Zeitschrift für die gesamte Versicherungswissenschaft, 114 (2025) 3: 293 – 317
https://doi.org/10.3790/zverswiss.2025.1467101

Risk assessment of long-term cancer survivors in complete remission – an insurance medicine point-of-view

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Abstract

Background

Cancer survivors differ in survival depending on cancer type, stage, age, and on the already survived time after diagnosis or end of treatment, respectively. Here we present an approach to evaluate extramortality loadings for cancer survivors in long-term complete remission based on these factors.

Methods and Results

We analyzed relative survival (ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of expected survivors in a comparable set of cancer free individuals; adjusted for sex and age) of patients with major cancers from the Surveillance, Epidemiology, and End Results database of the US National Cancer Institute. Conditional relative survival was used to determine improvements according to time already survived after diagnosis. For a qualitative analysis, we defined in complete remission as being cancer-free. For retrieving information on risk for recurrences, second primary malignancy and treatment-related sequelea, we performed a literature review.

Results

Our insurance medicine approach categorizes cancer constellations in 3 risk categories: Category A, based on current data, has a normal relative survival already from time of diagnosis onwards; category B has a normal relative survival after having survived several years as measured by conditional relative survival; and category C has a persisting lower relative survival. For the latter, impaired survival can be due to recurrences of the same cancer, second primary malignancies, cancer- and treatment related sequelae, or

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comorbidities. Based on comorbidity data, which is usually not available in cancer registry data, and expert insurance medicine knowledge, we strive to identify and select favorable risk profiles, which we term the underwriting effect, to improve insurability of applicants with category C cancers.

Conclusion

Our rationale for medical underwriting of long-term cancer survivors combines contemporary medical data and insurance expertise. This combination enables adequate reflection of the specific characteristics of cancer survivors within an insurance population, which differs from the general population. As a result, Life insurance might be offered to many long-term cancer survivors who did not suffer from recurrence, secondary malignancy, and other sequelae if all available information is taken into account. On the other side, some cancer types show excess mortality risk compared to the general population even many years in remission.

Zusammenfassung

Hintergrund

Krebsüberlebende unterscheiden sich in ihrer Überlebensrate je nach Krebsart, Stadium, Alter und der bereits überlebten Zeit nach Diagnosestellung bzw. dem Ende der Behandlung. Wir stellen einen Ansatz zur Bewertung der Übersterblichkeit und daraus folgender Risikozuschläge für Krebsüberlebende in langfristiger kompletter Remission vor.

Methoden und Ergebnisse

Wir analysierten die relative Überlebensrate (Verhältnis der Überlebensrate von Patienten zu einem definierten Zeitpunkt in Verhältnis zur erwarteten Überlebensrate der Allgemeinbevölkerung, adjustiert für Geschlecht und Alter) von Patienten mit häufigen Krebserkrankungen basierend auf Daten aus der Surveillance, Epidemiology, and End Results-Datenbank des US National Cancer Institute. Die konditionale relative Überlebensrate wurde verwendet, um Verbesserungen der Überlebensrate entsprechend der bereits nach der Diagnose überlebten Zeit zu bestimmen. Für eine qualitative Analyse definierten wir eine vollständige Remission als Zustand ohne Nachweis von Krebs. Um Informationen über das Risiko von Rezidiven, Zweittumoren und behandlungsbedingten Folgeerkrankungen zu erhalten, führten wir eine systematische Literaturrecherche durch.

Ergebnisse

Unser versicherungsmedizinischer Ansatz kategorisiert Krebserkrankungen in drei Risikokategorien: Kategorie A, basierend auf aktuellen Daten, zeigt bereits ab dem Zeitpunkt der Diagnose eine normale relative Überlebensrate; Kategorie B weist eine normale relative Überlebensrate auf, nachdem mehrere Jahre überlebt wurden, gemessen anhand der konditionalen relativen Überlebensrate; und Kategorie C weist eine anhaltend niedrigere relative Überlebensrate auf. Bei letzterer Kategorie kann die eingeschränkte Überlebensrate auf Rezidive derselben Krebserkrankung, weitere Primärtumore, krebs- und behandlungsbedingte Folgeerkrankungen oder Komorbiditäten zurückzuführen sein. Auf der Grundlage von Komorbiditätsdaten, die in Krebsregisterdaten

in der Regel nicht verfügbar sind, und versicherungsmedizinischem Fachwissen können günstige Risikoprofile identifiziert werden. Diesen Vorgang bezeichnen wir als „Underwriting-Effekt", der die Versicherbarkeit von Antragstellern mit Krebserkrankungen der Kategorie C verbessert.

Schlussfolgerung

Unser Ansatz für die medizinische Risikoprüfung von Langzeitüberlebenden von Krebserkrankungen kombiniert aktuelle medizinische Daten und versicherungsmedizinische Expertise. Diese Kombination ermöglicht eine angemessene Berücksichtigung der spezifischen Merkmale von Krebsüberlebenden innerhalb der Versichertenpopulation, die sich von der Allgemeinbevölkerung unterscheidet. Daher könnte vielen Langzeitüberlebenden von Krebs, die nicht an einem Rezidiv, zusätzlichem Primärtumor oder anderen Folgeerkrankungen leiden, eine Lebensversicherung wahrscheinlich angeboten werden, wenn alle verfügbaren Informationen berücksichtigt werden. Andererseits weisen einige Krebsarten im Vergleich zur Allgemeinbevölkerung auch viele Jahre nach der Remission ein erhöhtes Sterblichkeitsrisiko auf.

JEL classification: G22

Keywords: Insurance Medicine, Conditional Relative Survival, Underwriting, Cancer, Tumor, Second Primary Malignancy

1. Introduction

Providing access to financial services for people with pre-existing conditions enables social and economic participation. This access depends on the long-term risk (Scocca/Meunier 2022). Determining medical loadings according to risk should be evidence-based, as exact as possible and fair for all parties involved, first and foremost for the applicant. Despite advances in survival over the last decades, there is clear evidence that cancer patients substantially differ in their survival pattern from the general population (Dal Maso et al. 2019; Van Ginckel A. 2022). Consequently, medical loadings and therefore insurability are cancer-specific, as are the survival periods after which, if at all, a normal survival is achieved compared to the general population.

Long-term survival of cancer patients depends on a multitude of factors, e. g. age, stage of cancer, choice of therapy, socioeconomic situation and quality of the healthcare system. As overall long-term survival has improved in recent years, insurability for cancer survivors has been extended continuously over the last decades. Still, there are cancers and stages which are associated with decreased survival compared to the survival level of the general population (relative survival, RS), even many years after diagnosis. This excess mortality determines, among other factors, medical loadings for life insurance. As RS can vary from year to year, and especially over the first years after diagnosis, it might not be representative for the underwriting situation. In reality, cancer survivors usu-

ally apply for insurance after they have survived a certain amount of time after diagnosis.

To capture the time-dependence of survival development, a useful type of analysis is conditional relative survival (CRS). CRS is defined as the relative survival for a subsequent number of years, given the person has already survived previously a defined number of years. The general hypothesis is that this CRS increases with succeeding years. At some point and for some cancer stages, CRS can reach levels equal to the general population, i. e. 100 %, despite the fact that relative survival at time of diagnosis or shortly thereafter could be in fact reduced. Using CRS resembles the underwriting reality, where cancer survivors apply for insurance after they have survived a certain amount of time after diagnosis. This parameter is also useful for assessing the scientific appropriateness of fixed time periods to realize standard conditions for cancer survivors, as proposed by different cancer patient lobbying groups under the umbrella of the 2021 European Commission's Beating Cancer Plan ("The right to be forgotten" regulations, EUROPEAN COMMISSION 2021).

Survival data for cancers can be retrieved from single study data or cancer registries. For the latter, cancer patients are recorded at the time of diagnosis, and ultimately at time of death. Interim data, e. g. at end of treatment, recurrences or complications, is rarely documented in public cancer registries. This is in contrast to the clinical reality of cancer survivors, as these events are highly relevant. Also underwriting of cancer survivors for life insurance products takes information of these interim events after the diagnosis into consideration.

In the case of cancer, achieving a comparable CRS to the general population would imply surviving without developing serious complications of either the cancer itself or due to the specific therapy applied. In addition, it might imply a low likelihood of recurrence of the cancer, as this is often an event impacting survival. As a consequence, if registry data can deliver long-term CRS data for a specific cancer type, stage and time period, and is able to show equal CRS compared to the general population, loadings for an applicant presenting with this specific cancer type, stage and time period are not justifiable. If CRS is not equal to the general population, risk assessment and underwriting for these cancer survivors must take into account relevant information to provide a risk-adequate medical loading.

2. Methods

2.1 SEER data survival analysis

Data were obtained from the US Surveillance, Epidemiology, and End Results (SEER) 17 registries database (2000 – 2021, November 2023 submission) from

the National Cancer Institute. We used the Survival Session within SEER*stat 8.4.4 version with the following settings.

Inclusion criteria: Cases were selected if cancer was microscopically confirmed with malignant behavior. Therefore we did not investigate in situ cancer. We selected cancer types according to ICD-0-3/WHO 2008 site coding, with the respective stage. Stage was selected according to the combined summary stage (2004+) option with localized or regional cancers. Non-hispanic white was selected.

Exclusion criteria: Cases were excluded if the cancer was reported through a death certificate or autopsy only, as well as cases that were recorded as alive but have no survival time recorded. Distant cancers were not selected as we assume that distant metastases will lead to such dismal outcomes and/or these patients are not cancer-free in the vast majority of cases.

For the calculation method of relative survival, we used the actuarial method according to SEER. For calculating the expected survival, the Ederer II method was applied. If interval relative survival increased above 1.00, it was not adjusted down to 1.00 in the output. An increasing relative survival over time was also not adjusted down to 1.00. For age standardization, the respective International Cancer Survival Standard according to SEER recommendations was selected, depending on the cancer type. We used the age groups 15 – 44, 45 – 54, 55 – 64, 65 – 74 and 75+. The expected survival table was U.S. by SES/geography/race (NHW, NHB, NHAIAN, NHAPI, HISP) 1992 – 2021.

For CRS periods, we chose an 8 year period of follow-up, after having survived a defined number of consecutive years, starting with the first year after diagnosis (8-year conditional relative survival). As an example, a 9 – 17 conditional relative survival means that a person has survived 9 years (condition), and then the relative survival of the following 8 years (8-year) until year 17 is calculated. For longer time periods, the number of cancer patients in the SEER database diminished, therefore the 8 year follow-up period was a reasonable choice to ensure relevant numbers of patients. Normal relative survival was defined as having a relative survival of 1.00 (or 100 %).

2.2 Definition of long-term cancer survivor

For the literature analysis, we aimed at finding publications that provide long-term cancer survival data for more than 10 years of follow-up, if available. Information on recurrences, i. e. recurrence-, progression-, or disease-free survival was necessary to identify cancer patients without evidence of cancer at follow-up. According to this definition, we interpreted the results from the literature.

2.3 Literature search strategy

We retrieved relevant studies on the topic of CRS, recurrences, complications and second primary malignancy published as of June 2024 from electronic databases, including PubMed and GoogleScholar. The search terms were "conditional relative survival", "disease-free survival", "progression-free survival", "event-free survival", "recurrence-free survival", "long-term", "second primary malignancy", "second malignant neoplasm", "second primary cancer", "secondary cancer", "treatment complications", "treatment sequelea", in addition to the respective cancer type.

3. Results

3.1 Cancer-specific analysis of long-term CRS

3.1.1 All cancers combined

All malignant tumors with the exception of non-melanoma skin cancer were combined and analyzed according to age group and stage. All age groups show a continuous increase in multi-year CRS with increasing time after diagnosis (Figure 1). The age group 75+ has the lowest multi-year CRS, but increases as well over time. The level and increase of multi-year CRS is relatively similar for all other age groups.

For regional stage cancer (Figure 2), CRS increased over time for all age groups as well. Differences of multi-year CRS between age groups at a given year after diagnosis were pronounced, ranging from 0.91 for age group 15 – 44 to 0.76 for 75+ after 5 years. The age group of 15 – 44 had the highest relative survival at every time point.

This analysis already shows that all cancer types taken together cannot have a normal survival. Thus a generalisation of cancer survival is not meaningful, and a one-size-fits-all perspective for setting extramortality loadings must be refuted.

Nevertheless, as this is an aggregated view of various cancer types which differ widely in prognosis, we selected the following cancer with high incidence for an individual analysis: Breast cancer, prostate cancer, colon cancer (excluding rectum), pancreatic cancer, lung cancer, malignant melanoma, leukemia, multiple myeloma, and Non-Hodgkin-lymphoma.

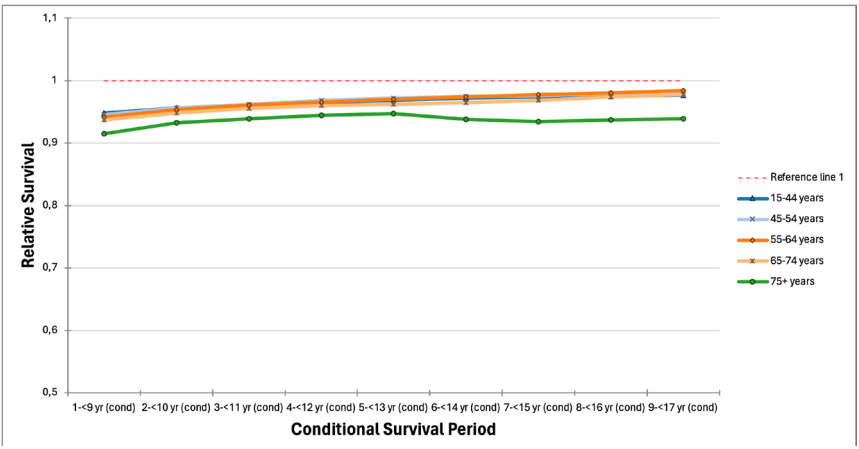

Figure 1: Localized Cancer

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. For example, if a person has survived the first 2 years, the relative survival for the next 8 years until year 10 after diagnosis is 0.93 for 75+ age group. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.

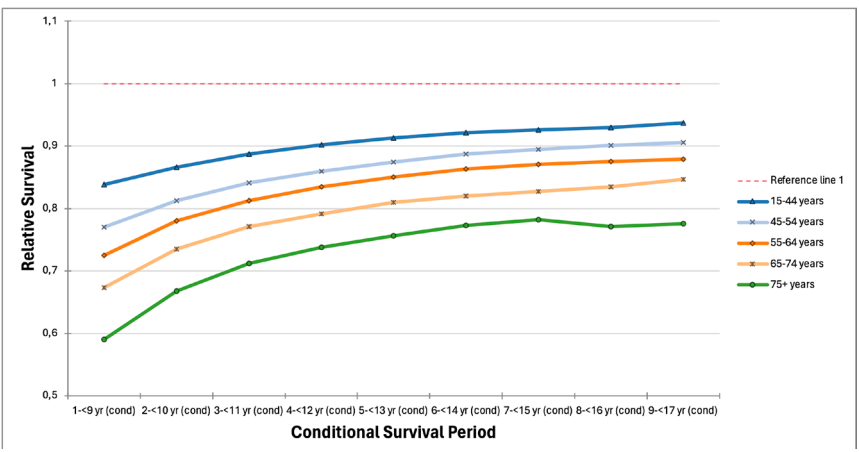

Figure 2: Regional Cancer

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.

3.1.2 Breast Cancer

Breast cancer is the most frequent female cancer. It has a different pattern of multi-year CRS compared to all cancers combined, especially for localized stage. Localized breast cancer patients in the age group 15 – 44 at diagnosis have the largest increase in multi-year CRS with time after diagnosis (0.95 to 0.97)(Figure 3). Patients in age group 45 – 54 and 55 – 64 have also an increase in multi-year CRS, but less pronounced. On the contrary, patients in age group 65 – 74 and especially in 75+ show a decrease of multi-year CRS over time (1.02 to 0.91 for 75+). For all age groups except 75+, which has normal relative survival in the first 4 years, relative survival does not reach normal levels at any given time.

Patients with regional breast cancer show a similar pattern of CRS development as all regional stage cancers combined (Figure 4). All age groups have an increase in CRS over time. This increase is most pronounced in the age group of 15 – 44 years (0.82 to 0.91). In all age groups, relative survival does not reach normal levels.

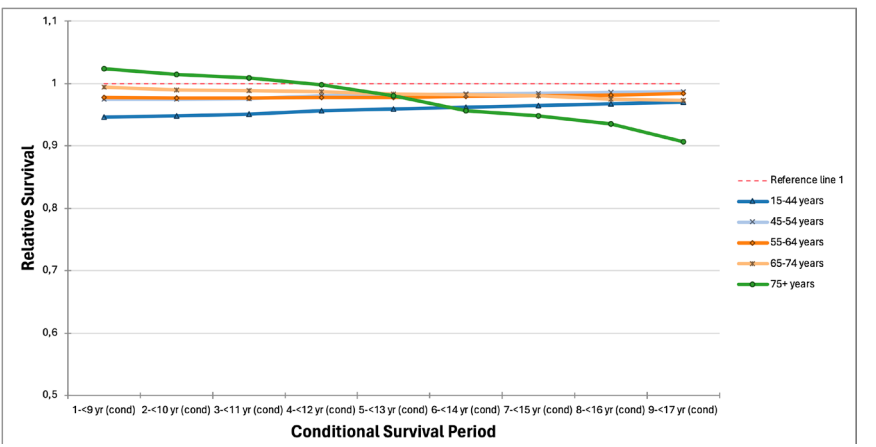

Figure 3: Localized Breast Cancer

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed horizontal line represents normal relative survival compared to reference population.

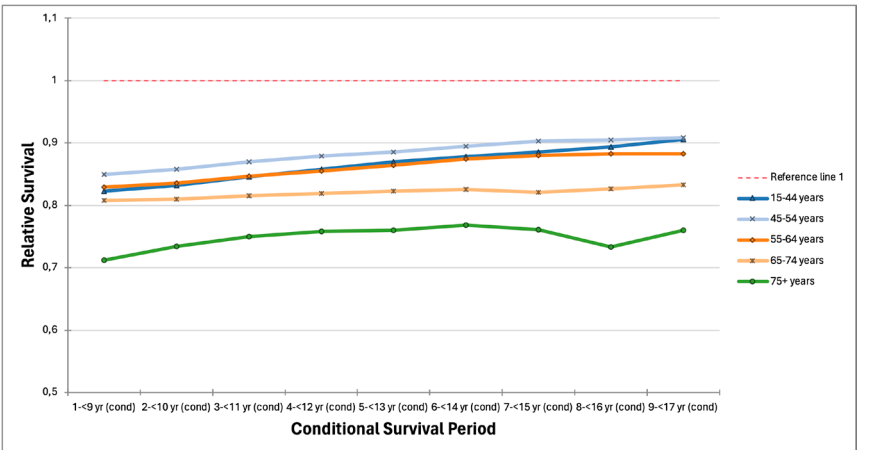

Figure 4: Regional Breast Cancer

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed horizontal line represents normal relative survival compared to reference population.

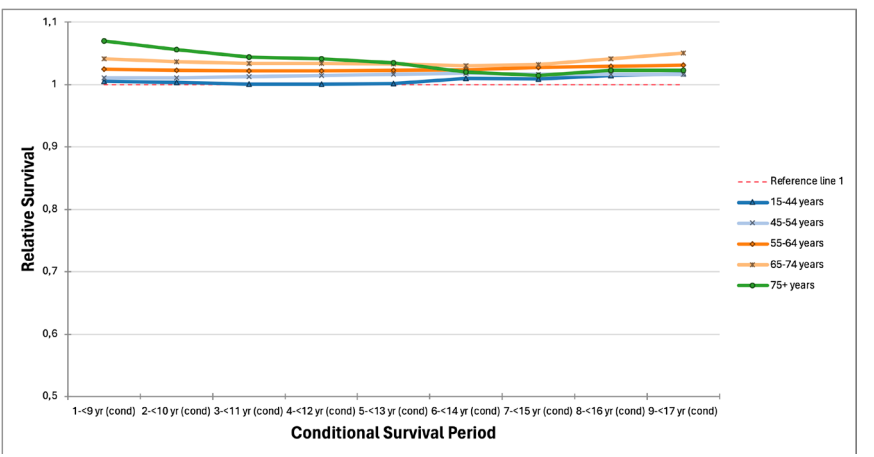

Figure 5: Localized Prostate Cancer

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.

3.1.3 Prostate Cancer

All age groups of localized prostate cancer with the exception of 75+ have an increase of multi-year CRS over time (Figure 5). This increase is relatively small. All age groups have a normal relative survival at any given timepoint, but patients in the age group 15 – 44 at diagnosis have the lowest multi-year CRS.

Regional prostate cancer patients in the age group 15 – 44 at diagnosis have the lowest multi-year CRS up until 9 years after diagnosis (Figure 6). Age groups 15 – 44, 65 – 74 and 75+ have an increase of multi-year CRS over time, age group 55 – 64 has no increase, and 45 – 54 has a decrease. Only the age groups 65 – 74 and 75+ have a normal relative survival at certain timepoints.

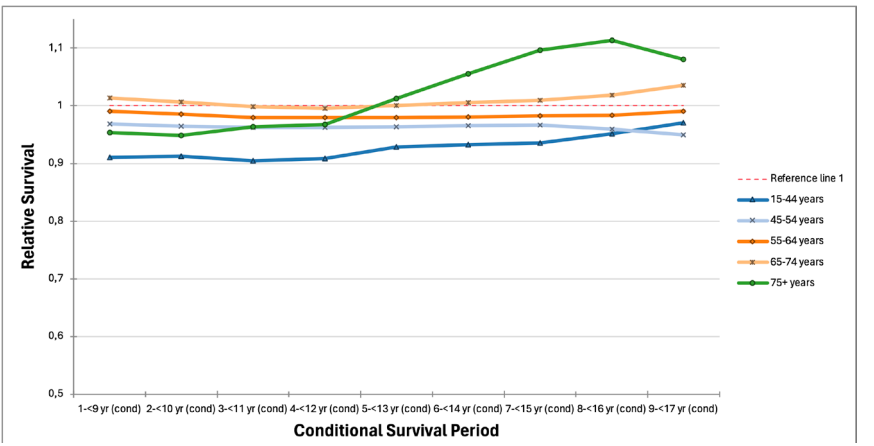

Figure 6: Regional Prostate Cancer

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.

3.1.4 Colon Cancer

Localized colon cancer patients in age groups 15 – 44 and 65 – 74 have no increases of multi-year CRS over time, 45 – 54 and 55 – 64 have a slight increase and age group 75+ has a slight decrease (Figure 7). No age group reaches normal CRS over time.

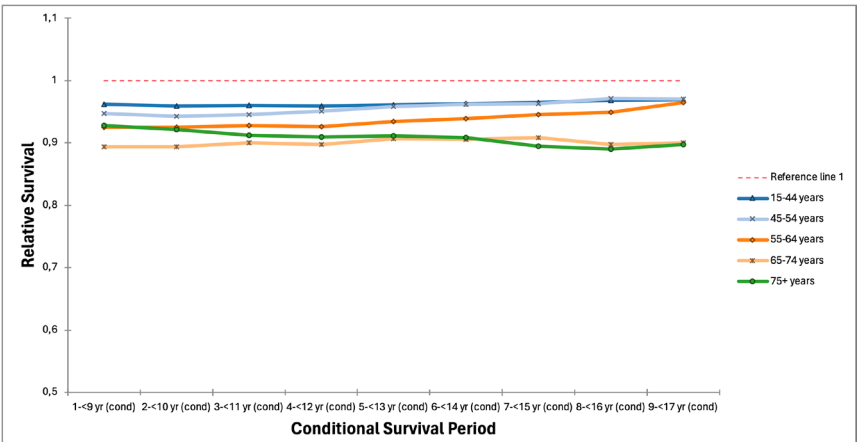

Figure 7: Localized Colon Cancer

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.

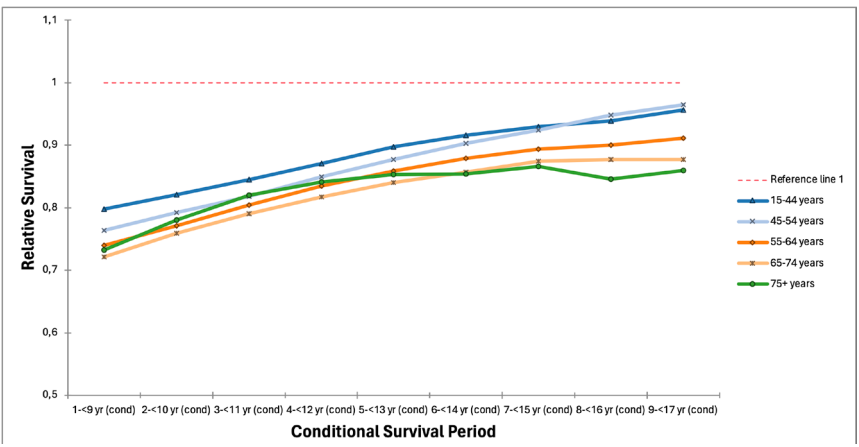

Figure 8: Regional Colon Cancer

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.

All age groups of regional colon cancer patients show an increase of multi-year CRS over time (Figure 8). Age group 75+ has the lowest increase over time. No age group reaches normal CRS level.

Results for pancreatic cancer, lung cancer, malignant melanoma, leukemia, multiple myeloma, and Non-Hodgkin-Lymphoma are shown in the supplement (Supplementary Appendix).

3.1.5 Cancer Categories from an Insurance Medicine Perspective

All cancers evaluated here did not have a common pattern of CRS level and/or development over time when considering age and stage (Table 1). Remarkable findings are that young breast cancer patients tend to have a stronger increase in CRS with subsequent years after diagnosis, and elderly breast cancer patients a decline. In contrast, colon cancer patients have a stable CRS over time in localized cases, and a strong increase of CRS if regional. Notably, the three hematologic malignancies Non-Hodgkin lymphoma, leukemia, multiple myeloma investigated in this study do not show a common pattern either. In addition, many stages of certain cancer types in defined age groups do not show normal CRS over time.

Based on contemporary survival data, our insurance medicine approach could categorize cancer constellations in three categories (Table 1).

Category A) Cancer stages that have a normal relative survival already from time of diagnosis onwards (example: localized prostate cancer)

Category B) Cancer stages that have a normal relative survival after having survived several years as measured by CRS (example: localized melanoma)

Category C) Cancer stages with a persisting lower relative survival (example: regional breast cancer)

Table 1

CRS development and CRS level according to cancer type and stage based on SEER registry data

	Localized		Regional		Systemic Disease	
	CRS development	CRS level	CRS development	CRS level	CRS development	CRS level
All cancer	increase	Age-independent	strong increase	Age-dependent		
Breast	Age-dependent	Age-dependent	weak increase	Age-dependent		
Colon	stable	Age-dependent	strong increase	Age-dependent		
Leukemia					Age-dependent	Age-dependent
Lung	weak increase	Age-dependent	increase	Age-dependent		
Melanoma	weak increase	Age-independent	strong increase	Age-independent		
Multiple myeloma					weak increase	Age-dependent
Non-Hodgkin Lymphoma	stable	Age-dependent	stable	Age-dependent		
Pancreas	Age-dependent	Age-dependent	increase	Age-dependent		
Prostate	stable	Age-independent	Age-dependent	Age-dependent		

Age-dependent is defined as having either different changes of CRS according to age (CRS development) or differences of CRS level between ages at the majority of time points. Furthermore, CRS development can be stable (no relevant change of CRS in the majority of age bands over time) or increasing to different degrees. An age-independent CRS level is defined as having similar CRS across the majority of age bands (4 of 5 age bands within a 5 % CRS range at the majority of timepoints).

3.2 Assessing the mortality risk of long term cancer survivors in life insurance – Literature analysis

For category C cancer constellation, in which CRS is not normal at any given timepoint, we hypothesize that the following needs to be considered when underwriting long term cancer survivors in order to adequately estimate excess mortality:

1. What is the risk of a certain cancer recurring after long-term complete remission (e. g. 10 years)?
2. What is the risk of a second primary malignancy occurring after long-term complete remission?
3. What is the risk of developing complications after long-term complete remission?
4. Can we overcome data limitations of registries by application of the "underwriting effect"?

This information should be based on contemporary literature review, which would support life insurance risk assessment

3.2.1 What is the risk of a certain cancer recurring after long-term complete remission (e. g. 10 years)?

While there are cancer types that show late and very late recurrences such as breast cancer (Pedersen et al. 2022), the majority of cancers develop recurrences within the first years of diagnosis. Most cancers that are going to show recurrences will do so in the first 5 years after treatment. After 5 years recurrence rates have dropped to low levels for many cancers. In patients with colon cancer for example, >80 % of all recurrences have occurred by 5 years, as is the case for lung cancer or head-neck cancers (Tumorregister München 2021). Even cancers like breast cancer, which is infamous for late recurrences, show a typical recurrence pattern with higher recurrence rates in early years after diagnosis (Tumorregister München 2022). Admittedly, less than 60 % of breast cancer recurrence have occurred by year 5 after diagnosis, with 84 % by year 10 after diagnosis.

3.2.2 What is the risk of a second primary malignancy occurring after long-term complete remission?

The occurrence of another cancer type, which is not the same type as the first (primary) cancer diagnosis is a relevant risk for cancer survivors. These so-called second primary malignancies (SPM) can contribute to increased mortality. The risk for SPM probably decreases over time (Lee et al. 2016), and depends on the first cancer type and its associated risk factors. A recent study has quantified the risk of developing subsequent primary cancers in 5-year cancer survivors (Sung et al. 2020). The overall risk irrespective of initial type of cancer was 1.1 for women, and 1.0 for men. For the latter, removing prostate cancer from the analysis resulted also in an elevated risk of 1.1. However, the range of SIR between different cancer types differed substantially. Cancer types with a much higher risk for SPM were, for example, larynx (1.75 for men, 2.48 for women), esophagus (1.35 for men, 1.89 for women), or Hodgkin lymphoma (1.59 for men, 1.86 for women), which implies relevant heterogeneity between different cancer types. Therefore a general risk estimation across cancer types or a general time frame, from which SPM are unlikely, cannot be made. Notably, the all-cause mortality of persons with a SPM is reflected in the (conditional) relative survival of the original primary cancer, as death irrespective of cause is registered in this data. In persons without a SPM, the survival is probably even better (Donin et al. 2016).

3.2.3 What is the risk of developing complications after long-term complete remission?

Treatment-related sequelea can occur many years after diagnosis, but this depends on the treatment type and the initial cancer. This has recently been shown by a study investigating side effects of prostatectomy or radiotherapy versus untreated controls in prostate cancer patients. Over 12 years, the risk of developing complications could be as high as 6.6-fold for prostatectomy-treated patients (Unger et al. 2024) compared to untreated patients. Another recent study has shown that breast cancer survivors can have increased risk for heart failure compared to general population more than 10 years after diagnosis, but not for ischemic heart disease (Yang et al. 2022). Overall, the excess risk for comorbidities seems to decrease with time after diagnosis (Koric et al. 2022). Obviously, any of these events should be considered during underwriting.

Several articles show an overview of typical short- and long-term side effects (Gegechkori et al. 2017; Miller et al. 2022). As an example of these side effects and which kind of therapy potentially causes them, the following table 2 shows the effect regarding breast cancer.

Table 2

Potentially life insurance relevant long term and latent effects of breast cancer treatment

Side effect	Treatment type				
	Chemo	Hormonal	Trastuzumab	Radiation	Surgery
Cardiac					
Cardiomyopathy	X			X	
Thromboembolism		X			
Neurologic					
Cognitive dysfunction	X	X			X
Neuropathy	X				
Psychosocial (anxiety, depression)		X		X	X
Pulmonary (pneumonitis)				X	

Probably the most prominent example of long-term side effects is the cardiotoxicity of both chemo- and radiation therapy. However, even this prominent example actually shows that the latency to developing symptoms is covered within the first ten years after treatment.

Another study shows that in most cases, participants were diagnosed with cardiotoxicity within a year of having treatment, while most of the remaining were late-onset, being defined as 1 – 7 years after treatment (Clark et al. 2019).

3.2.4 Can we overcome data limitations of registries by application of the "underwriting effect"?

Cancer registries are a valuable tool to access and analyze mortality data. However, there are limitations to the data provided in these registries. Underwriting life insurance policies is based on the prerequisite that no recurrence of cancer has occurred since the end of treatment. This prerequisite is rarely reflected in cancer registries, unless the disease-free (or recurrence-free) survival is explicitly reported. The SEER registries do not provide recurrence-free survival. There is only a start-point (diagnosis) and an end-point (death). Interim data is therefore limited. Only a few cancer registries provide this information, and usually only in selected publications, such as the Tumorregister München.

Cancer registries also do not take any comorbidities explicitly into account. Hence there is no distinction of mortality between persons who are recurrence-

and complication-free and those who suffer from those sequelae. All the comorbidities that are developed after diagnosis, including those caused by therapy, could add to the extra mortality of the specific cancer (Henry et al. 2023; Sandini et al. 2019). Life insurance underwriting could control for these comorbidities and their risk. On the other hand, as this additional non-cancer mortality is within the all-cause mortality, there is potential to overestimate excess mortality for a group of recurrence- and complication-free survivors within an insurance population.

Cancer registries sometimes record cancer cases, not patients. This is often due to issues with collecting information and/or the quality of coding (Haejin et al. 2019; Haejin et al. 2014). Because a patient may have multiple primary cancers, the same person can appear more than once in a registry database. A person with primary cancers in the lung and breast (or both breasts) is then considered as 2 cases. This also leads to an overestimation of mortality, as having recurrences or second malignancies confers a worse prognosis but would just be registered as another cancer case in the registry (In et al. 2014; In et al. 2019). Some registries such as SEER do account for this issue by providing selection criteria based on the information of first malignant primary cancer or multiple primaries.

The incorporation of additional relevant medical information, which are usually not available in cancer registry data, into the mortality risk analysis of cancer survivors leads to an improved underwriting assessment, which we term the underwriting effect.

4. Discussion

The results of our study, in particular the observed heterogeneity of both CRS development, SPM occurrence and associated comorbidities, implies the following:

- Excess mortality must be determined by an evidence-based approach using high-quality cancer registry data and put into context by literature review and medical expert knowledge
- This approach must result in evidence-based, up-to-date medical underwriting rule books
- A one-size-fits-all (standard) rating for cancer survivors after an arbitrarily set time-point is not evidence-based, as survivors of major cancer types do not reach normal levels of relative survival even after a decade after diagnosis
- Based on contemporary survival data, our insurance medicine approach could categorize cancer constellations in three categories.

- Data base information should be enriched by information on treatment duration, recurrences of the original cancer and occurrence of secondary primary malignancies, as well as comorbidities, to improve prediction of overall survival among long-term cancer survivors

We can show that the development of conditional relative survival of cancer survivors over time is highly heterogeneous. No consistent pattern can be identified across major cancer types, stages and age groups, based on data from a large and comprehensive public cancer registry, and also shown by others (Dal Maso et al. 2019). A general, arbitrarily set date to determine normal relative survival, or cure, for all cancer types is therefore not evidence-based on publicly available data from large public cancer registries.

Calculation of CRS shows that for example localized breast cancer, as a highly relevant cancer for insurance medicine due to its relatively high incidence in working-age female population, shows a stronger increase of CRS in younger persons over time compared to elderly persons, who show in fact a decreasing CRS. Except for localized prostate cancer and melanoma, the other investigated cancer types and stages showed consistent difference in CRS levels across ages at a given timepoint after diagnosis. With some exceptions, younger cancer patients have higher CRS than older cancer patients at most timepoints. Notably, this higher CRS does not automatically translate into low standardized mortality ratio for young or middle-age cancer survivors.

Deriving medical risk loadings from available data for specific impairments is key to a fair risk assessment and adequate risk management during underwriting of life insurance.

For actuarial science and insurance medicine, relative survival, standardized mortality rates and excess death rates irrespective of the cause of death are relevant for the determination of medical risk loadings in life insurance.

If relative survival data from begin of diagnosis nor CRS data show similar survival compared to the general population, we have formulated 4 questions that should be answered during underwriting of these cancers with residual excess mortality:

1. What is the risk of a certain cancer recurring after long-term complete remission (e. g. 10 years)?
2. What is the risk of a second primary malignancy occurring after long-term complete remission?
3. What is the risk of developing complications after long-term complete remission?
4. Can we overcome data limitations of registries by application of the "underwriting effect"?

Our findings imply an extended insurability for cancer survivors of localized and regional cancer over time. If the CRS reaches a comparable survival additional risk premiums are not justified anymore from that timepoint on. Nevertheless, many cancer types do not show normal survival rates compared to the general population even many years after diagnosis. Whether these long-term survivors with residual excess mortality can be termed cured is therefore debatable. Definitions of cure vary in the literature, but the World Health Organization defines cure "as the attainment of normal life expectancy", including the three aspects of complete remission, minimal or no risk of recurrence or relapse, and restoration of health (WHO 2008). For patients and oncologists, freedom from cancer might be a more patient-centric outcome, but is not necessarily related to objective long-term survival data. But only data of overall survival in comparison to reference populations can enable objective assessment of medical loadings.

For cancer survivors with residual increased mortality risk according to registry data, further risk stratification taking into account comorbidities and general health status could potentially identify low-risk profiles. With such low-risk profiles, standard conditions for life insurance could be attained in selected cases. The role and expertise of insurance medicine is to integrate registry data and contemporary literature analysis to improve insurability.

5. Limitations

Even if conditional survival is used in registry data, the criterion used is number of years survived only, irrespective of which medical events happen between diagnosis/therapy and death. This does not reflect the actual and individual situation that is assessed in the case of long-term cancer survivors, as applicants for life insurance would only qualify as being long-term survivors (e. g., >10 years survival), if the period of survival was disease-free (without recurrence). Sequelea would be taken into account, if neither absent or irrelevant. Any recurrence of the disease would lead to a reset of the time the underwriting assessment would start at, and recurrences are associated with impaired prognosis as well. Furthermore, any complications appearing in this time frame would also be subject to underwriting and hence potential loadings for extra mortality. This added mortality risk is not reflected yet in registries, but would support fair and evidence-based extramortality ratings in the life insurance industry.

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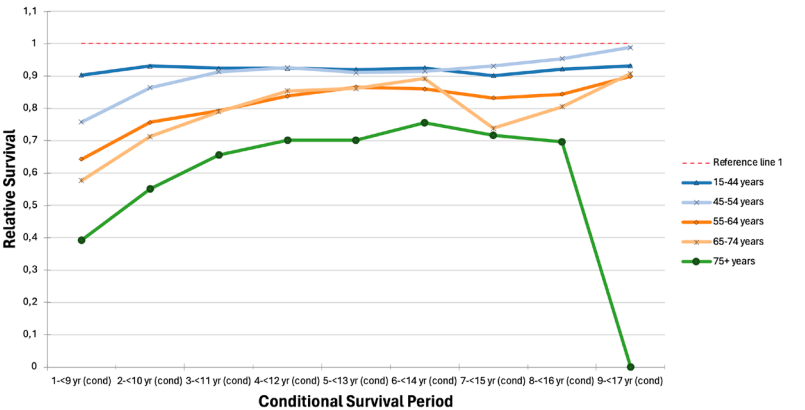
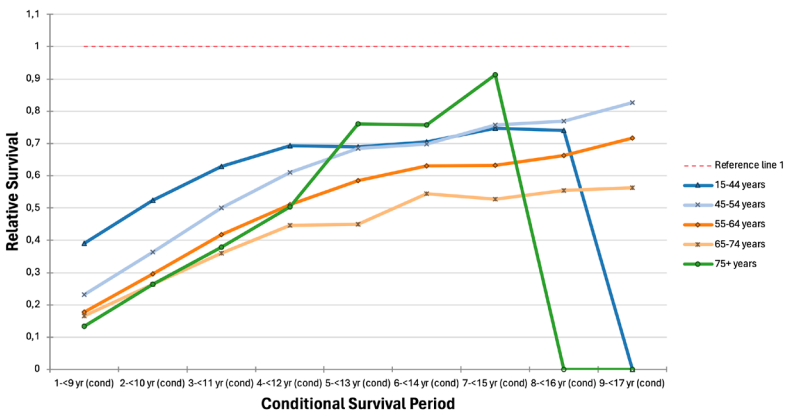
Supplement

Development of conditional relative survival (CRS) for pancreatic cancer, lung cancer, malignant melanoma, leukemia, multiple myeloma, and Non-Hodgkin-Lymphoma.



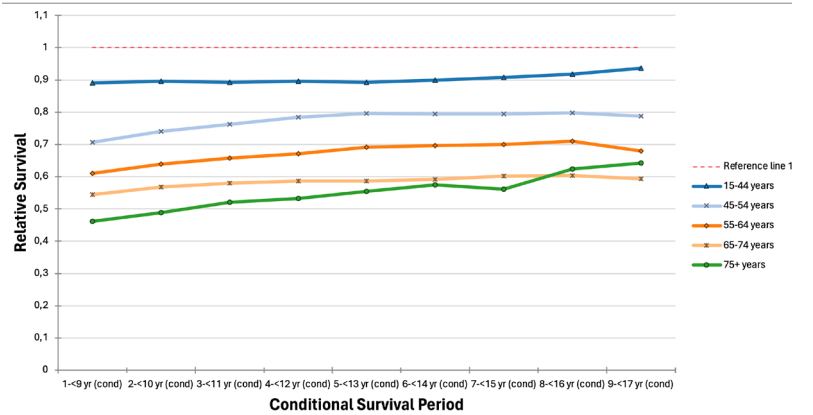
Supplementary Figure 1: Localized Pancreatic Cancer

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.



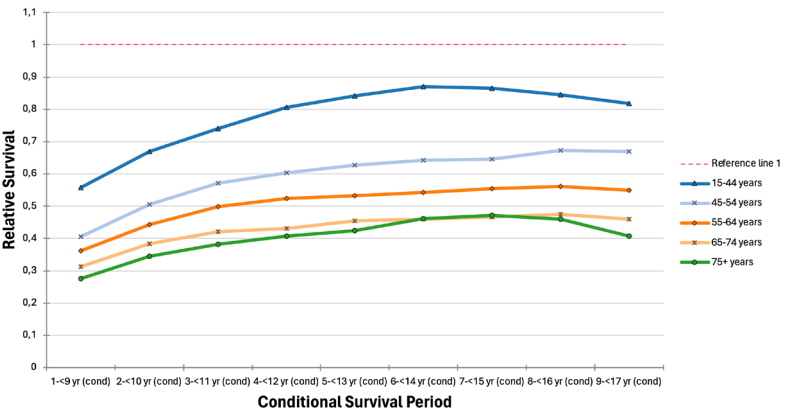
Supplementary Figure 2: Regional Pancreatic Cancer

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.



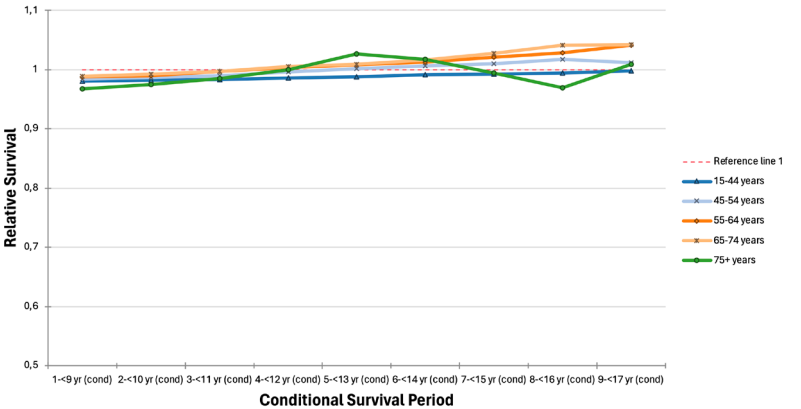
Supplementary Figure 3: Localized Lung Cancer

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.



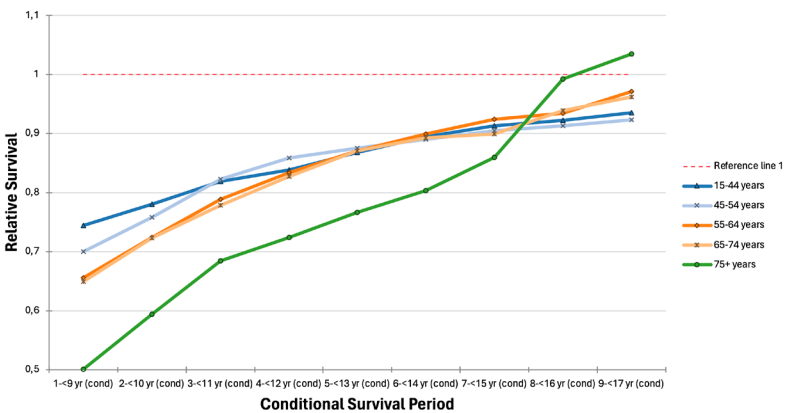
Supplementary Figure 4: Regional Lung Cancer

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.



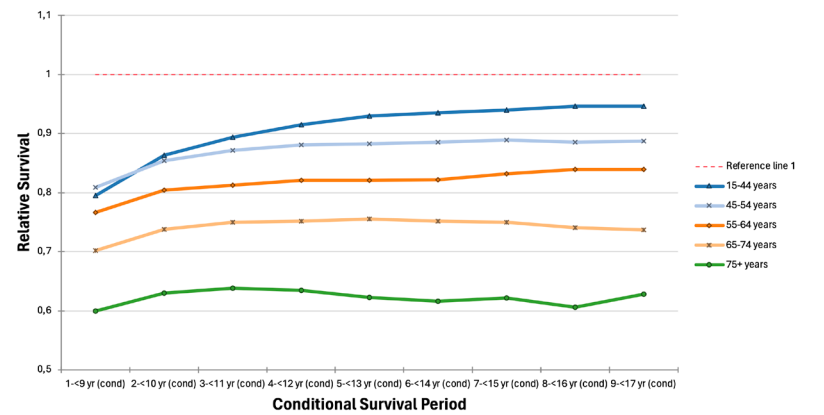
Supplementary Figure 5: Localized Malignant Melanoma

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.



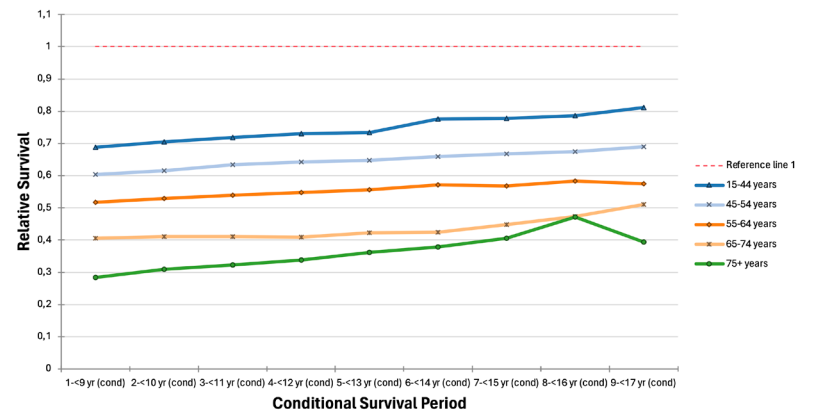
Supplementary Figure 6: Regional Malignant Melanoma

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.



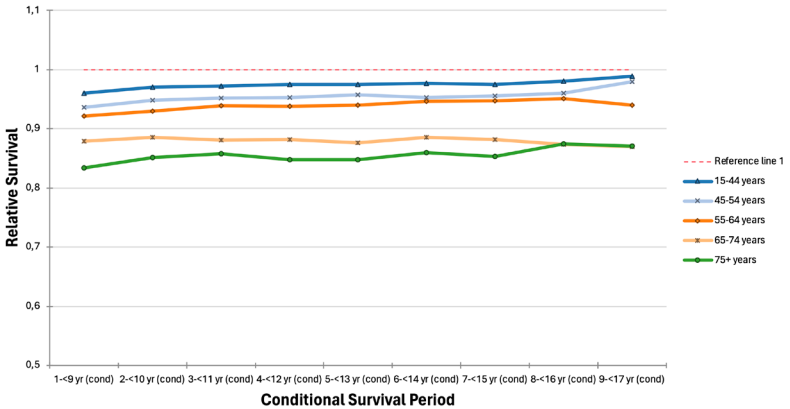
Supplementary Figure 7: Leukemia

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.



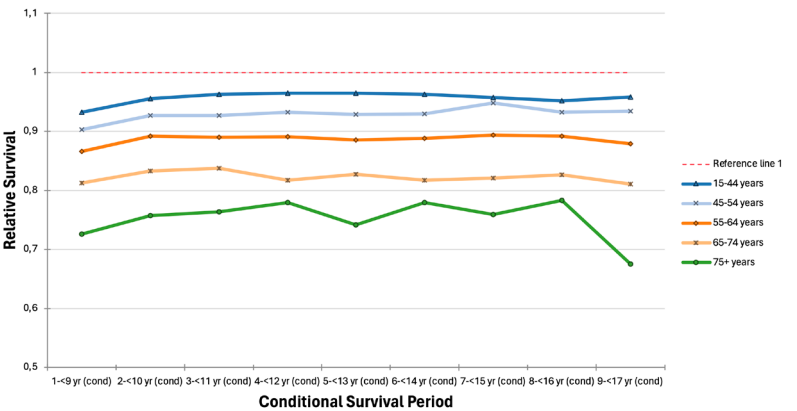
Supplementary Figure 8: Multiple Myeloma

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.



Supplementary Figure 9: Localized Non-Hodgkin-Lymphoma

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.



Supplementary Figure 10: Regional Non-Hodgkin-Lymphoma

Development of multi-year CRS with subsequent years after diagnosis. CRS is shown as the 8-year survival after having survived subsequent years as shown on the x-axis, from 1 to 9 years after diagnosis. Multi-year CRS are shown for different age groups. Dashed red horizontal line represents normal relative survival compared to reference population.