Higher risk of cardiovascular death than cancer death among long-term cancer survivors

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Abstract

Background

Most previous studies have focused more on the short-term risk of cardiovascular death related to traumatic psychological stress after cancer diagnosis, but less on the long-term risk of cardiovascular death. Recent studies suggested that the risk of cardiovascular death would probably outweigh the risk of index cancer death among long-time cancer survivors. However, it has not received enough attention.

Methods

Temporal trends in the proportions of cardiovascular death (P_{CV}), cancer death (P_{CA}), and other causes in all-cause deaths were used to show preliminary relationships between three causes of death in 4,806,064 cancer patients from the SEER Program. Competing mortality risk curves were used to investigate when cumulative cardiovascular mortality rate (CMR_{CV}) began to outweigh cumulative cancer mortality rate (CMR_{CA}) for cancer patients survived more than 10 years. Competing risk models were used to investigate independent factors associated with cardiovascular death in long-time cancer survivors.

Results

For all cancer patients, the P_{CV} increased from 22.8% in the 5th year after cancer diagnosis, to 31.0% in 10th year, and 35.7% in the 20th year, while the P_{CA} decreased from 57.7%, to 41.2% and 29.9%, respectively. The P_{CV} outweighed the P_{CA} (34.6% vs. 34.1%) since the 15th year for all cancer patients, as early as the ninth year for colorectal cancer patients (37.5% vs. 33.2%), and as late as the 22nd year for breast cancer patients (33.5% vs. 30.6%). The CMR_{CV} outweighed CMR_{CA} since the 15th year for cancer patients survived more than 10 years, the 5th year for those survived more than 15 years, and the 1st for those survived more than 20 years. Among cancer patients survived more than 20 years, elder age at diagnosis, male, local metastasis, and radiotherapy were associated with increased risk of cardiovascular death, while surgery and chemotherapy were associated with decreased risk of cardiovascular death. Sensitivity analysis by cancer sites showed similar results.

Conclusions

Cardiovascular death will gradually outweigh cancer death as survival time increases for most cancer patients. Cardio-oncologist should be involved as early as possible in the anti-cancer treatments to reduce cardiovascular death in long-term cancer survivors.

Introduction

Cancer ranks as the leading cause of death and the single most important barrier to increasing life expectancy in every country of the world in the 21st century.¹ According to estimates from the World Health Organization (WHO) in 2015, cancer is the first or second leading cause of death before age 70 years in 91 of 172 countries, and it ranks third or fourth in an additional 22 countries.¹ Moreover, based on the Global Burden of Disease study 2016, cancer cases increased by 28% from 2006 to 2016.² This increase seems to continue currently. As reported in the latest GLOBOCAN estimates of cancer incidence and mortality produced by the International Agency for Research on Cancer, there will be 19.3 million new cases and almost 10 million cancer death worldwide in 2020.³

A cancer diagnosis often associated with immediately and traumatically psychological stress, thereby increasing the risk of short-term cardiovascular death.^{4–6} As reported by Fang, risk of cardiovascular death after cancer diagnosis is 6–10 times higher than that in cancer-free persons.⁵ However, with the follow-up of treatment and the deepening of cancer awareness, the risk of cardiovascular death due to psychological stress began to decline rapidly one year after cancer diagnosis.^{5,7,8} Therefore, most of previous studies pay more attention to the immediate risks of cardiovascular death, but less attention to the long-time risk of cardiovascular death. Due to the long-term cumulative cardiotoxicity of anticancer treatments, the potential long-time risk of cardiovascular death after anticancer treatments among cancer patients has always been a great concern for both oncologists and cardiologists.^{9–12} Recent studies suggested that cardiovascular death would probably outweigh that of cancer death, particularly for young patients and colorectal cancer patients survived more than 10 years.^{13,14} However, it has not received enough attention. Moreover, it's still unclear whether long-term cardiovascular mortality risk will outweigh cancer mortality risk in other cancer patients, and when does cardiovascular mortality risk begin to outweigh cancer mortality risk. Therefore, this study aims to investigate long-time risk of cardiovascular death among cancer patients and investigate whether and when cardiovascular death outweighs cancer death for cancers in different sites.

Methods

Study cohort

The Surveillance, Epidemiology, and End Results (SEER) program of the National Cancer Institute is a network of population-based incident tumor registries from geographically distinct regions in the United States.^{15,16} The SEER program collects uniformly reported data on patient demographics, month and year of diagnosis, tumor characteristics, treatment utilization and mortality for all incident cancers from selected population-based cancer registries in the United States.

We used the SEER 9 data released in April 2018, which covered 10% of the entire US population.^{15,17} SEER 9 included all cancer patients diagnosed from January 1, 1973, through December 31, 2015 in the nine original registries (San Francisco-Oakland, Connecticut, Detroit, Hawaii, Iowa, New Mexico, Seattle, Utah, and Atlanta).¹⁸ In the latest SEER data, all cancer had been classified into nine sites: RESPIR, respiratory, BREAST, breast, COLRECT, colon and rectum, URINARY, urinary, LYMYLEUK, lymphoma of all sites and leukemia, FEMGEN, female genital, MALEGEN, male genital, DIGOTHR, other digestive except colon and rectum, OTHER, all other sites except above sites.

The radiation treatment variables were removed from the public research database since November 2016, and chemotherapy had never been released in the research data. Therefore, radiation and chemotherapy data were available through a custom data.¹⁹ Finally, a total of 5,094,238 patients with cancer diagnosed as their first primary malignancy were initially identified. After excluding 48,820 (1.0%) cancer patients without clear cause of death, 67,735 (1.3%) cancer loss to follow-up, and 171,619 (3.3%) cancer patients diagnosed in 2015 due to less than one-year follow-up after diagnosis, a total of 4,806,064 patients were included in the final analyses.

Ascertainment of mortality and survival time

SEER data were linked with data from the National Center for Health Statistics to determine death and cause of death. Survival time, as recorded in months, started at the date of cancer diagnosis and ended at date of death, date last known to be alive, or end of follow-up (December 31, 2015), whichever came first.

Definition of cardiovascular death

According to previous study,¹³ based on the SEER Causes of Death Register and International Classification of Diseases (10th Revision, ICD10), cardiovascular death included death of heart diseases (ICD10: I00-I09, I11, I13, I20-I51), hypertension without heart disease (ICD10: I10, I12), cerebrovascular diseases (ICD10: I60-I69), atherosclerosis (ICD10: I70), and diabetes mellitus (ICD10: E10-E14).

Statistical analysis

Temporal trends in the proportions of cardiovascular death (P_{CV}), cancer death (P_{CA}), and other causes in all-cause deaths were used to show preliminary relationships between above three causes of death in cancer patients. In order to investigate when cumulative cardiovascular mortality rate (CMR_{CV}) began to outweigh cumulative cancer mortality rate (CMR_{CA}) for cancer patients survived more than 10 years, cumulative incidence functions based on Fine-Gray hypothesis were first used to calculate the CMR_{CV} and CMR_{CA} , respectively. Fine-Gray tests were then used to select potential factors associated with cardiovascular death in long-time cancer survivors. Multivariate competing risk models based on Fine-Gray tests were further used to investigate the independent factors associated with cardiovascular death.²⁰⁻²² Hazard ratio (HR) and 95% confidence intervals were calculated based on multivariate competing risk models to measure the associations between risk factors and cardiovascular death. Since the potential higher risk of arterial thromboembolic events caused by tumor thrombus among LYMYLEUK patients,²³ LYMYLEUK patients were used as the reference group in the multivariate competing risk models.

In order to reduce the “dilution” effect of short-time follow up on the long-time risk of cardiovascular death, we selected cancer patients who survived for more than 15 years and 20 years for subgroup analysis. Moreover, in order to determine whether some cancer patients will never have a higher risk of cardiovascular death than cancer death during their lifetime, we further selected cancer patients who survived for more than 25 years for sensitivity analysis.

All analyses were performed with R software (version 4.0.3). All the statistics were tested on two-sided, and P values less than 0.05 were considered as statistically significant.

Results

Overall mortality rates of cardiovascular death among cancer patients

After an average of 6.90 years follow-up, 563,848 cancer patients died of CARDIOVASCULAR DISEASE (16.99/1000 person-years), which accounted for 17.9% of all-cause deaths (3,149,601) and 51.4% non-cancer death (1,095,209). Fine-Gray tests showed that significant higher overall mortality rate of CARDIOVASCULAR DISEASE were found among cancer patients with elder age at diagnosis, male, widow, African American, RESPIR patients, no surgery, no radiation therapy, no chemotherapy, and distant metastasis (all p values <0.001, **table 1**).

Temporal trends in the proportions of cardiovascular death (P_{CV}) and cancer death (P_{CA})

As shown in **figure 1**, for all cancer patients, the P_{CV} increased from 22.8% in the 5th year after cancer diagnosis, to 31.0% in 10th year, and 35.7% in the 20th year, while the P_{CA} decreased from 57.7%, to 41.2% and 29.9%, respectively. The P_{CV} outweighed the P_{CA} (34.6% vs. 34.1%) since the 15th year for all cancer patients, as early as the ninth year for colorectal cancer patients (37.5% vs. 33.2%), and as late as the 22nd year for breast cancer patients (33.5% vs. 30.6%). For respiratory and hematological cancers patients, it was not observed that the P_{CV} obviously outweighed the P_{CA} , even at follow-up ≥ 30 year. So was for digestive cancers patients other than colorectal cancer and cancers at all other sites.

Cumulative risk of cardiovascular death (CMR_{CV}) and cancer death (CMR_{CA})

For all cancer patients, the CMR_{CV} outweighed CMR_{CA} since the 15th year for cancer patients survived more than 10 years (**supplementary figure S1**), 5th year for cancer patients survived more than 15 years (**supplementary figure S1**), and the 1st for cancer patients survived more than 20 years (**figure 2**). For cancers

in different sites, it was observed that CMR_{CV} finally outweighed CMR_{CA} in most cancer patients survived more than 10 years, except respiratory cancers, hematological cancers, digestive cancers other than colorectal cancer, and cancers at all other sites (**supplementary figure S1**). For cancer patients survived more than 20 years, it was only observed that CMR_{CV} finally did not outweigh CMR_{CA} in respiratory cancers and hematological cancers patients (**figure 2**). Sensitivity analyses showed that the CMR_{CV} began to outweigh CMR_{CA} in the 10th year for respiratory cancer patients survived more than 25 years, and 7th year for respiratory cancer patients survived more than 30 years (**supplementary figure S2, supplementary figure S3**).

Factors associated with cardiovascular death for long-time cancer survivors

As shown in **table 2**, multivariate competing risk models showed that increased risk of cardiovascular death was independently associated with elder age at diagnosis, male, no surgery, no chemotherapy, and local metastasis among cancer patients survived more than 10 years. Further analyses for cancer patients survived more than 20 years showed similar results, while showing that radiotherapy significantly increased the risk of cardiovascular death in long-term cancer survivors. Among all risk factors associated with cardiovascular death, elder age at diagnosis was the most important factor. Compared with cancer patients who survived more than 20 year and diagnosed ≤ 30 years, the HRs for the risk of cardiovascular death increased from 2.07 (95%CI: 1.91-2.25) for patients diagnosed at 31-39 years, to 27.08 (95%CI: 21.26-34.49) for patients diagnosed at 71-77 years, and 40.66 (95%CI: 26.13-63.25) for patients diagnosed at ≥ 80 years. Sensitivity analysis by cancer sites showed similar results (**figure3, supplementary table S1**).

Discussion

In this cohort of more than 4.8 million cancer patients, the risk of cardiovascular death begins to climb after cancer diagnosis and will eventually outweigh the risk of cancer death for most cancer patients. This is the first study to investigate when cardiovascular mortality risk begin to outweigh cancer mortality risk. This is also the first systematic report on whether cardiovascular deaths outnumber cancer deaths in all cancer patients. We also observed that elder age at diagnosis was the most important factor associated with increasing risk of cardiovascular death in cancer patients. Therefore, cardio-oncologist should be involved as early as possible in the anti-cancer treatments to reduce cardiovascular death in long-term cancer survivors for cancer patients, especially elderly cancer patients.^{24–29}

Previous studies have suggested that cardiovascular death in cancer patients can be majorly attributed to cardiovascular toxicity of various anti-cancer treatments, including chemotherapy, radiotherapy, endocrine therapy,^{10,30–32} and targeted therapy (such as trastuzumab).^{33,34} Cancer patients are also potentially at high cardiovascular risk when undergoing surgery. This would due to the traumatic stress on the cardiovascular system caused by surgery and chronic inflammation after surgery.^{35,36} The increased risk of stress-induced cardiovascular death caused by surgery was usually an immediate risk but not a long-term risk.³⁶ The difference between this study and previous studies is that chemotherapy and surgery did not significantly increase the risk of cardiovascular death, but reduced the risk. Even though long-term cancer survivors were selected to minimize the dilution effect of short-term follow-up, the protective effect of cardiovascular death for chemotherapy was still observed, even further adjusting the main confounding factors, such as age at diagnosis, cancer stage, and competing risk of death. The potential explanation for the protective effect of chemotherapy in cardiovascular death is that chemotherapy generally reduces local and distant metastasis of cancer cells, thereby reduced cancer cell invasion of blood vessels, and ultimately reduced cardiovascular time risk indirectly. These results suggested that the combined effect of chemotherapy on cardiovascular death for cancer patients should be re-evaluated in addition to the well-established cardiovascular toxicity. This re-evaluation is also needed for the combined effect of surgery on cardiovascular death for cancer patients. Differ from protective effect of chemotherapy and surgery, the combined effect of radiotherapy changed from no effect to a significant increased risk of cardiovascular death (Table 2). The results suggest that cardio-oncologists should pay more attention to the cardiovascular toxicity of radiotherapy than chemotherapy.

Compared with the associations between other factors and the risk of cardiovascular death, this study suggests that the most important risk factor of cardiovascular death was elder age at diagnosis. The risk of cardiovascular death was even 40 times higher in cancer patients diagnosed at ≥ 80 years compared to those diagnosed ≤ 30 years. This is indeed an unexpected result. Although we cannot rule out the influence of underlying cardiovascular disease, we rarely see such huge differences in cardiovascular mortality risk among different age groups in other populations.^{35,37,38} This probably due to the presence of multiple shared cardiovascular risk factors and chronic inflammation from cancer.³⁵ However, this huge difference has not received enough attention at present. This results also suggested that controlling multiple shared cardiovascular risk factors and chronic inflammation from cancer may be more important than reducing the abovementioned cardio-toxic effects of different anti-cancer therapy.

Another important finding of this study is that the timing of cardiovascular death over cancer death varies among different types of cancer patients. It first appeared in colorectal cancer patients and last observed in breast cancer patients. However, we also found that not all cancer patients will experience more cardiovascular deaths than cancer deaths. This is likely to be related to the different treatment regimens of different cancer patients. But it may also be related to the potential for local/distant metastases of cancers at different sites. Distant metastasis is based on the cancer cell invasion of blood vessels. Cancer patients may be in a state where the cardiovascular system continuously face the invasion process of cancer cells and inflammatory factors. The more prone to distant metastasis, the more prone to cardiovascular invasion. Therefore, prevention of distant metastasis in cancer patients may be an effective way to reduce the risk of cardiovascular death.

Several limitations deserved the attentions in this study. First, preexisting illnesses, especially preexisting cardiovascular disease, may modify the risk of cardiovascular death after cancer diagnosis. Second, shared causal factors between cancer and cardiovascular disease, as residual confounding, may bias our findings. Third, since the data were collected from the cancer registries rather than cardiovascular registries, underreporting or misclassification of cardiovascular disease would also bias our results. Despite these limitations in our analysis, we believe that such a large real-world cohort study with relatively reasonable analyses would bring a lot of indications to the current practice of cardio-oncology.

Conclusions

In conclusion, for cancer patients, cardiovascular death is a risk that persists throughout the whole life and will likely exceed the risk of cancer death over time. Although drug therapy may increase the known risk of cardiovascular death, the necessary chemotherapy and surgery are likely to provide combined cardiovascular protection. Cardiovascular risk in elderly cancer patients and radiotherapy, as well as prevention of cardiovascular death by reducing local/distant metastases, will be the focus in the field of cardio-oncology.

Abbreviations

- P_{CV}
cardiovascular death
- P_{CA}
cancer death
- CMR_{CV}
cumulative cardiovascular mortality rate
- CMR_{CA}
cumulative cancer mortality rate
- SEER
Surveillance, Epidemiology, and End Results
- RESPIR
respiratory
- BREAST
breast
- COLRECT
colon and rectum
- URINARY
urinary
- LYMYLEUK
lymphoma of all sites and leukemia
- FEMGEN
female genital
- MALEGEN
male genital
- DIGOTHR
other digestive except colon and rectum
- OTHER
all other sites except above sites
- CVD
cardiovascular disease.

Declarations

Ethics approval and consent to participate

Not applicable

Consent for publication

Not applicable

Availability of data and materials

The datasets generated and/or analysed during the current study are available in the SEER repository(<https://seer.cancer.gov/>).

Competing interests

The authors declare that they have no competing interests.

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Authors’ contributions

ZW and YH designed the study and drafted the manuscript. LY. and ZW analyzed the data. CS performed the statistical analysis. SW, LL, KC, YH, made critical revision of the manuscript. All authors read and approved the final manuscript.

References

1. World Health Organization. Global Health Observatory. Geneva: World Health Organization, 2018.
2. Fitzmaurice C, Akinyemiju TF, Al LF, Alam T, Alizadeh-Navaei R, Allen C, Alsharif U, Alvis-Guzman N, Amini E, Anderson BO, Aremu O, Artaman A, Asgedom SW, Assadi R, Atey TM, Avila-Burgos L, Awasthi A, Ba SH, Barac A, Bennett JR, Bensenor IM, Bhakta N, Brenner H, Cahuana-Hurtado L, Castaneda-Orjuela CA, Catala-Lopez F, Choi JJ, Christopher DJ, Chung SC, Curado MP, Dandona L, Dandona R, Das NJ, Dey S, Dharmaratne SD, Doku DT, Driscoll TR, Dubey M, Ebrahimi H, Edessa D, El-Khatib Z, Endries AY, Fischer F, Force LM, Foreman KJ, Gebrehiwot SW, Gopalani SV, Grosso G, Gupta R, Gyawali B, Hamadeh RR, Hamidi S, Harvey J, Hassen HY, Hay RJ, Hay SI, Heibati B, Hiluf MK, Horita N, Hosgood HD, Ilesanmi OS, Innos K, Islami F, Jakovljevic MB, Johnson SC, Jonas JB, Kasaieian A, Kassa TD, Khader YS, Khan EA, Khan G, Khang YH, Khosravi MH, Khubchandani J, Kopec JA, Kumar GA, Kutz M, Lad DP, Lafranconi A, Lan Q, Legesse Y, Leigh J, Linn S, Lunevicius R, Majeed A, Malekzadeh R, Malta DC, Mantovani LG, McMahon BJ, Meier T, Melaku YA, Melku M, Memiah P, Mendoza W, Meretoja TJ, Mezgebe HB, Miller TR, Mohammed S, Mokdad AH, Moosazadeh M, et al. Global, Regional, and National Cancer Incidence, Mortality, Years of Life Lost, Years Lived With Disability, and Disability-Adjusted Life-Years for 29 Cancer Groups, 1990 to 2016: A Systematic Analysis for the Global Burden of Disease Study. *JAMA Oncol* 2018;4(11):1553–1568.
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, Bray F. Global cancer statistics 2020: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin* 2021;71(3):209–249.
4. Fang F, Keating NL, Mucci LA, Adami HO, Stampfer MJ, Valdimarsdottir U, Fall K. Immediate risk of suicide and cardiovascular death after a prostate cancer diagnosis: cohort study in the United States. *J Natl Cancer Inst* 2010;102(5):307–14.
5. Fang F, Fall K, Mittleman MA, Sparen P, Ye W, Adami HO, Valdimarsdottir U. Suicide and cardiovascular death after a cancer diagnosis. *N Engl J Med* 2012;366(14):1310–8.
6. Fall K, Fang F, Mucci LA, Ye W, Andren O, Johansson JE, Andersson SO, Sparen P, Klein G, Stampfer M, Adami HO, Valdimarsdottir U. Immediate risk for cardiovascular events and suicide following a prostate cancer diagnosis: prospective cohort study. *PLoS Med* 2009;6(12):e1000197.
7. Zhou H, Xian W, Zhang Y, Chen G, Zhao S, Chen X, Zhang Z, Shen J, Hong S, Huang Y, Zhang L. Trends in incidence and associated risk factors of suicide mortality in patients with non-small cell lung cancer. *Cancer Med* 2018;7(8):4146–4155.
8. Wang SM, Chang JC, Weng SC, Yeh MK, Lee CS. Risk of suicide within 1 year of cancer diagnosis. *Int J Cancer* 2018;142(10):1986–1993.
9. Khosrow-Khavar F, Fillion KB, Al-Qurashi S, Torabi N, Bouganim N, Suissa S, Azoulay L. Cardiotoxicity of aromatase inhibitors and tamoxifen in postmenopausal women with breast cancer: a systematic review and meta-analysis of randomized controlled trials. *Ann Oncol* 2017;28(3):487–496.
10. Haque R, Shi J, Schottinger JE, Chung J, Avila C, Amundsen B, Xu X, Barac A, Chlebowski RT. Cardiovascular Disease After Aromatase Inhibitor Use. *JAMA Oncol* 2016;2(12):1590–1597.
11. Van Hemelrijck M, Garmo H, Holmberg L, Ingelsson E, Bratt O, Bill-Axelsson A, Lambe M, Stattin P, Adolfsson J. Absolute and relative risk of cardiovascular disease in men with prostate cancer: results from the Population-Based PCBaSe Sweden. *J Clin Oncol* 2010;28(21):3448–56.
12. Albin A, Pennesi G, Donatelli F, Cammarota R, De Flora S, Noonan DM. Cardiotoxicity of anticancer drugs: the need for cardio-oncology and cardio-oncological prevention. *J Natl Cancer Inst* 2010;102(1):14–25.
13. Zaorsky NG, Churilla TM, Egleston BL, Fisher SG, Ridge JA, Horwitz EM, Meyer JE. Causes of death among cancer patients. *Ann Oncol* 2017;28(2):400–407.
14. Feng Y, Jin H, Guo K, Wasan HS, Ruan S, Chen C. Causes of Death After Colorectal Cancer Diagnosis: A Population-Based Study. *Front Oncol* 2021;11:647179.
15. Merrill RM, Dearden KA. How representative are the surveillance, epidemiology, and end results (SEER) program cancer data of the United States? *Cancer Causes Control* 2004;15(10):1027–34.
16. Zippin C, Lum D, Hankey BF. Completeness of hospital cancer case reporting from the SEER Program of the National Cancer Institute. *Cancer* 1995;76(11):2343–50.
17. Warren JL, Klabunde CN, Schrag D, Bach PB, Riley GF. Overview of the SEER-Medicare data: content, research applications, and generalizability to the United States elderly population. *Med Care* 2002;40(8 Suppl):IV-3-18.
18. Surveillance, Epidemiology, and End Results (SEER) Program. Research Data (1973–2015), National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission. Vol. 2018, 2018.
19. Surveillance, Epidemiology, and End Results (SEER) Program. Radiation/Chemotherapy Databases, National Cancer Institute, DCCPS, Surveillance Research Program, released April 2018, based on the November 2017 submission., 2018.
20. Austin PC, Fine JP. Practical recommendations for reporting Fine-Gray model analyses for competing risk data. *Stat Med* 2017;36(27):4391–4400.
21. DirkF. Moore. Applied Survival Analysis Using R Springer International Publishing, 2016.
22. Fine J, Gray R. A proportional hazards model for the subdistribution of a competing risk. *JASA* 1999;94(446):496–509.
23. Navi BB, Reiner AS, Kamel H, Iadecola C, Okin PM, Tagawa ST, Panageas KS, DeAngelis LM. Arterial thromboembolic events preceding the diagnosis of cancer in older persons. *Blood* 2018.
24. Totzeck M, Schuler M, Stuschke M, Heusch G, Rassaf T. Cardio-oncology - strategies for management of cancer-therapy related cardiovascular disease. *Int J Cardiol* 2019;280:163–175.

25. Varricchi G, Galdiero MR, Tocchetti CG. Cardiac Toxicity of Immune Checkpoint Inhibitors: Cardio-Oncology Meets Immunology. *Circulation* 2017;136(21):1989–1992.
26. Jovenaux L, Cautela J, Resseguier N, Pibarot M, Taouqi M, Orabona M, Pinto J, Peyrol M, Barraud J, Laine M, Bonello L, Paganelli F, Barlesi F, Thuny F. Practices in management of cancer treatment-related cardiovascular toxicity: A cardio-oncology survey. *Int J Cardiol* 2017;241:387–392.
27. Gujral DM, Lloyd G, Bhattacharyya S. Provision and Clinical Utility of Cardio-Oncology Services for Detection of Cardiac Toxicity in Cancer Patients. *J Am Coll Cardiol* 2016;67(12):1499–1500.
28. Hampton T. Cardio-Oncology Programs Strive to Balance Cancer Care With Heart Health. *Circulation* 2016;134(4):353–4.
29. Bellinger AM, Arteaga CL, Force T, Humphreys BD, Demetri GD, Druker BJ, Moslehi JJ. Cardio-Oncology: How New Targeted Cancer Therapies and Precision Medicine Can Inform Cardiovascular Discovery. *Circulation* 2015;132(23):2248–58.
30. Matthews A, Stanway S, Farmer RE, Strongman H, Thomas S, Lyon AR, Smeeth L, Bhaskaran K. Long term adjuvant endocrine therapy and risk of cardiovascular disease in female breast cancer survivors: systematic review. *BMJ* 2018;363:k3845.
31. Mouridsen H, Keshaviah A, Coates AS, Rabaglio M, Castiglione-Gertsch M, Sun Z, Thurlimann B, Mauriac L, Forbes JF, Paridaens R, Gelber RD, Colleoni M, Smith I, Price KN, Goldhirsch A. Cardiovascular adverse events during adjuvant endocrine therapy for early breast cancer using letrozole or tamoxifen: safety analysis of BIG 1–98 trial. *J Clin Oncol* 2007;25(36):5715–22.
32. Lyon AR, Dent S, Stanway S, Earl H, Brezden-Masley C, Cohen-Solal A, Tocchetti CG, Moslehi JJ, Groarke JD, Bergler-Klein J, Khoo V, Tan LL, Anker MS, von Haehling S, Maack C, Pudil R, Barac A, Thavendiranathan P, Ky B, Neilan TG, Belenkov Y, Rosen SD, Iakobishvili Z, Sverdllov AL, Hajjar LA, Macedo A, Manisty C, Ciardiello F, Farmakis D, de Boer RA, Skouri H, Suter TM, Cardinale D, Witteles RM, Fradley MG, Herrmann J, Cornell RF, Wechelaker A, Mauro MJ, Milojkovic D, de Lavallade H, Ruschitzka F, Coats A, Seferovic PM, Chioncel O, Thum T, Bauersachs J, Andres MS, Wright DJ, Lopez-Fernandez T, Plummer C, Lenihan D. Baseline cardiovascular risk assessment in cancer patients scheduled to receive cardiotoxic cancer therapies: a position statement and new risk assessment tools from the Cardio-Oncology Study Group of the Heart Failure Association of the European Society of Cardiology in collaboration with the International Cardio-Oncology Society. *Eur J Heart Fail* 2020;22(11):1945–1960.
33. He X, Dai X, Ji J, Liu H, Shi G, Yeung SJ. Nine-Year Median Follow-up of Cardiotoxicity and Efficacy of Trastuzumab Concurrently With Anthracycline-Based and Anthracycline-Free Neoadjuvant Chemotherapy in HER2-Positive Breast Cancer Patients. *Clin Breast Cancer* 2022;22(1):e80-e90.
34. Gonciar D, Mocan L, Zlibut A, Mocan T, Agoston-Coldea L. Cardiotoxicity in HER2-positive breast cancer patients. *Heart Fail Rev* 2021;26(4):919–935.
35. Zaorsky NG, Churilla TM, Egleston BL, Fisher SG, Ridge JA, Horwitz EM, Meyer JE. Causes of death among cancer patients. *Ann Oncol* 2017;28(2):400–407.
36. Fang F, Keating NL, Mucci LA, Adami HO, Stampfer MJ, Valdimarsdottir U, Fall K. Immediate risk of suicide and cardiovascular death after a prostate cancer diagnosis: cohort study in the United States. *J Natl Cancer Inst* 2010;102(5):307–14.
37. Neal B, Wu Y, Feng X, Zhang R, Zhang Y, Shi J, Zhang J, Tian M, Huang L, Li Z, Yu Y, Zhao Y, Zhou B, Sun J, Liu Y, Yin X, Hao Z, Yu J, Li KC, Zhang X, Duan P, Wang F, Ma B, Shi W, Di Tanna GL, Stepien S, Shan S, Pearson SA, Li N, Yan LL, Labarthe D, Elliott P. Effect of Salt Substitution on Cardiovascular Events and Death. *N Engl J Med* 2021;385(12):1067–1077.
38. Hu Y, Zong G, Liu G, Wang M, Rosner B, Pan A, Willett WC, Manson JE, Hu FB, Sun Q. Smoking Cessation, Weight Change, Type 2 Diabetes, and Mortality. *N Engl J Med* 2018;379(7):623–632.

Tables

Table 1. Cardiovascular mortality risk in cancer patients by baseline characteristics.

Variable		Number of subgroup	Number of CVD death	Mean follow-up years	CVD-specific mortality rate, 1/1000 person-years	P value for Fine- Gray test
Age at diagnosis, years	≤ 30	177119	2308	13.14	0.99	<0.001
	31-39	247533	5863	11.51	2.06	
	41-49	522030	21271	9.87	4.13	
	51-59	917621	65447	8.10	8.80	
	61-69	1123669	123222	6.91	15.87	
	71-77	1075716	184835	5.09	33.77	
	≥ 80	742376	160902	2.93	73.92	
Sex	Male	2385471	298205	6.03	20.71	<0.001
	Female	2420593	265643	7.76	14.14	
Marital status at diagnosis	Married	2710794	301105	7.61	14.60	<0.001
	Single	579805	45349	7.20	10.86	
	Separated	58599	9224	5.43	28.98	
	Divorced	360536	30966	6.29	13.66	
	Widowed	770078	143570	4.51	41.38	
	Unmarried	2229	18	2.26	3.57	
	Unknown	324023	33616	7.15	14.52	
Race	White	4045601	489894	7.05	17.16	<0.001
	Black	432341	48756	5.65	19.97	
	Indian/Alaska Native	23651	1661	6.12	11.48	
	Asian/Pacific Islander	276870	22916	6.65	12.45	
	Unknown	27601	621	7.65	2.94	
Cancer site	RESPIR	642669	45141	2.49	28.24	<0.001
	BREAST	786979	96593	10.19	12.04	
	COLRECT	529644	93863	6.73	26.33	
	URINARY	326229	54657	7.15	23.43	
	LYMYLEUK	387832	35673	5.95	15.47	
	FEMGEN	316790	39091	9.95	12.40	
	MALEGEN	641129	111865	8.60	20.28	
	DIGOTHR	364418	20575	2.19	25.84	
	OTHER	810374	66390	7.27	11.27	
Surgery	No	1770680	158700	3.62	24.79	<0.001
	Yes	2951990	396461	8.97	14.97	
	Unknown	83394	8687	3.53	29.49	
Radiotherapy	No	4107490	504379	6.64	18.50	<0.001
	Yes	695019	59146	8.48	10.04	
	Unknown	3555	323	6.84	13.28	
Chemotherapy	None/Unknown	3712398	513612	7.46	18.53	<0.001
	Yes	1093666	50236	5.00	9.19	
SEER historic stage	In situ	295848	31025	10.41	10.08	<0.001
	Distant	828146	42268	2.33	21.91	

	Localized/Regional	2610184	346802	8.62	15.42
	Unknown	1071886	143753	5.30	25.32
Total		4806064	563848	6.90	16.99

Note: CVD, cardiovascular disease, RESPIR, respiratory, BREAST, breast, COLRECT, colon and rectum, URINARY, urinary, LYMYLEUK, lymphoma of all sites and leukemia, FEMGEN, female genital, MALEGEN, male genital, DIGOTHR, other digestive, OTHER, all other sites.

Table 2. Cardiovascular mortality risk and its influencing factors in long-term cancer survivors*.

Variable	Groups	Cancer patients survived ≥ 10 years (n=1160503)			Cancer patients survived ≥ 15 years (n=652029)			Cancer patients survived ≥ 20 years (n=301000)	
		Number of subgroups	Number of cardiovascular death	HR (95%CI)	Number of subgroups	Number of cardiovascular death	HR (95%CI)	Number of subgroups	Number of cardiovascular death
Age at diagnosis, years	≤ 30	87197	1469	Reference	65994	1235	Reference	48153	983
	31-39	110462	3368	2.12 (1.89, 2.37)	78689	2639	2.10 (1.92, 2.30)	52347	1944
	41-49	200749	10840	4.16 (3.53, 4.91)	130276	8136	4.20 (3.74, 4.73)	78600	5676
	51-59	277205	28688	8.18 (6.45, 10.38)	161845	20178	8.36 (7.08, 9.88)	85736	13098
	61-69	271128	46748	14.36 (9.99, 20.65)	145603	29487	15.40 (11.70, 20.27)	63619	15494
	71-77	173992	46333	27.27 (15.61, 47.66)	62999	18368	28.37 (17.98, 44.75)	14137	4626
	≥ 80	39770	14386	43.39 (21.33, 88.28)	6623	2589	42.58 (23.55, 76.97)	597	257
Sex	Male	444613	56090	Reference	220643	26382	Reference	99120	11505
	Female	715890	95742	0.82 (0.76, 0.88)	431386	56250	0.83 (0.78, 0.88)	244069	30573
Cancer site	LYMYLEUK	79645	7666	Reference	43846	3965	Reference	24381	1995
	RESPIR	32409	5054	1.07 (0.98, 1.18)	15344	2306	1.04 (0.96, 1.13)	6646	924
	BREAST	326879	40587	0.98 (0.95, 1.02)	194104	23537	0.95 (0.90, 0.99)	104204	12268
	COLRECT	133896	30416	1.11 (1.06, 1.16)	74949	16312	1.06 (1.01, 1.12)	38681	7864
	URINARY	86578	16034	1.06 (1.02, 1.11)	46076	8185	1.02 (0.97, 1.07)	23783	3852
	FEMGEN	122576	19527	1.12 (1.03, 1.21)	85246	13476	1.05 (0.99, 1.13)	54335	8567
	MALEGEN	144313	11207	0.83 (0.79, 0.87)	57834	3249	0.79 (0.75, 0.84)	13627	484
	DIGOTHR	21007	3123	1.08 (1.03, 1.14)	10152	1539	1.03 (0.96, 1.10)	4864	724
	OTHER	213200	18218	0.94 (0.90, 0.98)	124478	10063	0.87 (0.83, 0.92)	72668	5400
Surgery	No	177140	19437	Reference	78577	8023	Reference	33840	3385
	Yes	976002	130897	0.90 (0.87, 0.94)	568238	73680	0.91 (0.88, 0.95)	305451	38138
	Unknown	7361	1498	1.01 (0.95, 1.07)	5214	929	1.01 (0.94, 1.09)	3898	555
Radiotherapy	No	936411	129347	Reference	526478	69621	Reference	280841	35211
	Yes	223221	22353	0.99	125034	12932	1.03	62059	6814

				(0.97, 1.02)			(1.00, 1.06)		
	Unknown	871	132	1.23 (1.03, 1.46)	517	79	1.23 (0.98, 1.54)	289	53
Chemotherapy	None/Unknown	978119	139567	Reference	554562	76168	Reference	294774	38940
	Yes	182384	12265	0.85 (0.81, 0.90)	97467	6464	0.88 (0.85, 0.91)	48415	3138
SEER historic stage	In situ	128461	12864	Reference	72907	7101	Reference	36890	3534
	Distant	47601	4826	0.92 (0.83, 1.03)	25260	2467	0.98 (0.91, 1.06)	13677	1138
	Localized/Regional	877458	122427	1.07 (1.04, 1.10)	494097	66742	1.08 (1.05, 1.11)	258074	34010
	Unknown	106983	11715	1.08 (1.02, 1.15)	59765	6322	1.12 (1.07, 1.18)	34548	3396

*, marital status at diagnosis, race, calendar years at diagnosis according to 1970s, 1980s, 1990s, 2000s, 2010s, nine original registries, and all variables listed in the table were adjusted in the multivariate competing risk regression models. Note: HR (95%CI), Hazard ratio (95% confidence intervals), RESPIR, respiratory, BREAST, breast, COLRECT, colon and rectum, URINARY, urinary, LYMYLEUK, lymphoma of all sites and leukemia, FEMGEN, female genital, MALEGEN, male genital, DIGOTHR, other digestive, OTHER, all other sites.

Figures

Figure 1

Temporal trends in the proportions of cardiovascular death (P_{CV}), cancer death (P_{CA}), and other causes in all-cause deaths in cancer patients. Note: CVD, cardiovascular disease, RESPIR, respiratory, BREAST, breast, COLRECT, colon and rectum, URINARY, urinary, LYMYLEUK, lymphoma of all sites and leukemia, FEMGEN, female genital, MALEGEN, male genital, DIGOTHR, other digestive, OTHER, all other sites.

Figure 2

Competing mortality risk curves for cancer patients survived more than 20 years by cancer sites. Note: CVD, cardiovascular disease, RESPIR, respiratory, BREAST, breast, COLRECT, colon and rectum, URINARY, urinary, LYMYLEUK, lymphoma of all sites and leukemia, FEMGEN, female genital, MALEGEN, male genital, DIGOTHR, other digestive, OTHER, all other sites.

Figure 3

Cardiovascular mortality risk and anti-cancer treatments for cancer patients survived more than 20 years by cancer sites. Note: *, P value less than 0.05. Note: marital status at diagnosis, race, calendar years at diagnosis according to 1970s, 1980s, 1990s, 2000s, 2010s, nine original registries, sex, SEER historic stage, surgery, radiotherapy and chemotherapy were adjusted in the multivariate competing risk regression models. HR (95%CI), Hazard ratio (95% confidence intervals), RESPIR, respiratory, BREAST, breast, COLRECT, colon and rectum, URINARY, urinary, LYMYLEUK, lymphoma of all sites and leukemia, FEMGEN, female genital, MALEGEN, male genital, DIGOTHR, other digestive, OTHER, all other sites.

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