our study also the hazard ratio for mortality from cardiovascular disease peaked in the 1980s (1.55, 95% CI 1.14 – 2.11), then declined in recent years with a non-significant trend test in adjusted estimates compared to mortality in 1960-69. Declines in mortality from heart disease in the general population occur concurrently with our study (35), and could account for at least some of the trends that we and others see. However, it is likely that most of the cardiac disease in survivors is attributable to cancer treatment. For instance, in the CCSS the prevalence of four types of heart disease was between 3 and 9 times greater in survivors than their siblings (34). This ratio may change as survivors age and as they acquire the same increasing risk of cardiac disease as the general population. This aspect of long-term survival deserves further study.

We also saw a steady drop in deaths from infections, possibly related to changes in treatment -- less radiotherapy (36), better management of asplenia (37) for the primary malignancy, and improved supportive therapies, and deserving of further study. Deaths from external causes (accidents, homicides and suicides) dropped by one-third over the

observation period (p for trend <0.005), maybe due to survivors' improved overall health, since the presence of chronic medical conditions may be linked to risky behaviours (38).

Changes in medical practices that have led to reduced mortality rates in this population of long-term survivors include shifts from radiotherapy to chemotherapy, seen in our data also (Supplementary Figure 2), reduction in splenectomy and in cardiotoxic drugs, the introduction of other supportive measures, including antibiotics and immunizations. Concomitant changes in the underlying population that will impact cancer survivors also include lower rates of heart disease, fewer cancer deaths, and reduction of direct and indirect smoking patterns. These changes may account for the relatively high cumulative mortality from the primary neoplasm diagnosed before 1980 (Figure 4) and require more detailed investigations than our data allow.

Most data providers to PCSF are population-based registries so that our results can be generalised to the broader European population. PCSF covers mortality in five-year survivors who were diagnosed over a period spanning nearly 70 years from 1940 to 2008, allowing us to assess the overall effects of improving treatments introduced in these decades, and suggesting how late toxicities from successful front-line therapies may have contributed to excess mortality even decades later (39). Differences between our results and those from other studies may arise due to differences between study coverage (i.e., selected US and Canadian hospitals in the Childhood Cancer Survivor Study (CCSS); population coverage in PCSF).

The high SMR for those diagnosed between 2000 and 2008 is likely related to the short follow-up. The mortality rate as a function of time since diagnosis is for most diagnoses U-shaped or L-shaped. Many patients diagnosed after 2000 have not yet reached the follow-up time where mortality is relatively low, so their mortality rates are dominated by the early high mortality rates. Further, background mortality has also decreased over time. Since the SMR is on a multiplicative scale whereas AER is on an additive scale, changes in background mortality will affect these parameters in different ways. Therefore, for any given mortality rate among the childhood cancer survivors a small increase in the low background mortality rate may have a substantial impact on the SMR but a lesser impact on the AER.

Inferences concerning excess cause-specific mortality are limited as PCSF does not have detailed treatment information, nor information on stage at diagnosis. The requirements of coding rules concerning the underlying cause of death can

result in over-counts of deaths attributed to the first malignancy (40), and under-estimation of deaths due to other causes. Our results may reflect these biases. Concomitant secular trends in mortality reductions due to cancer, heart disease and infections (35, 41, 42) may influence the relative decline in cause-specific mortality seen in our data. Changes in medical practices, mentioned above, may mean that cases and deaths registered before 1960 may differ from later eras, both in diagnostic criteria and ability to accurately ascertain causes of death. The very different picture of cumulative mortality of deaths from infections (Supplemental Figure 1a) shows this clearly. However, we believe, that in addition to their novelty, the value of these data lies in the ways that they highlight the improvements in survival in subsequent eras.

Many unanswered questions remain concerning the excess risk for late mortality in survivors of childhood and adolescent cancer. Among them are the impacts of new treatments, the differing risks by sex, continuing deaths from the primary cancer, controlling for the background mortality rate. Additional studies of these data will address some of these questions. PanCareSurFup confirms the steady decline in deaths overall during long-term follow-up after cancer treatment during childhood or adolescence, but also shows the persisting excess mortality risks for aging European survivors. Improved treatments that have led to better five-year survival rates have continued to exert their beneficial effects into long-term follow-up. But the impact of other outcomes, especially cardiac disease and second tumours, requires more consideration of mechanisms that produce these life-threatening complications. In addition, new therapies may bring new late effects, necessitating life-long follow-up for newer cohorts. The development of evidence-based guidelines for the delivery of long-term follow-up and for surveillance for late effects may reduce late mortality by enabling earlier detection of serious chronic medical conditions, offering the potential for medical or lifestyle interventions to allow survivors to reach their full life-span potential.

**Conflict of interest**

The authors declare that they have no conflict of interest.

**Data Availability Statement**

Individual PanCareSurFup patient data are not publicly available due to potential identification of individuals. PanCareSurFup data, aggregated for the purposes of the Late Mortality analysis, is available to approved researchers. Access to this and other anonymised, aggregated data may be granted under conditions agreed with the **PanCareSurFup Sustainability, Publication and Authorship Group (PCSF-SPAG),** and with appropriate data sharing agreements and permissions from data providers in place. All outputs are subject to the codes of practice for official statistics. Further information is available from the corresponding author upon request.

**Ethics Statement**

All participating institutions received approval for the study from their relevant Ethics Committees. Written informed consent was obtained as needed. Patient data was de-identified before pooling.

**Acknowledgements**

We are grateful to all the survivors who allowed their personal information to be used for research and in PanCareSurFup. We thank all those involved in the data collection, and data management, including Tina Žagar from the Slovenian Cancer Registry; Klaus Bjerregaard and Bo Midberg, Regional Cancer Centre South, Lund, Sweden; the Italian Association of Cancer Registries (AIRTUM), the Italian Registry of Off-Therapy (OTR) of the Italian Association of Pediatric Hematology and Oncology (AIEOP).

**Funding**

This project has received funding from the European Union's Seventh Framework Programme for research, technological development and demonstration under grant agreement no 257505 (PanCareSurFup). The material presented and views

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Additional financial support was received from: The Swedish Childhood Cancer Fund (Lund University); The Italian Association for Cancer Research and the Compagnia San Paolo (University of Turin); the Italian Ministry of Health Ricerca Corrente (Istituto Giannina Gaslini, University of Turin); The Fondo Chiara Rama ONLUS (Istituto Giannina Gaslini); La Ligue Nationale Contre le Cancer (Université Paris-Sud, Orsay; The French Agence Nationale Pour la Recherche Scientifique (Hope-Epi project; Université Paris-Sud Orsay); the Institut National du Cancer (Université Paris-Sud Orsay); Fondation Pfizer pour la santé de l'enfant et de l'adolescent (Université Paris-Sud Orsay); Slovenian Research Agency (Institute of Oncology); the Swiss Paediatric Oncology Group (University of Bern); The Swiss Cancer League (KLS-3412-02-2014; University of Bern); The Swiss Cancer Research Foundation (KFS-02783-02-2011 and KFS-4157-02-2017; University of Bern); The Swiss National Science Foundation Grant Number (PDFMP3_141775 and KFS-4157-02-2017; University of Bern); Dutch Cancer Society (UVA 2012-5517; Academic Medical Center, Amsterdam, the Netherlands). The material presented and views expressed here are the responsibility of the authors only. Neither the EU Commission nor any other funder takes responsibility for any use made of the information set out. Where authors are identified as personnel of the International Agency for Research on Cancer/World Health Organization the authors alone are responsible for the views expressed in this article and they do not necessarily represent the decisions, policy or views of the International Agency for Research on Cancer/World Health Organization.

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FIGURE LEGENDS

FIGURE 1. FLOW CHART FOR THE PANCARESURFUP LATE MORTALITY STUDY

FIGURE 2. OVERALL CUMULATIVE LATE MORTALITY BY ERA OF DIAGNOSIS AMONG FIVE-YEAR SURVIVORS FROM THE PANCARESURFUP STUDY OF LATE MORTALITY.

FIGURE 3. CUMULATIVE CAUSE-SPECIFIC MORTALITY AMONG FIVE-YEAR SURVIVORS FROM THE PANCARESURFUP STUDY OF LATE MORTALITY.

FIGURE 4. CUMULATIVE LATE MORTALITY BY ERA OF DIAGNOSIS FOR SPECIFIC CAUSES OF DEATH FOR FIVE-YEAR SURVIVORS OF CHILDHOOD AND ADOLESCENT CANCER IN THE PANCARESURFUP LATE MORTALITY STUDY. Cause of death=First neoplasm. Scale from 0% to 15%.

FIGURE 5. CUMULATIVE MORTALITY BY ERA OF DIAGNOSIS FOR SPECIFIC CAUSES OF DEATH FOR FIVE-YEAR SURVIVORS OF CHILDHOOD AND ADOLESCENT CANCER IN THE PANCARESURFUP LATE MORTALITY STUDY. Cause of death= (A) Second or subsequent neoplasms. Scale from 0% to 12%; (B) Cardiovascular disease. Scale from 0% to 6%.

TABLE 1. CHARACTERISTICS OF SURVIVORS ENROLLED IN THE PANCARESURFUP LATE MORTALITY STUDY AND COMPARISON WITH THE GENERAL POPULATION

| | | N | Person years at risk | Observed deaths N | Expected deaths N | Standardized mortality ratio SMR | 95% confidence interval | | Absolute excess risk per 1000 person-years AER | 95% confidence interval | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | lower limit | upper limit | | lower limit | upper limit |
| ***Total*** | **Total** | 77,423 | 1273414 | 9166 | 927.1 | 9.89 | 9.69 | 10.09 | 6.47 | 6.32 | 6.62 |
| | **male** | 42,237 | 686149 | 5324 | 650.6 | 8.18 | 7.97 | 8.41 | 6.81 | 6.60 | 7.02 |
| | **female** | 35,186 | 587265 | 3842 | 276.6 | 13.89 | 13.46 | 14.34 | 6.07 | 5.87 | 6.28 |
| | *P for heterogeneity* | | | | | *<0.00001* | | | *< 0.00001* | | |
| ***Age at diagnosis*** | **0-4 years** | 30682 | 56672 | 3057 | 253.7 | 12.05 | 11.62 | 12.48 | 5.25 | 5.05 | 5.46 |
| | | | | | | | | | | | |
| | **5-9** | 18,189 | 306279 | 2417 | 202.7 | 11.92 | 11.45 | 12.41 | 7.23 | 6.92 | 7.55 |
| | **10-14** | 17,135 | 280143 | 2438 | 273.9 | 8.90 | 8.55 | 9.26 | 7.72 | 7.38 | 8.08 |
| | **15-20** | 11,417 | 153320 | 1254 | 196.7 | 6.37 | 6.03 | 6.74 | 6.90 | 6.45 | 7.36 |
| | *P for heterogeneity* | | | | | *<0.0001* | | | *<0.0001* | | |
| | *P for trend* | | | | | *<0.0001* | | | *<0.0001* | | |
| ***Era of diagnosis*** | **1940-1959** | 1,548 | 56672 | 579 | 113.5 | 5.10 | 4.69 | 5.53 | 8.21 | 7.40 | 9.08 |
| | **1960-1969** | 6,039 | 186487 | 1669 | 247.6 | 6.74 | 6.42 | 7.07 | 7.62 | 7.20 | 8.06 |
| | **1970-1979** | 14,129 | 344413 | 2885 | 259.2 | 11.13 | 10.73 | 11.54 | 7.62 | 7.32 | 7.94 |
| | **1980-1989** | 22,490 | 404957 | 2493 | 211.7 | 11.78 | 11.32 | 12.25 | 5.63 | 5.39 | 5.88 |
| | **1990-1999** | 22,490 | 241605 | 1268 | 85.0 | 14.91 | 14.10 | 15.76 | 4.90 | 4.61 | 5.19 |
| | **2000-2008** | 10,727 | 39280 | 272 | 10.0 | 27.08 | 23.96 | 30.50 | 6.67 | 5.87 | 7.54 |
| | *P for heterogeneity* | | | | | *<0.0001* | | | *<0.0001* | | |
| | *P for trend* | | | | | *<0.0001* | | | *<0.0001* | | |
| ***Attained age*** | **< 20** | 18,296 | 501135 | 4421 | 161.7 | 27.34 | 26.54 | 28.16 | 8.50 | 8.24 | 8.76 |
| | **20-29** | 25,468 | 442106 | 2454 | 282.3 | 8.69 | 8.35 | 9.04 | 4.91 | 4.69 | 5.14 |
| | **30-39** | 20,323 | 227403 | 1200 | 199.9 | 6.00 | 5.67 | 6.35 | 4.40 | 4.10 | 4.71 |
| | **40-49** | 9,322 | 77914 | 699 | 151.4 | 4.62 | 4.28 | 4.97 | 7.03 | 6.38 | 7.72 |
| | **50-59** | 3,186 | 21684 | 316 | 100.3 | 3.15 | 2.81 | 3.52 | 9.95 | 8.38 | 11.64 |
| | **60-68** | 828 | 3172 | 76 | 31.5 | 2.41 | 1.90 | 3.02 | 14.04 | 8.95 | 20.07 |
| | *P for heterogeneity* | | | | | *<0.0001* | | | *0.0001* | | |
| | *P for trend* | | | | | *<0.0001* | | | *<0.0001* | | |
| ***…st malignant neoplasm*** | **Lymphoid leukemia** | 18,046 | 273944 | 1959 | 124.6 | 15.73 | 15.04 | 16.44 | 6.70 | 6.38 | 7.02 |
| | **Other leukemias** | 2,653 | 32312 | 353 | 16.9 | 20.86 | 18.74 | 23.15 | 10.40 | 9.29 | 11.60 |
| | **Hodgkin's lymphoma** | 7,049 | 110240 | 1010 | 103.9 | 9.72 | 9.13 | 10.34 | 8.22 | 7.66 | 8.80 |
| | **Other lymphomas** | 5,539 | 89105 | 355 | 73.5 | 4.83 | 4.34 | 5.36 | 3.16 | 2.76 | 3.60 |
| | **Central nervous system** | 14,427 | 233602 | 2699 | 193.3 | 13.96 | 13.44 | 14.50 | 10.73 | 10.29 | 11.17 |

| | | N | Person years at risk | Observed deaths N | Expected deaths N | Standardized mortality ratio SMR | 95% confidence interval | | Absolute excess risk per 1000 person-years AER | 95% confidence interval | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | | | | | lower limit | upper limit | | lower limit | upper limit |
| | **Sympathetic nervous system** | 4,156 | 70654 | 376 | 33.3 | 11.29 | 10.18 | 12.49 | 4.85 | 4.33 | 5.42 |
| | **Retinoblastoma** | 2,519 | 57824 | 210 | 38.9 | 5.40 | 4.70 | 6.18 | 2.96 | 2.48 | 3.49 |
| | **Renal tumors** | 5,712 | 113534 | 406 | 63.5 | 6.39 | 5.79 | 7.05 | 3.02 | 2.68 | 3.38 |
| | **Hepatic tumors** | 466 | 6159 | 31 | 2.5 | 12.21 | 8.30 | 17.33 | 4.62 | 3.01 | 6.73 |
| | **Bone tumors** | 3,273 | 53149 | 501 | 55.7 | 8.99 | 8.22 | 9.81 | 8.38 | 7.57 | 9.24 |
| | **Soft-tissue sarcomas** | 4,912 | 87784 | 590 | 74.1 | 7.96 | 7.33 | 8.63 | 5.88 | 5.34 | 6.44 |
| | **Germ-cell tumors** | 3,613 | 57200 | 231 | 47.7 | 4.84 | 4.24 | 5.51 | 3.20 | 2.70 | 3.76 |
| | **Carcinomas** | 4,392 | 74170 | 360 | 85.4 | 4.22 | 3.79 | 4.68 | 3.70 | 3.21 | 4.23 |
| | **Other malignant neoplasms** | 666 | 13736 | 85 | 13.8 | 6.16 | 4.92 | 7.62 | 5.18 | 3.94 | 6.65 |
| | *P for heterogeneity* | | | | | *<0.0001* | | | *<0.0001* | | |
| ***Treatment*** | **Incomplete information on surgery, chemotherapy and radiotherapy** | 35,092 | 511101 | 3637 | 422.6 | 8.61 | 8.33 | 8.89 | 6.29 | 6.06 | 6.52 |
| | **Surgery only** | 5,571 | 104630 | 395 | 81.8 | 4.83 | 4.36 | 5.33 | 2.99 | 2.63 | 3.38 |
| | **Chemotherapy, no radiotherapy, possibly surgery** | 13,,500 | 193772 | 764 | 86.4 | 8.84 | 8.23 | 9.49 | 3.50 | 3.22 | 3.79 |
| | **Radiotherapy, no chemotherapy, possibly surgery** | 5,442 | 131463 | 1438 | 140.3 | 10.25 | 9.73 | 10.79 | 9.87 | 9.31 | 10.45 |
| | **Chemotherapy and radiotherapy, possibly surgery** | 17,818 | 332447 | 2932 | 196.0 | 14.96 | 14.43 | 15.51 | 8.23 | 7.91 | 8.56 |
| | *P for heterogeneity* | | | | | *<0.0001* | | | *<0.0001* | | |
| ***Years since diagnosis*** | **5-9** | 13,120 | 351667 | 4330 | 127.7 | 33.92 | 32.91 | 34.94 | 11.95 | 11.59 | 12.32 |
| | **10-14** | 11,242 | 294180 | 1506 | 139.4 | 10.80 | 10.26 | 11.36 | 4.65 | 4.39 | 4.91 |
| | **15-19** | 14,342 | 228820 | 874 | 145.7 | 6.00 | 5.61 | 6.41 | 3.18 | 2.93 | 3.44 |
| | **20-24** | 12,000 | 162341 | 681 | 123.6 | 5.51 | 5.10 | 5.94 | 3.43 | 3.12 | 3.76 |
| | **25-29** | 9,639 | 108776 | 582 | 105.8 | 5.50 | 5.06 | 5.97 | 4.38 | 3.95 | 4.83 |
| | **30-34** | 7,488 | 65529 | 476 | 91.6 | 5.20 | 4.74 | 5.69 | 5.87 | 5.23 | 6.55 |
| | **35-39** | 4,626 | 35394 | 336 | 77.7 | 4.33 | 3.88 | 4.81 | 7.30 | 6.31 | 8.37 |
| | **40-44** | 2,787 | 17395 | 194 | 60.1 | 3.23 | 2.79 | 3.72 | 7.70 | 6.18 | 9.38 |
| | **45-49** | 1,433 | 6695 | 117 | 34.8 | 3.36 | 2.78 | 4.03 | 12.28 | 9.26 | 15.75 |
| | **50-54** | 545 | 2113 | 59 | 15.7 | 3.75 | 2.85 | 4.83 | 20.47 | 13.81 | 28.57 |
| | **55-59** | 178 | 439 | 9 | 4.1 | 2.17 | 0.99 | 4.13 | 11.07 | -0.06 | 29.48 |
| | **60-69** | 23 | 64 | 2 | 0.8 | 2.37 | 0.29 | 8.55 | 17.99 | -9.39 | 99.36 |
| | *P for heterogeneity* | | | | | *<0.0001* | | | *<0.0001* | | |
| | *P for trend* | | | | | *<0.0001* | | | *<0.0001* | | |

*P for heterogeneity* measures differences between strata

*P for trend* evaluates trends across strata

TABLE 2. DISTRIBUTION OF SPECIFIC CAUSES OF DEATH ACCORDING TO THE FIRST MALIGNANT NEOPLASM AMONG FIVE-YEAR SURVIVORS OF CHILDHOOD AND ADOLESCENT CANCER FROM THE PANCARESURFUP STUDY OF LATE MORTALITY

| | Specific cause of death | | | | | | | | | | | | | | All deaths | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | First neoplasm | | Second neoplasm | | Cardiovascular | | Infections | | External causes | | Other known cause | | Unknown | | | |
| | N | % | N | % | N | % | N | % | N | % | N | % | N | % | N | % |
| **Lymphoid leukemia** | 1376 | 70.2 | 164 | 8.4 | 44 | 2.2 | 135 | 6.9 | 68 | 3.5 | 101 | 5.2 | 71 | 3.6 | 1959 | 100.0 |
| **Other leukemias** | 226 | 64.0 | 25 | 7.1 | 21 | 5.9 | 20 | 5.7 | 15 | 4.2 | 24 | 6.8 | 22 | 6.2 | 353 | 100.0 |
| **Hodgkin's lymphoma** | 447 | 44.3 | 221 | 21.9 | 117 | 11.6 | 49 | 4.9 | 42 | 4.2 | 70 | 6.9 | 64 | 6.3 | 1010 | 100.0 |
| **Other lymphomas** | 120 | 33.8 | 73 | 20.6 | 42 | 11.8 | 17 | 4.8 | 27 | 7.6 | 44 | 12.4 | 32 | 9.0 | 355 | 100.0 |
| **Central nervous system** | 1666 | 61.7 | 280 | 10.4 | 102 | 3.8 | 67 | 2.5 | 119 | 4.4 | 321 | 11.9 | 144 | 5.3 | 2699 | 100.0 |
| **Sympathetic nerv. syst.** | 217 | 57.7 | 40 | 10.6 | 23 | 6.1 | 10 | 2.7 | 22 | 5.9 | 36 | 9.6 | 28 | 7.4 | 376 | 100.0 |
| **Retinoblastoma** | 31 | 14.8 | 121 | 57.6 | 8 | 3.8 | 5 | 2.4 | 13 | 6.2 | 20 | 9.5 | 12 | 5.7 | 210 | 100.0 |
| **Renal tumors** | 122 | 30.0 | 106 | 26.1 | 27 | 6.7 | 14 | 3.4 | 43 | 10.6 | 59 | 14.5 | 35 | 8.6 | 406 | 100.0 |
| **Hepatic tumors** | 19 | 61.3 | 2 | 6.5 | 2 | 6.5 | 1 | 3.2 | 4 | 12.9 | 3 | 9.7 | . | . | 31 | 100.0 |
| **Bone tumors** | 306 | 61.1 | 87 | 17.4 | 23 | 4.6 | 14 | 2.8 | 21 | 4.2 | 22 | 4.4 | 28 | 5.6 | 501 | 100.0 |
| **Soft-tissue sarcomas** | 321 | 54.4 | 101 | 17.1 | 29 | 4.9 | 20 | 3.4 | 27 | 4.6 | 50 | 8.5 | 42 | 7.1 | 590 | 100.0 |
| **Germ-cell tumors** | 90 | 39.0 | 49 | 21.2 | 14 | 6.1 | 13 | 5.6 | 23 | 10.0 | 29 | 12.6 | 13 | 5.6 | 231 | 100.0 |
| **Carcinomas** | 149 | 41.4 | 77 | 21.4 | 29 | 8.1 | 13 | 3.6 | 25 | 6.9 | 48 | 13.3 | 19 | 5.3 | 360 | 100.0 |
| **Other neoplasms** | 48 | 56.5 | 9 | 10.6 | 8 | 9.4 | 1 | 1.2 | 6 | 7.1 | 7 | 8.2 | 6 | 7.1 | 85 | 100.0 |
| **Total** | 5138 | 56.1 | 1355 | 14.8 | 489 | 5.3 | 379 | 4.1 | 455 | 5.0 | 834 | 9.1 | 516 | 5.6 | 9166 | 100.0 |

TABLE 3. MULTIVARIABLE PROPORTIONAL HAZARDS MODELS OF FACTORS AFFECTING LATE MORTALITY BY CAUSE OF DEATH*

| | All causes | | First Neoplasm | | Second Neoplasm | | Cardiovascular Causes | | Infections | | External Causes | | Other known cause | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hazard Ratio | | Hazard Ratio | | Hazard Ratio | | Hazard Ratio | | Hazard Ratio | | Hazard Ratio | | Hazard Ratio | |
| | Point estimate | 95% CI | Point estimate | 95% CI | Point estimate | 95% CI | Point estimate | 95% CI | Point estimate | 95% CI | Point estimate | 95% CI | Point estimate | 95% CI |
| **Era of diagnosis** | | | | | | | | | | | | | | |
| 1940-1959 | 1.01 | [0.91, 1.12] | 1.19 | [1.04, 1.38] | 1.13 | [0.90, 1.40] | 1.27 | [0.89, 1.82] | 0.23 | [0.09, 0.54] | 0.95 | [0.62, 1.46] | 0.79 | [0.58, 1.09] |
| 1960-1969 | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| 1970-1979 | 0.95 | [0.89, 1.01] | 0.80 | [0.73, 0.87] | 1.25 | [1.06, 1.47] | 1.47 | [1.12, 1.91] | 0.59 | [0.44, 0.79] | 0.90 | [0.68, 1.18] | 1.11 | [0.91, 1.36] |
| 1980-1989 | 0.63 | [0.59, 0.68] | 0.47 | [0.43, 0.52] | 1.05 | [0.87, 1.26] | 1.55 | [1.14, 2.11] | 0.33 | [0.24, 0.45] | 0.81 | [0.60, 1.09] | 0.84 | [0.66, 1.06] |
| 1990-1999 | 0.41 | [0.38, 0.44] | 0.32 | [0.29, 0.36] | 0.83 | [0.66, 1.05] | 0.74 | [0.47, 1.18] | 0.10 | [0.07, 0.16] | 0.61 | [0.42, 0.88] | 0.50 | [0.36, 0.69] |
| 2000-2008 | 0.34 | [0.30, 0.39] | 0.23 | [0.20, 0.27] | 0.84 | [0.53, 1.34] | 0.50 | [0.16, 1.58] | 0.03 | [0.01, 0.11] | 0.48 | [0.22, 1.04] | 0.45 | [0.25, 0.81] |
| *P for linear trend* | *<0.0001* | | *<0.0001* | | *0.1105* | | *0.0829* | | *<0.0001* | | *0.0968* | | *0.0040* | |
| **Sex** | | | | | | | | | | | | | | |
| female | 0.85 | [0.81, 0.88] | 0.89 | [0.84, 0.94] | 0.95 | [0.86, 1.07] | 0.77 | [0.64, 0.93] | 0.80 | [0.65, 0.98] | 0.49 | [0.40, 0.60] | 0.86 | [0.75, 0.99] |
| male | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| *P for heterogeneity* | *<0.0001* | | *<0.0001* | | *0.4056* | | *0.0058* | | *0.0343* | | *<0.0001* | | *0.0329* | |
| **First neoplasm** | | | | | | | | | | | | | | |
| Lymphoid leukemia | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | |
| Other leukemias | 1.50 | [1.34, 1.68] | 1.32 | [1.15, 1.52] | 1.33 | [0.87, 2.02] | 4.10 | [2.43, 6.91] | 1.23 | [0.77, 1.97] | 1.81 | [1.04, 3.16] | 1.99 | [1.27, 3.12] |
| Hodgkin's lymphoma | 1.07 | [0.99, 1.16] | 0.69 | [0.62, 0.78] | 2.90 | [2.35, 3.57] | 4.39 | [3.07, 6.28] | 0.64 | [0.46, 0.91] | 1.10 | [0.73, 1.64] | 1.24 | [0.90, 1.70] |
| Other lymphomas | 0.50 | [0.45, 0.56] | 0.25 | [0.21, 0.30] | 1.27 | [0.96, 1.68] | 2.20 | [1.43, 3.38] | 0.34 | [0.20, 0.56] | 0.96 | [0.61, 1.51] | 1.11 | [0.77, 1.59] |
| Central nervous system tumours | 1.34 | [1.26, 1.43] | 1.21 | [1.12, 1.31] | 1.66 | [1.35, 2.03] | 1.88 | [1.31, 2.69] | 0.42 | [0.30, 0.58] | 1.62 | [1.19, 2.20] | 2.76 | [2.17, 3.50] |
| Sympathetic nervous system tumours. | 0.71 | [0.64, 0.80] | 0.61 | [0.53, 0.70] | 0.88 | [0.62, 1.24] | 1.93 | [1.15, 3.22] | 0.27 | [0.14, 0.52] | 1.27 | [0.79, 2.05] | 1.30 | [0.89, 1.91] |
| Retinoblastoma | 0.41 | [0.36, 0.48] | 0.10 | [0.07, 0.14] | 2.69 | [2.11, 3.45] | 0.57 | [0.27, 1.22] | 0.14 | [0.06, 0.36] | 0.78 | [0.42, 1.43] | 0.69 | [0.42, 1.13] |
| Renal tumors | 0.46 | [0.41, 0.51] | 0.21 | [0.17, 0.25] | 1.38 | [1.08, 1.76] | 1.26 | [0.78, 2.04] | 0.22 | [0.13, 0.38] | 1.44 | [0.98, 2.11] | 1.21 | [0.87, 1.68] |
| Hepatic tumors | 0.72 | [0.50, 1.02] | 0.61 | [0.39, 0.97] | 0.58 | [0.15, 2.35] | 2.40 | [0.58, 9.95] | 0.36 | [0.05, 2.56] | 2.87 | [1.05, 7.85] | 1.49 | [0.47, 4.71] |
| Bone tumors | 1.08 | [0.98, 1.20] | 1.00 | [0.87, 1.14] | 2.22 | [1.70, 2.91] | 1.61 | [0.95, 2.74] | 0.38 | [0.22, 0.67] | 1.17 | [0.70, 1.94] | 0.77 | [0.48, 1.23] |
| Soft tissue sarcomas | 0.80 | [0.73, 0.88] | 0.66 | [0.58, 0.75] | 1.59 | [1.23, 2.05] | 1.39 | [0.86, 2.26] | 0.36 | [0.23, 0.58] | 0.99 | [0.63, 1.57] | 1.16 | [0.82, 1.63] |
| Germ-cell tumors | 0.48 | [0.42, 0.56] | 0.28 | [0.22, 0.34] | 1.27 | [0.92, 1.75] | 1.08 | [0.58, 2.01] | 0.36 | [0.20, 0.63] | 1.34 | [0.83, 2.17] | 1.06 | [0.69, 1.62] |
| Carcinomas | 0.53 | [0.47, 0.59] | 0.33 | [0.28, 0.40] | 1.33 | [0.99, 1.78] | 1.29 | [0.79, 2.10] | 0.23 | [0.13, 0.43] | 1.06 | [0.65, 1.74] | 1.11 | [0.77, 1.60] |
| Other malignant neoplasms. | 0.67 | [0.53, 0.83] | 0.59 | [0.44, 0.79] | 0.81 | [0.41, 1.59] | 2.02 | [0.94, 4.31] | 0.09 | [0.01, 0.67] | 1.30 | [0.56, 3.02] | 0.87 | [0.40, 1.88] |
| *P for heterogeneity* | *<0.0001* | | *<0.0001* | | *<0.0001* | | *<0.0001* | | *<0.0001* | | *0.0237* | | *<0.0001* | |
| **Attained age** | | | | | | | | | | | | | | |
| < 20 | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | | 1.00 | |

| | All causes | | First Neoplasm | | Second Neoplasm | | Cardiovascular Causes | | Infections | | External Causes | | Other known cause | |
|---|---|---|---|---|---|---|---|---|---|---|---|---|---|---|
| | Hazard Ratio | | Hazard Ratio | | Hazard Ratio | | Hazard Ratio | | Hazard Ratio | | Hazard Ratio | | Hazard Ratio | |
| | Point estimate | 95% CI | Point estimate | 95% CI | Point estimate | 95% CI | Point estimate | 95% CI | Point estimate | 95% CI | Point estimate | 95% CI | Point estimate | 95% CI |
| [illegible]29 | 1.08 | [1.02, 1.15] | 1.08 | [1.00, 1.16] | 0.90 | [0.76, 1.07] | 1.02 | [0.74, 1.41] | 1.60 | [1.20, 2.14] | 1.90 | [1.42, 2.54] | 1.62 | [1.29, 2.03] |
| 30-39 | 1.36 | [1.22, 1.52] | 1.56 | [1.32, 1.84] | 1.13 | [0.89, 1.43] | 1.54 | [1.01, 2.35] | 1.22 | [0.67, 2.20] | 1.86 | [1.23, 2.82] | 1.97 | [1.40, 2.78] |
| 40-49 | 1.90 | [1.62, 2.22] | 2.19 | [1.60, 3.01] | 1.35 | [0.97, 1.87] | 3.09 | [1.85, 5.17] | 2.83 | [1.41, 5.68] | 2.19 | [1.23, 3.89] | 2.68 | [1.76, 4.07] |
| [illegible]59 | 2.34 | [1.88, 2.92] | 3.73 | [2.15, 6.47] | 1.79 | [1.16, 2.76] | 6.99 | [3.69, 13.27] | 1.33 | [0.32, 5.62] | 2.47 | [1.05, 5.81] | 3.07 | [1.75, 5.38] |
| 60-78 | 2.57 | [1.81, 3.66] | 4.26 | [1.61, 11.30] | 2.23 | [1.18, 4.23] | 8.34 | [3.46, 20.10] | 0.00 | [0.00, 0.00] | 5.74 | [1.82, 18.09] | 4.03 | [1.82, 8.94] |
| *P for linear trend* | *<0.0019* | | *<0.0449* | | *0.0052* | | *<0.0001* | | *<0.0001* | | *0.08719* | | *<0.0001* | |

Footnote: * Cox regression for all cause hazard ratios, Fine and Gray subdistribution hazard ratios for competing causes of death.

Children and adolescents who survive cancer have increased mortality rates compared with the general population. Here, the authors investigated trends in mortality among European cancer survivors 5 or more years after diagnosis. They pooled data on more than 77,000 patients from 12 cancer registries and clinics across Europe. Patients were diagnosed between 1940 and 2018, and all-cause mortality fell steeply during this period. However, excess mortality remained high, even for subjects in their 60s, highlighting the need for long term care for childhood cancer survivors.