Journal of the American Heart Association

ORIGINAL RESEARCH

Specific Cardiovascular Mortality in Cancer Survivors: A Nationwide Population-Based Cohort Study in Japan

Yasufumi Gon, MD, PhD; Ling Zha, MPH; Tomohiro Kawano, MD, PhD; Haruka Kudo, PhD; Toshitaka Morishima, MD, PhD; Tsutomu Sasaki, MD, PhD; Isao Miyashiro, MD, PhD; Hideki Mochizuki, MD, PhD; Tomotaka Sobue, MD, MPH

BACKGROUND: Improvements in cancer survivorship have led to concern about cardiovascular disease (CVD) among cancer survivors. This study aimed to investigate CVD mortality in patients with cancer compared with the general population, with a focus on specific CVDs including ischemic heart disease, heart failure, aortic dissection, ischemic stroke, and hemorrhagic stroke.

METHODS: This nationwide population-based cohort study used data from the National Cancer Registry in Japan. Patients diagnosed with cancer between January 2016 and December 2019 were included. Standardized mortality ratios (SMRs) and their 95% CIs were calculated to compare the risk of CVD mortality between patients with cancer and the general population. The SMRs were also computed for each specific CVD.

RESULTS: The study included 3 972 603 patients, representing 6 212 672 person-years of follow-up. Patients with cancer had a 2.39-fold higher risk of cardiovascular death compared with the general population. The SMR was highest for nonlymphoid hematologic malignancies (4.32 [95% CI, 4.15–4.50]). The mortality risk varied across specific types of CVD. Nonlymphoid hematologic malignancies had the highest SMRs for ischemic heart disease (3.15 [95% CI, 2.87–3.45]) and heart failure (7.65 [95% CI, 7.07–8.27]). The SMR for aortic dissection, ischemic stroke, and hemorrhagic stroke were highest for laryngeal (3.31 [95% CI, 2.29–4.79]), pancreatic (5.39 [95% CI, 4.79–6.05]), and liver (3.75 [95% CI, 3.36–4.18]) cancers, respectively.

CONCLUSIONS: Patients with cancer had a higher CVD mortality risk, which was prominent in nonlymphoid hematologic malignancies. The mortality risk varied considerably by cancer type and specific CVD type.

Key Words: cancer survivors ■ cardiovascular mortality ■ cohort study

Advancements in cancer care and treatment have led to significant improvements in cancer survivorship.[1] With this increased survival, cardiovascular disease (CVD) has emerged as a major concern for cancer survivors.[2,3] Compared with those without cancer, patients with cancer have a higher risk of developing CVD, which is associated with an increased risk of mortality.[4,5] Multiple factors, including patient-related, cancer-related, and cancer treatment–related factors, contribute to the increased risk of CVD in patients with cancer.[6,7] Shared risk factors between cancer and CVD, such as smoking and obesity, elevate the cardiovascular risk for patients with cancer.[6,7] Cancer-associated coagulopathy increases the incidence of thromboembolic events, such as ischemic stroke and myocardial infarction.[8] Radiotherapy and certain chemotherapeutic agents also raise the long-term risk of cardiovascular complications in this population.[9,10]

Correspondence to: Yasufumi Gon, MD, PhD, Department of Neurology, Osaka University Graduate School of Medicine, 2-2, Yamada-oka, Suita, Osaka, 565-0871, Japan. Email: gon@neurol.med.osaka-u.ac.jp

This article was sent to Tochukwu M. Okwuosa, DO, Associate Editor, for review by expert referees, editorial decision, and final disposition.

Supplemental Material is available at https://www.ahajournals.org/doi/suppl/10.1161/JAHA.124.037965

For Sources of Funding and Disclosures, see page 10.

JAHA is available at: www.ahajournals.org/journal/jaha

CLINICAL PERSPECTIVE

What Is New?

- The risk of death from cardiovascular diseases was highest in patients with nonlymphoid hematologic malignancies (standardized mortality ratio, 4.32 [95% CI, 4.15–4.50]).
- When analyzing by specific cancer types and cardiovascular diseases, the highest standardized mortality ratios were found as follows: nonlymphoid hematologic malignancies for ischemic heart disease and heart failure, pancreatic cancer for ischemic stroke, laryngeal cancer for aortic dissection, and liver cancer for hemorrhagic stroke.

What Are the Clinical Implications?

- Understanding the associations between specific cancer types and cardiovascular disease–related mortality can help identify high-risk populations and guide long-term surveillance strategies for cancer survivors.

Nonstandard Abbreviations and Acronyms

NCR	National Cancer Registry
SMR	standardized mortality ratio

Consequently, addressing CVD has become an essential component of comprehensive care for cancer survivors.[2]

Recent studies have identified CVD as the leading cause of noncancer mortality among cancer survivors.[11–13] Research using the Surveillance, Epidemiology, and End Results (SEER) database found that patients with cancer are approximately twice as likely to die from heart and cerebrovascular diseases as the general population.[14–16] Similar findings have been reported from studies analyzing data from the Osaka Cancer Registry.[17,18] Although studies have investigated the risk of mortality from heart and cerebrovascular disease in patients with cancer, few have focused on specific CVDs, such as ischemic heart disease and ischemic stroke.[16–18] We previously reported on the mortality risks associated with specific CVDs, such as heart failure (HF) and ischemic stroke.[17,18] A limitation of our previous study was the use of cancer registries from specific regions in Japan, as the National Cancer Registry (NCR) was not available for research purposes at the time the study was conducted. Understanding the cardiovascular mortality risks associated with cancer for specific conditions in an aging population such as Japan's could offer valuable insights for global cancer care strategies, especially in regions with aging demographics.

This study aimed to investigate the risk of cardiovascular mortality among patients with cancer in Japan, using NCR data. In addition to evaluating the overall CVD risk, specific CVDs, including ischemic heart disease, HF, aortic dissection or aneurysm, ischemic stroke, and hemorrhagic stroke, were analyzed.

METHODS

Ethics Approval and Consent to Participate

The study was approved by the institutional review board of Osaka University Hospital (approval number: 21438-2), and the requirement for obtaining informed consent was waived due to the use of anonymized data.

Data Availability

As the dataset analyzed in this study was provided in accordance with the Cancer Registration Promotion Act and used with the permission of the NCR Information Provision and Review Committee of the National Cancer Center in Japan, it is not available for public sharing. However, data can be accessed by submitting an application to the NCR Information Desk (https://ganjoho.jp/med_pro/cancer_control/can_reg/national/datause/index.html), following the specified study protocol. The data presented in the article originated from and were processed independently of the provided data set.

Study Design and Participants

This is a nationwide population-based cohort study using NCR in Japan. Details of the study design have been described elsewhere.[19] Briefly, the NCR was launched in 2016 based on the Act on the Promotion of Cancer Registries and covers the entire population of Japan.[20] The NCR registers all cancer diagnoses and regularly updates survival, including the cause of death. The data from patients diagnosed with cancer between January 1, 2016, and December 31, 2019, were accessed after permission from the NCR Information Provision and Review Committee of the National Cancer Center. The exclusion criteria were as follows: (1) uncertain sex, (2) uncertain age at the time of cancer diagnosis, (3) death certificate notification or death certification only, (4) registration for second and subsequent cancers, (5) age at cancer diagnosis <20 years, and (6) male breast cancer. Figure S1 shows a chart of eligible patients.

Variable Definition

The age at diagnosis was grouped into 4 categories: 20 to 39, 40 to 59, 60 to 79, and ≥80 years. The year

of diagnosis was classified into 4 periods: 2016, 2017, 2018, and 2019. The stage at diagnosis was categorized into 6 groups: (1) intraepithelial (abnormal cells were present but have not spread to nearby tissues); (2) localized (cancer was limited to the organ of origin where it originated, with no sign of spread); (3) regional (cancer had spread to nearby tissue or regional lymph nodes); (4) distant metastasis (cancer had metastasized to distant parts of the body); (5) unstaged (there was insufficient information to determine the stage); and (6) not applicable (leukemia or multiple myeloma). Cancer treatments were categorized as cancer surgery, chemotherapy, and radiotherapy, and were classified as follows: present (yes), absent (no), or unknown. The *International Classification of Diseases for Oncology, Third Edition*, was used to code the cancer (Table S1). The cause of death was determined based on *International Classification of Diseases, Tenth Revision* (*ICD-10*), codes registered in the NCR from the death certificate: CVD (I00-I99); ischemic heart disease (I20–I25); HF, (I50); aortic dissection or aneurysm (I71); ischemic stroke (I63 and I69.3); and hemorrhagic stroke (I60, I61, I69.0, and I69.1).

Statistical Analysis

The risk of death from CVD after cancer diagnosis was analyzed. CVD-related death was defined as CVD being the cause of death recorded on the death certificate. The observation period ranged from January 1, 2016, to December 31, 2019. Survival of <1 month was recorded as 0 days in the NCR. Therefore, patients with 0 survival months in the NCR were assigned a value of 0.5 months.[20–22] The start date of the follow-up period was defined as the date of cancer diagnosis. The end date of the follow-up was defined as either the date of death, 4 years after the cancer diagnosis, or December 31, 2019, whichever came first. Thus, the cohort included patients diagnosed with cancer between January 2016 and December 2019, with a follow-up period until December 31, 2019.

Standardized mortality ratios (SMRs) and their 95% CIs were calculated to compare the risk of fatal CVD in patients with cancer with that in the general population. SMRs were calculated as the ratio of the observed to the expected number of deaths. The observed number of deaths was obtained from the NCR database. The expected number of deaths was calculated by applying national cause-specific mortality rates stratified by 5-year age group, sex, and calendar year to the corresponding person-years contributed by each patient in the study cohort, thereby accounting for variations in individual follow-up durations. Both the national population and mortality data, including in patients with and without cancer, were sourced from the Portal Site of Official Statistics of Japan (https://www.e-stat.go.jp/en). SMRs were further stratified by both cancer type and time since cancer diagnosis. To investigate changes in SMR over time since cancer diagnosis, each patient's follow-up was divided into predefined time intervals after diagnosis (eg, 0–6 months and 6–12 months) using the *stsplit* command in Stata. SMRs were then calculated for each time interval to capture changes in CVD mortality risk.

The mortality risk for specific CVD was evaluated by calculating separate SMRs for ischemic heart disease, HF, aortic dissection or aneurysm, ischemic stroke, and hemorrhagic stroke. As with the analysis of CVD, SMRs were analyzed by cancer type and time since cancer diagnosis.

All statistical analyses were performed using Stata 17/MP (StataCorp LLC) and R (https://cran.r-project.org/) software (R Foundation for Statistical Computing). All tests were 2-tailed, and statistical significance was defined as $P<0.05$.

RESULTS

Patients' Demographics and Overall Cardiovascular Mortality

Among the 4 686 949 patients registered in the NCR during the study period, 3 972 603 patients (45.8% women) were included in the analysis, yielding 6 212 672 person-years of follow-up. Table shows the cohort's characteristics.

Figure 1 shows the SMR for CVD. Compared with the general population, patients with cancer had a 2.39-fold higher risk of death due to CVD. The SMR was higher in women than in men. The SMR was highest in the 20- to 39-year age group (5.56 [95% CI, 4.22–7.31]) and lowest in the 60- to 79-year age group (2.16 [95% CI, 2.12–2.19]) at cancer diagnosis. Regarding the known stage at diagnosis, the SMR was highest for distant metastatic cancers (2.86 [95% CI, 2.79–2.94]) and lowest for intraepithelial cancers (1.62 [95% CI, 1.56–1.68]). Among all cancer treatments, patients who received intervention exhibited the lowest SMR for CVD, while those with unknown treatment status showed the highest. Patients with unknown cancer treatment had a high proportion of "not applicable" classifications for stage at diagnosis. Detailed data are presented in Tables S2 and S3.

CVD Mortality Risk by Cancer Type and Time Since Cancer Diagnosis

Figure 2 illustrates CVD mortality risks by cancer type. The risk was highest for nonlymphoid hematologic malignancies (SMR, 4.32 [95% CI, 4.15–4.50]), followed by pancreatic cancer (SMR, 3.17 [95% CI, 2.99–3.35]) and brain tumors (SMR, 3.13 [95% CI, 2.94–3.34]). The

Table. Patient Characteristics

	Number	Percentage
Sex		
Female	1 819 130	45.8%
Male	2 153 473	54.2%
Age at diagnosis, y		
20–39	142 588	3.6%
40–59	686 386	17.3%
60–79	2 157 813	54.3%
≥80	985 816	24.8%
Period of diagnosis		
2016	999 535	25.2%
2017	994 169	25.0%
2018	987 452	24.9%
2019	991 447	25.0%
Stage at diagnosis		
Intraepithelial	398 687	10.0%
Localized	1 663 734	41.9%
Regional	796 030	20.0%
Distant	640 547	16.1%
Unstaged	118 774	3.0%
Not applicable	354 831	8.9%
Cancer surgery		
Yes	1 165 463	29.3%
No	2 425 505	61.1%
Unknown	381 635	9.6%
Chemotherapy		
Yes	1 061 126	26.7%
No	2 529 554	63.7%
Unknown	381 923	9.6%
Radiotherapy		
Yes	395 527	10.0%
No	3 194 934	80.4%
Unknown	382 142	9.6%

risk was lowest for prostate cancer (SMR, 1.52 [95% CI, 1.48–1.57]), followed by thyroid cancer (SMR, 1.77 [95% CI, 1.56 –1.99]) and laryngeal cancer (SMR, 1.87 [95% CI, 1.65–2.12]). Importantly, all cancers showed an elevated SMR >1.0, indicating an increased risk of CVD mortality for every patient with cancer. Figure 3 shows how the risk of CVD death changes over time after cancer diagnosis. The risk is highest immediately after cancer diagnosis and gradually decreases over time. In addition, women have a higher risk than men. Further demographic details by sex are provided in Table S4.

Mortality Risk by Specific CVD

Figure 4 presents the mortality risks for specific CVDs, including ischemic heart disease, HF, aortic dissection or aneurysm, ischemic stroke, and hemorrhagic stroke. The risks varied among different diseases. Nonlymphoid hematologic malignancies had the highest SMR for ischemic heart disease (SMR, 3.15 [95% CI, 2.87–3.45]) and HF (SMR, 7.65 [95% CI, 7.07–8.27]), while pancreatic cancer showed the highest risks for ischemic stroke (SMR, 5.39 [95% CI, 4.79–6.05]). Notably, laryngeal cancer had the highest SMR for aortic dissection or aneurysm (SMR, 3.31 [95% CI, 2.29–4.79]), and liver cancer had the highest SMR for intracerebral hemorrhage (SMR, 3.75 [95% CI, 3.36–4.18]). Figure 5 shows the risks associated with specific CVDs over time. Women had higher risks than men for HF, aortic dissection, and ischemic stroke.

DISCUSSION

This nationwide population cohort study using data from the NCR in Japan found a 2.39-fold higher risk of CVD mortality among patients with cancer compared with the general population. The risks varied according to cancer type, with nonlymphoid hematologic malignancies having the highest mortality risk for CVD. Notably, the mortality risk for specific CVDs varied by cancer type, with laryngeal cancer associated with a higher risk of aortic dissection, pancreatic cancer with ischemic stroke, and liver cancer with hemorrhagic stroke.

Our finding of a higher CVD mortality risk in patients with cancer compared with the general population aligns with previous studies.[11,14–18] Notably, our study revealed that CVD mortality risks differ according to cancer type, with nonlymphoid hematological malignancies exhibiting the highest risk. Sturgeon et al investigated CVD mortality risks using SEER data and reported that endometrial cancer had the highest CVD mortality risk.[16] Ye et al examined CVD mortality risks utilizing the Tasmania Cancer Registry and reported that lung cancer exhibited the highest risk.[13] The exact causes behind these discrepancies remain unclear; however, we hypothesize the following explanations. First, our study used data from patients diagnosed with cancer between 2016 and 2019, while the previous studies covered the periods 1973 to 2012[16] and 2006 to 2013.[13] The significant advancements in cancer treatments from the late 1900s to the early 2000s might have influenced mortality risk variations. Second, our study involved a Japanese population, whereas the previous studies were conducted in the United States[16] and Australia,[13] respectively. Previous studies showed that patients with cancer of different races have different risks for CVD mortality.[23,24] Comparing SMRs between studies requires caution due to varying reference populations, but this racial difference likely contributed to the observed variations. Variations in cancer survival rates and healthcare systems across these

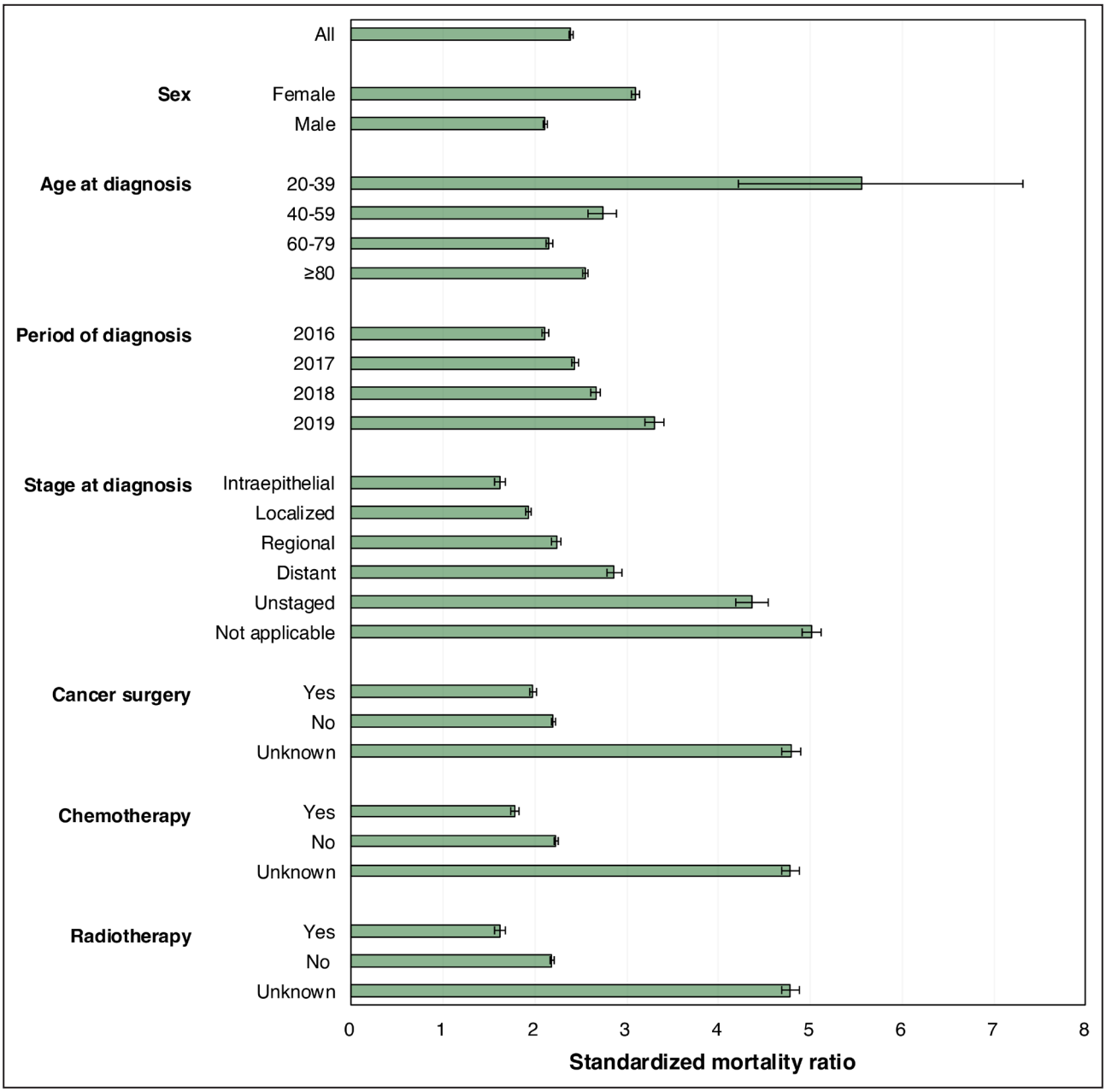

Figure 1. **Cardiovascular disease mortality by patient characteristics.**

regions might also have contributed to the observed differences in CVD mortality risk. In hematological malignancies, disruption of coagulation profiles increases the risk of thromboembolic events.[25] The frequent use of cytotoxic anticancer agents as the primary treatment modality contributes to the elevated risk of CVD mortality via vascular toxicity.[25–27] Hematological malignancies have been reported to confer a higher risk of arterial thromboembolic events compared with solid tumors.[28] Therefore, careful attention to hematological malignancies in the management of CVD risks in patients with cancer is imperative.

The SMRs for cardiovascular mortality increased with higher stages of cancer diagnosis. There are several factors explaining this finding. First, as cancer progresses, coagulation abnormalities become more severe,[29] increasing the incidence of potentially fatal ischemic stroke and myocardial infarction among patients with advanced cancer. Second, the administration of anticancer drugs for advanced cancer treatment can increase cardiovascular risk.[27] Third, the elevation of inflammatory cytokines as cancer progresses promotes atherosclerotic changes and thromboembolic events.[30] Collectively, these factors contribute to the

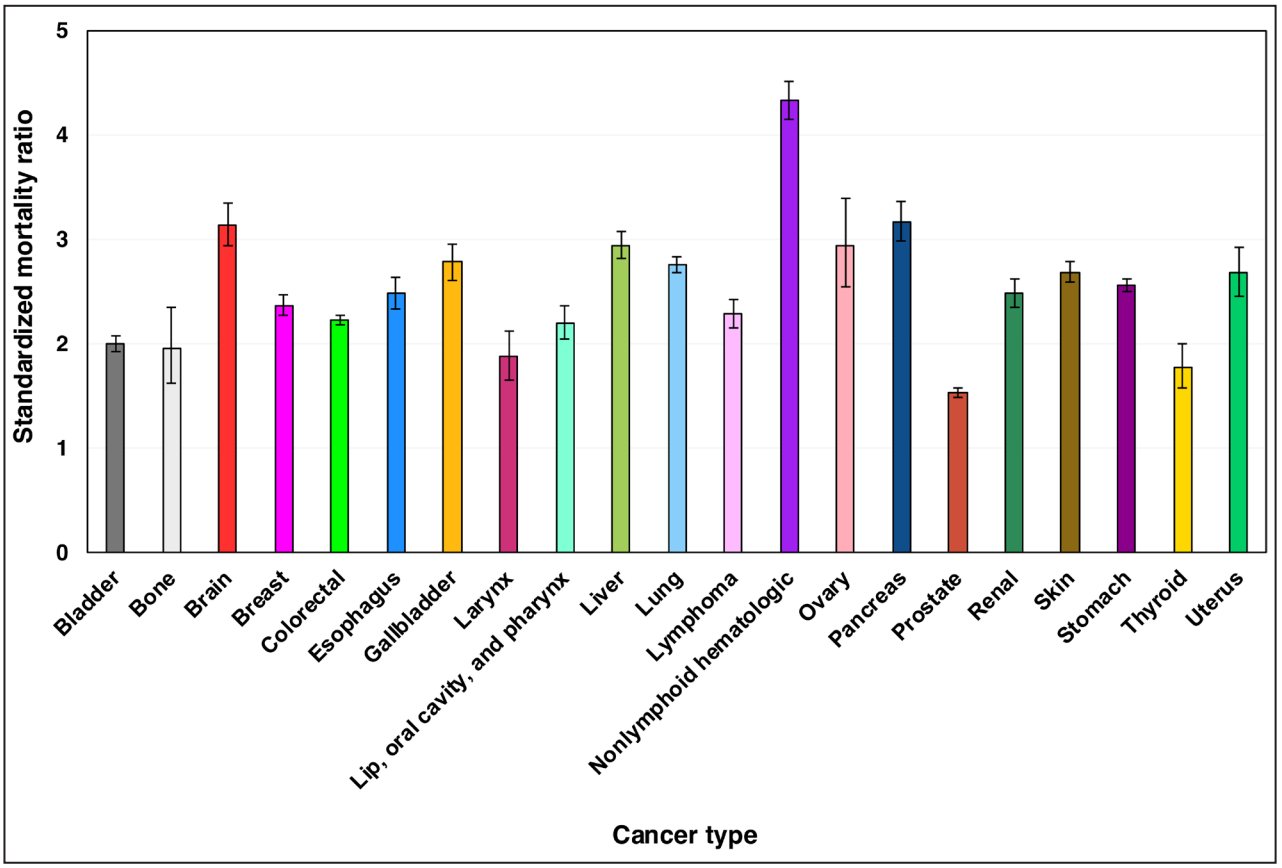

Figure 2. Cardiovascular disease mortality by cancer type.
The vertical axis represents the standardized mortality ratio (SMR) for cardiovascular disease, while the horizontal axis indicates the cancer type. The error bars in the figure represent the 95% CIs. Nonlymphoid hematologic malignancies had the highest SMR (4.32 [95% CI, 4.15–4.50]), followed by pancreatic cancer (3.17 [95% CI, 2.99–3.35]) and brain tumors (3.13 [95% CI, 2.94–3.34]). Prostate cancer had the lowest SMR (1.52 [95% CI, 1.48–1.57]), followed by thyroid cancer (1.77 [95% CI, 1.56–1.99]) and laryngeal cancer (1.87 [95% CI, 1.65–2.12]).

elevated risk of cardiovascular mortality observed in patients diagnosed with advanced-stage cancer.

It is noteworthy that the CVD mortality was greatest among young cancer survivors. This finding is consistent with previous studies.[16,31] Henson et al followed more than 20 000 young patients with cancer (15–39 years) and reported that age at cancer diagnosis was critical in determining subsequent cardiac mortality risk. The marked increase of CVD mortality in the young cancer group is likely related to the higher risk of developing CVD among them.[32] This may be attributed to cancer-specific factors such as cancer-associated coagulation disorders and cardiovascular side effects from cancer treatments.[27,29] These results will likely provide useful data for managing CVD mortality risk in young individuals diagnosed with cancer.

An interesting finding was the increased mortality risk from aortic dissection or aneurysm in patients with laryngeal cancer. Smoking not only increases the risk of developing laryngeal cancer but also accelerates the progression of atherosclerosis.[33,34] Advanced atherosclerosis predisposes individuals to aortic aneurysms and dissections. Consequently, patients with laryngeal cancer may have an increased risk of developing and potentially dying from aortic aneurysms and aortic dissections. In addition, radiation therapy, which is often used for organ preservation in laryngeal cancer,[35] exposes the aorta to radiation, potentially causing vascular damage[36] and increasing the risk of dissection or rupture. Perioperative manipulation can further injure the blood vessels.[37] In addition, although rare, the proximity of the larynx to the aorta allows laryngeal cancers to directly invade the aorta, posing a risk of dissection or rupture.[38] The site of aortic dissection was not specified in this study. Thus, it is uncertain whether cancer treatment or cancer progression elevated the risk of aortic dissection. Another notable finding was that the mortality risk from hemorrhagic stroke was highest among patients with liver cancer. This may be attributed to the associated thrombocytopenia and bleeding tendency caused by liver dysfunction.[39,40] Although referred to as cardiovascular

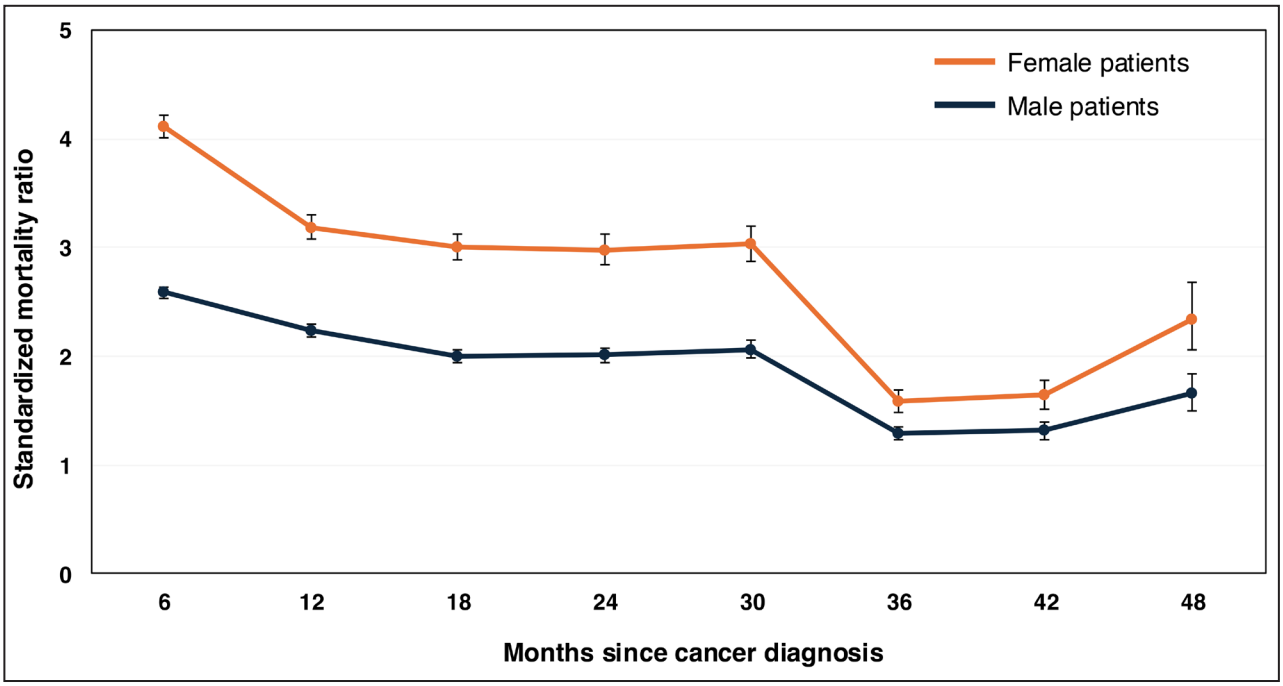

Figure 3. Cardiovascular disease mortality by time since cancer diagnosis.
The vertical axis represents the standardized mortality ratio (SMR) for cardiovascular disease, while the horizontal axis indicates the time since cancer diagnosis in months. The error bars in the figure represent the 95% CIs. The orange line represents female patients and the navy blue line represents male patients. The mortality risk for cardiovascular diseases decreased as the time since cancer diagnosis increased. Overall, female patients had a higher risk than male patients.

mortality risk, these findings crucially underscore the varying risk based on the cancer location and associated organ impairment.

Cardiovascular mortality risk peaked immediately after cancer diagnosis, likely due to complications associated with cancer surgery and anticancer treatment, and gradually decreased with time, likely due to tumor volume reduction through cancer treatment. These findings suggest that the detection and management of cardiotoxic events should be optimized during antineoplastic treatments and in the first year of follow-up to more effectively mitigate long-term complications and associated cardiovascular mortality. Our study also found that younger age at cancer diagnosis and advanced cancer stage were associated with increased cardiovascular mortality risks, which is consistent with previous studies.[11,13–18] These findings highlight the importance of cardiovascular risk assessment, particularly in young adult patients with cancer and those with advanced stages.

While cancer treatment is associated with an increased risk of CVD,[9,10] this study suggests that patients who received interventions had the lowest SMR for CVD. Several factors may explain this discrepancy. First, selection bias may play a role, as patients eligible for cancer treatment generally have better overall health; those ineligible due to severe comorbidities or advanced age may have an inherently increased risk of CVD mortality. Second, a surveillance effect may be present, whereby patients receiving treatment undergo regular monitoring, potentially allowing for early detection and management of CVD, which may lower mortality risk. Last, disease severity is a crucial factor; patients unable to receive treatment, particularly cancer surgery, often have more advanced disease stages, potentially contributing to the higher observed SMR. These factors suggest that the relationship between cancer treatment and CVD mortality is complex and influenced by multiple variables beyond the treatment itself.

The higher SMR for CVD mortality in female patients with cancer suggests that female-specific cancers, such as gynecologic malignancies and breast cancer, may contribute to an elevated risk of cardiovascular mortality. Gynecologic malignancies such as ovarian and uterine cancers carry a high risk of tumor-associated coagulopathy, potentially leading to cerebral ischemia.[41–43] For breast cancer, trastuzumab and anthracycline chemotherapeutic agents are known to be cardiotoxic and increase the risk of HF.[44,45] Although the risk has been reduced in recent years due to advances in radiation techniques, exposure of surrounding tissues to radiation during breast irradiation may still increase the risk of CVD.[46] However, the SMR for HF among patients with breast cancer was not markedly elevated in this study. This finding may be partly

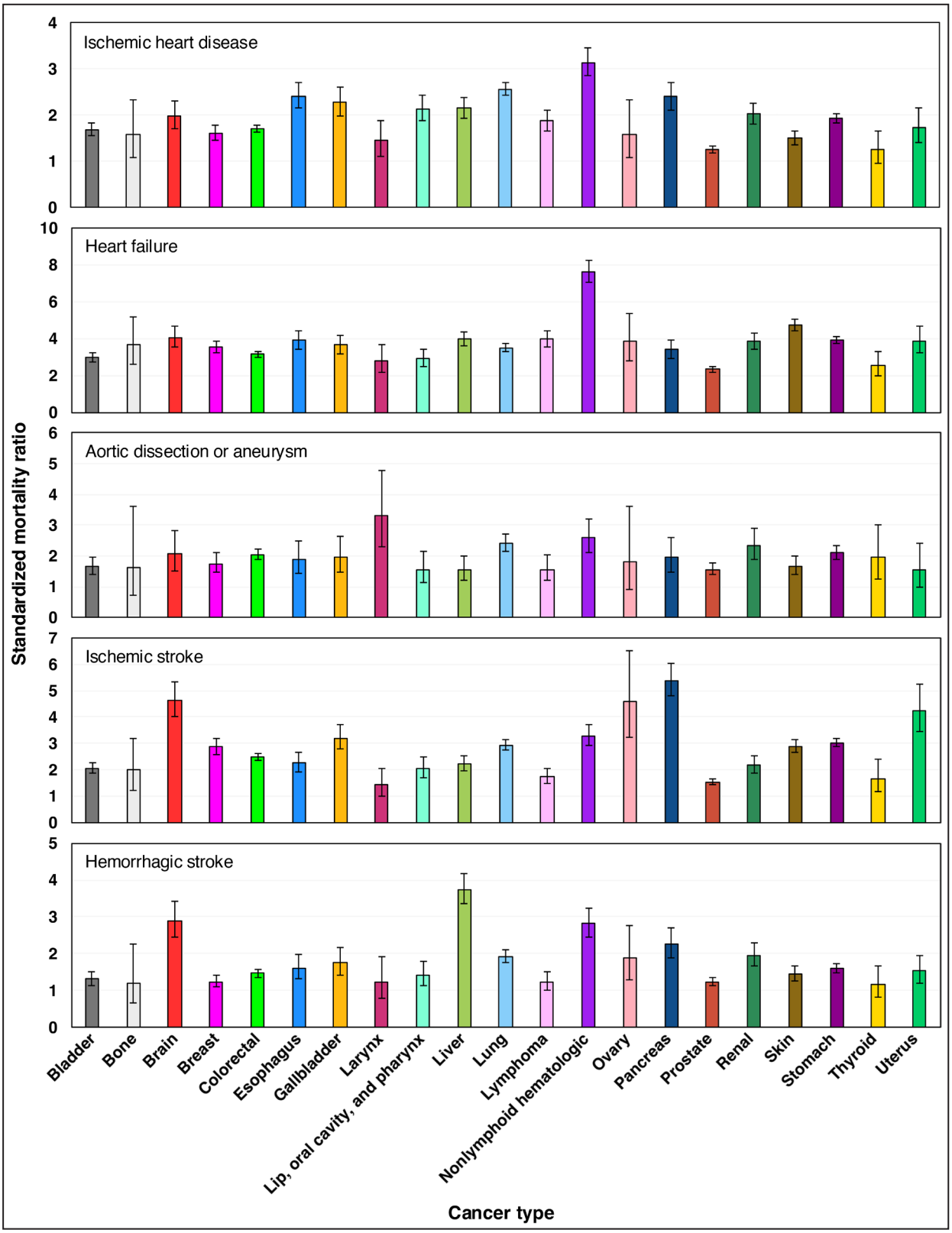

Figure 4. Specific cardiovascular disease mortality by cancer type.
The vertical axis represents the standardized mortality ratio (SMR), while the horizontal axis indicates the cancer type. The error bars in the figure represent the 95% CIs. For cardiac diseases such as ischemic heart disease and heart failure, the SMR was highest in nonlymphoid hematologic malignancies. For aortic dissection, laryngeal cancer had the highest SMR; for ischemic stroke, pancreatic cancer had the highest SMR; and for hemorrhagic stroke, liver cancer had the highest SMR.

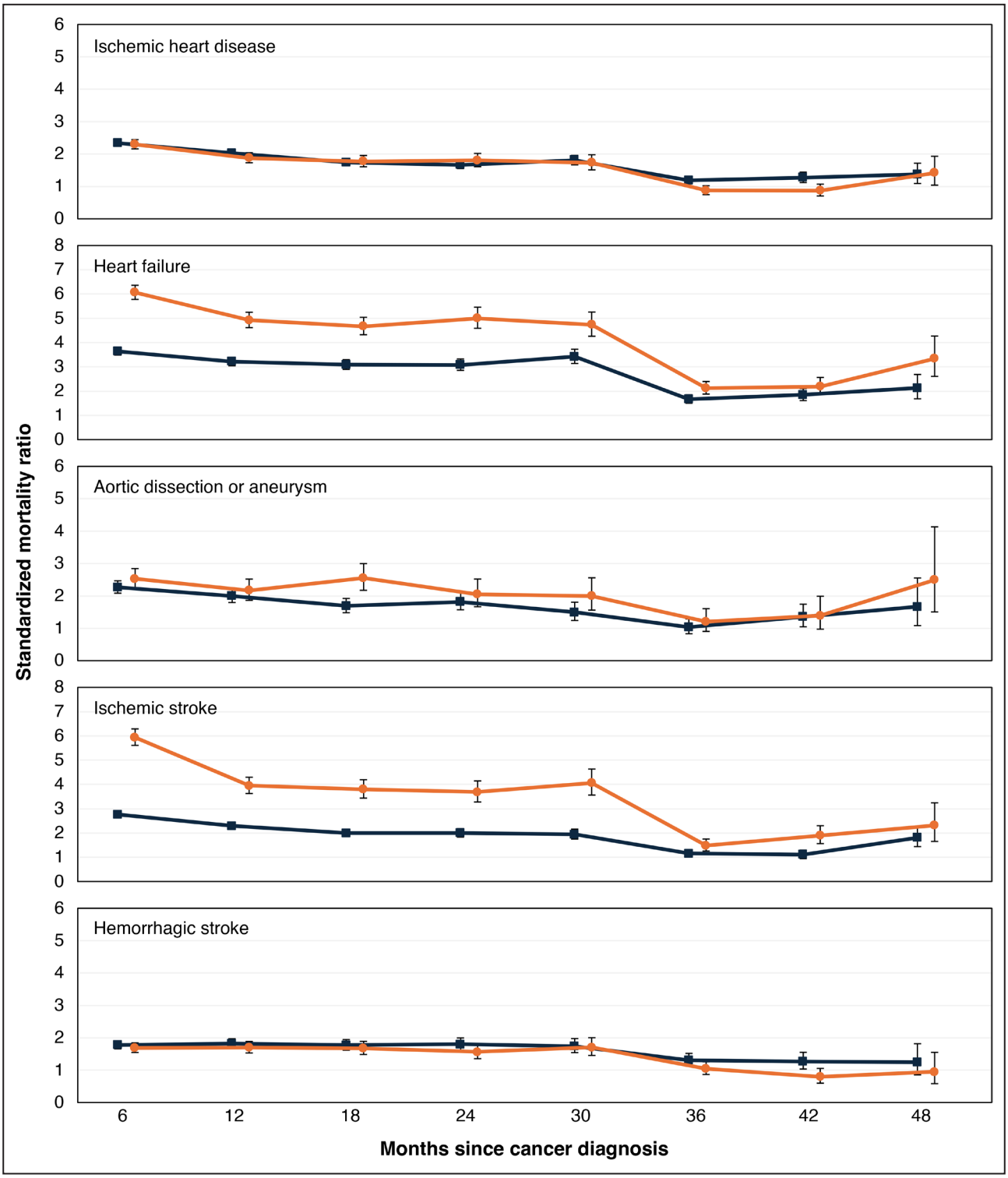

Figure 5. Specific cardiovascular disease mortality risk by time since cancer diagnosis.
The vertical axis represents the standardized mortality ratio (SMR), while the horizontal axis indicates the time since cancer diagnosis in months. The error bars in the figure represent 95% CIs. Orange represents female patients and navy blue represents male patients. Male and female groups are evaluated at the same observation points marked on the horizontal axis, but they are displayed slightly offset for better visibility. For ischemic heart disease, aortic dissection, and hemorrhagic stroke, there were no clear differences between male patients and female patients. In contrast, for heart failure and ischemic stroke, female patients had higher SMRs than male patients. Overall, the SMR was high immediately after cancer diagnosis and tended to gradually decrease over the 4 years following diagnosis.

attributed to the relatively short observation period of 4 years. Further research is warranted to elucidate the underlying mechanisms contributing to the increased risk of CVD mortality observed in female patients with cancer.

Study Limitations

Despite the valuable insights provided by this study, several limitations should be acknowledged. First, the cause of death in the NCR was recorded based on the death certificates using *ICD-10* code, which may be inaccurate at times.[47] Nonetheless, this method is currently the most reliable information source of cause of death and widely used.[11,14–19,21–24] Second, being an observational study, it cannot firmly establish causal relationships between cancer and CVD. Third, potential confounding factors, such as shared risk factors (eg, smoking and obesity) and the direct cardiovascular toxicities of cancer treatments, might have influenced the observed associations. Fourth, while the NCR recorded whether chemotherapy was administered or not, it lacked information on the specific drugs used or adjuvant therapies. Therefore, a detailed examination of the relationship between chemotherapy implementation and the risk of CVD mortality could not be conducted. Fifth, our analysis of the association between cancer treatment and CVD mortality risk was limited by the categorization of patients into 3 groups: those who received cancer surgery, chemotherapy, or radiotherapy; those who did not; and those with unknown treatment status. This simplification may not adequately reflect clinical practice, where combination therapies are common. In addition, potential cardiotoxic interventions such as hematopoietic stem cell transplantation may have been overlooked if not explicitly considered as antineoplastic therapy. Moreover, we lacked data on the specific anatomical targets of radiotherapy, particularly regarding mediastinal irradiation, which is crucial in assessing cardiovascular risk. The 2022 European Society of Cardiology guidelines on cardio-oncology emphasize the necessity of a tailored approach to cardiovascular follow-up management in cancer survivors.[2] Future research should aim to address these limitations, providing a more nuanced evaluation of treatment-related cardiovascular risks and enabling the development of personalized surveillance strategies.

CONCLUSIONS

In conclusion, this nationwide study highlights the substantial burden of cardiovascular mortality among patients with cancer in Japan. Our findings offer important insights for advancing cancer care, especially in the context of aging populations worldwide. Moreover, they emphasize the critical need for tailored cardiovascular risk management strategies for cancer survivors. Multidisciplinary collaborations involving oncologists, cardiologists, and other healthcare professionals are essential for developing comprehensive care models that address the unique cardiovascular challenges faced by this vulnerable population. Future research should prioritize elucidating the mechanisms underlying the observed associations, identifying high-risk subgroups, and developing evidence-based interventions to mitigate cardiovascular morbidity and mortality in cancer survivors.

ARTICLE INFORMATION

Received July 29, 2024; accepted February 7, 2025.

Affiliations

Department of Neurology, Osaka University Graduate School of Medicine, Osaka, Japan (Y.G., T.K., T.S., H.M.); Cancer Control Center, Osaka International Cancer Institute, Osaka, Japan (Y.G., H.K., T.M., I.M.); Department of Medical Innovation, Academic Clinical Research Center, Osaka University Hospital, Osaka, Japan (Y.G.); Department of Social Medicine, Environmental Medicine and Population Science (L.Z., T.S.) and StemRIM Institute of Regeneration-Inducing Medicine (T.S.), Osaka University Graduate School of Medicine, Suita, Japan.

Acknowledgments

We thank the staff at the NCR Information Desk for their assistance in providing the NCR data for our research.

Sources of Funding

This work was supported by Grants-in-Aid for Scientific Research of the Japan Society for the Promotion of Science (grant number: JP23K09713).

Disclosures

None.

Supplemental Material

Tables S1–S4
Figure S1

REFERENCES

1. Miller KD, Nogueira L, Devasia T, Mariotto AB, Yabroff KR, Jemal A, Kramer J, Siegel RL. Cancer treatment and survivorship statistics, 2022. *CA Cancer J Clin*. 2022;72:409–436.
2. Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, Boriani G, Cardinale D, Cordoba R, Cosyns B, et al. 2022 ESC guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). *Eur Heart J*. 2022;43:4229–4361.
3. Ameri P, Canepa M, Anker MS, Belenkov Y, Bergler-Klein J, Cohen-Solal A, Farmakis D, López-Fernández T, Lainscak M, Pudil R, et al. Cancer diagnosis in patients with heart failure: epidemiology, clinical implications and gaps in knowledge. *Eur J Heart Fail*. 2018;20:879–887. doi: 10.1002/ejhf.1165
4. Strongman H, Gadd S, Matthews A, Mansfield KE, Stanway S, Lyon AR, Dos-Santos-Silva I, Smeeth L, Bhaskaran K. Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study using multiple linked UK electronic health records databases. *Lancet*. 2019;394:1041–1054.
5. Paterson DI, Wiebe N, Cheung WY, Mackey JR, Pituskin E, Reiman A, Tonelli M. Incident cardiovascular disease among adults with cancer: a population-based cohort study. *JACC CardioOncol*. 2022;4:85–94. doi: 10.1016/j.jaccao.2022.01.100

6. de Boer RA, Meijers WC, van der Meer P, van Veldhuisen DJ. Cancer and heart disease: associations and relations. *Eur J Heart Fail*. 2019;21:1515–1525. doi: 10.1002/ejhf.1539
7. Koene RJ, Prizment AE, Blaes A, Konety SH. Shared risk factors in cardiovascular disease and cancer. *Circulation*. 2016;133:1104–1114. doi: 10.1161/CIRCULATIONAHA.115.020406
8. Khorana AA. Cancer and coagulation. *Am J Hematol*. 2012;87:S82–S87.
9. Belzile-Dugas E, Eisenberg MJ. Radiation-induced cardiovascular disease: review of an underrecognized pathology. *J Am Heart Assoc*. 2021;10:e021686.
10. Moslehi JJ. Cardiovascular toxic effects of targeted cancer therapies. *N Engl J Med*. 2016;375:1457–1467. doi: 10.1056/NEJMra1100265
11. Zaorsky NG, Churilla TM, Egleston BL, Fisher SG, Ridge JA, Horwitz EM, Meyer JE. Causes of death among cancer patients. *Ann Oncol*. 2017;28:400–407. doi: 10.1093/annonc/mdw604
12. Oh CM, Lee D, Kong HJ, Lee S, Won YJ, Jung KW, Cho H. Causes of death among cancer patients in the era of cancer survivorship in Korea: attention to the suicide and cardiovascular mortality. *Cancer Med*. 2020;9:1741–1752. doi: 10.1002/cam4.2813
13. Ye Y, Otahal P, Marwick TH, Wills KE, Neil AL, Venn AJ. Cardiovascular and other competing causes of death among patients with cancer from 2006 to 2015: an Australian population-based study. *Cancer*. 2019;125:442–452. doi: 10.1002/cncr.31806
14. Stoltzfus KC, Zhang Y, Sturgeon K, Sinoway LI, Trifiletti DM, Chinchilli VM, Zaorsky NG. Fatal heart disease among cancer patients. *Nat Commun*. 2020;11:2011. doi: 10.1038/s41467-020-15639-5
15. Zaorsky NG, Zhang Y, Tchelebi LT, Mackley HB, Chinchilli VM, Zacharia BE. Stroke among cancer patients. *Nat Commun*. 2019;10:5172.
16. Sturgeon KM, Deng L, Bluethmann SM, Zhou S, Trifiletti DM, Jiang C, Kelly SP, Zaorsky NG. A population-based study of cardiovascular disease mortality risk in US cancer patients. *Eur Heart J*. 2019;40:3889–3897.
17. Gon Y, Zha L, Sasaki T, Morishima T, Ohno Y, Mochizuki H, Sobue T, Miyashiro I. Heart disease mortality in cancer survivors: a population-based study in Japan. *J Am Heart Assoc*. 2023;12:e029967. doi: 10.1161/JAHA.123.029967
18. Gon Y, Zha L, Sasaki T, Morishima T, Ohno Y, Mochizuki H, Sobue T, Miyashiro I. Stroke mortality in cancer survivors: a population-based study in Japan. *Thromb Res*. 2023;222:140–148. doi: 10.1016/j.thromres.2023.01.005
19. Gon Y, Zha L, Morishima T, Kimura Y, Asai K, Kudo H, Sasaki T, Mochizuki H, Miyashiro I, Sobue T. Non-cancer-related deaths in cancer survivors: a nationwide population-based study in Japan. *J Epidemiol*. 2025;35:147–153. doi: 10.2188/jea.JE20240230
20. Matsuda T, Sobue T. Recent trends in population-based cancer registries in Japan: the Act on Promotion of Cancer Registries and drastic changes in the historical registry. *Int J Clin Oncol*. 2015;20:11–20. doi: 10.1007/s10147-014-0765-4
21. Kurisu K, Fujimori M, Harashima S, Akechi T, Matsuda T, Saika K, Yoshiuchi K, Miyashiro I, Uchitomi Y. Suicide, other externally caused injuries, and cardiovascular disease within 2 years after cancer diagnosis: a nationwide population-based study in Japan (J-SUPPORT 1902). *Cancer Med*. 2023;12:3442–3451. doi: 10.1002/cam4.5122
22. Harashima S, Fujimori M, Akechi T, Matsuda T, Saika K, Hasegawa T, Inoue K, Yoshiuchi K, Miyashiro I, Uchitomi Y, et al. Death by suicide, other externally caused injuries and cardiovascular diseases within 6 months of cancer diagnosis (J-SUPPORT 1902). *Jpn J Clin Oncol*. 2021;51:744–752. doi: 10.1093/jjco/hyab001
23. Sung H, Nisotel L, Sedeta E, Islami F, Jemal A. Racial and ethnic disparities in survival among people with second primary cancer in the US. *JAMA Netw Open*. 2023;6:e2327429. doi: 10.1001/jamanetworkopen.2023.27429
24. Zhu C, Shi T, Jiang C, Liu B, Baldassarre LA, Zarich S. Racial and ethnic disparities in all-cause and cardiovascular mortality among cancer patients in the U.S. *JACC CardioOncol*. 2023;5:55–66. doi: 10.1016/j.jaccao.2022.10.013
25. Horowitz NA, Brenner B. Thrombosis in hematological malignancies: mechanisms and implications. *Thromb Res*. 2020;191:S58–S62. doi: 10.1016/S0049-3848(20)30398-4
26. Falanga A, Marchetti M. Venous thromboembolism in the hematologic malignancies. *J Clin Oncol*. 2009;27:4848–4857. doi: 10.1200/JCO.2009.22.8197
27. Grover SP, Hisada YM, Kasthuri RS, Reeves BN, Mackman N. Cancer therapy-associated thrombosis. *Arterioscler Thromb Vasc Biol*. 2021;41:1291–1305. doi: 10.1161/ATVBAHA.120.314378
28. Gon Y, Morishima T, Kawano T, Okazaki S, Todo K, Sasaki T, Mochizuki H, Miyashiro I. Arterial thromboembolism in Japanese patients with cancer: incidence, predictors, and survival impact. *JACC CardioOncol*. 2024;6:283–297. doi: 10.1016/j.jaccao.2024.01.006
29. Falanga A, Marchetti M, Vignoli A. Coagulation and cancer: biological and clinical aspects. *J Thromb Haemost*. 2013;11:223–233. doi: 10.1111/jth.12075
30. Crusz SM, Balkwill FR. Inflammation and cancer: advances and new agents. *Nat Rev Clin Oncol*. 2015;12:584–596. doi: 10.1038/nrclinonc.2015.105
31. Henson KE, Reulen RC, Winter DL, Bright CJ, Fidler MM, Frobisher C, Guha J, Wong KF, Kelly J, Edgar AB, et al. Cardiac mortality among 200 000 five-year survivors of cancer diagnosed at 15 to 39 years of age: the teenage and young adult cancer survivor study. *Circulation*. 2016;134:1519–1531. doi: 10.1161/CIRCULATIONAHA.116.022514
32. Chao C, Xu L, Bhatia S, Cooper R, Brar S, Wong FL, Armenian SH. Cardiovascular disease risk profiles in survivors of adolescent and young adult (AYA) cancer: the Kaiser permanente AYA cancer survivors study. *J Clin Oncol*. 2016;34:1626–1633.
33. Gandini S, Botteri E, Iodice S, Boniol M, Lowenfels AB, Maisonneuve P, Boyle P. Tobacco smoking and cancer: a meta-analysis. *Int J Cancer*. 2008;122:155–164. doi: 10.1002/ijc.23033
34. Ockene IS, Miller NH. Cigarette smoking, cardiovascular disease, and stroke: a statement for healthcare professionals from the American Heart Association. *Circulation*. 1997;96:3243–3247.
35. Forastiere AA, Ismaila N, Lewin JS, Nathan CA, Adelstein DJ, Eisbruch A, Fass G, Fisher SG, Laurie SA, Le QT, et al. Use of larynx-preservation strategies in the treatment of laryngeal cancer: American Society of Clinical Oncology Clinical Practice Guideline Update. *J Clin Oncol*. 2018;36:1143–1169. doi: 10.1200/JCO.2017.75.7385
36. Venkatesulu BP, Mahadevan LS, Aliru ML, Yang X, Bodd MH, Singh PK, Yusuf SW, Abe JI, Krishnan S. Radiation-induced endothelial vascular injury: a review of possible mechanisms. *JACC Basic Transl Sci*. 2018;3:563–572. doi: 10.1016/j.jacbts.2018.01.014
37. Rimmer J, Giddings CE, Vaz F, Brooks J, Hopper C. Management of vascular complications of head and neck cancer. *J Laryngol Otol*. 2012;126:111–115.
38. Salvador-Coloma C, Cohen E. Multidisciplinary care of Laryngeal cancer. *J Oncol Pract*. 2016;12:717–724. doi: 10.1200/JOP.2016.014225
39. Afdhal N, McHutchison J, Brown R, Jacobson I, Manns M, Poordad F, Weksler B, Esteban R. Thrombocytopenia associated with chronic liver disease. *J Hepatol*. 2008;48:1000–1007. doi: 10.1016/j.jhep.2008.03.009
40. Lisman T, Leebeek FW, de Groot PG. Haemostatic abnormalities in patients with liver disease. *J Hepatol*. 2002;37:280–287.
41. Tsai SJ, Huang YS, Tung CH, Lee CC, Lee MS, Chiou WY, Lin HY, Hsu FC, Tsai CH, Su YC, et al. Increased risk of ischemic stroke in cervical cancer patients: a nationwide population-based study. *Radiat Oncol*. 2013;8:41. doi: 10.1186/1748-717X-8-41
42. Kuan AS, Teng CJ, Wu HH, Su VY, Chen YT, Chien SH, Yeh CM, Hu LY, Chen TJ, Tzeng CH, et al. Risk of ischemic stroke in patients with ovarian cancer: a nationwide population-based study. *BMC Med*. 2014;12:53.
43. Wang X, Wang E, Kavanagh JJ, Freedman RS. Ovarian cancer, the coagulation pathway, and inflammation. *J Transl Med*. 2005;3:25. doi: 10.1186/1479-5876-3-25
44. Larsen CM, Garcia Arango M, Dasari H, Arciniegas Calle M, Adjei E, Rico Mesa J, Scott CG, Thompson CA, Cerhan JR, Haddad TC, et al. Association of anthracycline with heart failure in patients treated for breast cancer or lymphoma, 1985-2010. *JAMA Netw Open*. 2023;6:e2254669.
45. Sengupta PP, Northfelt DW, Gentile F, Zamorano JL, Khandheria BK. Trastuzumab-induced cardiotoxicity: heart failure at the crossroads. *Mayo Clin Proc*. 2008;83:197–203. doi: 10.4065/83.2.197
46. Shah C, Al-Hilli Z, Vicini F. Advances in breast cancer radiotherapy: implications for current and future practice. *JCO Oncol Pract*. 2021;17:697–706. doi: 10.1200/OP.21.00635
47. Mieno MN, Tanaka N, Arai T, Kawahara T, Kuchiba A, Ishikawa S, Sawabe M. Accuracy of death certificates and assessment of factors for misclassification of underlying cause of death. *J Epidemiol*. 2016;26:191–198. doi: 10.2188/jea.JE20150010