Association Between Radiotherapy and Death From Cardiovascular Disease Among Patients With Cancer: A Large Population-Based Cohort Study

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BACKGROUND: This study aimed to investigate the association between radiotherapy for cancer and cardiovascular disease (CVD) deaths and evaluate the relative risk for CVD deaths in the general population and among patients with cancer treated with radiotherapy.

METHODS AND RESULTS: The statistics of cancers from 16 sites were extracted from the Surveillance, Epidemiology, and End Results database and evaluated. Multivariable Cox proportional hazards regression analysis was used to analyze the association between radiotherapy and cardiovascular-specific survival. The standardized mortality ratio for CVD deaths was estimated by comparing the observed deaths of patients with cancer treated with radiotherapy to the expected deaths of the general population. Of the 2,214,944 patients identified from the database, 292,102 (13.19%) died from CVD. Multivariable Cox proportional hazards regression analyses demonstrated that radiotherapy was an independent risk factor for cardiovascular-specific survival among patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers. The long-term cardiovascular-specific survival of patients with cancer who underwent radiotherapy was significantly lower than that of patients who did not undergo radiotherapy. The incidence of CVD deaths among patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers who underwent radiotherapy was higher than that among the general population. Standardized mortality ratio significantly decreased with increasing age at cancer diagnosis, gradually decreased within 10 years of diagnosis and increased after 10 years of diagnosis.

CONCLUSIONS: Radiotherapy is associated with worse cardiovascular-specific survival in patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers. Long-term surveillance of cardiovascular conditions should be performed after radiotherapy.

Key Words: cardiovascular disease ■ neoplasms ■ radiotherapy ■ standardized mortality ratio

Cardiovascular disease (CVD) and cancer, which are the leading causes of mortality worldwide, have a complex relationship.1–3 Previous studies have shown that smoking, alcohol abuse, obesity, and poor lifestyle habits are common modifiable risk factors for CVD and cancer, increasing a considerable overlap between both diseases.4–6 The incidence of CVD in patients with cancer, especially lung cancer, is almost twice that of the general population, which provides evidence of a higher rate of cardiovascular mortality in patients with cancer.7 As the age and life expectancy of a population improve, CVD deaths...
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among patients with cancer steadily increase. CVD, rather than the cancer itself, has even become the leading cause of death among patients with endometrial cancer, indicating that patients with cancer may require heightened surveillance to prevent CVD deaths.

Cancer-related treatment, such as chemotherapy with anthracycline antibiotics and/or radiotherapy, may be responsible for the increased incidence of CVD deaths among patients with cancer, especially if the heart is in the radiation field. The available evidence indicates that irradiation of the heart and major blood vessels could promote CVD deaths in patients with breast cancer many years later. Furthermore, it has been reported that radiotherapy is associated with an increased absolute risk of breast cancer of 125.5 cases of CVD deaths per 100 000 person-years. Hence, ignoring the negative effects of cancer-related treatment may increase the incidence of CVD deaths.

Considering the findings of previous studies, we performed a comprehensive analysis to investigate the association between radiotherapy and CVD deaths in patients with cancer. In addition, we compared the incidence of CVD deaths among patients with cancer who underwent radiotherapy with the incidence of CVD deaths in the general population.

Nonstandard Abbreviations and Acronyms

CVSS  cardiovascular-specific survival
SMR  standardized mortality ratio

CLINICAL PERSPECTIVE

What Is New?
- Radiotherapy increases the incidence of cardiovascular disease deaths among patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers.
- Our results showed a higher incidence of cardiovascular disease deaths among patients with these aforementioned cancers who underwent radiotherapy than among the general population.

What Are the Clinical Implications?
- The findings of this study highlight the importance of cardiovascular care and provide the reference for the prevention of cardiovascular disease deaths in patients with cancer undergoing radiotherapy.

METHODS

Data Source
All data are available at the Surveillance, Epidemiology, and End Results (SEER) database (https://seer.cancer.gov/) using the SEER*Stat 8.3.9 software (https://seer.cancer.gov/seerstat/). The demographic characteristics, treatment, and survival data of patients with cancer were extracted from the SEER database, which covers approximately 28% of the population of the United States. Cause of death was categorized using the International Classification of Diseases, Eighth Revision (ICD-8; 1968–1978), Ninth Revision (ICD-9; 1979–1998), and Tenth Revision (ICD-10; 1999+) codes. CVD was coded with heart disease, hypertension, cerebrovascular disease, atherosclerosis, aortic aneurysm/dissection, and other diseases of arteries, arterioles, or capillaries.

Standardized mortality ratios (SMRs) were introduced to estimate the relative risk for CVD deaths among patients with cancer compared with the general population of the United States (standard population of the United States in 2000), adjusted for race, sex, and age at the same time.

Study Population
The inclusion criteria for this study were as follows: (1) first primary solid malignant tumors; (2) diagnosis between January 1, 1975 and December 31, 2014; and (3) patients with cancer who have more than 100 000 person-years of survival time. Patients with less than 2 months of survival time were excluded to maintain consistency with the minimum period following cancer diagnosis in which SMR can be estimated (starts at 2 months).

We identified 16 cancer sites from the database. The sites included the brain, breast, cervix uteri, colon and rectum, corpus uteri, kidney and renal pelvis, larynx, lung and bronchus, melanoma of the skin, ovary, prostate, soft tissue including heart, stomach, testis, thyroid, and urinary bladder.

All procedures performed in this study involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. For this study, informed consent was not required.

Statistical Analysis
The distributions of baseline characteristics of the patients with cancer were compared using the chi-square test. The multivariable Cox proportional hazards regression analyses were performed to estimate the hazard ratios (HRs) and 95% CIs for the association between radiotherapy and cardiovascular-specific survival.
survival (CVSS), adjusted for race, sex, age at diagnosis, and year at diagnosis. The Kaplan–Meier method was used to analyze CVSS in patients with cancer who underwent radiotherapy and in those who did not undergo radiotherapy. Adjusted \( P \) values were estimated using the multivariable Cox proportional hazards regression analyses to reduce confounding effects. SMRs and 95% CIs for CVD were calculated using the SEER*Stat 8.3.9 software.

**RESULTS**

**Patient Characteristics**
A total of 2,214,944 patients with cancer were identified from the SEER database. Of these, 292,102 (13.19%) died of CVD (Table 1). A total of 718,979 patients were included in the radiotherapy group, whereas 1,495,965 patients were in the no-radiotherapy group. Of the patients in the radiotherapy group, 67,003 (9.32%) died of CVD, whereas 225,099 (15.05%) patients in the no-radiotherapy group died of CVD. The percentage of patients who died from CVD increased with increasing age at diagnosis in both the groups. In the radiotherapy group, patients with cancer of the larynx had the highest percentage of those who died from CVD (20%), followed by those with corpus uteri (19.19%), prostate (17.88%), urinary bladder (14.49%), and cervix uteri (10.2%) cancers. In the no-radiotherapy group, those with cancer of the urinary bladder had the highest percentage of those who died from CVD (23.29%), followed by those with cancer of the larynx (21.54%), prostate (19.42%), colon and rectum (18.51%), and breast (17%).

**Multivariable Cox Proportional Hazards Regression Analysis**
In the multivariable Cox proportional hazards regression analyses, radiotherapy was considered an independent risk factor for CVSS among patients with lung and bronchus (HR, 1.09; 95% CI, 1.06–1.13; adjusted \( P<0.001 \)), cervix uteri (HR, 1.47; 95% CI, 1.36–1.59; adjusted \( P<0.001 \)), corpus uteri (HR, 1.13; 95% CI, 1.09–1.17; adjusted \( P<0.001 \)), and urinary bladder (HR, 1.13; 95% CI, 1.07–1.20; adjusted \( P<0.001 \)) cancers (Figure 1 and Tables S1 through S16). Potential confounders were adjusted for race, sex, and age at the same time.

**Cardiovascular-Specific Survival of 4 Cancers**
The long-term CVSS of 4 cancers was estimated using the Kaplan-Meier method (Figure 2). Among patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers, those who underwent radiotherapy had significantly lower 40-year CVSS than those who did not undergo radiotherapy (lung and bronchus: 21.9% versus 33.3%, adjusted \( P<0.001 \)); cervix uteri: 52.0% versus 80.6%, adjusted \( P<0.001 \); corpus uteri: 29.1% versus 38.1%, adjusted \( P<0.001 \); and urinary bladder: 26.0% versus 33.4%, adjusted \( P<0.001 \)).

**Standardized Mortality Ratios**
When the incidence of CVD deaths among patients with cancer treated using radiotherapy was compared with that of the general population, the overall SMR indicated a 13% increase in CVD deaths among all patients with cancer (SMR, 1.13 [1.13–1.14]) (Table 2). The incidence of CVD deaths among patients with lung and bronchus (SMR, 2.83 [2.61–3.07]), cervix uteri (SMR, 1.67 [1.59–1.74]), corpus uteri (SMR, 1.13 [1.10–1.16]), and urinary bladder (SMR, 1.51 [1.43–1.59]) cancers who underwent radiotherapy was higher than that in the general population.

**Cardiovascular Deaths According to Age at Diagnosis**
Different age groups showed higher-than-expected incidences of CVD deaths. In addition, SMRs decreased with increasing age at cancer diagnosis among patients with lung and bronchus (≤39 years old: SMR, 25.00 [13.31–42.75]; 40–59 years old: SMR, 5.95 [5.57–6.35]; 60–79 years old: SMR, 3.09 [3.00–3.18]; ≥80 years old: SMR, 1.33 [1.27–1.40]), cervix uteri (≤39 years old: SMR, 4.81 [2.07–9.47]; 40–59 years old: SMR, 3.06 [2.62–3.56]; 60–79 years old: SMR, 2.11 [1.97–2.26]; ≥80 years old: SMR, 2.29 [2.12–1.38]), corpus uteri (≤39 years old: SMR, 6.46 [0.78–23.32]; 40–59 years old: SMR, 2.32 [2.02–2.81]; 60–79 years old: SMR, 1.33 [1.28–1.39]; ≥80 years old: SMR, 1.03 [1.00–1.06]), and urinary bladder cancers (≤39 years old: SMR, 17.08 [0.43–95.14]; 40–59 years old: SMR, 3.92 [2.85–5.26]; 60–79 years old: SMR, 1.86 [1.70–2.02]; ≥80 years old: SMR, 1.29 [1.19–1.38]) (Figure 3A).

**Cardiovascular Deaths According to Year of Diagnosis**
The historical trends of CVD deaths among patients who underwent radiotherapy for lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers are shown in Figure 3B. Patients with these cancers showed higher incidences of CVD deaths than the general population in different eras. In addition, SMRs decreased with advancing time among patients with lung and bronchus (1985–1994: SMR, 2.73 [2.36–2.63]; 1995–2004: SMR, 2.61 [2.50–2.72]; 2005–2014: 2.26 [2.16–2.37]) and cervix uteri cancers (1995–2004: SMR, 1.76 [1.62–1.91]; 2005–2014: 1.60 [1.46–1.75]).
Table 1. Baseline Characteristics of Patients With Cancer According to Treatment Modality

| Characteristic          | Radiotherapy   | CVD deaths (%) | No radiotherapy | CVD deaths (%) |
|-------------------------|----------------|----------------|-----------------|----------------|
|                         | Overall        |                | Overall         |                |
| All patients            | 718 979        | 67 003 (9.32)  | 1 495 965       | 225 099 (15.05) |
| Race                    |                |                |                 |                |
| White                   | 588 034        | 56 366 (9.59)  | 1 257 323       | 196 386 (15.62) |
| Black                   | 75 714         | 70 333 (9.29)  | 132 008         | 18 620 (14.11)  |
| Other*                  | 53 073         | 35 660 (6.71)  | 94 842          | 97 671 (10.29)  |
| Unknown                 | 2158           | 44 (2.04)      | 11 792          | 332 (2.82)      |
| Sex                     |                |                |                 |                |
| Female                  | 370 142        | 28 133 (7.60)  | 739 775         | 102 783 (13.89) |
| Male                    | 348 837        | 38 870 (11.14) | 756 190         | 122 316 (16.18) |
| Age at diagnosis, y     |                |                |                 |                |
| ≤39                     | 50 821         | 657 (1.29)     | 107 112         | 1203 (1.12)     |
| 40–59                   | 236 548        | 8848 (3.74)    | 413 743         | 21 988 (5.31)   |
| 60–79                   | 382 428        | 47 847 (12.51) | 739 609         | 132 545 (17.92) |
| ≥80                     | 49 182         | 9651 (19.62)   | 235 501         | 69 363 (29.45)  |
| Year at diagnosis       |                |                |                 |                |
| 1975–1984               | 114 016        | 16 254 (14.26) | 275 164         | 70 444 (25.60)  |
| 1985–1994               | 154 289        | 22 753 (14.75) | 355 418         | 78 972 (22.22)  |
| 1995–2004               | 206 684        | 20 647 (9.98)  | 396 093         | 54 163 (13.67)  |
| 2005–2014               | 243 990        | 7349 (3.01)    | 469 290         | 21 520 (4.59)   |
| Tumor stage             |                |                |                 |                |
| Localized/regional      | 461 179        | 44 930 (9.74)  | 1 058 923       | 163 236 (15.42) |
| Distant                 | 108 887        | 3126 (2.87)    | 202 686         | 8222 (4.06)     |
| Unknown                 | 148 913        | 18 947 (12.72) | 234 356         | 53 641 (22.89)  |
| Surgery                 |                |                |                 |                |
| Yes                     | 393 442        | 35 390 (8.99)  | 1 161 459       | 185 616 (15.98) |
| No                      | 209 865        | 30 168 (9.74)  | 315 656         | 37 157 (11.77)  |
| Unknown                 | 15 672         | 1447 (9.23)    | 18 850          | 2326 (12.34)    |
| Chemotherapy            |                |                |                 |                |
| Yes                     | 243 154        | 8267 (3.40)    | 259 245         | 11 508 (4.44)   |
| No                      | 475 825        | 58 736 (12.34) | 1 236 720       | 213 591 (17.27) |
| Primary cancer site     |                |                |                 |                |
| Larynx                  | 17 618         | 3523 (20.00)   | 5822           | 1254 (1.54)     |
| Corpus uteri            | 32 172         | 6174 (19.19)   | 64 445         | 10 056 (15.80)  |
| Prostate                | 145 996        | 26 102 (17.88) | 305 388       | 59 293 (19.42)  |
| Urinary bladder         | 9145           | 1325 (14.49)   | 101 089        | 23 539 (23.29)  |
| Cervix uteri            | 18 297         | 1866 (10.20)   | 16 652         | 1080 (6.49)     |
| Colon and rectum        | 38 803         | 3352 (8.64)    | 266 007        | 49 232 (18.51)  |
| Ovary                   | 2295           | 181 (7.89)     | 47 471         | 2554 (5.38)     |
| Breast                  | 185 898        | 14 193 (7.63)  | 246 309        | 41 874 (17.00)  |
| Soft tissue including heart | 7889      | 530 (6.72)     | 11 135         | 988 (8.87)      |
| Stomach                 | 10 825         | 485 (4.48)     | 40 168         | 3545 (8.83)     |
| Lung and bronchus       | 172 697        | 7400 (4.28)    | 167 036        | 13 195 (7.90)   |
| Testis                  | 7864           | 302 (3.84)     | 14 804         | 277 (1.87)      |
| Kidney and renal pelvis | 6726           | 209 (3.11)     | 61 548         | 7295 (11.85)    |
| Melanoma of the skin    | 2441           | 70 (2.87)      | 101 601        | 8837 (8.70)     |
| Thyroid                 | 28 916         | 688 (2.38)     | 33 390         | 1717 (5.14)     |
| Brain                   | 31 397         | 603 (1.92)     | 13 100         | 364 (2.78)      |

CVD indicates cardiovascular disease.
*Other refers to American Indian/Alaskan Native, Asian/Pacific Islander.
P values were calculated using χ² test and all P values <0.001.
However, SMR gradually increased with advancing time among patients with urinary bladder cancer (1975–1984: SMR, 1.37 [1.21–1.53]; 1985–1994: SMR, 1.40 [1.27–1.55]; 1995–2004: SMR, 1.60 [1.44–1.78]; 2005–2014: SMR, 1.74 [1.54–1.95]).

**Cardiovascular Deaths According to Time After Diagnosis**

We estimated the relative risk of CVD deaths according to time after diagnosis and compared the results of patients with cancer who underwent radiotherapy with those of the general population. The results showed that patients with cancer who underwent radiotherapy had a higher incidence of CVD deaths than the general population from the time of diagnosis onward (Figure 3C). SMRs gradually decreased within 10 years of diagnosis and increased after 10 years of diagnosis among patients with lung and bronchus (2–11 months: SMR, 2.63 [2.54–2.73]; 12–59 months: SMR, 2.39 [2.31–2.48]; 60–119 months: SMR, 2.38 [2.23–2.54]; 120+ months: SMR, 2.97 [2.74–3.22]), cervix uteri (2–11 months: SMR, 1.99 [1.71–2.31]; 12–59 months: SMR, 1.87 [2.17–2.04]; 60–119 months: SMR, 1.49 [1.34–1.66]; 120+ months: SMR, 1.59 [1.48–1.70]), corpus uteri (2–11 months: SMR, 1.29 [1.15–1.45]; 12–59 months: SMR, 1.10 [1.03–1.16]; 60–119 months: SMR, 1.06 [1.00–1.13]; 120+ months: SMR, 1.39 [1.24–1.56]), and urinary bladder cancer (2–11 months: SMR, 1.88 [1.67–2.10]; 12–59 months: SMR, 1.50 [1.37–1.64]; 60–119 months: SMR, 1.33 [1.17–1.51]; 120+ months: SMR, 1.39 [1.24–1.56]).

**DISCUSSION**

In this large population-based cohort study, we evaluated the association between radiotherapy and CVD deaths among patients with cancer treated with radiotherapy. The results showed that radiotherapy was a significant independent risk factor for CVSS among patients with 4 cancers: lung and bronchus, urinary bladder, cervix uteri, and corpus uteri cancers. In addition, radiotherapy was associated with worse CVSS in patients with these cancers. Furthermore, a comparison of the relative risk of CVD deaths between patients with cancer and the general population showed a higher incidence of CVD deaths among patients with these 4 cancers who underwent radiotherapy than among the general population. We also found that the SMR for CVD among patients with these cancers significantly decreased with increasing age at cancer diagnosis, gradually decreased within 10 years of diagnosis, and increased after 10 years of diagnosis.
These epidemiological characteristics provided a reference for the implementation of strategies for the prevention of CVD deaths in patients with cancer after radiotherapy.

To our knowledge, this is the most comprehensive population-based study of the association between radiotherapy and CVD deaths in patients with cancer of 16 different sites. Previous studies have reported elevated incidences of CVD deaths among patients with solid tumors after radiotherapy. However, some previous studies have also reported that the incidence of CVD deaths among patients with cancer is not elevated. Hence, a unified conclusion on the relationship between radiotherapy and CVD deaths in patients with solid tumors has not yet been reached. In addition, knowledge of the tumors that increase the incidence of CVD deaths after radiotherapy is particularly important. In a previous population-based study, CVD deaths in patients with 10 common malignant tumors were evaluated and the results indicated that radiotherapy is an independent risk factor for CVSS in lung cancer, a finding that is in line with our results. However, a recent study showed that the incidence of CVD deaths among patients with non-small cell lung cancer who underwent chemotherapy and/or radiotherapy decreased. The conflicting result could be explained by the advent of chemotherapy, which may affect the survival outcome. Another explanation may be the tumor heterogeneity between non-small cell lung cancer and other types of lung cancer. We also found that radiotherapy could promote the likelihood of CVD deaths among patients with urinary bladder, cervix uteri, and corpus uteri cancers, a finding that could not be obtained from the aforementioned study. This difference might be caused by the fact that only patients with more than 5 years of survival were included in the aforementioned study, whereas patients with almost all types of cancer were included in the present study. The Kaplan–Meier

Figure 2. Cardiovascular-specific survival in patients with lung and bronchus (A), cervix uteri (B), corpus uteri (C), and urinary bladder cancers (D) in the radiotherapy vs no radiotherapy group. P values were calculated using the multivariable Cox proportional hazards regression analyses, adjusted for race, sex, age at diagnosis, and year of diagnosis. NRT indicates no radiotherapy; and RT, radiotherapy.
analysis demonstrated worse CVSS after radiotherapy in patients with lung and bronchus, urinary bladder, cervix uteri, and corpus uteri cancers. This is the first study to demonstrate an association between radiotherapy and CVD deaths among patients with urinary bladder, cervix uteri, and corpus uteri cancers. Some existing evidence alludes to the robustness of our findings. A previous retrospective study demonstrated that patients with uterine cancer who underwent radiotherapy are more likely to die from intercurrent illness, including cardiac arrhythmia, congestive heart failure, cardiac arrest, and other complications, 10 years later than from cancer. Okajima et al. discovered that 13% of patients with urinary cancer died within 10 years after radiotherapy and that except for cancer, CVD was the leading cause of death among them. These previous studies suggest that CVD deaths are associated with cancer-related radiotherapy. In addition, reports in recently published literature indicate that short- and long-term radiotherapy elevates the incidence of adverse cardiovascular events in patients with multiple types of cancer, especially breast, lung, and esophagus cancer, which often require mediastinal radiotherapy. Although these studies only focused on the incidence of CVD in patients with cancer, they provided a theoretical basis for our results.

### Table 2. Standardized Mortality Ratios of Patients With Different Cancers According to Treatment Modality

| Primary cancer site               | Total SMR (95% CI) | Radiotherapy SMR (95% CI) | No radiotherapy SMR (95% CI) |
|----------------------------------|-------------------|--------------------------|-----------------------------|
| Brain                            | 2.60* (2.44–2.77) | 2.83* (2.61–3.07)        | 2.29* (2.06–2.54)           |
| Lung and bronchus                | 2.04* (2.02–2.07) | 2.52* (2.48–2.58)        | 1.85* (1.82–1.88)           |
| Larynx                          | 1.81* (1.76–1.86) | 1.83* (1.77–1.89)        | 1.76* (1.67–1.86)           |
| Cervix uteri                     | 1.53* (1.47–1.58) | 1.67* (1.59–1.74)        | 1.33* (1.25–1.41)           |
| Stomach                          | 1.43* (1.39–1.48) | 1.79* (1.63–1.96)        | 1.39* (1.35–1.44)           |
| Kidney and renal pelvis          | 1.40* (1.37–1.43) | 1.73* (1.50–1.98)        | 1.39* (1.36–1.43)           |
| Urinary bladder                  | 1.29* (1.27–1.31) | 1.51* (1.43–1.59)        | 1.28* (1.26–1.30)           |
| Soft tissue including heart      | 1.21* (1.15–1.27) | 1.12* (1.02–1.21)        | 1.26* (1.19–1.35)           |
| Colon and rectum                 | 1.15* (1.14–1.16) | 1.14* (1.10–1.18)        | 1.15* (1.14–1.16)           |
| Ovary                            | 1.08* (1.04–1.12) | 1.19* (1.02–1.38)        | 1.08* (1.03–1.12)           |
| Corpus uteri                     | 1.08* (1.06–1.10) | 1.13* (1.10–1.16)        | 1.05* (1.03–1.07)           |
| Breast                           | 1.06* (1.05–1.07) | 0.92* (0.91–0.94)        | 1.11* (1.10–1.12)           |
| Testis                           | 1.01 (0.93–1.09)  | 1.00 (0.89–1.12)         | 1.02 (0.90–1.14)            |
| Prostate                         | 0.99 (0.99–1.00)  | 0.92* (0.91–0.93)        | 1.03* (1.02–1.04)           |
| Melanoma of the skin             | 0.98* (0.96–1.00) | 1.06 (0.83–1.34)         | 0.98 (0.96–1.00)            |
| Thyroid                          | 0.87* (0.84–0.91) | 0.78* (0.73–0.84)        | 0.92* (0.87–0.96)           |
| Overall                          | 1.13* (1.13–1.14) | 1.09* (1.08–1.10)        | 1.14* (1.14–1.15)           |

SEER indicates Surveillance, Epidemiology, and End Results; and SMR, standardized mortality ratio. SMRs and 95% CIs were calculated using SEER*Stat 8.3.9, adjusted for age, race, and sex at the same time. *P values <0.05.

### Figure 3. Standardized mortality ratios for cardiovascular disease among patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers after radiotherapy according to age at diagnosis (A), year at diagnosis (B), and time after diagnosis (C).

Standardized mortality ratios represent the relative risk of cardiovascular disease deaths in patients with cancer compared with the general population, adjusted for age, race, and sex at the same time.
In this study, we also observed a lower incidence of CVD deaths in patients who underwent radiotherapy for breast, thyroid, and colorectal cancer than among the general population. It is generally agreed that radiotherapy is associated with a high incidence of CVD deaths in patients with cancer. However, the latest randomized trials showed no increase in CVD deaths among patients with breast and colorectal cancer who underwent radiotherapy. In addition, Killander emphasized that serious late side effects of radiation are limited and that with the current therapeutic strategies, the risk for cardiac events due to exposure of the breasts to radiation is likely to be decreased. Significantly, breast, thyroid, and colorectal cancers have good oncological prognoses and long survival times, which may increase the incidence of CVD deaths. However, radiotherapy may be used to treat patients with more advanced cancers with poor oncological prognoses. Therefore, patients with cancer who undergo radiotherapy are more likely to die from tumors than from CVD. In addition, elderly patients may reject recommendations for radiotherapy because of concomitant CVD, which might increase the risk of CVD deaths. Previous studies have reported that CVD deaths often occur 15 years after cancer diagnosis. In the present study, patients were diagnosed between 1975 and 2014, and more than a quarter of them were followed up for less than 15 years, which may have affected the incidence of CVD deaths. However, Greenlee et al. reported that patients with breast cancer are at an increased risk for cardiovascular-related diseases. Furthermore, Guan et al. reported that the tumor itself, not just the cardiotoxicity of radiotherapy, might increase the incidence of CVD deaths in patients who did not undergo radiotherapy. Given these findings, the limitations of the present study led to the misconception that radiotherapy reduced CVD deaths in patients with breast, thyroid, and colorectal cancers. Radiotherapy is an effective treatment for tumors that can kill tumor cells and shrink tumors through high doses of ionizing radiation. Although this local treatment may control tumor progression and improve survival time, it also leads to several adverse events, especially CVD. The potential mechanisms behind this are not fully clear, however, the results of some studies suggest that pathogenesis of radiotherapy-induced CVD is related to inflammatory activation, production of reactive oxygen species, and oxidative stress. This may be because radiotherapy could directly cause cell death and premature endothelial senescence and could impair endothelium-dependent vasodilation. In addition, the promotion of coagulation and thrombosis could influence the incidence of CVD. Radiotherapy-induced CVD is also affected by the dose of cardiac radiation. Therefore, radiotherapy-induced CVD is a complex and modifiable pathophysiological process.

Radiologists have been trying to find the most effective treatment method that limits the risk of developing CVD. Radiation techniques are constantly being updated with newer methods, such as intensity-modulated radiotherapy, image-guided radiotherapy, and proton therapy. In addition, advances in radiation techniques have reduced accidental cardiac radiation. In the present study, the risk of CVD deaths decreased significantly with increasing years of diagnosis in the radiotherapy and no-radiotherapy cohorts, especially in the last decade. However, radiation-induced CVD most often occurs several years after radiation therapy, and late cardiovascular toxicity still causes CVD deaths. Therefore, a short follow-up duration may be one of the reasons for the reduced risk of CVD deaths in recent years. Thus, this conclusion should be interpreted with caution.

We used SMR to compare the relative risk for CVD between patients with cancer and the general population. The results demonstrated that patients with 4 different types of cancer who underwent radiotherapy had higher incidences of CVD deaths than the general population. The underlying CVD was a critical factor; however, the cardiotoxicity associated with treatment should not be overlooked. Epidemiological studies have shown that risk factors for cancer and CVD have significant overlaps, which suggests that patients with cancer may be more susceptible to CVD. These are some possible explanations for the higher incidence of CVD deaths among patients with cancer than in the general population.

We found that patients with the 4 aforementioned cancers who underwent radiotherapy had a higher incidence of CVD deaths than the general population. Tukkenova reported a similar conclusion, which is that cardiovascular SMRs for cancer survivors increase after radiotherapy. On the other hand, Boekel et al. emphasized that the SMR of CVD for patients with breast cancer who underwent surgery plus radiotherapy or surgery alone did not vary. However, the author also explained that the impact of radiotherapy on CVD deaths may be underestimated because of short follow-up durations and low doses of radiation. As mentioned previously, the results of the present study showed that patients with cancer who underwent radiotherapy had a higher incidence of CVD deaths than the general population. Similar trends were observed in subgroups stratified according to age at diagnosis, year of diagnosis, and follow-up duration. These results suggest that attention should be paid to the risk of CVD deaths in patients with cancer undergoing radiotherapy. Efforts should be made to prevent cardiotoxicity and maximize outcomes, while ensuring that the therapeutic effect of the treatment is not compromised.
we could not access detailed information on the indications for radiotherapy (or exceptions of user-patient or provider preferences/refusals/access to care), individual-level patient data on comorbidities (or underlying CVD), or prognostic information on individual tumors (which may affect the CVD deaths studied). Thus, these factors were not adjusted in the analysis. Second, the general population represents individuals not exposed to radiation. However, as we did not exclude patients with a history of cancer from this population or adjust for potential CVD risk factors, this is inevitably a comparison biased in favor of the cancer population. Therefore, future prospective randomized trials are necessary to verify the reliability and accuracy of the findings of this study. Third, the wide period is a notable limitation of the study, as indications and modalities for radiotherapy continued to improve during this period. Moreover, advances in radiation techniques might influence CVD mortality. However, CVD deaths were few and mostly occurred several years after radiotherapy; hence, we had to expand the period and sample size to enhance the credibility of this study.

CONCLUSIONS
In summary, this study demonstrated that radiotherapy increases the incidence of CVD deaths among patients with lung and bronchus, cervix uteri, corpus uteri, and urinary bladder cancers. The findings of this study highlight the importance of cardiovascular care in patients with cancer undergoing radiotherapy.

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Disclosures
None.

Supplemental Material
Table S1–S16

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SUPPLEMENTAL MATERIAL
Table S1. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with prostate cancer.

| Variables                       | HR  | 95% CI   | P      |
|---------------------------------|-----|----------|--------|
| **Race**                        |     |          |        |
| White                           | Reference | /       | /     |
| Black                           | 1.29 | 1.26-1.31 | <0.001 |
| Other                           | 0.87 | 0.84-0.9  | <0.001 |
| Unknown                         | 0.32 | 0.27-0.37 | <0.001 |
| **Sex**                         |     |          |        |
| Female                          | Reference | /       | /     |
| Male                            | NA  | NA       | NA    |
| **Age at diagnosis (Years)**    |     |          |        |
| ≤39                             | Reference | /       | /     |
| 40-59                           | 2.89 | 1.20-6.96 | 0.018  |
| 60-79                           | 13.44 | 5.59-32.31 | <0.001 |
| ≥80                             | 54.47 | 22.67-130.91 | <0.001 |
| **Year at diagnosis**           |     |          |        |
| 1975-1984                       | Reference | /       | /     |
| 1985-1994                       | 0.67 | 0.66-0.68 | <0.001 |
| 1995-2004                       | 0.42 | 0.42-0.43 | <0.001 |
| 2005-2014                       | 0.25 | 0.24-0.25 | <0.001 |
| **Radiotherapy**                |     |          |        |
| No                              | Reference | /       | /     |
| Yes                             | 0.99 | 0.97-1.00 | 0.127  |

HR, hazard ratio; CI, confidence interval.
Table S2. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with soft tissue including heart

| Variables                      | HR     | 95% CI    | P       |
|--------------------------------|--------|-----------|---------|
| **Race**                       |        |           |         |
| White                          | Reference | /         | /       |
| Black                          | 1.59   | 1.34-1.88 | <0.001  |
| Other                          | 0.88   | 0.71-1.10 | 0.259   |
| Unknown                        | 0.51   | 0.19-1.35 | 0.173   |
| **Sex**                        |        |           |         |
| Female                         | Reference | /         | /       |
| Male                           | 1.43   | 1.29-1.58 | <0.001  |
| **Age at diagnosis (Years)**   |        |           |         |
| ≤39                            | Reference | /         | /       |
| 40-59                          | 9.35   | 6.90-12.68| <0.001  |
| 60-79                          | 63.05  | 47.00-84.59| <0.001 |
| ≥80                            | 288.89 | 212.39-392.93| <0.001 |
| **Year at diagnosis**          |        |           |         |
| 1975-1984                      | Reference | /         | /       |
| 1985-1994                      | 0.79   | 0.69-0.90 | <0.001  |
| 1995-2004                      | 0.58   | 0.50-0.67 | <0.001  |
| 2005-2014                      | 0.44   | 0.37-0.52 | <0.001  |
| **Radiotherapy**               |        |           |         |
| No                             | Reference | /         | /       |
| Yes                            | 0.88   | 0.79-0.98 | 0.016   |

HR, hazard ratio; CI, confidence interval.
Table S3. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with urinary bladder cancer

| Variables                  | HR   | 95% CI      | P     |
|----------------------------|------|-------------|-------|
| **Race**                   |      |             |       |
| White                      | Reference | /        | /     |
| Black                      | 1.27 | 1.19-1.36   | <0.001|
| Other                      | 0.76 | 0.71-0.82   | <0.001|
| Unknown                    | 0.21 | 0.14-0.32   | <0.001|
| **Sex**                    |      |             |       |
| Female                     | Reference | /        | /     |
| Male                       | 1.36 | 1.33-1.40   | <0.001|
| **Age at diagnosis (Years)** |      |             |       |
| ≤39                        | Reference | /        | /     |
| 40-59                      | 8.43 | 6.58-10.79  | <0.001|
| 60-79                      | 37.06| 29.00-47.35 | <0.001|
| ≥80                        | 131.51| 102.8-168.23| <0.001|
| **Year at diagnosis**      |      |             |       |
| 1975-1984                  | Reference | /        | /     |
| 1985-1994                  | 0.80 | 0.77-0.82   | <0.001|
| 1995-2004                  | 0.60 | 0.58-0.62   | <0.001|
| 2005-2014                  | 0.41 | 0.40-0.43   | <0.001|
| **Radiotherapy**           |      |             |       |
| No                         | Reference | /        | /     |
| Yes                        | 1.13 | 1.07-1.20   | <0.001|

HR, hazard ratio; CI, confidence interval.
Table S4. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with ovary cancer

| Variables           | HR  | 95% CI      | P      |
|---------------------|-----|-------------|--------|
| **Race**            |     |             |        |
| White               | Reference | /            | /      |
| Black               | 1.79 | 1.56-2.05   | <0.001 |
| Other               | 0.89 | 0.75-1.07   | 0.217  |
| Unknown             | 0.50 | 0.19-1.33   | 0.164  |
| **Sex**             |     |             |        |
| Female              | Reference | /            | /      |
| Male                | NA  | NA          | NA     |
| **Age at diagnosis (Years)** |     |             |        |
| ≤39                 | Reference | /            | /      |
| 40-59               | 9.09 | 6.88-12.01  | <0.001 |
| 60-79               | 52.03| 39.48-68.57 | <0.001 |
| ≥80                 | 238.63| 178.78-318.51 | <0.001 |
| **Year at diagnosis** |     |             |        |
| 1975-1984           | Reference | /            | /      |
| 1985-1994           | 0.67 | 0.62-0.74   | <0.001 |
| 1995-2004           | 0.47 | 0.42-0.52   | <0.001 |
| 2005-2014           | 0.33 | 0.29-0.39   | <0.001 |
| **Radiotherapy**    |     |             |        |
| No                  | Reference | /            | /      |
| Yes                 | 1.00 | 0.86-1.17   | 0.958  |

HR, hazard ratio; CI, confidence interval.
Table S5. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with thyroid cancer

| Variables                  | HR   | 95% CI          | P     |
|----------------------------|------|-----------------|-------|
| **Race**                   |      |                 |       |
| White                      |      | Reference       |       |
| Black                      | 1.86 | 1.61-2.15       | <0.001|
| Other                      | 0.94 | 0.82-1.07       | 0.33  |
| Unknown                    | 0.16 | 0.04-0.65       | 0.01  |
| **Sex**                    |      |                 |       |
| Female                     |      | Reference       |       |
| Male                       | 1.63 | 1.50-1.78       | <0.001|
| **Age at diagnosis (Years)**|      |                 |       |
| ≤39                        |      | Reference       |       |
| 40-59                      | 7.07 | 5.97-8.38       | <0.001|
| 60-79                      | 59.68| 50.39-70.68     | <0.001|
| ≥80                        | 316.01| 258.66-386.08  | <0.001|
| **Year at diagnosis**      |      |                 |       |
| 1975-1984                  |      | Reference       |       |
| 1985-1994                  | 0.72 | 0.64-0.80       | <0.001|
| 1995-2004                  | 0.50 | 0.44-0.57       | <0.001|
| 2005-2014                  | 0.31 | 0.27-0.36       | <0.001|
| **Radiotherapy**           |      |                 |       |
| No                         |      | Reference       |       |
| Yes                        | 0.83 | 0.76-0.91       | <0.001|

HR, hazard ratio; CI, confidence interval.
| Variables                | HR   | 95% CI     | P        |
|--------------------------|------|------------|----------|
| **Race**                 |      |            |          |
| White                    | Reference | /           | /        |
| Black                    | 1.44 | 1.12-1.85  | 0.004    |
| Other                    | 0.89 | 0.69-1.15  | 0.38     |
| Unknown                  | 0.27 | 0.20-0.37  | <0.001   |
| **Sex**                  |      |            |          |
| Female                   | Reference | /           | /        |
| Male                     | 1.54 | 1.48-1.61  | <0.001   |
| **Age at diagnosis (Years)** |     |            |          |
| ≤39                      | Reference | /           | /        |
| 40-59                    | 8.94 | 7.58-10.55 | <0.001   |
| 60-79                    | 74.97| 63.74-88.19| <0.001   |
| ≥80                      | 427.57| 361.82-505.25| <0.001  |
| **Year at diagnosis**    |      |            |          |
| 1975-1984                | Reference | /           | /        |
| 1985-1994                | 0.77 | 0.73-0.82  | <0.001   |
| 1995-2004                | 0.56 | 0.53-0.60  | <0.001   |
| 2005-2014                | 0.36 | 0.33-0.39  | <0.001   |
| **Radiotherapy**         |      |            |          |
| No                       | Reference | /           | /        |
| Yes                      | 1.03 | 0.81-1.30  | 0.815    |

HR, hazard ratio; CI, confidence interval.
Table S7. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with stomach cancer

| Variables                  | HR   | 95% CI     | P     |
|----------------------------|------|------------|-------|
| **Race**                   |      |            |       |
| White                      | Reference | /     | /     |
| Black                      | 1.42 | 1.29-1.55  | <0.001|
| Other                      | 0.73 | 0.67-0.80  | <0.001|
| Unknown                    | 0.61 | 0.29-1.29  | 0.197 |
| **Sex**                    |      |            |       |
| Female                     | Reference | /     | /     |
| Male                       | 1.28 | 1.2-1.36   | <0.001|
| **Age at diagnosis (Years)** |    |            |       |
| ≤39                        | Reference | /     | /     |
| 40-59                      | 5.94 | 3.49-10.13 | <0.001|
| 60-79                      | 23.53| 13.88-39.89| <0.001|
| ≥80                        | 72.90| 42.9-123.89| <0.001|
| **Year at diagnosis**      |      |            |       |
| 1975-1984                  | Reference | /     | /     |
| 1985-1994                  | 0.81 | 0.75-0.88  | <0.001|
| 1995-2004                  | 0.67 | 0.62-0.73  | <0.001|
| 2005-2014                  | 0.43 | 0.39-0.48  | <0.001|
| **Radiotherapy**           |      |            |       |
| No                         | Reference | /     | /     |
| Yes                        | 1.03 | 0.93-1.13  | 0.61  |

HR, hazard ratio; CI, confidence interval.
Table S8. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with testis cancer

| Variables                              | HR   | 95% CI      | P   |
|----------------------------------------|------|-------------|-----|
| **Race**                               |      |             |     |
| White                                  | Reference | /         | /   |
| Black                                  | 2.06 | 1.28-3.30   | 0.003 |
| Other                                  | 0.87 | 0.54-1.41   | 0.574 |
| Unknown                                | /    | /           | /   |
| **Sex**                                |      |             |     |
| Female                                 | Reference | /         | /   |
| Male                                   | NA   | NA          | NA  |
| **Age at diagnosis (Years)**           |      |             |     |
| ≤39                                    | Reference | /         | /   |
| 40-59                                  | 4.97 | 4.11-6.01   | <0.001 |
| 60-79                                  | 40.25 | 31.45-51.52 | <0.001 |
| ≥80                                    | 144.09 | 82.04-253.07 | <0.001 |
| **Year at diagnosis**                  |      |             |     |
| 1975-1984                              | Reference | /         | /   |
| 1985-1994                              | 0.46 | 0.38-0.56   | <0.001 |
| 1995-2004                              | 0.27 | 0.21-0.35   | <0.001 |
| 2005-2014                              | 0.21 | 0.14-0.32   | <0.001 |
| **Radiotherapy**                       |      |             |     |
| No                                     | Reference | /         | /   |
| Yes                                    | 1.11 | 0.94-1.32   | 0.213 |

HR, hazard ratio; CI, confidence interval.
### Table S9. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with lung and bronchus cancer

| Variables                  | HR  | 95% CI          | P    |
|----------------------------|-----|-----------------|------|
| Race                       |     |                 |      |
| White                      | Reference / | / |<0.001 |
| Black                      | 1.47 | 1.41-1.53       |<0.001 |
| Other                      | 0.81 | 0.76-0.86       |<0.001 |
| Unknown                    | 0.33 | 0.18-0.61       |<0.001 |
| Sex                        |     |                 |      |
| Female                     | Reference / | / |<0.001 |
| Male                       | 1.48 | 1.44-1.52       |<0.001 |
| Age at diagnosis (Years)   |     |                 |      |
| ≤39                        | Reference / | / |      |
| 40-59                      | 5.37 | 4.28-6.74       |<0.001 |
| 60-79                      | 14.20 | 11.32-17.8     |<0.001 |
| ≥80                        | 35.50 | 28.25-44.61    |<0.001 |
| Year at diagnosis          |     |                 |      |
| 1975-1984                  | Reference / | / |      |
| 1985-1994                  | 0.88 | 0.84-0.91       |<0.001 |
| 1995-2004                  | 0.67 | 0.65-0.70       |<0.001 |
| 2005-2014                  | 0.47 | 0.45-0.49       |<0.001 |
| Radiotherapy               |     |                 |      |
| No                         | Reference / | / |      |
| Yes                        | 1.09 | 1.06-1.13       |<0.001 |

HR, hazard ratio; CI, confidence interval.
Table S10. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with corpus uteri cancer

| Variables                        | HR   | 95% CI       | P      |
|----------------------------------|------|--------------|--------|
| **Race**                         |      |              |        |
| White                            | Reference | / | / |
| Black                            | 1.64 | 1.53-1.76    | <0.001 |
| Other                            | 0.86 | 0.8-0.94     | 0.001  |
| Unknown                          | 0.36 | 0.22-0.58    | <0.001 |
| **Sex**                          |      |              |        |
| Female                           | Reference | / | / |
| Male                             | NA   | NA           | NA     |
| **Age at diagnosis (Years)**     |      |              |        |
| ≤39                              | Reference | / | / |
| 40-59                            | 3.14 | 2.61-3.77    | <0.001 |
| 60-79                            | 13.72| 11.44-16.46  | <0.001 |
| ≥80                              | 73.88| 61.35-88.97  | <0.001 |
| **Year at diagnosis**            |      |              |        |
| 1975-1984                        | Reference | / | / |
| 1985-1994                        | 0.89 | 0.86-0.93    | <0.001 |
| 1995-2004                        | 0.68 | 0.65-0.71    | <0.001 |
| 2005-2014                        | 0.45 | 0.42-0.48    | <0.001 |
| **Radiotherapy**                 |      |              |        |
| No                               | Reference | / | / |
| Yes                              | 1.13 | 1.09-1.17    | <0.001 |

HR, hazard ratio; CI, confidence interval.
Table S11. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with kidney and renal pelvis cancer

| Variables                | HR   | 95% CI     | P   |
|--------------------------|------|------------|-----|
| Race                     |      |            |     |
| White                    | Reference | /         | /   |
| Black                    | 1.59 | 1.47-1.71  | <0.001 |
| Other                    | 0.88 | 0.79-0.98  | 0.018 |
| Unknown                  | 0.23 | 0.11-0.49  | <0.001 |
| Sex                      |      |            |     |
| Female                   | Reference | /         | /   |
| Male                     | 1.29 | 1.23-1.35  | <0.001 |
| Age at diagnosis (Years) |      |            |     |
| ≤39                      | Reference | /         | /   |
| 40-59                    | 7.65 | 6.11-9.59  | <0.001 |
| 60-79                    | 31.77| 25.42-39.71| <0.001 |
| ≥80                      | 110.55| 87.93-138.99| <0.001 |
| Year at diagnosis        |      |            |     |
| 1975-1984                | Reference | /         | /   |
| 1985-1994                | 0.83 | 0.78-0.88  | <0.001 |
| 1995-2004                | 0.59 | 0.55-0.63  | <0.001 |
| 2005-2014                | 0.40 | 0.37-0.43  | <0.001 |
| Radiotherapy             |      |            |     |
| No                       | Reference | /         | /   |
| Yes                      | 0.98 | 0.85-1.12  | 0.734 |

HR, hazard ratio; CI, confidence interval.
Table S12. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with larynx cancer

| Variables                  | HR     | 95% CI       | P       |
|----------------------------|--------|--------------|---------|
| **Race**                   |        |              |         |
| White                      | Reference | /           | /       |
| Black                      | 1.37   | 1.25-1.49    | <0.001  |
| Other                      | 0.76   | 0.64-0.90    | 0.002   |
| Unknown                    | 0.27   | 0.10-0.73    | 0.010   |
| **Sex**                    |        |              |         |
| Female                     | Reference | /           | /       |
| Male                       | 1.12   | 1.04-1.21    | 0.004   |
| **Age at diagnosis (Years)** |        |              |         |
| ≤39                        | Reference | /           | /       |
| 40-59                      | 4.95   | 3.24-7.55    | <0.001  |
| 60-79                      | 13.44  | 8.82-20.47   | <0.001  |
| ≥80                        | 36.06  | 23.46-55.43  | <0.001  |
| **Year at diagnosis**      |        |              |         |
| 1975-1984                  | Reference | /           | /       |
| 1985-1994                  | 0.87   | 0.81-0.93    | <0.001  |
| 1995-2004                  | 0.71   | 0.66-0.77    | <0.001  |
| 2005-2014                  | 0.50   | 0.45-0.56    | <0.001  |
| **Radiotherapy**           |        |              |         |
| No                         | Reference | /           | /       |
| Yes                        | 1.03   | 0.97-1.1     | 0.342   |

HR, hazard ratio; CI, confidence interval.
Table S13. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with colon and rectum cancer

| Variables          | HR    | 95% CI      | P      |
|--------------------|-------|-------------|--------|
| **Race**           |       |             |        |
| White              | Reference | /          | /      |
| Black              | 1.26  | 1.22-1.30   | <0.001 |
| Other              | 0.76  | 0.73-0.79   | <0.001 |
| Unknown            | 0.33  | 0.25-0.43   | <0.001 |
| **Sex**            |       |             |        |
| Female             | Reference | /          | /      |
| Male               | 1.32  | 1.3-1.35    | <0.001 |
| **Age at diagnosis (Years)** |       |             |        |
| ≤39                | Reference | /          | /      |
| 40-59              | 6.04  | 4.95-7.37   | <0.001 |
| 60-79              | 31.15 | 25.58-37.93 | <0.001 |
| ≥80                | 116.66| 95.75-142.13| <0.001 |
| **Year at diagnosis** |       |             |        |
| 1975-1984          | Reference | /          | /      |
| 1985-1994          | 0.81  | 0.79-0.83   | <0.001 |
| 1995-2004          | 0.63  | 0.62-0.65   | <0.001 |
| 2005-2014          | 0.44  | 0.43-0.46   | <0.001 |
| **Radiotherapy**   |       |             |        |
| No                 | Reference | /          | /      |
| Yes                | 0.85  | 0.82-0.89   | <0.001 |

HR, hazard ratio; CI, confidence interval.
| Variables                  | HR     | 95% CI   | P    |
|---------------------------|--------|----------|------|
| **Race**                  |        |          |      |
| White                     | Reference | /      | /    |
| Black                     | 1.42   | 1.37-1.46 | <0.001 |
| Other                     | 0.75   | 0.72-0.79 | <0.001 |
| Unknown                   | 0.45   | 0.34-0.6  | <0.001 |
| **Sex**                   |        |          |      |
| Female                    | Reference | /      | /    |
| Male                      | 1.57   | 1.44-1.72 | <0.001 |
| **Age at diagnosis (Years)** |      |          |      |
| ≤39                       | Reference | /      | /    |
| 40-59                     | 4.04   | 3.63-4.50 | <0.001 |
| 60-79                     | 31.35  | 28.2-34.85 | <0.001 |
| ≥80                       | 154.74 | 139.03-172.22 | <0.001 |
| **Year at diagnosis**     |        |          |      |
| 1975-1984                 | Reference | /      | /    |
| 1985-1994                 | 0.76   | 0.74-0.77 | <0.001 |
| 1995-2004                 | 0.58   | 0.57-0.59 | <0.001 |
| 2005-2014                 | 0.39   | 0.38-0.41 | <0.001 |
| **Radiotherapy**          |        |          |      |
| No                        | Reference | /      | /    |
| Yes                       | 0.78   | 0.76-0.79 | <0.001 |

HR, hazard ratio; CI, confidence interval.
Table S15. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with cervix uteri cancer

| Variables               | HR  | 95% CI   | P    |
|-------------------------|-----|----------|------|
| **Race**                |     |          |      |
| White                   | Reference | /       | /    |
| Black                   | 1.60 | 1.46-1.75| <0.001|
| Other                   | 0.74 | 0.64-0.85| <0.001|
| Unknown                 | 0.81 | 0.42-1.57| 0.54  |
| **Sex**                 |     |          |      |
| Female                  | Reference | /       | /    |
| Male                    | NA  | NA       | NA   |
| **Age at diagnosis (Years)** |     |          |      |
| ≤39                     | Reference | /       | /    |
| 40-59                   | 6.39 | 5.44-7.52| <0.001|
| 60-79                   | 35.39 | 30.04-41.69| <0.001|
| ≥80                     | 139.66 | 115.84-168.37| <0.001|
| **Year at diagnosis**   |     |          |      |
| 1975-1984               | Reference | /       | /    |
| 1985-1994               | 0.81 | 0.74-0.88| <0.001|
| 1995-2004               | 0.64 | 0.57-0.71| <0.001|
| 2005-2014               | 0.41 | 0.34-0.49| <0.001|
| **Radiotherapy**        |     |          |      |
| No                      | Reference | /       | /    |
| Yes                     | 1.47 | 1.36-1.59| <0.001|

HR, hazard ratio; CI, confidence interval.
Table S16. Multivariable Cox proportional hazards regression analysis of cardiovascular-specific survival in patients with brain cancer

| Variables                | HR     | 95% CI       | P     |
|--------------------------|--------|--------------|-------|
| **Race**                 |        |              |       |
| White                    | Reference | /            | /     |
| Black                    | 2.23   | 1.80-2.75    | <0.001|
| Other                    | 1.00   | 0.74-1.36    | 0.976 |
| Unknown                  | 1.00   | 0.25-4.00    | 0.996 |
| **Sex**                  |        |              |       |
| Female                   | Reference | /            | /     |
| Male                     | 1.18   | 1.04-1.34    | 0.011 |
| **Age at diagnosis (Years)** |    |              |       |
| ≤39                      | Reference | /            | /     |
| 40-59                    | 9.32   | 7.57-11.48   | <0.001|
| 60-79                    | 43.81  | 35.07-54.73  | <0.001|
| ≥80                      | 154.09 | 115.01-206.46 | <0.001|
| **Year at diagnosis**    |        |              |       |
| 1975-1984                | Reference | /            | /     |
| 1985-1994                | 0.68   | 0.58-0.80    | <0.001|
| 1995-2004                | 0.45   | 0.38-0.55    | <0.001|
| 2005-2014                | 0.33   | 0.27-0.41    | <0.001|
| **Radiotherapy**         |        |              |       |
| No                       | Reference | /            | /     |
| Yes                      | 0.97   | 0.85-1.12    | 0.70  |

HR, hazard ratio; CI, confidence interval.