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Temporal Trend of Cardiovascular Disease Burden Among Cancer Patients Between 2005 and 2022: Nationwide Population-Based Cohort Study in South Korea

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AUTHOR'S SUMMARY

Although overall and cancer-specific mortality have significantly decreased in cancer patients, cardiovascular disease (CVD)-related mortality has remained stable, leading to an increasing proportion of deaths attributable to CVD among cancer patients. Heart failure (HF) has emerged as a major concern in cancer patients, with a significant increase in HF burden. These findings underscore the need for enhanced cardiovascular monitoring in cancer patients.

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Conflict of Interest
Dr. You reports being a chief executive officer of the PHI Digital Healthcare; grants from Daiichi Sankyo. Hasung Kim and Jungkuk Lee are employees of Hanmi Pharm. Other authors have no conflicts of interest to disclose.

Data Sharing Statement
The datasets used during this study are available from the corresponding author upon reasonable request.

Author Contributions
Conceptualization: Cho I, Lee S, Kim H, Lee J, Hwang HJ, Cho EJ, Kim HJ, Park SM, Kim SE, Lee YG, Jung MH, Youn JC, Park CS, Shim CY,

ABSTRACT

Background and Objectives: Comprehensive data on the changing landscape of cardiovascular disease (CVD) burden in cancer patients remains limited. We aimed to analyze the temporal trend in the burden of CVD among cancer patients.
Methods: Using a nationwide administrative claims database in Korea, we analyzed 1,322,502 adults (aged ≥18) newly diagnosed with cancer (2005–2022). The primary outcomes were: 1) temporal trends in CVD incidence, including ischemic heart disease (IHD), heart failure (HF), and stroke; and 2) cause-specific mortality trends, focusing on cancer and CVD-related deaths. Both crude and age-standardized rates were calculated for CVD incidence and mortality.
Results: The 1-year age-standardized cancer mortality rate showed a substantial decline from 134.0 to 76.3 per 1,000 person-years. While the age-standardized 1-year CVD incidence initially decreased from 91.7 to 50.6 per 1,000 person-years (2005–2014), this improvement plateaued and showed an upward trend thereafter. Analysis of CVD subtypes revealed divergent patterns: age-standardized IHD incidence declined, while HF incidence rose by 136%, 52%, and 37% at 1-, 3-, and 5-year follow-ups. Despite improvements in cancer mortality, the proportion of deaths attributed to CVD increased from 1.0% to 1.5% at 1-year, corresponding to a 50% relative rise and showed a similar upward trend at 5-year follow-up, with HF emerging as an increasingly cause of cardiovascular death (increasing from 10.8% to 26.3% of CVD mortality).
Conclusions: While cancer-specific mortality has improved significantly, cardiovascular mortality remains a growing concern, due to the increasing burden of HF in cancer patients. Ongoing CVD pattern surveillance in cancer patients is crucial for targeted interventions and prevention.

Keywords: Cardio-oncology; Cancer; Cardiovascular disease; Heart failure; Epidemiology

INTRODUCTION

Cardiovascular disease (CVD) and cancer share multiple risk factors, including aging, obesity, smoking, and inflammation, creating a complex interrelationship between these 2 major health conditions.[1)2)] This connection is further complicated by cancer therapies themselves, because many treatments, including certain chemotherapeutics, targeted therapies, and radiation, can induce various cardiovascular complications such as heart failure, coronary artery disease, hypertension (HTN), and thromboembolism.

The landscape of cancer care has evolved significantly in recent decades, with remarkable improvements in survival rates due to early detection and advanced therapeutic options.[3)4)] As patients with cancer live longer, they face an increasing risk of developing cardiovascular complications, either as a consequence of their cancer therapy or due to shared underlying risk factors.[5)]

Recent evidence suggests that the incidence of CVD among cancer patients has been fluctuating over time, reflecting the dynamic interaction between improved cancer survival and cardiovascular complications.[6)] Recent data from the United States indicates concerning trends, with CVD mortality rates increasing since 2020 in the general population.[7)] This broader cardiovascular trend intersects with the complex landscape of cancer care, where improved cancer survival may paradoxically contribute to increased cardiovascular burden. Despite these

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shifting patterns, comprehensive data on the changing CVD burden in cancer patients remain limited. Thus, we aimed to analyze the temporal trend of CVD burden in patients with cancer using a large-scale, nationwide database spanning nearly 2 decades (2005–2022). Specifically, we examined changes in CVD prevalence, incidence, and mortality patterns, while also investigating the relationship between cardiovascular outcomes and cancer-specific survival.

METHODS

Ethical statement

The Institutional Review Board of Severance Hospital approved the study protocol (4-2023-0011) and waived the requirement of informed consent because the data provided by National Health Insurance Service (NHIS) were deidentified. This study was conducted in accordance with the latest version of the Declaration of Helsinki.

Data source

We used the nationwide de-identified healthcare database of the NHIS, which is the single provider of mandatory health insurance, covering approximately 97% of the Korean population.[8)9)] The NHIS includes diagnostic codes, prescribed medications, health examinations, demographic data, and death records. This study used NHIS data from 2005 to 2022 and employed stratified random sampling, extracting a 50% sample based on sex and birthdate.

Study population

From the NHIS Sample Cohort 2005 to 2022 database, we extracted patients with cancer (n=2,372,511). In this study, we included the following 18 common adult solid and hematologic cancers using International Classification of Diseases, Tenth Revision (ICD-10) codes: gastric cancer (C16), colon cancer (C18–C20), lung cancer (C34), gallbladder cancer (C23), liver cancer (C22), pancreatic cancer (C25), breast cancer (C50), ovarian cancer (C56), prostate cancer (C61), and renal cell carcinoma (C64), Hodgkin's disease (C81), non-Hodgkin's disease (C82–C86), multiple myeloma (C90), lymphoid leukemia (C91), myeloid leukemia (C92-94), Leukemia of unspecified cell type (C95). We excluded patients with previous cancer at the baseline (from 2002 to 2004) to focus our study population on those with newly diagnosed cancer (n=252,702) and patients <18 years of age at the date of their first cancer diagnosis (n=7,070). Additionally, patients without the critical condition code (V193, V194 and V027) were excluded to improve the accuracy of the cancer diagnosis (n=790,237). Finally, 1,322,502 patients were included in this study.

Clinical outcome

The main outcome was CVD which includes ischemic heart disease (IHD; I20–I25), heart failure (HF; I40–I43, I50–I52, I110, I130, I132, I255) and stroke (I60–I64). Each newly diagnosed cancer patient was tracked throughout the study period to identify incident CVD events. We also assessed survival status and causes of death during the follow-up period.

Statical analysis

Categorical variables are presented as frequency and percentage of total patients.
We analyzed both crude and age-standardized prevalence, incidence rates, and mortality of cancer patients (per 1,000 person-years) throughout the duration of the study period. Direct age-standardized rates were calculated using the 2005 Korean population to facilitate the comparison of yearly rates. Additionally, we examined incidence and mortality in 3 forms

(1-, 3-, and 5-year incidence rates) and 2 forms (1- and 5-year mortality), respectively. Also, we analyzed the all-cause mortality, cancer-specific mortality and CVD mortality according to prevalence and incidence of CVD within first year after cancer diagnosis. All statistical analyses were performed using SAS software for Windows version 9.4 (SAS Institute Inc., Cary, NC, USA).

RESULTS

Population characteristics

A total of 1,322,502 patients were included in the analysis. **Table 1** presents the demographics of the cohort. Among these patients, the most prevalent types of cancer were gastrointestinal cancer (stomach; 18.23%, colo-rectum;19.45%) followed by lung cancer (14.11%) and breast cancer (13.22%). The proportion of cancer patients aged over 80 years showed a consistent and significant increase from 2005 to 2022. Cardiotoxic agents were administered to 32.6% of all cancer patients.

Trends of cardiovascular disease prevalence at cancer diagnosis

Over the study period, the crude and age-standardized prevalence of CVD at cancer diagnosis exhibited a decreasing trend until 2012 but has remained relatively stable since then. The age-standardized prevalence of CVD (per 1,000 person-years) decreased from 127.4 (men 143.2, women 117.6) in 2005 to 102.5 (men 114.8, women 93.4) in 2012 (**Supplementary Figure 1**).

Trends of newly developed cardiovascular disease incidence among cancer patients

When examining the CVD incidence rates by time since cancer diagnosis (**Figure 1**), the 1-year crude incidence rate of CVD (per 1,000 person-years) showed a downward trend until 2014 (**Figure 1A**). However, from 2015 to 2022, the rate increased, reaching a peak of 131.6. Similarly, the 1-year age-standardized incidence rate of CVD (per 1,000 person-years) exhibited a decline, dropping from 91.7 (men 101.1, women 86.2) in 2005 to 50.6 (men 55.7, women 44.6) in 2014. Thereafter, the 1-year age-standardized incidence rate of CVD showed a gradual increase. In the 3-year incidence rate of CVD (**Figure 1B**), the 3-year crude incidence rate of CVD showed a decline until 2012, followed by a slight upward trend. Likewise, the 3-year age-standardized incidence rates of CVD also decreased from 61.5 (men 70.1, women 55.9) in 2005 to 36.3 (men 41.4, women 31.9) in 2012. From 2013 to 2020, the 3-year age-standardized incidence rate showed an increasing trend from 38.9 (men 45.5, women 34.4) to 44.4 (men 50.5, women 40.4). The 5-year age-standardized incidence rate of CVD (**Figure 1C**) also decreased from 51.8 to 33.5, until around 2010, and then plateaued.

Figure 2 and **Supplementary Figure 2** show the temporal trends of incidence rates by specific causes of CVD (per 1,000 person-years). In 2005, the most common 1-year incidence of CVD was IHD, followed by stroke and HF. Notably, from 2005 to 2022, the proportion of CVD incidents attributed to IHD and stroke declined, while HF incidents increased by 91% (**Supplementary Figure 2A**). The trends for 3- and 5-year incidence rates by specific causes of CVD were consistent, with HF incidents rising by 40% and 33%, respectively (**Supplementary Figure 2B and C**). The age-standardized incidence rates showed similar trends (**Figure 2**). The age-standardized incidence of IHD decreased consistently, while the HF incidence rate increased from 25.0 to 59.4 at 1 year. The trends in 3-year and 5-year incidence rates for CVD subtypes were similar, with HF incidents increasing by 52% and 37%, respectively.

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Table 1. Baseline characteristics

	Percentage of frequency (%)				
	2005	2009	2014	2018	2022
Demographics					
Age at diagnosis (years)					
18–29	1.5	1.0	0.9	0.9	1.0
30–39	5.3	4.3	3.8	3.6	3.5
40–49	15.6	13.7	12.5	12.0	12.0
50–59	22.0	21.9	23.2	21.6	20.3
60–69	29.0	27.2	24.7	26.4	28.4
70–79	20.6	23.8	24.8	23.3	21.4
≥80	6.0	8.0	10.1	12.2	13.4
Female	40.5	41.0	43.2	45.7	49.1
Cancer type					
Stomach	22.6	20.7	18.1	16.0	14.8
Colon and rectum	17.3	19.0	20.1	18.8	21.0
Liver	17.6	15.6	13.8	11.0	8.7
Gall bladder	1.5	1.6	1.5	1.5	1.3
Pancreas	5.2	5.7	6.7	7.3	6.8
Lung	14.0	13.5	13.8	14.6	14.3
Breast	10.0	10.6	12.8	15.4	18.6
Ovary	2.9	2.6	2.6	3.2	3.0
Prostate	8.8	10.2	10.0	11.0	9.4
Kidney	2.1	2.4	2.6	2.9	3.0
Lymphoma	2.4	2.6	2.9	3.4	3.9
Multiple myeloma	0.6	0.7	0.9	1.2	1.2
Leukemia	1.5	1.5	1.6	1.7	2.0
Previous medical history					
Diabetes mellitus	13.3	16.4	18.5	19.7	20.6
Hypertension	30.2	39.2	42.6	43.7	44.4
Dyslipidemia	8.7	17.1	26.0	33.6	39.5
Chronic kidney disease	1.2	1.6	2.3	3.0	3.5
Medication use					
Statins	10.1	18.8	27.5	35.0	41.4
ACEi/ARB	18.5	27.1	33.3	35.9	37.8
Beta blockers	16.9	19.6	16.4	14.1	13.8
CCB	28.2	35.9	36.1	36.3	37.4
Antiplatelet	22.3	30.2	28.8	26.0	21.8
Anticoagulant	1.4	2.6	3.7	4.6	5.4
Cardiotoxic agents					
Adriamycin	10.7	11.3	12.6	11.2	7.3
Herceptin	0.3	1.0	2.5	3.1	2.5
Alkylating agents	8.0	8.9	10.6	10.7	8.2
ALK inhibitors	0.0	0.0	0.1	0.3	0.2
Proteasome inhibitor	0.2	0.4	0.6	0.7	0.7
Fluoropyrimidines	3.6	3.9	5.1	5.9	4.6
BCR-ABL TKI	0.4	0.5	0.6	0.7	0.7
Income level*					
0	7.4	8.1	6.6	6.5	6.1
1	17.0	16.5	17.9	18.7	20.6
2	16.8	16.7	17.4	18.2	17.6
3	24.1	23.1	22.8	22.6	22.1
4	34.7	35.6	35.3	34.0	33.6

ACEi = angiotensin-converting enzyme inhibitor; ALK = anaplastic lymphoma kinase; ARB = angiotensin II receptor blocker; CCB = calcium channel blocker; TKI = tyrosine kinase inhibitor.
*Income level was classified into 5 categories (0–4) according to quintiles of National Health Insurance Service insurance, serving as a surrogate marker of socioeconomic status. Level 4 corresponded to the highest income group.

When analyzing the incidence of CVD associated with the most prevalent cancers, lung cancer showed the highest occurrence of CVD (**Supplementary Figure 3**). Markedly high incidence of CVD was also demonstrated in hematological malignancies such as

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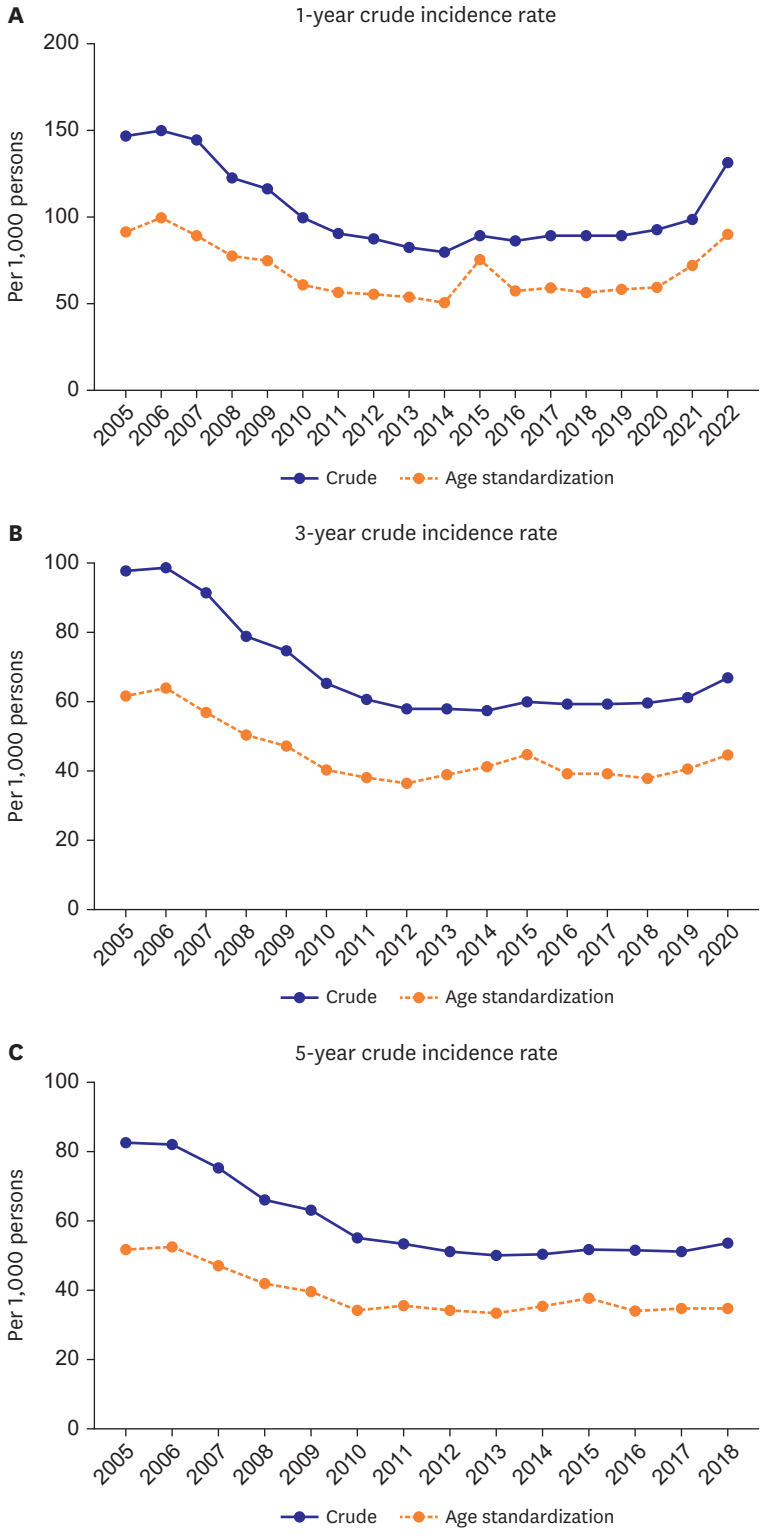

Figure 1. Incidence rate of cardiovascular disease by timing after cancer diagnosis. (A) One-year incidence rate. (B) Three-year incidence rate. (C) Five-year incidence rate.

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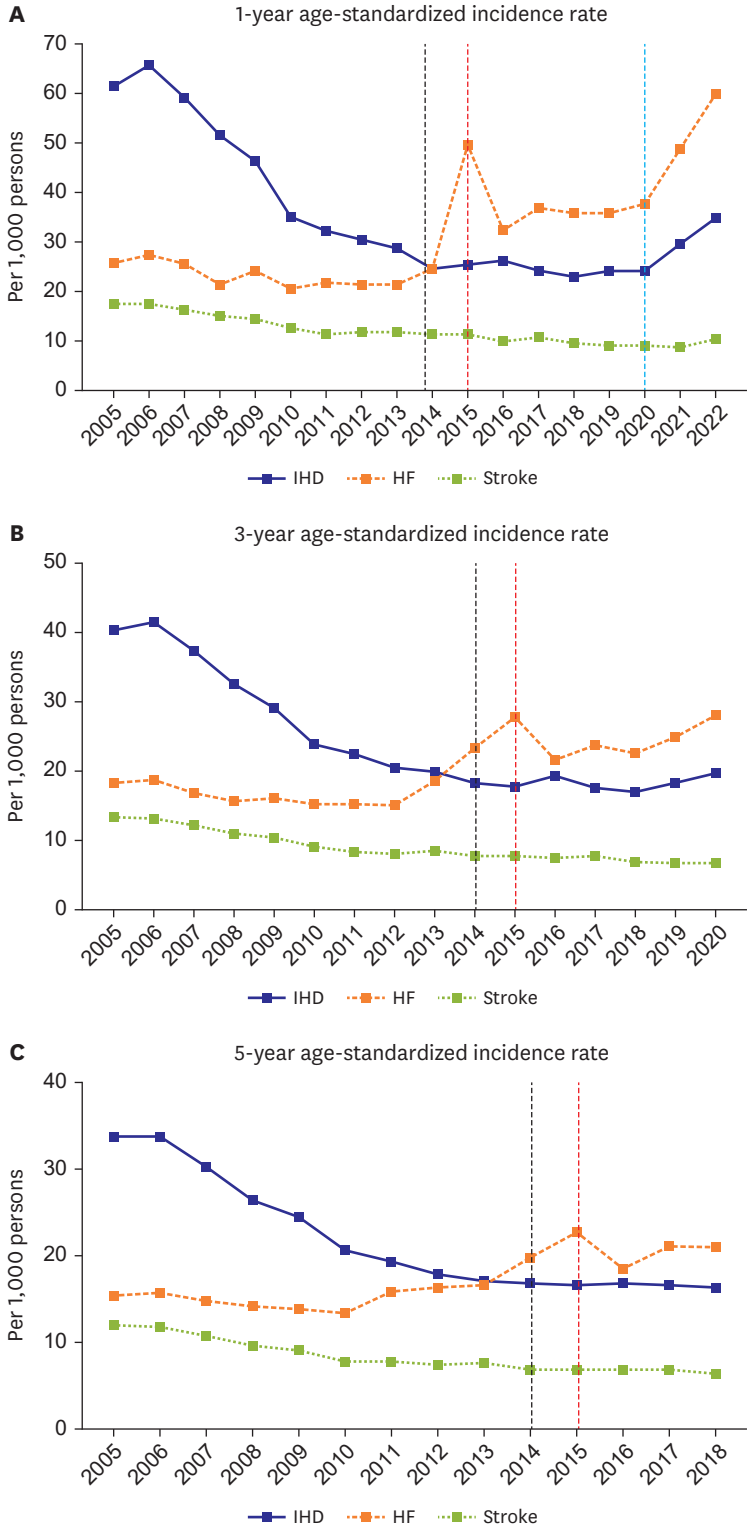

Figure 2. Disease-specific causes of cardiovascular age-standardized incidence rate. (A) One-year incidence rate. (B) Three-year incidence rate. (C) Five-year incidence rate.
Black dashed line indicates the first approval of ICIs in Korea; red dashed line indicates the introduction of NT-proBNP test reimbursement; and blue dashed line indicates the onset of the COVID-19 pandemic.
HF = heart failure; ICI = immune checkpoint inhibitor; IHD = ischemic heart disease; NT-proBNP = N-terminal pro-brain natriuretic peptide.

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leukemia and lymphoma, with 1-year age-adjusted incidence rates of 239 and 149 per 1,000 person-years at 2022, respectively. Across all cancer types, the trends were similar to the overall pattern, with the incidence of CVD demonstrating a decline until approximately 2010, after which it exhibited either a stabilization or a slight increase.

To analyze the risk factors for cardiovascular events, we performed a multivariable Cox regression analysis, which showed that age, diabetes mellitus (DM), HTN, chronic kidney disease (CKD), and atrial fibrillation were significant independent risk factors, whereas female sex was associated with a lower risk. When evaluating anticancer agents, anthracyclines, human epidermal growth factor receptor 2-targeted therapy, immune checkpoint inhibitors (ICIs), proteasome inhibitors, and anaplastic lymphoma kinase inhibitors were all significantly associated with increased CVD incidence and HF incidence (**Supplementary Tables 1** and **2**).

Trends of mortality in cancer patients: overall, cancer, and cardiovascular disease mortality

From 2005 to 2022, both the crude mortality rate and the age-standardized mortality rate for all causes and cancer showed a decreasing trend, except in 2022 (**Supplementary Figure 4**). The 1-year crude mortality rate of CVD (per 1,000 person-years) showed an overall upward trend. In contrast, the age-standardized 1-year CVD mortality rate remained relatively stable, with no significant changes (**Figure 3A**). The age-standardized 5-year CVD mortality rate slightly decreased from 0.8 to 0.6 (**Figure 3B**).

When comparing the changes in causes of death among the total death of cancer patients, from 2005 to 2022, the proportion of 1-year cancer-related deaths among all-cause deaths declined from 93.8% to 89.0%, while the proportion of deaths from CVD increased from 1.0% to 1.5%, corresponding to a 50% relative rise over the study period (**Figure 4A**). This trend also showed similar results in the 5-year mortality rates. (**Figure 4B**).

In disease-specific causes of CVD mortality among cancer patients (**Figure 5A**), the proportion of 1-year CVD mortality attributed to stroke gradually decreased from 2005 to 2022 (from 51.3% to 32.6%). The proportion of 1-year CVD mortality attributed to IHD increased until around 2010 but has since shown a declining trend (from 45.3% to 36.3%), while HF accounted for a gradually increasing proportion of CVD mortality (from 10.8% to 26.3%). Similarly, disease-specific causes of CVD mortality over 5 years showed a decrease in mortality attributed to IHD and stroke (from 85.3% to 72.1%), while the proportion of CVD deaths due to HF increased (from 15.9% to 26.2%) (**Figure 5B**). When examining CVD mortality by cancer type, although there were variations across years, lung cancer and hepatic cancer exhibited the highest CVD mortality rates, with the overall trend showing a slight increase in mortality rates after around 2010 (**Supplementary Figure 5**).

Mortality according to presence of cardiovascular disease

We evaluated all-cause mortality, cancer mortality, and CVD mortality for cancer patients with and without CVD (**Figure 6A-C**). Compared to patients without pre-existing CVD, cancer patients with pre-existing CVD had a significantly higher risk of all-cause, cancer and CVD mortality even after adjusting for confounding factors, including age, sex, HTN, DM, and CKD. Additionally, cancer patients who newly developed CVD had a worse prognosis in terms of all-cause mortality, cancer mortality, and CVD mortality compared to those who did not develop CVD (**Figure 6D-F**).

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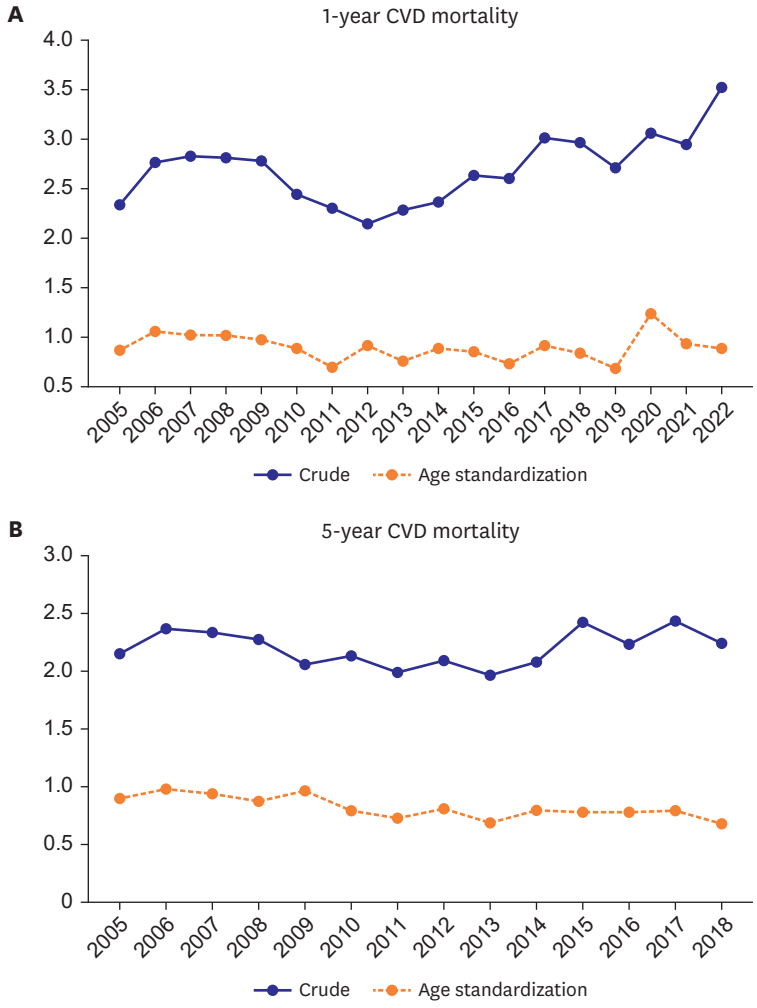

Figure 3. Mortality of CVD by timing after cancer diagnosis. (A) One-year mortality. (B) Five-year mortality.
CVD = cardiovascular disease.

DISCUSSION

Our long-term comprehensive analysis of CVD trends among cancer patients from 2005 to 2022 reveals several findings with important clinical implications. First, we observed a substantial decline in both crude and age-standardized CVD incidence rates among cancer patients until 2014, particularly for IHD and stroke. However, this improvement plateaued and subsequently exhibited a concerning upward trend, predominantly driven by HF. Second, while overall and cancer-specific mortality have significantly decreased in cancer patients, CVD mortality has remained stable, leading to CVD accounting for an increasing proportion of deaths among cancer patients. Third, we identified a notable shift in the pattern of CVD mortality, with HF becoming an increasingly dominant cause of death, rising from 10.8% to 26.3% of CVD-related mortality. Fourth, the presence of CVD, whether pre-existing or newly developed, significantly impacted patient outcomes, leading to increased risks of all-cause, cancer-specific, and CVD mortality.

Our large-scale East Asian cohort study reveals that while the prevalence of traditional cardiovascular risk factors has increased, similar to previous nationwide study,[10] the incidence

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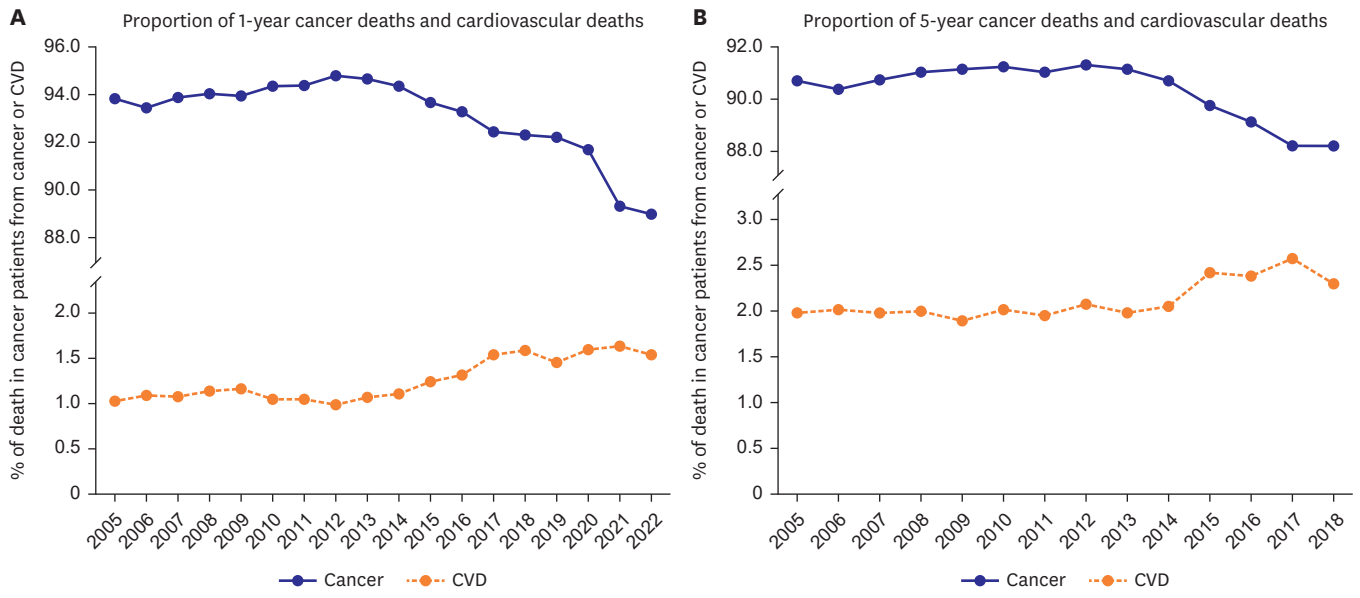

Figure 4. Changes in the proportion of cancer deaths and cardiovascular deaths by the time of cancer diagnosis. (A) One-year mortality. (B) Five-year mortality.
CVD = cardiovascular disease.

of newly developed CVD showed a marked decline through 2014. However, the subsequent plateau and recent increase in CVD incidence are concerning. While our observational study design prevents definitive causal inference, several factors may explain these trends. One possibility is the growing complexity of modern cancer therapies,[11][12] which, despite their enhanced efficacy against cancer, can trigger various cardiovascular complications, including myocardial infarction, stroke, HF, HTN, thromboembolism, and arrhythmias.[6][13][14] Supporting this hypothesis, Kobo et al.[15] recently showed that cardiovascular admission rates have increased in cancer patients while decreasing in those without cancer. In addition to changes in cancer therapy, the rise in CVD incidence since 2015 may reflect the increasing proportion of patients aged ≥80 years, improved detection through greater use of diagnostic tools such as echocardiography and N-terminal pro-brain natriuretic peptide (NT-proBNP) testing, and a genuine increase in CVD burden. The parallel rise in incidence of HF after 2015

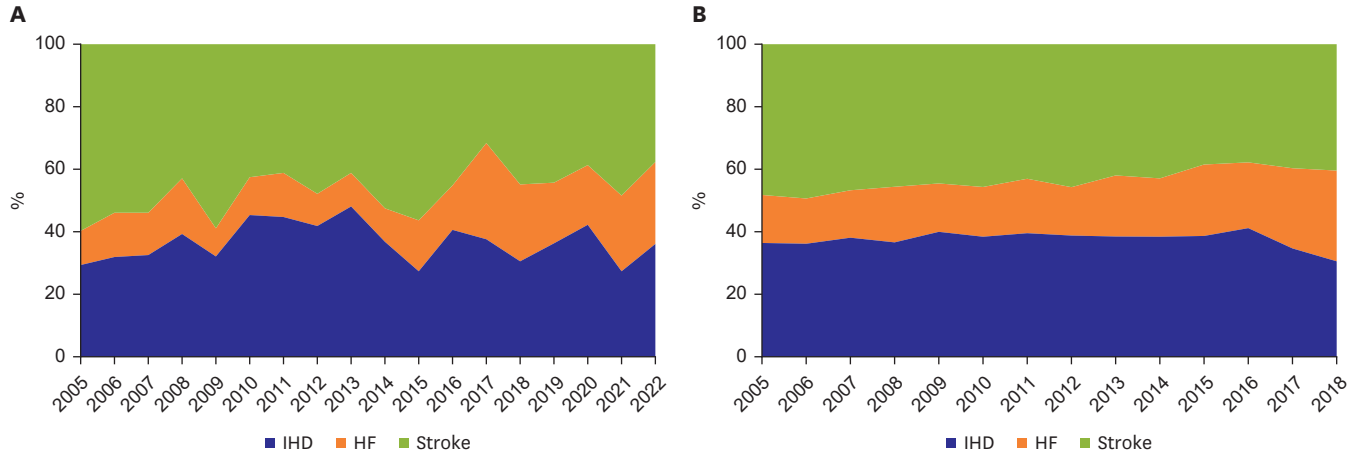

Figure 5. Disease-specific causes of cardiovascular mortality expressed as percentage of total cardiovascular mortality. (A) One-year mortality of CVD. (B) Five-year mortality of CVD.
CVD = cardiovascular disease; HF = heart failure; IHD = ischemic heart disease.

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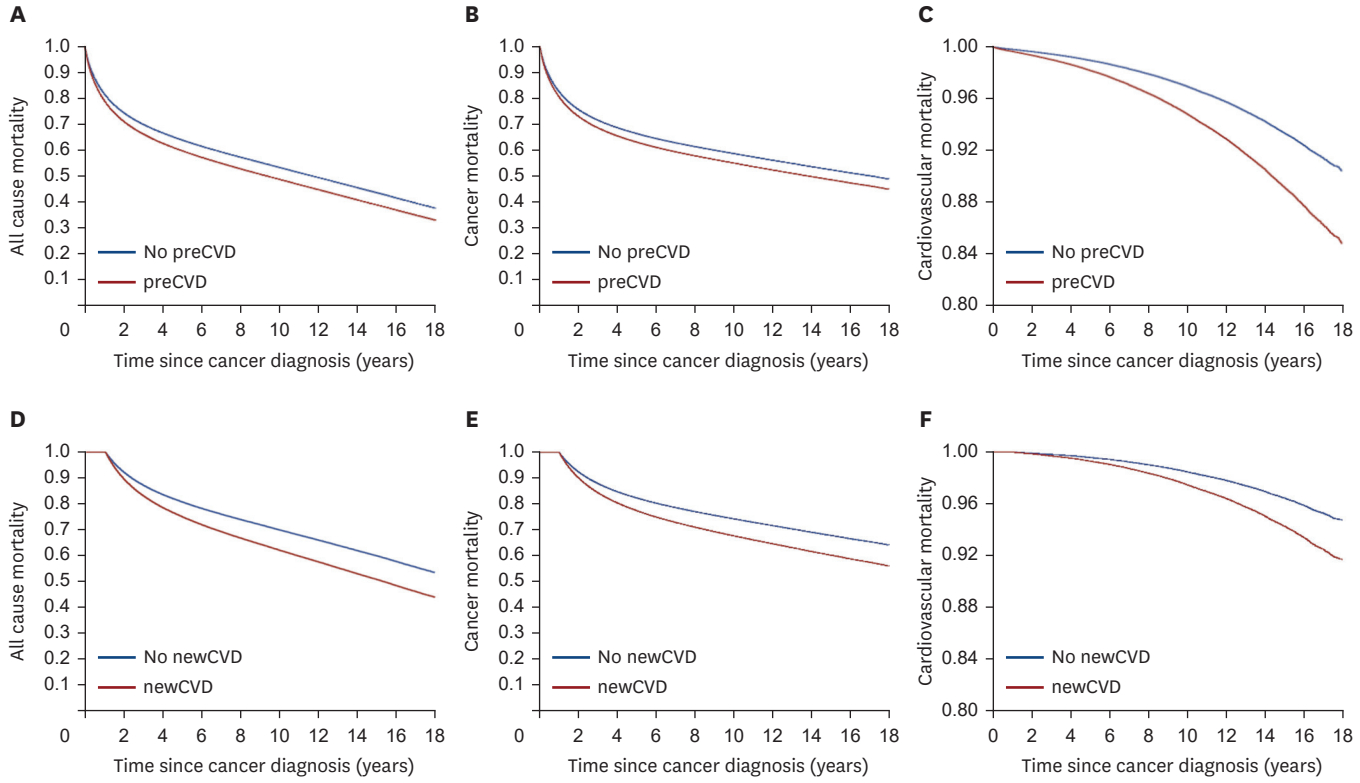

Figure 6. Mortality according to presence of CVD after adjusting confounding factors (age, sex, hypertension, diabetes and chronic kidney disease). (A) All-cause mortality according to pre-existing CVD. (B) Cancer mortality according to pre-existing CVD. (C) CVD mortality according to pre-existing CVD. (D) All-cause mortality according to newly developed CVD. (E) Cancer mortality according to newly developed CVD. (F) CVD mortality according to newly developed CVD.
CVD = cardiovascular disease.

mirrors national trends in the general population as reported in the 2022 HF Fact Sheet, which showed an increasing trend during the 2015–2016 period,[16] underscoring the need for targeted cardiovascular risk management in cancer patients.

Most notably, the increasing burden of HF emerges as a particular concern in our findings. We observed substantial increases in HF incidence of 136%, 52%, and 37% at 1-, 3-, and 5-year follow-up, respectively. This trend is particularly alarming as HF has become an increasingly dominant cause of cardiovascular death in cancer patients. Recent changes in cancer therapy, particularly the increased use of ICIs, have been linked to cardiotoxicity, including myocarditis, arrhythmias, and HF, with meta-analyses demonstrating a significantly elevated risk.[17] However, as these results are based on composite cardiotoxicity endpoints, caution is needed when applying them to HF, whose incidence appears low and likely represents a distinct phenotype from myocarditis. In addition, well-established agents such as anthracyclines and trastuzumab can induce cardiac dysfunction, and their incorporation into multimodal regimens may have exacerbated the observed rise in HF cases.[18] In this study, proteasome inhibitors were a strong risk factor for CVD, which may be explained by the older age and high baseline cardiovascular risk of multiple myeloma patients, prior exposure to cardiotoxic therapies, and age-related impairment of proteasome and ubiquitin–proteasome pathway function.[19] Furthermore, improved cancer survival may have prolonged exposure to cardiovascular risk factors, thereby contributing to the observed increase in HF incidence. A similar pattern was observed in a U.S. study of cancer patients from 1999 to 2019, where the proportion of cardiovascular deaths attributed to IHD decreased,

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while HF-related mortality increased.[7] In addition, in terms of the risk of HF according to cancer type, the age-adjusted incidence rate of HF over 5 years was notably higher for lung cancer (80.8 per 1,000 person-years, 740/10,278 patients) and hematological malignancies, including lymphoma (82.5 per 1,000 person-years, 206/2828 patients) and leukemia (103 per 1,000 person-years, 100/1414 patients), than for other cancer types. This pattern is consistent with the findings of a Danish population-based registries,[20] which reported an increase in HF mortality, particularly among patients with lung and hematological cancers. These elevated rates may reflect the combined effects of intensive, potentially cardiotoxic treatment regimens, a higher prevalence of comorbidities and the intrinsic disease burden of these malignancies. These findings underscore the need for enhanced vigilance in monitoring cardiovascular health, particularly in patients undergoing cancer treatments with known cardiotoxic effects.[21] Furthermore, this concerning trend aligns with broader population-wide cardiovascular patterns, in which CVD-associated mortality, particularly related to HF-related mortality, continues to rise despite the approval of several notable drug and device therapies.[22] Taken together, these findings suggest a fundamental shift in CVD patterns with HF emerging as a dominant concern in cancer population as well as general population.[18-20]

Our findings demonstrate that CVD significantly worsens cancer outcomes. In line with previous studies,[23-26] both pre-existing and newly developed CVD were found to be associated with an increased risk of both overall and cancer-specific mortality, regardless of confounding factors. This relationship may reflect the direct impact of comorbidity on mortality, reduced treatment efficacy due to heightened toxicity, and biological mechanisms, such as chronic inflammation, that promote cancer progression. Taken together, these pathways suggest that CVD compromises the effectiveness, tolerance and survival of treatment, emphasizing the importance of integrated cardiovascular care from the time of cancer diagnosis. Although the absolute increase in CVD specific mortality among cancer patients was small, this trend is notable in the context of declining cancer mortality. This suggests that CVD may become an increasingly important factor in determining long-term survival in this population.

The present study has several potential limitations. While the Korean NHIS dataset provides comprehensive longitudinal data on a national scale, it lacks detailed information on cancer stages, specific treatments, and lifestyle factors. However, this limitation is partially offset by the large sample size and comprehensive population coverage. Additionally, while the NHIS diagnostic codes have been validated in previous studies,[27][28] diagnostic accuracy varies by disease entity. Reliance solely on ICD-10 codes may therefore fail to capture real-world diagnostic complexity fully. In particular, our definition of IHD (I20–I25) included angina and myocardial infarction, as well as other related conditions. However, the diagnostic accuracy of subcategories such as atherosclerosis and angina is lower than that of myocardial infarction. Secondly, we were unable to apply a more stringent operational definition of HF, such as incorporating left ventricular ejection fraction, brain natriuretic peptide (BNP) levels, which could have improved diagnostic specificity. Also, to better capture the real-world disease burden, CVD diagnoses were identified from both inpatient and outpatient records, rather than relying solely on primary inpatient diagnoses. Although this approach increases sensitivity, it may also reduce specificity, resulting in cases where CVD was not the primary cause of hospitalization being included. Thirdly, the competing risk of non-CVD death was not explicitly accounted for in this study. However, because cancer-related mortality may influence the estimation of cardiovascular outcomes, we analyzed incidence and mortality at fixed time points (1, 3, and 5 years after cancer diagnosis) to minimize potential bias related

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to competing risks. Fourth, A trend such as the sharp increase in HF cases in 2015 and 2020 may have been influenced by changes in diagnostic practices and insurance coverage, such as NT-proBNP test coverage in 2015, as well as the potential effects of the COVD-19 pandemic. However, trends in test utilization, including echocardiography and BNP testing, could not be directly quantified from the current claims data, which limits the ability to determine their precise contribution to the observed increase in HF diagnoses.

Although the overall use of cardiotoxic agents did not increase significantly, newer agents such as ICIs and other non-reimbursed therapies were not fully captured in our dataset, which may have influenced treatment patterns during the study period.

Consequently, the prevailing explanation for the rise in HF induced by cardiotoxic agents might require refinement. Finally, our 5-year follow-up period, while capturing the period of most intensive cancer treatment and highest cardiovascular risk,[29)30)] limits our understanding of longer-term cardiovascular outcomes. Future studies should focus on examining long-term cardiovascular outcomes in cancer survivors.

While cancer-specific mortality has improved, cardiovascular mortality has remained stable and has become an increasingly important cause of death in cancer patients. Although the burden of CVD initially decreased, further progress has stalled, with HF emerging as a major concern. These findings emphasize the need for enhanced cardiovascular monitoring and integrated cardio-oncology care to improve cancer outcomes.

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SUPPLEMENTARY MATERIALS

Supplementary Table 1
Multivariable Cox regression analysis of clinical factors associated with cardiovascular events in cancer patients

Supplementary Table 2
Multivariable Cox regression analysis of cancer therapy associated with newly developed HF in cancer patients

Supplementary Figure 1
Prevalence of CVD at the time of cancer diagnosis. This graph shows the crude and age-standardized prevalence of CVD at the time of cancer diagnosis.

Supplementary Figure 2
Disease-specific causes of cardiovascular crude incidence rate.

Supplementary Figure 3
Incidence rate of CVD for cancer type.

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Supplementary Figure 4
Overall mortality and cancer mortality.

Supplementary Figure 5
CVD mortality for cancer type.

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