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ORIGINAL RESEARCH

Heart Disease Mortality in Cancer Survivors: A Population-Based Study in Japan

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BACKGROUND: Data on the risk of cardiovascular-related mortality in patients with cancer are limited.

METHODS AND RESULTS: This retrospective cohort study used data from the Osaka Cancer Registry and vital statistics in Japan between 1985 and 2013. The causes of death were investigated, and the risk of fatal heart disease was analyzed. Standardized mortality ratios were calculated to compare the risk of fatal heart disease between patients with cancer and the general population. Fine and Gray competing risk regression models were used to assess the risk of fatal heart disease among patients with cancer. In total, 682 886 patients with cancer were included in the analysis, and 335 635 patients died during the study period. Heart disease was the leading cause of noncancer deaths, with 10 686 deaths. Among the patients who died of heart disease, 5017 had ischemic heart disease, 3598 had heart failure, 356 had hypertensive disease, and 1715 had other heart diseases. The standardized mortality ratio for heart disease was 2.80 (95% CI, 2.74–2.85). The standardized mortality ratio for ischemic heart disease, heart failure, and hypertensive disease were 3.26 (95% CI, 3.17–3.35), 2.69 (95% CI, 2.60–2.78), and 5.97 (95% CI, 5.38–6.63), respectively. The risk of fatal heart disease increased over time after cancer diagnosis. Men were more likely to die of heart disease than women (subdistribution hazard ratio, 1.08 [95% CI, 1.02–1.16]). The risk of fatal heart disease among cancer survivors has decreased in recent years.

CONCLUSIONS: Cancer survivors have a higher risk of fatal heart disease than the general population.

Key Words: cancer ■ cancer survivors ■ cohort study ■ heart disease ■ mortality

Advances in cancer care have prolonged survival.[1] With population aging, patients with cancer have also become older and more highly comorbid.[2,3] The number of elderly cancer survivors is expected to increase in the coming decades, and, thus, the management of comorbidities is becoming a more significant concern.

Patients with cancer are at a high risk of developing heart disease.[4] Cancer and heart disease share common risk factors such as hypertension, diabetes, and smoking.[4,5] In addition, neuroendocrine factors, oxidative stress, inflammatory cytokines, and impaired immune system have been implicated in the increased risk of heart disease in patients with cancer.[4,5] With respect to mortality, an increased risk of death from heart disease has been reported for breast,[6,7] head and neck,[8] testicular,[9] and hematopoietic malignancies.[10] Zaorsky et al recently found that heart disease was the most common noncancer cause of death in patients with cancer.[11] Stoltzfus et al evaluated the data of ≈7.5 million patients with cancer from the Surveillance, Epidemiology, and End Results (SEER)

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CLINICAL PERSPECTIVE

What Is New?

- It is widely acknowledged that patients with cancer have a higher risk of developing cardiovascular disease; however, limited evidence is available regarding the specific population of patients with cancer at an increased risk of mortality from heart disease.
- We conducted a retrospective analysis of the risk of fatal heart disease among patients with cancer using the Osaka Cancer Registry and the vital statistics in Japan.
- Patients with cancer had a significantly higher risk of fatal heart disease than the general population, with a standardized mortality ratio of 2.80, and the risk varied depending on the type of heart disease, with a 3.26-fold increase for ischemic heart disease, 2.69-fold risk for heart failure, and 5.97-fold risk for hypertensive disease.

What Are the Clinical Implications?

- Cancer survivors have a higher risk of fatal heart disease than the general population.
- Clinicians should recognize the risk of fatal heart disease in patients with cancer.
- Careful clinical management, including of both cancer and heart disease, may be beneficial to improve the survival of cancer survivors.

Nonstandard Abbreviations and Acronyms

NANDE	Neoplasms and Other Causes of Death
OCR	Osaka Cancer Registry
SHR	subdistribution hazard ratio
SMR	standardized mortality ratio

database and reported a 2.2-fold higher risk of death from heart disease in patients with cancer than in the general population.[12] However, different findings have been reported in the literature. A study using the Korean Cancer Registry reported a lower risk of heart disease–related mortality among cancer survivors.[13] Another study using the Tasmanian Cancer Registry demonstrated that the risk of heart disease mortality in patients with cancer was similar to that in the general population.[14] It is widely acknowledged that patients with cancer have a higher risk of developing cardiovascular disease, and, thus, cardio-oncology guidelines have been developed.[15] However, there is limited evidence available regarding the specific population of patients with cancer at higher risk of mortality from heart disease.

In an era of increasing numbers of older cancer survivors, clinicians, including both oncologists and cardiologists, must recognize the significance of the risk of fatal heart disease in patients with cancer. Evidence about the association between cancer and fatal heart disease worldwide needs to be accumulated. However, many of the previous studies have been conducted in Europe and the United States, with only a limited number of studies conducted in Asia, including Japan.[7–14] Japan has one of the most aged populations worldwide, and 1 of 2 Japanese people is predicted to develop cancer.[15] The distribution of cancer types in Japan differs from that in Europe and the United States, with a higher prevalence of cancer types associated with high fatality rates (eg, esophageal and liver cancers) and a lower prevalence of cancer types with lower fatality rates (eg, prostate and breast cancers).[16–18] Data on the association between cancer and heart disease mortality in the super-aging society of Japan will be valuable in advancing research in cardio-oncology.

This study aimed to evaluate the risk of fatal heart disease after cancer diagnosis in Japan. We analyzed the risk of fatal heart disease in patients with cancer, and by cancer subgroup, compared with the general population.

METHODS

Data Availability

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethics Approval and Consent to Participate

Informed consent was waived owing to the retrospective nature of the study. The institutional review board of Osaka University, Suita, Japan, approved the study protocol (approval number: 17315–3).

Study Design and Data Source

This retrospective study was conducted as part of the NANDE (Neoplasms and Other Causes of Death) study, which investigated the causes of death in patients with cancer.[19–21] Briefly, the NANDE database was created by linking OCR (Osaka Cancer Registry) with official statistics in Japan. The OCR has been in operation since 1962, covering more than 8 million residents in Osaka Prefecture, Japan. All patients registered in OCR are followed for 10 years. OCR includes data on age at diagnosis, sex, year of diagnosis, cancer type,

stage at diagnosis, histology, follow-up period, and death. OCR also contains information on survival or death status, and official statistics in Japan include the individual causes of death based on the death certificate completed by a doctor. Therefore, we merged the 2 databases by sex, date of birth, date of death, and municipality of residence data and collected details on the causes of death from official statistics. Thereafter, information on 96.6% of the patients with cancer was collated. The NANDE database contains cancer-related information on age at diagnosis, sex, year of diagnosis, cancer type, stage at diagnosis, histology, survival time, and cause of death.

Patients

The current study used data of patients diagnosed with cancer between 1985 and 2013 and registered in the NANDE database. The exclusion criteria were as follows: (1) uncertain date of death, (2) uncertain final date of survival confirmation, (3) uncertain date of first cancer diagnosis, (4) uncertain date of second cancer diagnosis, (5) uncertain age at first cancer diagnosis, (6) death certificate notification or death certification only, (7) simultaneous cancer (ie, multiple tumors identified at the time of diagnosis) or synchronous cancer (ie, diagnosed within 2 months of each other), (8) age at cancer diagnosis <18 years, and (9) male breast cancer. The definition of synchronous tumors varies among studies, ranging from 2 to 6 months between diagnoses.[22,23] The details are summarized in Figure S1.

Variable Definition

Age at diagnosis was grouped into 6 categories: ≤39, 40 to 49, 50 to 59, 60 to 69, 70 to 79, and ≥80 years. Meanwhile, the year of diagnosis was classified into 3 periods: 1985 to 1995, 1995 to 2004, and 2005 to 2013. The stage at diagnosis was classified into 7 categories: (1) intraepithelial (abnormal cells were present but have not spread to nearby tissues), (2) localized (cancer was limited to the organ where it originated, with no sign of spread), (3) lymph node metastasis (cancer had spread to regional lymph nodes), (4) infiltration to adjacent organs (cancer had spread to nearby tissues or organs), (5) distant metastasis (cancer had metastasized to distant parts of the body), (6) unknown (there is insufficient information to determine the stage), and (7) not available (missing data on the stage). Histology was classified into 6 categories according to Berg classification[24]: squamous or basal cell carcinoma, adenocarcinoma, other carcinoma, lymphoma (non-Hodgkin and Hodgkin lymphoma), hematopoietic tumors (excluding lymphoma), and other histology. The detailed histological groupings are provided in Table S1.

Diseases were coded based on the *International Classification of Diseases* (*ICD*), and cancers were coded according to the *International Classification of Diseases for Oncology, Third Edition*. Details concerning the assignment of codes and number of patients (those included, excluded, and lost to follow-up) are shown in Table S2. Heart diseases, including ischemic heart disease (IHD), heart failure (HF), hypertensive disease, and other heart diseases, were identified using the *International Classification of Diseases, Ninth Revision* (*ICD-9*), and *International Statistical Classification of Diseases, Tenth Revision* (*ICD-10*), codes. In Japan, the causes of death were officially registered based on the *ICD-9* codes from 1979 to 1994; thereafter, the *ICD-10* codes were used. Details on the assignment of *ICD-9* and *ICD-10* codes were as follows: heart disease, *ICD-9* (390–398, 402, 404, 410–429) and *ICD-10* (I00–I09, I11, I13, I20–I52); IHD, *ICD-9* (410–414) and *ICD-10* (I20–I25); HF, *ICD*-9 (428) and *ICD-10* (I50); hypertensive disease, *ICD-9* (401, 403, 405) and *ICD-10* (I11, I13, I15); and other heart diseases, *ICD-9* (390–398, 415–429) and *ICD-10* (I00–I09, I26–I49, I51–I52).

Statistical Analysis

The risk of death from heart disease after cancer diagnosis was analyzed. Heart disease death was defined as heart disease being the cause of death recorded on the death certificate. The observation period was from January 1985 to December 2013. The survival time was measured in days, with a minimum of 1 day and a maximum of 3652 days. The index date for follow-up was the date of initial cancer diagnosis. The end date of follow-up was set as 10 years after the cancer diagnosis or until December 2013. Patients with <10 years of follow-up were censored at their last follow-up date. In patients diagnosed with a second cancer during the observation period, their follow-up was censored at the time of the second cancer diagnosis.

To compare the risk of fatal heart disease in patients with cancer with that in the general population, the standardized mortality ratios (SMRs) and their 95% CIs were calculated as the ratio of the observed to the expected number of deaths. The observed number of deaths was obtained from the NANDE database. The expected number was calculated by summing the products of multiplying the population in each 5-year age group of the study cohort by the national cause-specific mortality rate for the corresponding sex, age group, and calendar year in Japan. Information concerning both the national population and the number of deaths, including in patients with and without cancer, is available on the Portal Site of Official Statistics of Japan (https://www.e-stat.go.jp/en). The SMRs were calculated for heart disease, IHD, HF, and hypertensive disease.

To compare the risk of fatal heart disease among patients with cancer, a Fine and Gray competing risk

regression model was used to assess the influence of individual patient and tumor characteristics on heart disease mortality. Deaths from cancer and other causes were treated as competing risks. The results are presented as subdistribution hazard ratios (SHRs) and their 95% CIs, adjusted for sex, age at diagnosis, period of diagnosis, stage at diagnosis, and histology. We calculated the absolute numbers of cancer, heart disease, cerebrovascular disease, and noncancer (excluding heart and cerebrovascular disease) deaths for each specific cancer type, as well as the relative rates of death based on the number of years since cancer diagnosis.

All statistical analyses were performed using Stata 17/MP (StataCorp LLC) and R (https://cran.r-project.org/) software. All tests were 2-tailed, and $P<0.05$ was considered statistically significant.

RESULTS

Patient Characteristics

A total of 682 886 patients were included in the analysis, with 2 632 799 person-years at risk. Table 1 presents the demographics of the cohort. The distribution of cancer types in the groups of included and excluded patients is shown in Table S2. Stomach cancer was the most prevalent cancer type among the included patients (17.5%), followed by colorectal (16.2%) and lung (11.7%) cancers. Among patients ineligible for analysis, stomach cancer was the most common (16.6%), followed by lung (15.2%) and liver (14.6%) cancers. Among the patients lost to follow-up, liver cancer was the most common (17.5%), followed by stomach (15.8%) and lung (15.4%) cancers. In the comparison between included patients and those excluded from analysis, liver cancer was present in 7.4%

Table 1. Demographics of the Study Cohort

	Included (N=682 886)	Excluded (n=348 575)	
		Ineligible for analysis (n=324 313)	Lost to follow-up (n=24 262)
Sex			
Female	301 502	134 161	9394
Male	381 384	190 152	14 868
Age at diagnosis, y			
≤39	29 720	13 716	749
40–49	58 935	16 785	1508
50–59	119 476	44 201	3970
60–69	201 930	77 648	6787
70–79	190 506	89 644	7003
≥80	82 319	82 319	4245
Period of diagnosis			
1985–1994	137 882	107 517	7246
1995–2004	197 608	127 002	7723
2005–2013	347 396	89 794	9293
Stage at diagnosis			
Intraepithelial	36 309	3053	366
Localized	276 004	35 917	5973
Lymph node metastasis	87 496	14 088	2352
Infiltration to adjacent organs	90 916	20 251	3189
Distant metastasis	115 806	34 977	4553
Unknown	62 473	90 020	4201
N/A	13 882	12 075	666
Histology			
Adenocarcinoma	405 092	74 636	9738
Squamous or basal carcinoma	105 503	21 339	2933
Other carcinomas	77 013	43 658	4598
Lymphoma	17 390	6914	529
Hematopoietic tumors (excluding lymphoma)	13 766	13 232	679
Other histology	64 122	164 534	5785

N/A indicates not applicable.

of the included patients, in 14.6% of patients ineligible for analysis, and in 17.5% of patients lost to follow-up. In contrast, breast cancer was diagnosed in 9.7% of the included patients, in 3.7% of patients ineligible for analysis, and in 4.0% of patients lost to follow-up.

A total of 335 635 patients died during the study period. Of these, 85.2% (n=286 011) died of cancer, while the remaining 14.8% (n=49 624) died of noncancer-related causes. Heart disease was the leading cause of noncancer death, accounting for 10 686 deaths, followed by pneumonia (n=6603) and cerebrovascular disease (n=5489). Among the patients who died due to heart disease, the distribution of causes of death were as follows: IHD, 5017 patients; HF, 3598 patients; hypertensive disease, 356 patients; and other heart diseases, 1715 patients. The number of deaths due to IHD, HF, hypertensive disease, and other heart diseases according to cancer type is shown in Table S3.

Comparison of Risk of Heart Disease Death Between Patients With Cancer and the General Population

Among all patients with cancer, the crude rate of mortality due to heart disease was 405.88 per 100 000 person-years, and the overall SMR for heart disease was 2.80 (95% CI, 2.74–2.85). Table 2 presents the SMRs for heart disease death in patients with cancer

Table 2. SMRs for Heart Disease Death in Patients With Cancer Compared With the General Population

	Person-y	Heart disease death		Heart disease death rate*	SMR (95% CI)†
		Observed	Expected		
All patients	2 632 799	10 686	3821.29	405.88	2.80 (2.74–2.85)
Sex					
Female	1 311 831	4082	1407.50	301.07	2.90 (2.81–2.99)
Male	1 320 968	6604	2413.80	499.94	2.74 (2.67–2.80)
Age at diagnosis, y					
≤39	103 628	27	0.41	26.05	65.52 (44.93–95.54)
40–49	235 502	104	5.44	44.16	19.10 (15.75–23.15)
50–59	467 459	410	49.93	87.71	8.21 (7.45–9.05)
60–69	761 688	1537	261.98	201.79	5.87 (5.58–6.17)
70–79	738 086	3632	804.25	492.08	4.52 (4.37–4.67)
≥80	326 436	4976	2699.27	1524.34	1.84 (1.79–1.90)
Period of diagnosis					
1985–1994	606 537	3312	1366.52	527.77	2.42 (2.34–2.51)
1995–2004	1 012 667	3738	1576.10	357.48	2.37 (2.30–2.45)
2005–2013	1 013 595	3636	878.68	347.25	4.14 (4.01–4.28)
Stage at diagnosis					
Intraepithelial	176 871	379	99.94	214.28	3.79 (3.43–4.19)
Localized	1 440 128	5624	1948.79	390.52	2.89 (2.81–2.96)
Lymph node metastasis	387 374	1393	525.82	359.6	2.65 (2.51–2.79)
Infiltration to adjacent organs	233 041	1110	410.56	476.31	2.70 (2.55–2.87)
Distant metastasis	152 321	776	353.72	509.45	2.19 (2.05–2.35)
Unknown	207 140	1185	426.12	572.08	2.78 (2.63–2.94)
N/A	35 925	219	56.34	609.6	3.89 (3.41–4.44)
Histology					
Adenocarcinoma	1 757 558	6220	2246.74	353.9	2.77 (2.70–2.84)
Squamous or basal carcinoma	410 688	2153	722.97	524.24	2.98 (2.86–3.11)
Other carcinomas	207 607	796	389.05	383.42	2.05 (1.91–2.19)
Lymphoma	57 756	216	73.07	373.99	2.96 (2.59–3.38)
Hematopoietic tumors (excluding lymphoma)	40 323	220	61.04	545.59	3.60 (3.16–4.11)
Other histology	158 867	1081	328.42	680.44	3.29 (3.10–3.49)

N/A indicates not applicable.

*Per 100 000 person-years.

†Standardized mortality ratios (SMRs) may not equal the number of observed deaths divided by expected deaths because expected deaths are only listed to 2 decimal places.

in comparison to those in the general population. Patients who were diagnosed with cancer at a younger age had a higher SMR for heart disease, and the SMR gradually decreased as the age of diagnosis increased. The SMR was the highest when the diagnostic period was later than 2005. The SMR by stage at diagnosis was highest for intraepithelial disease and lowest for distant metastatic disease in patients with known stages. Regardless of the histology, the risk of death by heart disease was 2 to 3 times higher in patients with cancer than in the general population. The SMRs for lymphoma (non-Hodgkin and Hodgkin lymphoma) and hematopoietic tumors excluding lymphoma were 2.96 and 3.60, respectively.

Comparison of Risk of IHD, HF, and Hypertensive Disease Death Between Patients With Cancer and the General Population

Table 3 describes the SMRs for IHD, HF, and hypertensive disease. The number of deaths due to IHD, HF, and hypertensive disease is listed in Table S4. The crude mortality rates due to IHD, HF, and hypertensive

Table 3. SMRs for IHD, HF, and Hypertensive Disease in Patients With Cancer Compared With the General Population

	IHD		HF		Hypertensive disease	
	Rate*	SMR† (95% CI)	Rate*	SMR† (95% CI)	Rate*	SMR† (95% CI)
All patients	190.56	3.26 (3.17–3.35)	136.66	2.69 (2.60–2.78)	13.52	5.97 (5.38–6.63)
Sex						
Female	125.85	3.49 (3.33–3.67)	117.09	2.74 (2.61–2.89)	11.28	11.76 (10.01–13.81)
Male	254.81	3.16 (3.05–3.26)	156.1	2.65 (2.53–2.76)	15.75	4.42 (3.86–5.07)
Age at diagnosis, y						
≤39	7.72	86.80 (43.41–173.56)	14.47	93.34 (56.27–154.82)	0	…
40–49	14.86	15.63 (11.22–21.77)	17.83	23.67 (17.49–32.02)	0	…
50–59	40.64	7.67 (6.65–8.84)	31.02	10.95 (9.31–12.89)	0.64	4.63 (1.49–14.36)
60–69	104.9	5.71 (5.33–6.12)	57.64	7.16 (6.52–7.86)	6.04	12.37 (9.27–16.52)
70–79	257.56	4.67 (4.46–4.88)	143.89	5.05 (4.75–5.36)	16.8	9.44 (7.92–11.26)
≥80	638.41	2.16 (2.07–2.25)	580.51	1.80 (1.72–1.88)	56.06	4.35 (3.77–5.03)
Period of diagnosis						
1985–1994	203.78	2.23 (2.11–2.36)	254.23	2.94 (2.80–3.09)	15.83	3.23 (2.65–3.95)
1995–2004	191.57	2.98 (2.85–3.11)	99.34	1.96 (1.85–2.09)	13.43	6.81 (5.76–8.06)
2005–2013	181.63	5.51 (5.27–5.77)	103.59	3.48 (3.28–3.70)	12.23	12.49 (10.47–14.89)
Stage at diagnosis						
Intraepithelial	112.51	5.14 (4.48–5.91)	59.37	3.00 (2.48–3.63)	9.05	12.14 (7.44–19.81)
Localized	191.51	3.50 (3.37–3.63)	123.18	2.63 (2.51–2.76)	14.17	6.90 (6.01–7.91)
Lymph node metastasis	163.41	2.96 (2.73–3.20)	129.85	2.72 (2.50–2.97)	11.87	5.48 (4.11–7.32)
Infiltration to adjacent organs	220.13	3.13 (2.87–3.42)	166.49	2.66 (2.41–2.94)	17.59	6.39 (4.71–8.68)
Distant metastasis	227.81	2.39 (2.15–2.65)	188.42	2.31 (2.06–2.60)	11.82	2.94 (1.85–4.67)
Unknown	235.11	2.91 (2.66–3.18)	221.59	2.96 (2.70–3.24)	13.03	3.86 (2.65–5.63)
N/A	222.68	3.60 (2.89–4.48)	228.25	4.13 (3.32–5.12)	11.13	5.04 (1.89–13.42)
Histology						
Adenocarcinoma	169.61	3.31 (3.19–3.43)	112.88	2.52 (2.42–2.64)	12.97	6.68 (5.87–7.61)
Squamous or basal carcinoma	256.16	3.58 (3.37–3.80)	176.05	2.85 (2.65–3.06)	16.31	5.52 (4.35–7.01)
Other carcinomas	190.26	2.37 (2.15–2.62)	124.75	2.03 (1.80–2.29)	11.08	3.90 (2.59–5.87)
Lymphoma	155.83	3.07 (2.50–3.78)	121.20	2.78 (2.20–3.51)	6.93	3.92 (1.47–10.45)
Hematopoietic tumors (excluding lymphoma)	195.92	3.28 (2.63–4.09)	205.84	3.80 (3.07–4.72)	12.40	5.58 (2.32–13.41)
Other histology	264.26	3.36 (3.05–3.70)	301.51	3.84 (3.51–4.20)	18.25	5.25 (3.65–7.55)

HF indicates heart failure; IHD, ischemic heart disease; N/A, not applicable; and SMR, standardized mortality ratio.

*Per 100 000 person-years.

†SMRs may not equal the number of observed deaths divided by expected deaths (data are shown in Table S4) because expected deaths are only listed to 2 decimal places.

disease were 190.56, 136.66, and 13.52 per 100 000 person-years, respectively. The SMRs for IHD, HF, and hypertensive disease were 3.26 (95% CI, 3.17–3.35), 2.69 (95% CI, 2.60–2.78), and 5.97 (95% CI, 5.38–6.63), respectively. The SMRs for IHD, HF, and hypertensive disease were higher in women, patients diagnosed between 2005 and 2013, and patients with intraepithelial diseases than in other subgroups. Regarding age at diagnosis, the SMRs for IHD and HF were the highest in patients with a younger age at diagnosis. In contrast, the SMR for hypertensive disease was the highest in patients aged 60 to 69 years at diagnosis. The SMRs for lymphoma were lower than those for hematologic tumors excluding lymphoma.

SMR for Heart Disease According to Cancer Site

Figure 1 shows the SMRs for heart disease according to cancer site. The details are presented in Table S5. The SMR was the highest in brain cancer, followed by that in esophageal, bone, uterine, and hematopoietic tumors (excluding lymphoma). Meanwhile, the SMR was the lowest in liver cancer, followed by that in gallbladder, lung, pancreatic, and ovarian cancers.

Risk of Heart Disease Death According to Time After Cancer Diagnosis

Figure 2 shows the SMR trend after cancer diagnosis. The details are presented in Tables S6 through S10. The SMR for heart disease was 2.90 (95% CI, 2.73–3.08) within the first 3 months after cancer diagnosis, declined once, and then gradually increased thereafter. The trend of SMR for IHD and HF was similar to that of the SMR for overall heart disease. The SMRs for hypertensive disease varied with time after cancer diagnosis; however, in general, the SMRs increased over time. The SMR for hypertensive disease was the lowest within the first year (2.00 [95% CI,

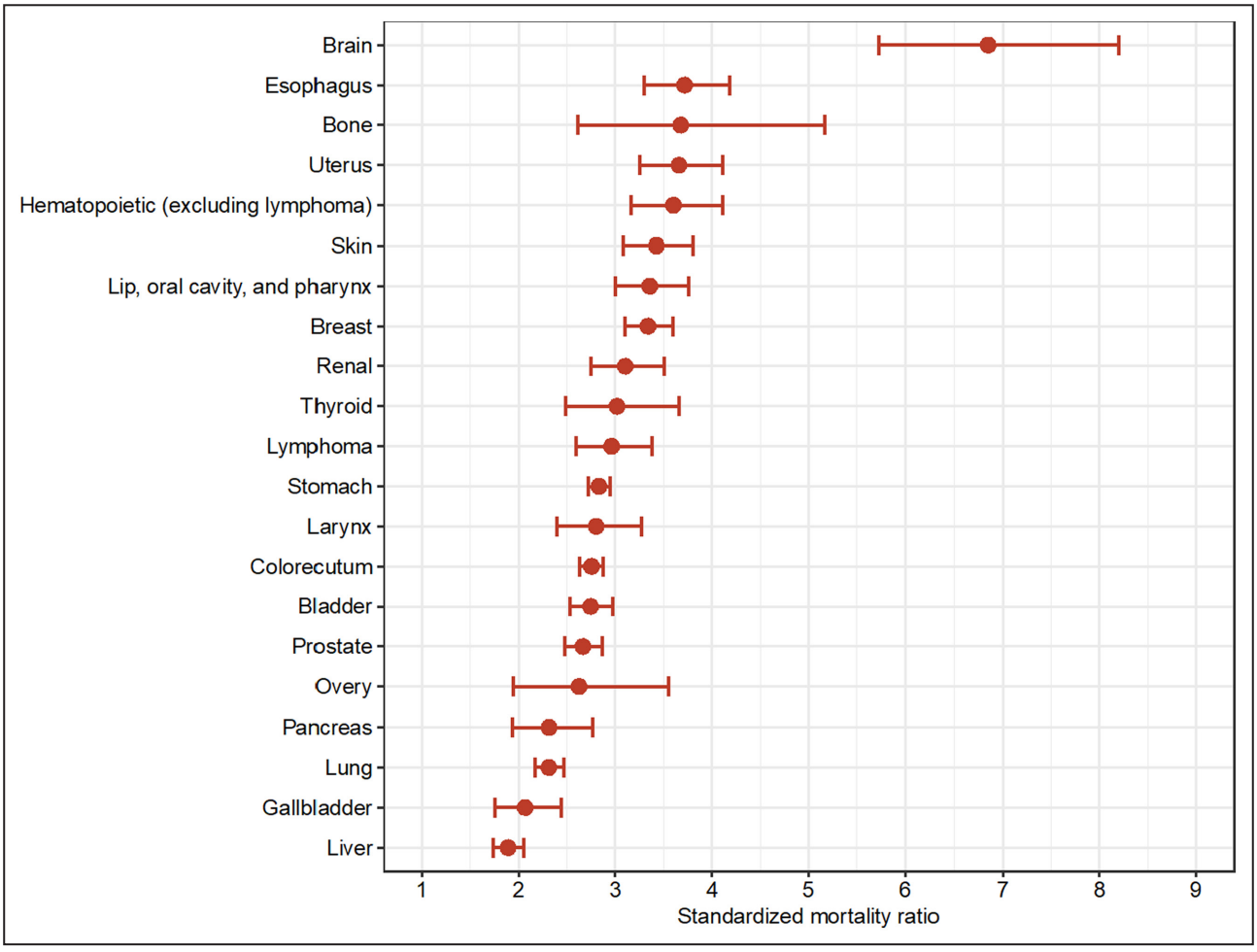

Figure 1. SMR for heart disease death stratified by cancer site.
The ordinate shows the cancer site, and the abscissa indicates the SMR for heart disease–related death. Error bars show the 95% CIs. The plots are in the order of increasing SMR. Patients with cancer have a higher SMR for heart disease–related death than the general population. SMR indicates standardized mortality ratio.

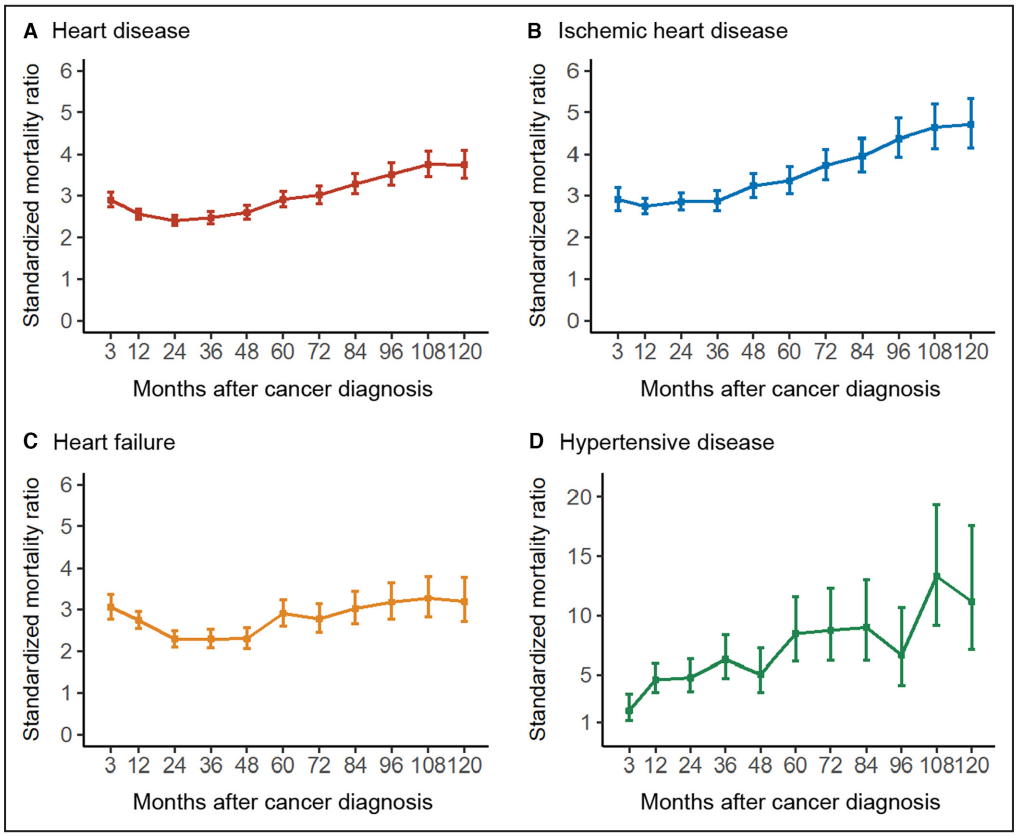

Figure 2. Trends in SMR according to time after cancer diagnosis.
The ordinate shows the SMR, and the abscissa indicates the time after cancer diagnosis. Error bars show the 95% CIs. **A**, The SMR for heart disease tends to be high immediately after diagnosis, declines once, and then increases with time. **B** and **C**, The SMR for ischemic heart disease and heart failure shows a trend similar to that of heart disease. **D**, In the analysis of hypertensive disease, SMR varies with time, but they are generally increased over time. SMR indicates standardized mortality ratio.

1.16–3.44] and highest in the ninth year (13.33 [95% CI, 9.21–19.31]) after cancer diagnosis.

Risk of Fatal Heart Disease Among Patients With Cancer

Table 4 shows the SHRs of patients with cancer for fatal heart disease. Men were 1.08 times more likely to die from heart disease than women. SHRs gradually increased as the age at diagnosis increased. Meanwhile, SHRs gradually decreased as the period of diagnosis became more recent. Patients with distant metastases had the lowest SHR among all cancer stages. Table 5 shows the SHRs for IHD, HF, and hypertensive disease. Men were more likely to die from IHD than were women. SHRs were higher for patients who were older at diagnosis with IHD and HF, while they were lower for those more recently diagnosed with IHD, HF, and hypertensive disease. When analyzed according to stage at diagnosis, the SHRs for death from IHD, HF, and hypertensive disease were the lowest for patients with distant metastasis. The SHRs varied according to histological stage and heart disease.

Distribution of Causes of Death by Cancer Type

Figure 3 illustrates the distribution of causes of death among various cancer types. Additional details are presented in Tables S11 through S14. In the first year following a cancer diagnosis, cancer-related mortality constituted the largest proportion (91.2%) of all recorded deaths, while heart disease deaths accounted for 1.7%, cerebrovascular disease accounted for 0.8%, and noncancer deaths (excluding heart and cerebrovascular disease deaths) accounted for 7.1%. The percentage of cancer-related deaths gradually declined over subsequent years, reaching 53.0% in the 10th year. Conversely, noncancer deaths showed a progressive increase, with heart disease death accounting for 10.2% of all deaths, cerebrovascular disease accounting for 6.4%, and noncancer deaths (excluding

Table 4. Risk of Heart Disease Death in Patients With Cancer

	SHR	95% CI	*P* value
Sex			
Female	1.00	…	
Male	1.08	1.02–1.16	0.01
Age at diagnosis, y			
≤39	1.00	…	
40–49	2.02	1.23–3.31	0.006
50–59	5.32	3.33–8.49	<0.001
60–69	12.16	7.60–19.43	<0.001
70–79	28.12	17.52–45.13	<0.001
≥80	57.06	35.52–91.66	<0.001
Period of diagnosis			
1985–1994	1.00	…	
1995–2004	0.65	0.59–0.73	<0.001
2005–2013	0.31	0.27–0.36	<0.001
Stage at diagnosis			
Intraepithelial	1.00	…	
Localized	1.10	0.96–1.25	0.16
Lymph node metastasis	0.69	0.59–0.81	<0.001
Infiltration to adjacent organs	0.46	0.39–0.55	<0.001
Distant metastasis	0.25	0.21–0.31	<0.001
Unknown	0.68	0.57–0.80	<0.001
N/A	0.77	0.57–1.03	0.08
Histology			
Adenocarcinoma	1.00	…	
Squamous or basal carcinoma	1.05	0.99–1.13	0.13
Other carcinomas	0.50	0.45–0.57	<0.001
Lymphoma	0.83	0.66–1.02	0.08
Hematopoietic tumors (excluding lymphoma)	0.84	0.66–1.07	0.15
Other histology	0.81	0.73–0.90	<0.001

N/A indicates not applicable; and SHR, subdistribution hazard ratio.

heart and cerebrovascular diseases) accounting for 36.8% of mortality in the 10th year since the cancer diagnosis. When considering specific cancer types, liver cancer had a high proportion of cancer-related deaths, whereas skin cancer was associated with a high proportion of noncancer deaths, including those due to heart diseases. Lymphoma, like liver and ovarian cancer, had a high rate of cancer deaths.

DISCUSSION

The risk of heart disease–related mortality in patients with cancer has not been elucidated to date. This study found the following findings. First, cancer survivors have a 2.80 times greater risk of heart disease death than the general population in the Japanese population. To the best of our knowledge, this study is the first to report the risk of heart disease–related mortality in the Japanese population of patients with cancer. Second, this risk varied by heart disease type: 3.26 times higher for IHD, 2.69 times higher for HF, and 5.97 times higher for hypertensive disease. Third, the risk of death from heart disease tended to increase with time after cancer diagnosis. Finally, the risk of fatal heart disease among cancer survivors has decreased in recent years.

There have been studies on the risk of heart disease–related mortality among cancer survivors.[6–14] We found similar associations in the current analysis: patients with cancer had a 2.80 times higher risk of death from heart disease than the general population. The results were similar in the subgroup analysis by sex, age at diagnosis, year of diagnosis, and stage at diagnosis. However, some results were in contrast to previous findings. For example, the SMR of lung cancer was not higher in our study compared with that in the report by Stolzfus et al in 2020, who retrospectively analyzed the SEER data from 1992 to 2015.[12] In addition, while the SMR by stage at diagnosis was the highest in distant metastases and lowest in localized cancers in previous research, opposite findings were noted in our analysis. The SMR was the lowest in distant metastasis and highest in intraepithelial cancer. However, this result was similar to that of our previous study on stroke deaths among cancer survivors.[21] Although the SMRs could not be compared due to the different populations studied, these findings are noteworthy in the context of prognosis and management of heart disease risk in cancer survivors. The factors that influenced these results are unclear, but regional differences and the extent of malignancies are possible contributing factors.

Several mechanisms explain the relationship between cancer and heart disease. Lifestyle factors such as diabetes and smoking are associated with the development of both cancer and heart disease.[4,5,25] Neuroendocrine factors, oxidative stress, inflammatory cytokines, and impaired immune system have been implicated in the increased risk of developing heart disease in patients with cancer.[4,5] Cancer-related coagulation abnormalities can cause arterial thromboembolisms, including myocardial infarction.[26] Certain anticancer agents, including anthracyclines,[27] tyrosine kinase inhibitors,[28] and immune checkpoint inhibitors,[29,30] have cardiotoxic adverse effects. Further, late-onset drug toxicity has been found to be associated with an increased risk of heart disease–related mortality among cancer survivors.[31] An increased risk of cardiovascular events with surgery[32] and radiotherapy[33] has also been reported.

The current study found that the risk of fatal heart disease increased over time after cancer diagnosis.

Table 5. Risk of IHD, HF, and Hypertensive Disease Death Among Patients With Cancer

	IHD			HF			Hypertensive disease		
	SHR	95% CI	*P* value	SHR	95% CI	*P* value	SHR	95% CI	*P* value
Sex									
Female	1.00	…		1.00	…		1.00	…	
Male	1.37	1.27–1.49	<0.001	0.93	0.84–1.04	0.19	1.30	0.96–1.77	0.09
Age at diagnosis, y									
≤39	1.00	…		1.00	…		…	…	
40–49	4.00	1.85–8.64	<0.001	1.34	0.68–2.66	0.39	…	…	
50–59	12.35	5.92–25.74	<0.001	2.76	1.47–5.18	0.002	1.00	…	
60–69	27.95	13.44–58.15	<0.001	5.94	3.17–11.16	<0.001	3.82	1.79–8.17	<0.001
70–79	56.63	27.09–118.38	<0.001	16.26	8.62–30.67	<0.001	10.10	4.82–21.16	<0.001
≥80	95.95	45.83–200.91	<0.001	37.54	19.91–70.80	<0.001	7.14	3.48–14.66	<0.001
Period of diagnosis									
1985–1994	1.00	…		1.00	…		1.00	…	
1995–2004	0.88	0.78–0.99	0.03	0.41	0.36–0.47	<0.001	0.90	0.63–1.28	0.56
2005–2013	0.39	0.34–0.47	<0.001	0.23	0.19–0.27	<0.001	0.36	0.25–0.53	<0.001
Stage at diagnosis									
Intraepithelial	1.00	…		1.00	…		1.00	…	
Localized	1.06	0.89–1.27	0.50	1.16	0.88–1.52	0.29	1.15	0.61–2.14	0.68
Lymph node metastasis	0.65	0.53–0.80	<0.001	0.80	0.60–1.08	0.15	0.59	0.30–1.17	0.13
Infiltration to adjacent organs	0.43	0.35–0.54	<0.001	0.54	0.39–0.74	<0.001	0.56	0.27–1.16	0.12
Distant metastasis	0.24	0.19–0.31	<0.001	0.32	0.23–0.45	<0.001	0.19	0.08–0.45	<0.001
Unknown	0.61	0.49–0.76	<0.001	0.78	0.57–1.07	0.12	0.64	0.30–1.41	0.27
N/A	0.73	0.45–1.16	0.18	1.04	0.60–1.79	0.89	0.20	0.04–0.96	0.04
Histology									
Adenocarcinoma	1.00	…		1.00	…		1.00	…	
Squamous or basal carcinoma	1.08	0.99–1.18	0.10	1.12	0.99–1.27	0.07	0.99	0.70–1.39	0.94
Other carcinomas	0.52	0.45–0.61	<0.001	0.55	0.45–0.67	<0.001	0.41	0.24–0.71	0.001
Lymphoma	0.66	0.47–0.92	0.02	0.91	0.60–1.38	0.66	1.13	0.31–4.13	0.85
Hematopoietic tumors (excluding lymphoma)	0.66	0.44–0.99	0.04	0.72	0.46–1.12	0.14	0.53	0.16–1.74	0.30
Other histology	0.78	0.67–0.90	<0.001	0.99	0.85–1.17	0.94	0.66	0.42–1.03	0.07

HF indicates heart failure; IHD, ischemic heart disease; N/A, not applicable; and SHR, subdistribution hazard ratio.

Notably, the risk was immediately high after cancer diagnosis. This trend may be due to cancer treatment initiated after diagnosis. Surgery increases the risk of major adverse cardiovascular disease,[32] and particular types of chemotherapy can cause vascular toxicity.[27–30] Cancer survivors develop a wide range of radiation-related cardiotoxic complications.[33] The subsequent increase in the risk of heart disease mortality over time may be due to a relative increase in cardiac mortality against cancer-related deaths. When analyzing the risk of death from heart disease based on the number of years after cancer diagnosis and cancer type, it was found that the SMR was low for cancers with a high fatality rate, such as lung and liver cancers. Conversely, the SMR was high for cancers with a low fatality rate, including skin and breast cancers. Collectively, these findings support that cancer treatment may be associated with an increase in the SMR after cancer diagnosis.

In this study, the risk of IHD-related death was 3.26 times greater in patients with cancer than in the general population. Paterson et al assessed the cardiovascular risk in more than 220 000 patients with cancer in the Canadian population. The HR of death from myocardial infarction was 1.01 (95% CI, 0.97–1.05), which did not differ from that in the general population.[34] The strength of their study is that the median observation period was >10 years, and the analysis was more in-depth, adjusting for vascular risk. Our study also

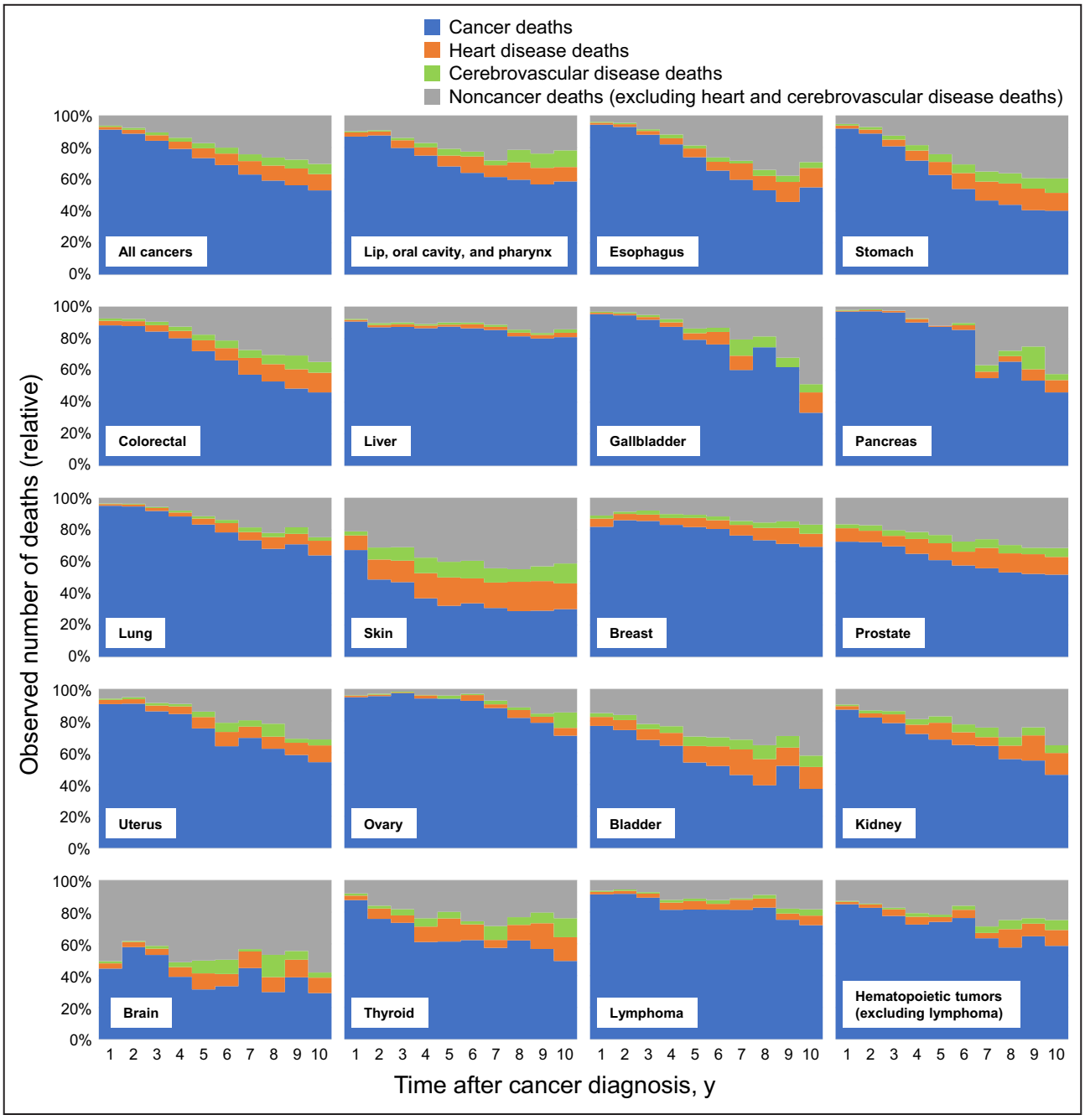

Figure 3. Observed number of deaths by time after cancer diagnosis and by cancer type.
The ordinate shows the relative percent of causes of death. The abscissa indicates the time (number of years) since cancer diagnosis. The causes of death are distinguished by color within the figure: blue for cancer deaths, orange for heart disease deaths, green for cerebrovascular disease, and gray for noncancer deaths (excluding heart and cerebrovascular disease deaths). As the number of years since cancer diagnosis increased, the proportion of cancer deaths decreased, while the proportion of noncancer deaths increased. Notably, liver cancer had a higher proportion of cancer deaths and a lower proportion of noncancer deaths than other malignancies. In contrast, skin cancer included a higher number of noncancer deaths, and there was a relatively high proportion of heart disease deaths. Detailed data, including results for other cancer types not presented here, are provided in Table S11 through S14.

analyzed the risk of death from IHD using data from more than 500 000 patients with cancer, but it was limited by a median observation period of ≈4 years and failure to adjust for the vascular risk factors such as hypertension and diabetes. Patients with cancer have been established to have a high risk of IHD.[35–37] Further studies are needed to determine whether cancer survivors have an elevated risk of mortality from IHD.

When examining the SMR by cancer site, the SMR from fatal heart disease was the highest for brain

cancers. One possible explanation for the increased risk of death from heart disease in brain tumors is the brain-heart connection.[38] Damage to the brain parenchyma affects the balance of neuromodulating hormones, triggering arrhythmias and impairing cardiac function.[38] Brain tumors can cause fatal neurogenic cardiac diseases. Reports of an increased risk of cardiovascular mortality in patients with brain tumors would support this hypothesis.[39] However, our analyses may have overestimated the risk of death from heart disease.[40] The causes of death in the NANDE database are collected through official Japanese statistics reports, which register the cause of death from death certificates. When a patient with a brain tumor dies suddenly, the cause of death may be listed as heart disease because the cause of death is unknown. There may also be instances in which the cause of death is listed as heart disease in patients with terminal disease. As for lymphoma, the SMR for heart disease was 2.96 in our study, ranking somewhere in the middle of all cancers. This finding is generally consistent with the study by Stoltzfus et al using SEER data.[12] A previous study has suggested that patients with Hodgkin lymphoma diagnosed at a young age and surviving over 5 years are known to have a high risk of cardiac death.[41] The risk of fatal heart disease would depend on factors such as the patient's age at cancer diagnosis and the timing of inclusion in the study (at the time of cancer diagnosis or after several years of survival).

The strength of the current study is that it assessed the risk of heart disease mortality among cancer survivors using a large cancer registry that spanned ≈30 years. However, this study also has some limitations. First, risks were analyzed without adjustment for confounding variables such as vascular risk factors. Second, advances in cancer treatment apparently influenced prognosis, but information regarding treatment was unavailable. Third, we excluded cases with incomplete information concerning survival days or diagnosis dates, death certificate notification, or death certificate only, as well as cases of simultaneous or synchronous cancers. Thus, ≈30% of the patients were excluded from the analysis. In addition, ≈2.4% of patients were lost to follow-up. When comparing cancer types between patients who were included, excluded, and lost to follow-up, the proportions were similar for many cancer types. However, colorectal, breast, uterine, and prostate cancers were more common in the study population. In contrast, liver, gallbladder, pancreatic, and lung cancers were more common in the excluded population and those lost to follow-up. It is possible that poor prognosis cancers were excluded from the analysis, leading to an overestimation of noncancer deaths in the target population. Therefore, selection bias may have been present. Fourth, biases associated with the application of SMR may exist, especially in relation to rare events, heterogeneous populations, and unmeasured confounders. Finally, a follow-up period of 10 years after cancer diagnosis may be inadequate to investigate heart disease–related deaths.

In conclusion, cancer survivors have a high risk of heart disease–related mortality. Thus, clinicians should recognize the risk of fatal heart disease in patients with cancer. Careful clinical management, including of both cancer and heart disease, will improve survival.

ARTICLE INFORMATION

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None.

Supplemental Material

Data 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. doi: 10.3322/caac.21731
2. Kadambi S, Loh KP, Dunne R, Magnuson A, Maggiore R, Zittel J, Flannery M, Inglis J, Gilmore N, Mohamed M, et al. Older adults with cancer and their caregivers–current landscape and future directions for clinical care. *Nat Rev Clin Oncol*. 2020;17:742–755. doi: 10.1038/s41571-020-0421-z
3. Bluethmann SM, Mariotto AB, Rowland JH. Anticipating the "silver tsunami": prevalence trajectories and comorbidity burden among older cancer survivors in the United States. *Cancer Epidemiol Biomark Prev*. 2016;25:1029–1036. doi: 10.1158/1055-9965.EPI-16-0133
4. 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
5. Meijers WC, de Boer RA. Common risk factors for heart failure and cancer. *Cardiovasc Res*. 2019;115:844–853. doi: 10.1093/cvr/cvz035
6. Ramin C, Schaeffer ML, Zheng Z, Connor AE, Hoffman-Bolton J, Lau B, Visvanathan K. All-cause and cardiovascular disease mortality among breast cancer survivors in CLUE II, a long-standing community-based cohort. *J Natl Cancer Inst*. 2021;113:137–145. doi: 10.1093/jnci/djaa096
7. Riihimäki M, Thomsen H, Brandt A, Sundquist J, Hemminki H. Death causes in breast cancer patients. *Ann Oncol*. 2012;23:604–610. doi: 10.1093/annonc/mdr160

8. Baxi SS, Pinheiro LC, Patil SM, Pfister DG, Oeffinger KC, Elkin EB. Causes of death in long-term survivors of head and neck cancer. *Cancer*. 2014;120:1507–1513. doi: 10.1002/cncr.28588
9. Fung C, Fossa SD, Milano MT, Sahasrabudhe DM, Peterson DR, Travis LB. Cardiovascular disease mortality after chemotherapy or surgery for testicular nonseminoma: a population-based study. *J Clin Oncol*. 2015;33:3105–3115. doi: 10.1200/JCO.2014.60.3654
10. Howlader N, Mariotto AB, Besson C, Suneja G, Robien K, Younes N, Engels EA. Cancer-specific mortality, cure fraction, and noncancer causes of death among diffuse large B-cell lymphoma patients in the immunochemotherapy era. *Cancer*. 2017;123:3326–3334. doi: 10.1002/cncr.30739
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. 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
13. 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
14. 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
15. 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. doi: 10.1093/eurheartj/ehac244
16. Cancer Statistics in Japan. Foundation for Promotion of Cancer Research. Accessed December 7, 2022. https://ganjoho.jp/public/qa_links/report/statistics/pdf/cancer_statistics_2021.pdf.
17. Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer statistics, 2021. *CA Cancer J Clin*. 2021;71:7–33. doi: 10.3322/caac.21654
18. Dyba T, Randi G, Bray F, Martos C, Giusti F, Nicholson N, Gavin A, Flego M, Neamtiu L, Dimitrova N, et al. The European cancer burden in 2020: incidence and mortality estimates for 40 countries and 25 major cancers. *Eur J Cancer*. 2021;157:308–347. doi: 10.1016/j.ejca.2021.07.039
19. Ohmori M, Ishihara R, Morishima T, Tabuchi T, Okada H, Ohno Y, Sobue T, Miyashiro I. Excessive risk of second-cancer incidence and cancer mortality in patients with esophageal cancer. *J Gastroenterol*. 2021;56:434–441. doi: 10.1007/s00535-021-01767-2
20. Kudo H, Morishima T, Fujii M, Nagayasu M, Sobue T, Ohno Y, Miyashiro I. Do prognoses of patients with second primary cancers differ from those of patients with no prior cancer? A population-based study. *Cancer Epidemiol*. 2022;80:102218. doi: 10.1016/j.canep.2022.102218
21. 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
22. Vogt A, Schmid S, Heinimann K, Frick H, Herrmann C, Cerny T, Omlin A. Multiple primary tumours: challenges and approaches, a review. *ESMO Open*. 2017;2:e000172. doi: 10.1136/esmoopen-2017-000172
23. Odani S, Tabuchi T, Nakata K, Morishima T, Kuwabara Y, Koyama S, Kudo H, Kato M, Miyashiro I. Incidence and relative risk of metachronous second primary cancers for 16 cancer sites, Osaka, Japan, 2000-2015: population-based analysis. *Cancer Med*. 2022;11:507–519. doi: 10.1002/cam4.4457
24. Sherman ME, Troester MA, Hoadley KA, Anderson WF. Morphologic and molecular classification of human cancer. In: Thun M, Linet MS, Cerhan JR, Hainman CA, Schottenfeld D, eds *Cancer Epidemiology and Prevention*. 4th ed. Oxford University Press; 2017.
25. 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
26. Bick RL. Cancer-associated thrombosis. *N Engl J Med*. 2003;349:109–111. doi: 10.1056/NEJMp030086
27. Narezkina A, Nasim K. Anthracycline cardiotoxicity. *Circ Heart Fail*. 2019;12:e005910. doi: 10.1161/CIRCHEARTFAILURE.119.005910
28. Lenihan DJ, Kowey PR. Overview and management of cardiac adverse events associated with tyrosine kinase inhibitors. *Oncologist*. 2013;18:900–908. doi: 10.1634/theoncologist.2012-0466
29. Lyon AR, Yousaf N, Battisti NML, Moslehi J, Larkin J. Immune checkpoint inhibitors and cardiovascular toxicity. *Lancet Oncol*. 2018;19:e447–e458. doi: 10.1016/S1470-2045(18)30457-1
30. Ball S, Ghosh RK, Wongsaengsak S, Bandyopadhyay D, Ghosh GC, Aronow WS, Fonarow GC, Lenihan DJ, Bhatt DL. Cardiovascular toxicities of immune checkpoint inhibitors: JACC review topic of the week. *J Am Coll Cardiol*. 2019;74:1714–1727. doi: 10.1016/j.jacc.2019.07.079
31. Bloom MW, Hamo CE, Cardinale D, Ky B, Nohria A, Baer L, Skopicki H, Lenihan DJ, Gheorghiade M, Lyon AR, et al. Cancer therapy-related cardiac dysfunction and heart failure: part 1: definitions, pathophysiology, risk factors, and imaging. *Circ Heart Fail*. 2016;9:e002661. doi: 10.1161/CIRCHEARTFAILURE.115.002661
32. Smilowitz NR, Gupta N, Ramakrishna H, Guo Y, Berger JS, Bangalore S. Perioperative major adverse cardiovascular and cerebrovascular events associated with noncardiac surgery. *JAMA Cardiol*. 2017;2:181–187. doi: 10.1001/jamacardio.2016.4792
33. Belzile-Dugas E, Eisenberg MJ. Radiation-induced cardiovascular disease: review of an underrecognized pathology. *J Am Heart Assoc*. 2021;10:e021686. doi: 10.1161/JAHA.121.021686
34. 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
35. Darby SC, Ewertz M, McGale P, Bennet AM, Blom-Goldman U, Brønnum D, Correa C, Cutter D, Gagliardi G, Gigante B, et al. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med*. 2013;368:987–998. doi: 10.1056/NEJMoa1209825
36. Navi BB, Reiner AS, Kamel H, Iadecola C, Okin PM, Elkind MSV, Panageas KS, DeAngelis LM. Risk of arterial thromboembolism in patients with cancer. *J Am Coll Cardiol*. 2017;70:926–938. doi: 10.1016/j.jacc.2017.06.047
37. Mulder FI, Horváth-Puhó E, van Es N, Pedersen L, Büller HR, Bøtker HE, Sørensen HT. Arterial thromboembolism in cancer patients: a Danish population-based cohort study. *JACC CardioOncol*. 2021;3:205–218. doi: 10.1016/j.jaccao.2021.02.007
38. Samuels MA. The brain-heart connection. *Circulation*. 2007;116:77–84. doi: 10.1161/CIRCULATIONAHA.106.678995
39. Jin K, Brennan PM, Poon MTC, Sudlow CLM, Figueroa JD. Raised cardiovascular disease mortality after central nervous system tumor diagnosis: analysis of 171,926 patients from UK and USA. *Neurooncol Adv*. 2021;3:vdab136. doi: 10.1093/noajnl/vdab136
40. Schuppener LM, Olson K, Brooks EG. Death certification: errors and interventions. *Clin Med Res*. 2020;18:21–26. doi: 10.3121/cmr.2019.1496
41. 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