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CLINICAL RESEARCH
Prevention and epidemiology

A population-based study of cardiovascular disease mortality risk in US cancer patients

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Aims This observational study characterized cardiovascular disease (CVD) mortality risk for multiple cancer sites, with respect to the following: (i) continuous calendar year, (ii) age at diagnosis, and (iii) follow-up time after diagnosis.

Methods and results The Surveillance, Epidemiology, and End Results program was used to compare the US general population to 3 234 256 US cancer survivors (1973–2012). Standardized mortality ratios (SMRs) were calculated using coded cause of death from CVDs (heart disease, hypertension, cerebrovascular disease, atherosclerosis, and aortic aneurysm/dissection). Analyses were adjusted by age, race, and sex. Among 28 cancer types, 1 228 328 patients (38.0%) died from cancer and 365 689 patients (11.3%) died from CVDs. Among CVDs, 76.3% of deaths were due to heart disease. In eight cancer sites, CVD mortality risk surpassed index-cancer mortality risk in at least one calendar year. Cardiovascular disease mortality risk was highest in survivors diagnosed at <35 years of age. Further, CVD mortality risk is highest (SMR 3.93, 95% confidence interval 3.89–3.97) within the first year after cancer diagnosis, and CVD mortality risk remains elevated throughout follow-up compared to the general population.

Conclusion The majority of deaths from CVD occur in patients diagnosed with breast, prostate, or bladder cancer. We observed that from the point of cancer diagnosis forward into survivorship cancer patients (all sites) are at elevated risk of dying from CVDs compared to the general US population. In endometrial cancer, the first year after diagnosis poses a very high risk of dying from CVDs, supporting early involvement of cardiologists in such patients.

Keywords Neoplasm • SEER • Heart disease • Epidemiology • Cardio-oncology

Introduction

Heart disease and cancer are the leading causes of mortality, both in the USA and worldwide.[1] During 2015, in the USA, 633 842 deaths were due to heart disease, while 595 930 deaths were due to cancer.[2] Worldwide, in 2015, 17.7 million deaths were due to cardiovascular diseases (CVDs),[3] while 8.8 million were due to cancer.[4]

Cancer survivors have an increased risk for CVDs,[5–7] either from shared lifestyles or from toxicities of cancer treatment.[8,9] With recent progress in screening, diagnosis, and treatment of many cancers, the population of cancer survivors is steadily increasing.[10] It is expected that by 2040, the number of Americans with a history of cancer will increase to more than 26 million.[11] Therefore, cardiology care of cancer survivors becomes increasingly important. For most cancer survivors, the most effective strategy for primary prevention, and or management, of CVD is likely achieved through modification of traditional risk factors.[12,13]

Long-term cancer survivorship care is an advancing field of research and the delineation of responsibility between primary care physicians (PCPs) and specialists (oncologists, cardiologists, etc.) is evolving.[14] Primary care physicians are to a large extent tasked with primary prevention and cardiologists oversee management of CVDs.

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Due to the complexities of specific cancer treatment effects, there may be uncertainty across a multidisciplinary care team as to the role of managing CV health for cancer survivors. Underestimation of the elevated risk that cancer survivors face may result in (i) missed opportunities for early intervention or (ii) treatment approaches that may not be aggressive enough. To better characterize the landscape of CVD mortality in cancer survivors, we conducted a comprehensive overview analysis of the risk of dying from CVDs in cancer survivors. Our goals were to analyse mortality due to CVDs in cancer patients (28 cancer sites) as a function of (i) calendar year, (ii) age at diagnosis, and (iii) follow-up time after cancer diagnosis. This study fills an important gap in the literature for both PCPs and specialists as we highlight both historical trends and observations regarding basic clinical presentations (age at cancer diagnosis and follow-up time after cancer diagnosis) which together may influence patient-level decisions on cardiovascular care.

Methods

Patients with invasive cancer, diagnosed between 1973 and 2015, were analysed from the Surveillance, Epidemiology, and End Results (SEER) program. The SEER program is a network of population-based incident tumour registries, covering 28% of the US population, including incidence, survival, and treatment.[15,16] Cause of death was categorized by the International Classification of Diseases (ICD)-9 code. Cause of death from clinician or coroner coded CVDs (heart disease, hypertension, cerebrovascular disease, atherosclerosis, aortic aneurysm/dissection, and other diseases of arteries, arterioles, or capillaries) was used. The methods and limitations for mortality rate calculation are described in the Supplementary material online, *Text* and *Figure S1*. Comorbidities, performance status, surgical pathology, margin status, doses, or agents are not coded in the SEER registry. SEER*Stat 8.2.2 was used for analysis.[15] Patients whose cancer were diagnosed only through autopsy or death certificate were excluded. Institutional Review Board approval was not necessary for publicly available information.

The analysis consists of three objectives. In Objective 1, we characterized CVD mortality risk in each continuous calendar year by cancer type. Death, based on death certificate, was coded as being due to 'index-cancer' or 'death from CVD' (defined above). Using standard methods, a competing risk model was also conducted for cancers at higher than average risk for death from CVD. The Fine and Gray model was applied to estimate the cumulative incidence function, which was implemented using SAS 9.4 software.[17,18] For Objectives 2 and 3, we describe the risk of death due to CVD as a function of age at cancer diagnosis, and follow-up time after cancer diagnosis, respectively. Standardized mortality ratios (SMRs) were used to estimate CVD mortality risk in cancer survivors using SEER data between 1973 and 2012 as well as SEER data in the modern treatment era from 2000 to 2015. Standardized mortality ratios provide the relative risk of death from CVD for cancer survivors as compared to all US residents, adjusted by age, race, and sex over the same time.[19] The reference cohort was US mortality as reported in the National Vital Statistics System and maintained by the National Center for Health statistics. Ninety-five percent confidence intervals (CIs) of the SMRs were calculated using SEER*Stat 8.2.1 and Microsoft Excel 15.0.4 (Microsoft, Redmond, WA, USA).[19–21] At least 1000 person-years at risk were necessary for each CVD cause of death with respect to cancer type in order to be included in the analysis.

Results

Patient characteristics

We identified 3 234 256 cancer patients among 28 cancer sites that were registered in the SEER program between years 1973 and 2012. In this representative sample, 49.3% of cancer patients died from either their cancer or from CVD during this time period (*Table 1*). The plurality (76.3%) of all cardiovascular-related deaths in cancer patients was from heart disease. We observed that increasing age at diagnosis was associated with both increased percent of cancer patients dying from index-cancer and increased percent of cancer patients dying from CVD. We also observed a trend for more recent years of cancer diagnosis to be associated with both decreased percent of cancer patients dying from index-cancer and decreased percent of cancer patients dying from CVD. These observations indicate that (i) with increasing age there is increased risk of dying, either from cancer or CVD; and (ii) cancer patients with a recent diagnosis have neither died of their cancer nor CVD yet. Consistent with these observations, there was a decrease in death from index-cancer and an increase in CVD death as months since diagnosis increased. Urinary bladder cancer patients have the highest risk of dying from a CVD with 19.4% of bladder cancer patients having died from CVD. The following cancer sites also displayed a higher than average (11.3%) risk for death from CVD in cancer patients: larynx (17.3%), prostate (16.6%), corpus uteri (15.6%), colorectal (13.7%), and breast (11.7%). To further contextualize our observations of decreased death from index-cancer and increased CVD death as time since diagnosis increases, we conducted a competing risk analysis for the above six cancer sites which have an elevated risk for death from CVD (Supplementary material online, *Figure S2*). Prostate and breast cancer patients have the largest absolute number of patients who have died of CVDs between 1973 and 2012, and therefore make up the largest percent (49.2%) of all cancer patients among the 28 cancer sites who have died from cardiovascular causes (*Figure 1*).

Objective 1: Cardiovascular deaths per calendar year

We examined historical trends in cancer patients by assessing deaths due to index-cancers (black lines) and deaths due to CVDs (red lines) in all 28 cancer sites (*Figures 2*, *3*, and *4*). Survivors who are least likely to die from CVDs (<10%) are those with cancers of the lung, liver, brain, stomach, gallbladder, multiple myeloma, pancreas, oesophagus, and ovary (*Figure 2*). These cancers are all associated with high mortality from index-cancer, and the prognosis has been relatively stable in the past decades. As prognosis for cancers improve (specifically: soft tissue, nasopharynx, anus, oropharynx, colorectal, non-Hodgkin's lymphoma, kidney, and cervix), there appears to be a concomitant increase in deaths due to CVD, yet death from index-cancer still remains >10% higher than death from CVD (*Figure 3*).

Figure 4 presents cancer sites where death from index-cancer is either <10% higher than death from CVD, or death from CVD has surpassed death from index-cancer. Variation by calendar year between CVD or index-cancer as the leading cause of death occurs for several cancers. In 2012, death from index-cancer was the leading cause of death among most cancer patients (24 of 28 cancer sites). The four cancer sites with CVD as the leading cause of death for cancer patients in 2012 were prostate, thyroid, Hodgkin's lymphoma, and testis (*Figure 4*).

Table I Cancer patients and death from cardiovascular disease between 1973 and 2012

	No. of cancer patients	Index-cancer deaths		CVD deaths		Heart disease deaths	
		No.	% of cancer patients	No.	% of cancer patients	No.	% of all CVD deaths
All patients	3 234 256	1 228 328	38.0	365 689	11.3	279 060	76.3
Sex							
Male	1 662 864	651 517	39.2	200 610	12.1	157 349	78.4
Female	1 571 392	576 811	36.7	165 079	10.5	121 711	73.7
Age at diagnosis							
0–19 years	43 263	10 156	23.5	278	0.6	232	83.5
20–39 years	210 699	54 047	25.7	2845	1.4	2330	81.9
40–59 years	932 545	326 003	35.0	41 356	4.4	32 622	78.9
60–79 years	1 636 489	656 668	40.1	224 173	13.7	171 137	76.3
80+ years	411 260	181 454	44.1	97 037	23.6	72 739	75.0
Year of diagnosis							
1973–82	564 129	294 723	52.2	109 144	19.3	82 941	76.0
983–92	766 593	356 095	46.5	127 992	16.7	97 955	76.5
1993–2002	911 959	338 260	37.1	97 014	10.6	73 780	76.1
2003–2012	991 575	239 250	24.1	31 539	3.2	24 384	77.3
Race							
White	2 731 980	1 027 442	37.6	319 537	11.7	243 887	76.3
Black	297 188	127 077	42.8	30 924	10.4	24 233	78.4
Other	205 088	73 809	36.0	15 228	7.4	10 940	71.8
Marital status							
Single	399 184	141 885	35.5	28 848	7.2	22 463	77.9
Married	1 894 691	699 628	36.9	200 897	10.6	153 711	76.5
Separated	42 498	20 794	48.9	6740	15.9	5244	77.8
Divorced	237 000	98 579	41.6	18 723	7.9	14 557	77.7
Widowed	484 770	224 723	46.4	91 850	18.9	68 835	74.9
Stage at presentation							
Localized	1 059 957	169 107	16.0	148 767	14.0	111 465	74.9
Regional	632 242	282 521	44.7	65 304	10.3	49 420	75.7
Distant	528 923	389 794	73.7	25 220	4.8	20 052	79.5
Months since diagnosis							
2–11 months	3 234 256	519 279	16.1	45 592	1.4	35 925	78.8
12–59 months	2 533 198	498 282	19.7	105 581	4.2	81 355	77.1
60–179 months	1 493 858	176 561	11.8	148 842	10.0	112 673	75.7
180–239 months	490 191	20 554	4.2	34 398	7.0	25 802	75.0
240+ months	257 961	13 652	5.3	31 276	12.1	23 305	74.5
Top 10 cancer sites with the largest percent of CVD deaths							
Urinary bladder	143 846	34 079	23.7	27 907	19.4	21 618	77.5
Larynx	32 564	12 019	36.9	5648	17.3	4393	77.8
Prostate	509 128	89 722	17.6	84 534	16.6	65 355	77.3
Corpus uteri	113 614	19 809	17.4	17 692	15.6	12 947	73.2
Rectum	76 448	31 266	40.9	10 440	13.7	8057	77.2
Breast	516 225	119 981	23.2	60 409	11.7	44 475	73.6
Kidney and renal pelvis	77 882	27 165	34.9	8032	10.3	6198	77.2
Non-Hodgkin lymphoma	125 567	50 504	40.2	10 989	8.8	8634	78.6
Melanoma of the skin	121 290	17 904	14.8	9315	7.7	6968	74.8
Lung and bronchus	377 956	289 842	76.7	22 463	5.9	18 076	80.5

In the SEER program, between 1973 and 2012, 3 234 256 cancer patients representing 28 different cancer sites were identified. Morality rates from index-cancer, cardiovascular diseases, and particularly heart disease are presented as a function of demographic variables.

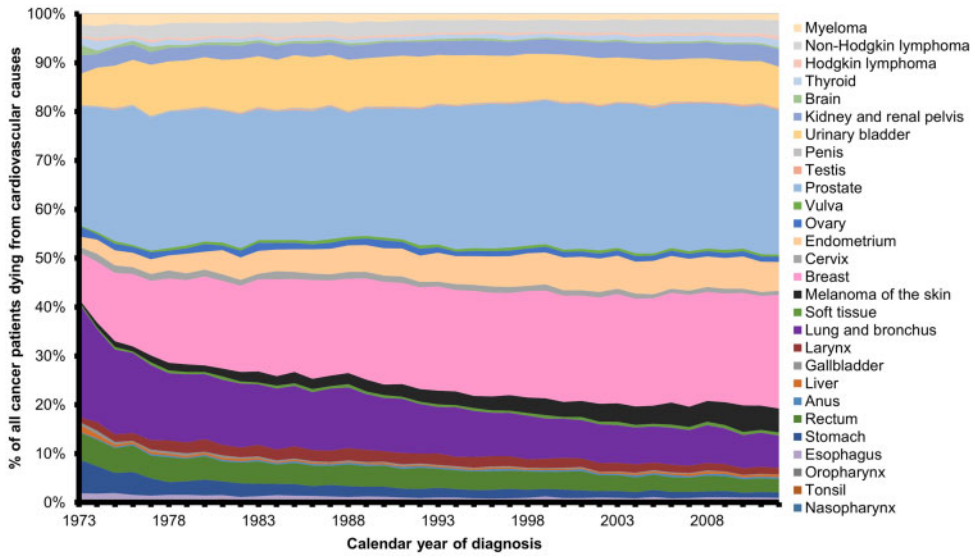


Figure 1 Yearly cardiovascular death in cancer patients by cancer site. All deaths from cardiovascular causes in cancer survivors between 1973 and 2012 are categorized by cancer site. Cancer site and its representative colour are listed to the right of the graph and in descending order of appearance on the graph.

Objective 2: Cardiovascular deaths by age at cancer diagnosis

Cancer patients diagnosed at age 85 or younger (all sites) have an increased risk of death from heart disease compared to men and women in the general US population (*Figure 5A, B*). The younger a cancer survivor is diagnosed (all sites), the higher their risk of death from heart disease. However, the prevalence of death from heart disease in cancer survivors is very low with 340 cases of death in patients 15–35 years of age between 1973 and 2012. For survivors with cancers (all sites) diagnosed before 55 years old, the risk of CV mortality is more than 10-fold greater than the general population (*Figure 5A*). Risk of death from CV causes in cancer survivors (all sites) gradually decreases as age at cancer diagnosis increases (55–64 years of age: SMR 7.5; 65–74 years of age: SMR 3.8; 75–84 years of age: SMR 2.4), and this trend is maintained in the modern treatment area (*Figure 5B*). This is due to the risk of CVD death increasing in the general population as age increases. Standardized mortality ratios and CIs for risk of CVD death by age at cancer diagnosis are presented in Supplementary material online, *Table S1*.

Objective 3: Cardiovascular deaths during follow-up

The first year following a cancer diagnosis (all sites) represents the period with the highest risk of CV mortality (*Figure 5C, D*). Additionally, cancer survivors (all sites) displayed SMRs that remained higher than the general population from diagnosis forward (*Figure 5C, D*). Standardized mortality ratios and CIs for risk of CVD death by follow-up time after cancer diagnosis are presented in Supplementary material online, *Table S2*.

Furthermore, we assessed cancer sites in which patients had both (i) ≤30% risk of death from the index-cancer and ≥20% risk of mortality from CVD (same cancer sites as *Figure 4*) and (ii) at least 1000 person-years of data at each time point in the modern treatment era (2000–15). In *Take home figure*, we observed that relative to the average SMR for all 28 cancer sites, endometrial cancer has the greatest risk of mortality from heart disease at all time points following diagnosis. We also observed that compared to the first year following a cancer diagnosis, breast, melanoma, and prostate cancer patients have a continually elevated risk of mortality from heart disease.

Discussion

Previous studies reported CVDs in malignancies of breast,[22,23] head and neck,[24] prostate,[24] testicular,[25] renal cell carcinoma,[26] endometrium,[27] and Hodgkin lymphoma.[28] A previous report by Abdel-Rahman assessed heart disease-specific mortality for 10 cancer sites in cancer survivors whom have lived 5+ years following diagnosis.[29] However, the current study is the largest and most comprehensive characterization of cardiovascular mortality among 28 individual cancer sites using a national cancer registry with 40 years of data. These data underscore the importance of multidisciplinary care for cancer patients. Cardio-oncology is a developing standard of care for cancer patients at the point of diagnosis, but it is also important to highlight the role of PCPs and cardiologists throughout survivorship as we have observed that cancer patients remain at elevated risk for CV mortality compared to the general US population.

In 2012, we observed that 61% of all cancer patients whom died from CVDs were diagnosed with either breast, prostate, or bladder cancer. For patients with cancers of the penis, vulva, bladder,

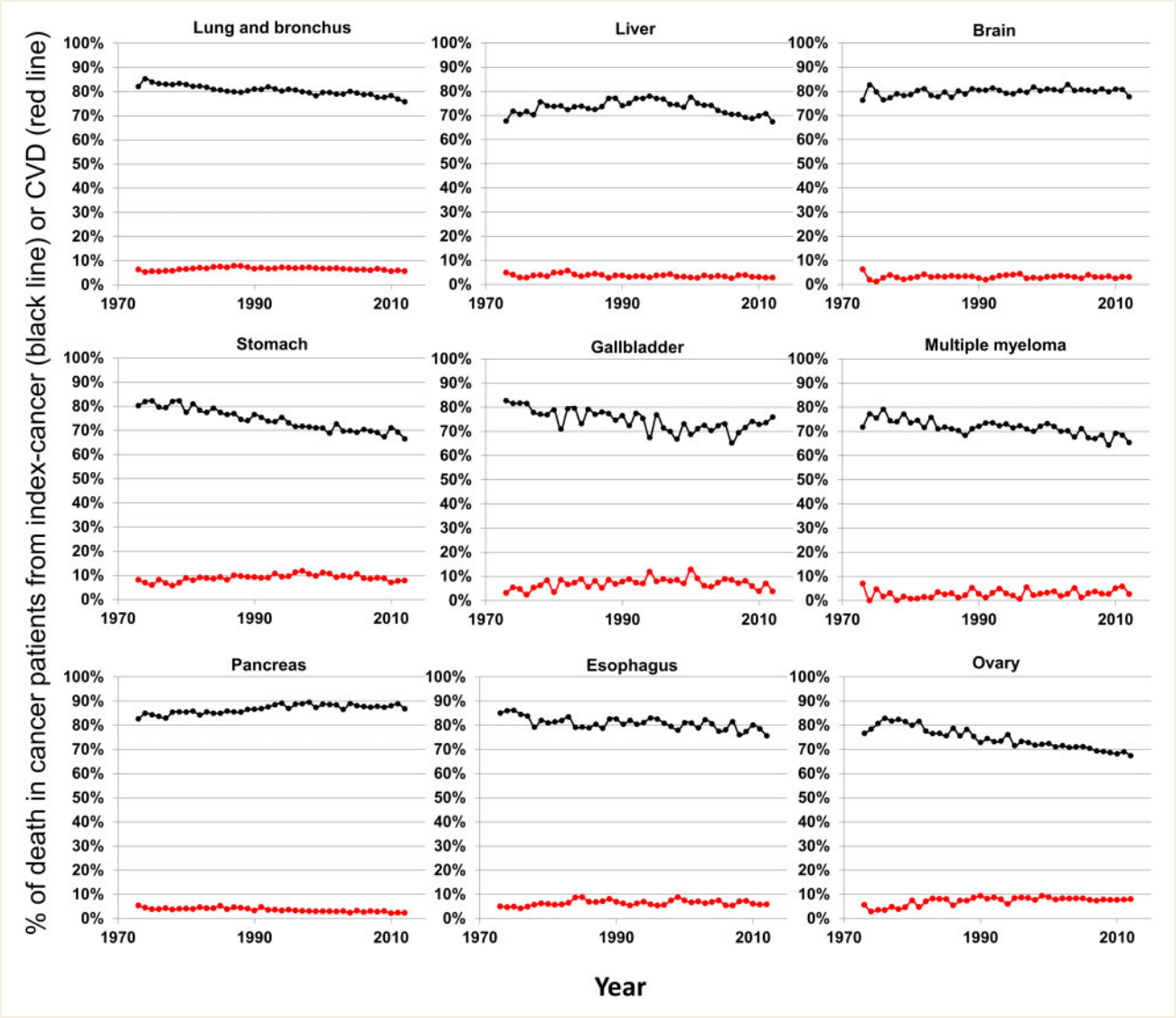


Figure 2 Plots of patient death vs. attained calendar year (from 1973 to 2012), for cancer sites with <20% decline in death due to index-cancer. Death was characterized as due to 'index-cancer', (black lines; i.e. the cancer originally diagnosed in the patient) and 'cardiovascular disease' (red lines). Attained calendar year refers to the year in which the death occurred.

endometrium, prostate, testes, thyroid, or Hodgkin's lymphoma, CV mortality has surpassed death from index-cancer during at least 1 year between 1973 and 2012. This study also describes the SMR of CVDs as a function of age at diagnosis and follow-up after diagnosis. We observed that cancer patients are perpetually at elevated risk of dying from CVDs compared to the general US population and the risk is negatively associated with age at diagnosis. Additionally, the first year following a cancer diagnosis represents the period with the highest SMR of CVDs.

We observed that in cancers with ≥20% risk of CVD mortality, these cancer were also all characterized by <30% risk of dying from index-cancer. Thus, this relationship seems to be the result of better prognosis in those cancers. For cancers with a more favourable prognosis, but still elevated risk of CV deaths, patients may benefit from clinical intervention by cardiologists at the point of diagnosis. Indeed, more research is needed to investigate the optimal approach in managing these patients and the collaboration between cardiologists and oncologists. Further, this study also highlights the need for ongoing and proactive surveillance by PCPs during cancer survivorship.

Evaluation of SMRs in this study provides important preliminary population-level data to support development of clinical screening tools which may aid clinicians in identifying cancer patients at risk for elevated CVD mortality. Consistent with previous reports, younger age of diagnosis is associated with higher SMR, both historically and in the modern treatment era.[6] Similarly, the first year of cancer diagnosis represents the greatest risk for CVD mortality. This finding may be explained by the aggressive treatment shortly after disease discovery and long-time at risk until death of the general population.[30,31] It could also be from the fact that patients who die early are those with the most severe co-existing CVDs, particularly in those with adult

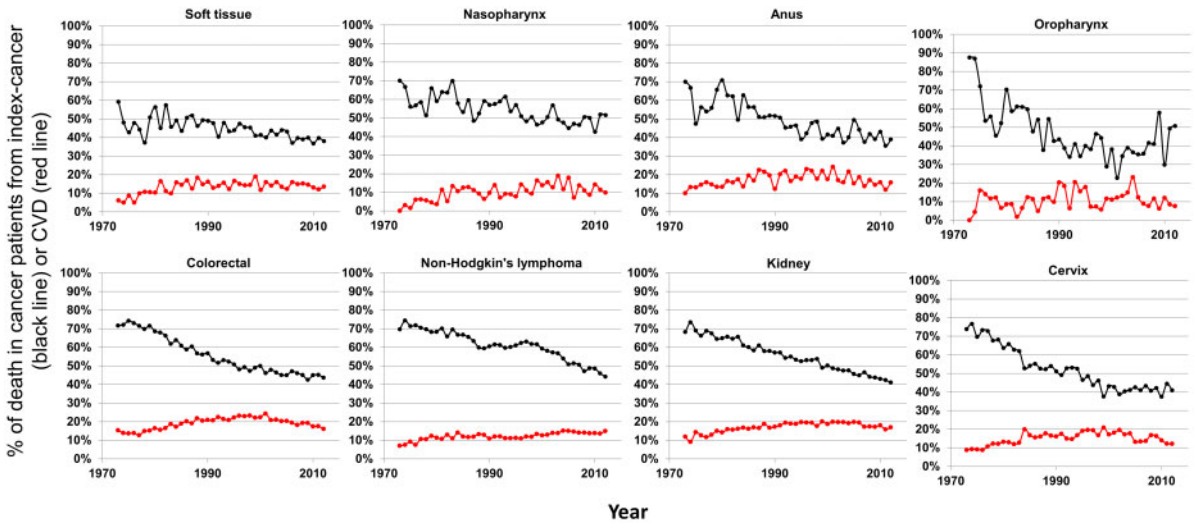


Figure 3 Plots of patient death vs. attained calendar year (from 1973 to 2012), for cancer sites with decreasing deaths due to index-cancer, yet, death from index-cancer still remains >10% higher than death from cardiovascular disease. Death was characterized as due to 'index-cancer', (black lines; i.e. the cancer originally diagnosed in the patient) and 'cardiovascular disease' (red lines). Attained calendar year refers to the year in which the death occurred.

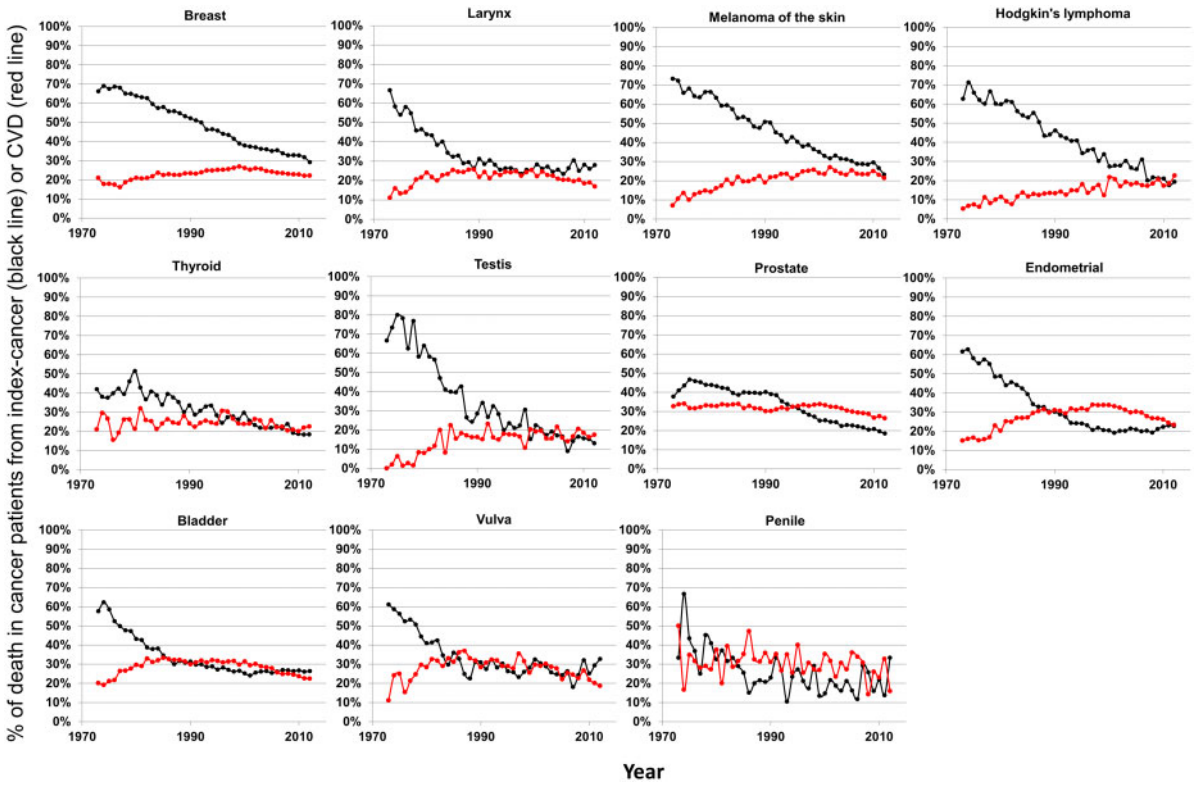


Figure 4 Plots of patient death vs. attained calendar year (from 1973 to 2012), for cancer sites where death from index-cancer is either <10% higher than death from cardiovascular disease, or death from cardiovascular disease has surpassed death from index-cancer. Death was characterized as due to 'index-cancer', (black lines; i.e. the cancer originally diagnosed in the patient) and 'cardiovascular disease' (red lines). Attained calendar year refers to the year in which the death occurred.

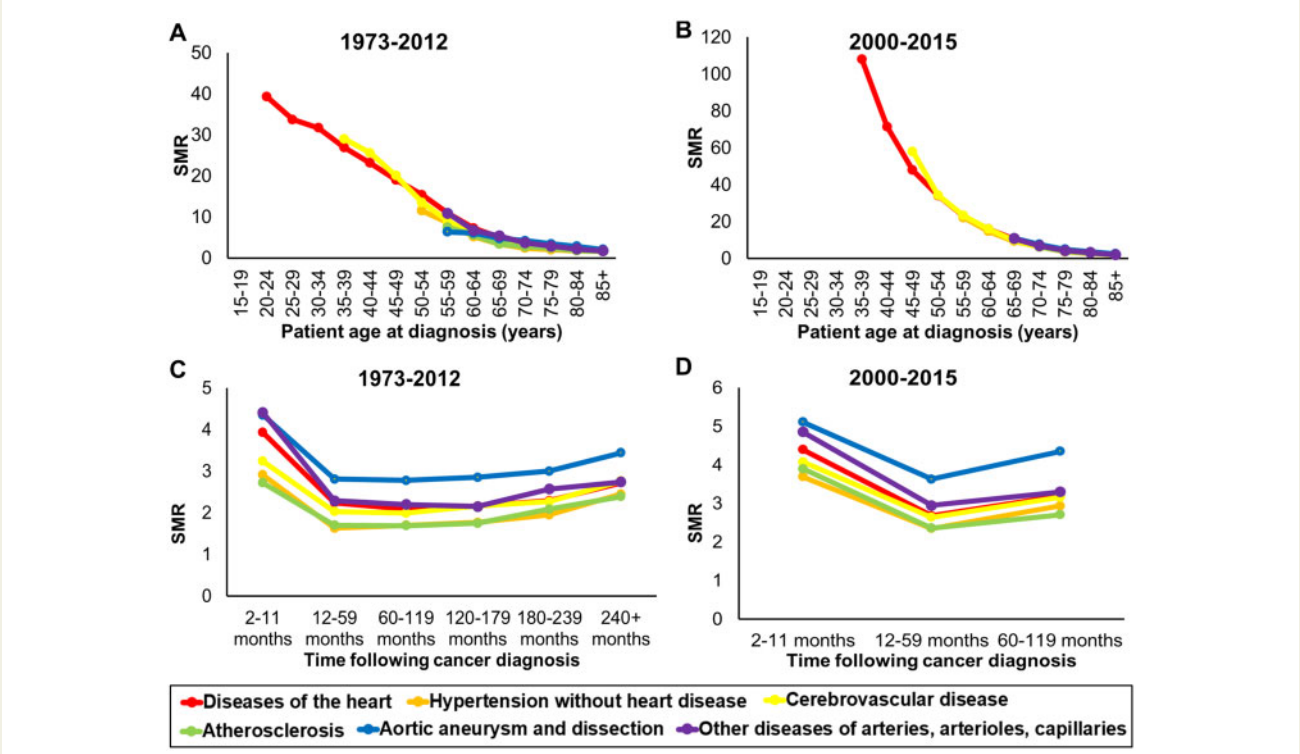
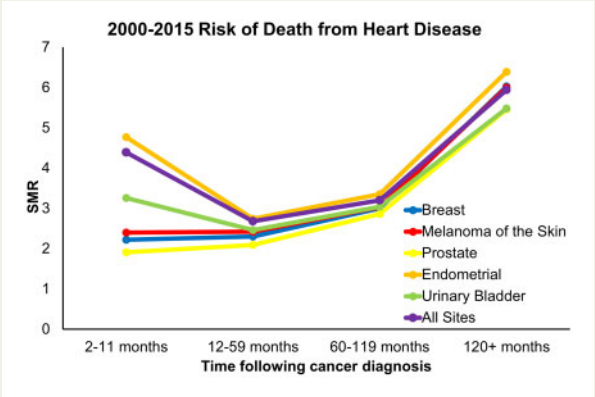


Figure 5 Cardiovascular disease mortality ratio by age at diagnosis and follow-up time in cancer patients. Standardized mortality ratios for the six types of cardiovascular diseases were characterized after diagnosis (all cancer sites), binned by patient age at diagnosis (*A* and *B*) and binned by period of follow-up time (*C* and *D*). Risk for cardiovascular disease mortality was assessed both historically (*A* and *C*) and specifically restricted to the modern treatment era (*B* and *D*). A standardized mortality ratio above 1 represents a higher relative risk of death for a type of cardiovascular cause, when compared to the general population (>1000 person years of risk for graphical inclusion).



Take home figure Standardized morality ratios for cancer sites with both ≤30% risk of death from the index-cancer and ≥20% risk of mortality from heart disease were calculated and binned by follow-up time. Cancers sites with at least 1000 person years of risk for death from heart disease between 2000 and 2015 were displayed.

cancers.[32] Patients with co-existing CVDs at cancer diagnosis are also at high risk of cardiotoxicity from cancer treatment.[33,34] Unfortunately, pre-existing diseases prior to cancer diagnosis are not entered into the SEER program. Nonetheless, this finding supports early involvement of cardiologists. Of particular importance would be future studies addressing early cardiology evaluation and how aggressive cardiology care should be in cancer patients. Such studies of interventional cardio-oncology following cancer diagnosis might focus on cancers of the larynx and endometrium as these patients have a good cancer prognosis but relatively high risk of CVD mortality, particularly in the first year following diagnosis.

This study has several limitations. First, death due to CVDs may be miscoded and bias may arise towards an overestimate of heart disease in death certificate data.[35] The long-range of accruing patients in the SEER database may contribute to the higher risk of death because of the smaller denominator. Patients diagnosed in recent years have short follow-up and therefore lower chance of dying from any cause (as observed in *Table 1*). We sought to mitigate this limitation by specifically examining a more modern treatment timeframe of 2000–15. All patients in the SEER registry were included to reduce the selection bias. For studies based on large population-based cancer registries, care is needed in interpretation as patients who are at increased risk of CVDs at cancer diagnosis, will tend not to be given potentially cardiotoxic chemotherapy if it can possibly be avoided. It is unknown what type of cancer treatment patients in the SEER database received though, and there is significant heterogeneity in cancer care and resulting impacts on cardiovascular biology. Moreover, our study did not

reveal the influence of immune checkpoint inhibitors on the trend of CVD mortality as recent studies showed these medications have potential cardiac toxicity.[36] Further, our analysis does not provide insight on the role of socioeconomic status (SES) in risk of CVD mortality following cancer diagnosis. Populations with low SES are more likely to have cancer and SES disparity may continue to contribute to CVD mortality risk in cancer survivors.[37,38] In line with these limitations, it is acknowledged that the SEER database does not provide information on comorbidities or modifiable risk factors. However, the broad presentation of mortality patterns holds considerable importance for physician approach to CV health in cancer patients.

The foundational evidence provided by this investigation is a seminal characterization of 28 cancer sites for CVD mortality risk and provides insight on the scope of CVD mortality risk in cancer patients that has not yet been fully reported. Future directions include assessing patient risk stratification (sex, race, ethnicity, disease stage, and geographical location). Such an analysis is possible without risking unstable estimates and will improve identification of patients at highest risk for CVD mortality.

Conclusion

The majority of deaths (absolute numbers) from CVD occur in patients diagnosed with breast, prostate, or bladder cancer. For patients with cancers of the penis, vulva, bladder, endometrium, prostate, testes, thyroid, or Hodgkin's lymphoma, there is year-to-year variation in leading cause of death (CV mortality or index-cancer mortality). We observed that from the point of cancer diagnosis forward into survivorship cancer patients (all sites) are at elevated risk of dying from CVDs compared to the general US population. In endometrial cancer patients, the first year of diagnosis poses a very high risk of dying from CVDs, which remains elevated compared to other cancer sites, supporting early involvement of cardiologists in such patients. Our observations highlight the need for earlier and more aggressive cardiovascular care in cancer patients which may require enhanced coordinated care between oncologists, cardiologists, and PCPs.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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