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ORIGINAL RESEARCH

Risk of Cardiovascular Disease in Cancer Survivors after Systemic Treatment

A Population-Based Cohort Study

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ABSTRACT

BACKGROUND Patients face an increased risk of cardiovascular disease shortly after a cancer diagnosis, but evidence on long-term risk among cancer survivors remains limited.

OBJECTIVES In this study the authors sought to estimate the risk of cardiovascular disease in cancer survivors previously treated with systemic cancer therapy.

METHODS Using Danish population-based registries, we identified individuals who had received systemic cancer treatment and were free of both cancer and treatment 3 years after diagnosis (index date). For each cancer survivor, 5 cancer-free individuals from the general population were randomly selected, matched by birth year, sex, and calendar year. Participants were followed from the index date for up to 5 years. HRs were estimated using Cox regression, adjusted for potential confounders.

RESULTS Compared with 457,035 matched individuals, the 91,407 cancer survivors had an increased risk of heart failure or cardiomyopathy (HR: 1.08; 95% CI: 1.02-1.15), venous thromboembolism (HR: 1.50; 95% CI: 1.41-1.61), pericarditis, endocarditis, or myocarditis (HR: 1.30; 95% CI: 1.11-1.52), and kidney failure (HR: 1.17; 95% CI: 1.10-1.25), but not of ischemic heart disease, stroke, or atrial fibrillation. Estimates varied substantially by cancer type and treatment agent. For example, venous thromboembolism risk was consistently increased across nearly all cancer types, whereas hypertension risk was elevated for none. Ischemic heart disease risk was increased only among lung cancer survivors. Stroke was associated with platinum compounds but not with other systemic treatments.

CONCLUSIONS Several cardiovascular disease risks were elevated among cancer survivors, with substantial variation by cancer type and treatment. (JACC CardioOncol. 2025;7:360-378) © 2025 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY-NC-ND license (http://creativecommons.org/licenses/by-nc-nd/4.0/).

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The number of patients cancer survivors has steadily grown in recent years.[1,2] An emerging concern is that the growing population of cancer survivors may face elevated long-term risks of cardiovascular disease.[3] Contributing factors include shared risk factors for cancer and cardiovascular diseases, such as diabetes and smoking, as well as the delayed cardiovascular effects of systemic cancer treatments.

It is well established that the risk of several cardiovascular diseases (eg, acute myocardial infarction, venous thromboembolism, and heart failure) is increased shortly after cancer diagnosis and during treatment.[4,5] However, less is known about these risks among patients who remain alive and cancer-free several years after diagnosis.[3,6]

Two large population-based studies recently reported an increased risk of several cardiovascular diseases among cancer patients who were alive 1 year after diagnosis, even after adjusting for comorbidities and other potential confounders.[7,8] Risks were particularly elevated among those who had received chemotherapy, suggesting that prior treatment may be a key driver. However, both studies could not confirm whether patients were cancer-free and off treatment during follow-up, leaving open the possibility that active cancer or ongoing cancer treatment contributed to the increased risk.

Estimating long-term cardiovascular risk after cancer treatment is important for cancer survivors, clinicians, and policymakers. If these risks are indeed higher than in the general population, closer monitoring and more aggressive management of cardiovascular risk factors may be warranted after cancer remission. In this study, we evaluated the long-term risk of several cardiovascular diseases and kidney failure in cancer survivors previously treated with systemic cancer therapy (oral or intravenous chemotherapy or targeted therapy) who were no longer undergoing treatment and had no evidence of active cancer. Their risks were compared with those of their matched comparators from the general population.

METHODS

DANISH POPULATION-BASED HEALTH CARE REGISTRIES. We used Danish population-based health care registries to conduct a cohort study of cancer survivors and their matched comparators from the general population. These registries are known for their completeness and high positive predictive value for cardiovascular disease diagnoses.[9,10] The DNPR (Danish National Patient Registry) supplied data on cardiovascular and kidney outcomes, comorbidities, and systemic cancer treatment.[11] The DNPR includes diagnosis codes, based on the *International Classification of Diseases,* from hospital admissions, emergency room contacts, and outpatient clinic visits. The Danish Cancer Registry was used to retrieve information on cancer diagnoses and stage.[12] Medication data were obtained from both the Danish National Prescription Registry and the DNPR.[13]

ABBREVIATION AND ACRONYM

HER2 = human epidermal growth factor receptor 2

The codes used for cancer diagnoses, treatments, study outcomes, and medication use are provided in Supplemental Table 1. Systemic cancer treatment was defined as any chemotherapy or targeted therapy. Chemotherapeutic agents were grouped and subclassified according to the Anatomical Therapeutic Chemical Classification System (Supplemental Table 2).[14] Targeted therapies comprised immunomodulating therapies (eg, lenalidomide), antiangiogenic agents, protein kinase inhibitors, and other targeted therapies. Immune checkpoint inhibitors were excluded because they were rarely used during the study period (2004-2019). This study was approved by the Danish Data Protection Agency through registration at Aarhus University (record number 2016-051-000001/812). Informed consent was not required, as participants were neither contacted nor assigned to an intervention.

CANCER SURVIVOR COHORT AND COMPARATOR COHORT. The cancer survivor cohort included all Danish residents aged 18 years or older who were alive 3 years after their first cancer diagnosis and had received systemic cancer therapy within 12 months of diagnosis. We focused on this cohort based on prior research suggesting that systemic therapy may contribute to the subsequent risk of cardiovascular diseases, including heart failure, arterial thromboembolism, venous thromboembolism, and valvular heart disease.[8]

All cancer types recorded in the Danish Cancer Registry since 2004 were included, except for nonmelanoma skin cancer and myelodysplastic disorders, as these are often not treated with conventional systemic cancer treatments. For patients with breast or prostate cancer, hormonal treatment was also considered a form of systemic treatment due to its central role in treatment strategies.

Follow-up for cancer survivors began 3 years after their cancer diagnosis (index date). To reduce the likelihood of active cancer at the index date, we excluded individuals with a new cancer diagnosis or a possible cancer relapse within the 12 months prior. A possible relapse was defined as a relapse diagnosis code, a new record of systemic cancer treatment,

or a code indicating cancer-related surgery or radiotherapy.

For each cancer survivor, 5 matched comparators were randomly selected from the general population, with replacement.[15] Matched comparators had no history of cancer and were alive and cancer-free on the survivor's diagnosis date, which served as the index date for the comparison cohort. Cancer survivors and comparison individuals were matched by year of birth, sex, and index year.[16]

FOLLOW-UP. Individuals in the cancer survivor and comparison cohorts were followed from their index date for up to 5 years. Follow-up was censored at the earliest occurrence of a new cancer diagnosis, cancer relapse, death, emigration, loss to follow-up, or end of study follow-up (December 31, 2022). Individuals in the comparison cohort who developed cancer during follow-up were censored at diagnosis and, if eligible, subsequently entered the cancer survivor cohort.

STUDY OUTCOMES. Outcomes included ischemic heart disease (a composite of myocardial infarction and chronic ischemic heart disease); heart failure or cardiomyopathy; stroke (ischemic, hemorrhagic, or unspecified); acute or chronic kidney failure (including kidney transplantation or dialysis); venous thromboembolism; atrial fibrillation or flutter; a composite of pericarditis, endocarditis, and myocarditis; other cardiac arrhythmias; valvular heart disease; aortic aneurysm or dissection; and hypertension.

CONFOUNDERS. The association between systemic cancer therapy and cardiovascular disease can be confounded by comorbidities related to cancer type, treatment type, and the outcome itself.[17,18] To address this, we accounted for established risk factors associated with certain cancer types (eg, smoking-related cancers and obesity-related cancers) and various cardiovascular diseases. These included kidney failure, obesity, liver disease, inflammatory bowel disease, alcoholism and related conditions, chronic obstructive pulmonary disease (as a proxy for smoking), and diabetes.

We also considered pre-existing cardiovascular diseases diagnosed before the index date as potential confounders, as they often share common risk factors with cancer, such as smoking, body weight, and lower socioeconomic status. These included atrial fibrillation or flutter, congestive heart failure, atherosclerosis and peripheral vascular disease, ischemic heart disease, venous thromboembolism, stroke, and hypertension. In addition, use of lipid-lowering therapies, antihypertensive drugs, or anticoagulation agents was included as a potential confounder. The same set of confounders was applied in each outcome analysis.

STATISTICAL ANALYSES. Baseline characteristics are presented as counts and percentages for categorical variables and as medians with first and third quartiles (Q1-Q3) for continuous variables. Cumulative risks of study outcomes during the 5-year follow-up period were calculated using the nonparametric Aalen-Johansen estimator, accounting for death as a competing risk.

To compare the cancer survivors with their matched comparators, we used Cox proportional hazards regression to estimate HRs with 95% CIs. A robust variance estimator was used to account for potential correlation due to sampling with replacement in the matched cohort. The proportional hazards assumption was verified by visual inspection of log(-log) survival plots and was found to be satisfied. HRs were adjusted for the potential confounders listed above.

Results are displayed in a forest plot and stratified by cancer type, type of systemic therapy received during the first 12 months after cancer diagnosis (chemotherapy vs targeted therapy), and subgroups of these treatments. Treatment groups were not mutually exclusive, as therapies are often given in combination. For selected outcomes, individuals with a history of the outcome were excluded to capture only incident cases. Because this exclusion could lead to underestimation of outcome incidence, a secondary analysis was conducted in which these individuals were retained. In that analysis, any new diagnosis code after the start of follow-up was considered a relapse or new event of the cardiovascular outcome of interest.

To present risks regardless of cancer recurrence, we repeated the analysis without censoring patients at the time of a new cancer diagnosis or relapse. In an exploratory analysis, we evaluated how often study outcomes preceded a new cancer diagnosis or relapse by calculating the proportion of patients with a new cancer diagnosis code, relapse code, or record of systemic therapy 30 days after a study outcome. All statistical analyses were performed using SAS version 9.4 (SAS Institute).

RESULTS

A total of 91,407 cancer survivors who received systemic cancer treatment and were cancer-free 3 years after diagnosis were included in the study. Cancers were diagnosed between January 2004 and December 2019, and follow-up ended in December 2022. The most common cancer types in the survivor cohort were breast cancer (n = 40,352; 44.1%), prostate cancer (n = 13,587; 14.9%), and colorectal cancer (n = 11,582; 12.7%).

At initial diagnosis, cancer stage was localized for 31,783 survivors (34.8%), regional for 32,485 (35.5%), distant metastasis for 6,786 (7.4%), and unknown for 20,353 (22.3%). Among cancer survivors who underwent systemic therapy, 57,779 (63.2%) received chemotherapy during the first 12 months following diagnosis. A total of 19,937 (21.8%) received alkylating agents, 15,390 (16.8%) antimetabolites, 18,500 (20.2%) cytotoxic antibiotics, 22,656 (24.8%) plant alkaloids, and 15,279 (16.7%) platinum compounds. In total, 13,756 patients (15.0%) received targeted therapies, and 46,540 (50.9%) received hormonal therapy (breast cancer and prostate cancer only). The matched comparator cohort comprised 457,035 individuals without cancer on the index date. Baseline characteristics of both cohorts are shown in Table 1 and the study flow chart (Figure 1).

CARDIOVASCULAR OUTCOMES IN CANCER SURVIVORS AND THEIR MATCHED COMPARATORS. Ischemic heart disease. The 5-year cumulative incidence of ischemic heart disease was 3.24% (95% CI: 3.10%-3.40%) in the cancer survival cohort and 3.21% (95% CI: 3.15%-3.27%) in the comparison cohort (HR: 0.96; 95% CI: 0.91-1.01). Among all cancer types, only lung cancer survivors had an increased risk of ischemic heart disease compared with their matched counterparts (HR: 1.47; 95% CI: 1.11-1.96) (Figure 2). There was no evidence of increased ischemic heart disease risk among cancer survivors who received chemotherapy (HR: 0.94; 95% CI: 0.87-1.01) or targeted therapy (HR: 1.03; 95% CI: 0.88-1.19), compared with their matched comparators (Figure 3). Figure 4 shows the cumulative incidence of ischemic heart disease for survivors of breast, colorectal, hematological and lung cancer, and for their matched cancer-free comparison individuals during the 5-year study period. It visually shows that the cumulative incidence for survivors of hematological and lung cancers is higher compared to their matched cancer-free cohorts, whereas this is not observed for other cancer types. Likewise, Figure 5 shows the cumulative incidence of ischemic heart disease for recipients of chemotherapy, targeted therapy and hormonal therapy and their matched comparison groups. None of the systemic treatments was associated with increased risk of ischemic heart disease.

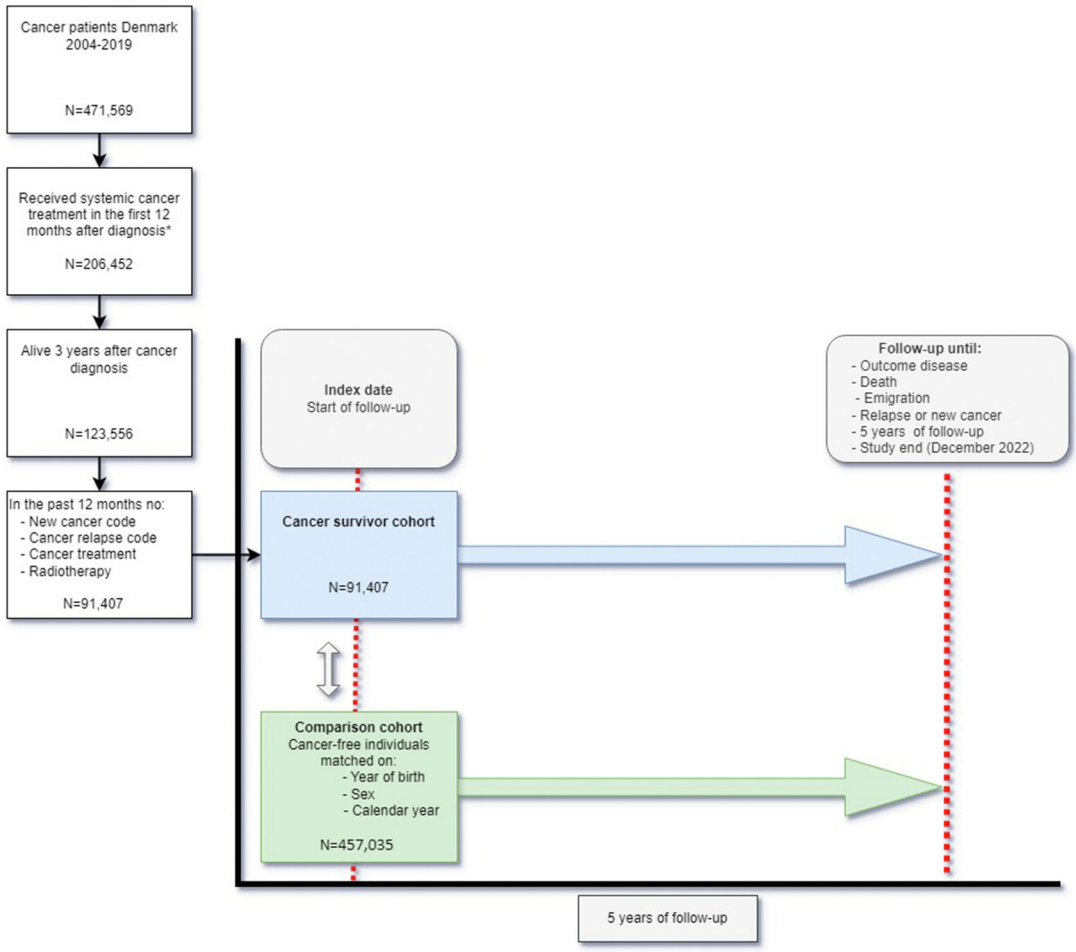
Heart failure or cardiomyopathy. The 5-year cumulative incidence of heart failure or cardiomyopathy was 2.73% (95% CI: 2.60%-2.86%) in the cancer survivor cohort and 2.42% (95% CI: 2.37%-2.47%) in the comparison cohort (HR: 1.08; 95% CI: 1.02-1.15) (Figure 2). Survivors of hematological malignancies

TABLE 1 Baseline Characteristics of Cancer Survivors and Their Matched Comparators in Denmark

	Cancer Survivors (n = 91,407)	Cancer-Free Comparators (n = 457,035)
Sex, female	57,881 (63.3)	289,405 (63.3)
Age, y	67 (57-75)	61 (57-75)
<50	11,320 (12.4)	56,600 (12.4)
50-59	16,615 (18.2)	83,075 (18.2)
60-69	25,885 (28.3)	129,425 (28.3)
70-79	25,927 (28.4)	129,635 (28.4)
≥80	11,660 (12.8)	58,300 (12.8)
Previous cancer type		
Breast	40,352 (44.1)	–
Prostate	13,587 (14.9)	–
Colorectal	11,582 (12.7)	–
Hematological	10,200 (11.2)	–
Other	4,518 (4.9)	–
Gynecological	3,819 (4.2)	–
Lung	2,875 (3.1)	–
Urogenital	1,931 (2.1)	–
Gastroesophageal	929 (2.1)	
Pancreas	368 (0.4)	–
Brain	324 (0.4)	–
Melanoma	241 (0.3)	–
Hepatobiliary	179 (0.2)	–
Cancer stage at diagnosis[a]		
Localized	31,783 (34.8)	–
Regional	32,485 (35.5)	–
Distant	6,786 (7.4)	–
Unknown	20,353 (22.3)	–
Cancer treatment[b]		
Chemotherapy	57,779 (63.2)	–
Alkylating agents	19,937 (21.8)	–
Antimetabolites	15,390 (16.8)	–
Cytotoxic antibiotics	18,500 (20.2)	–
Plant alkaloids	22,656 (24.8)	–
Platinum compounds	15,279 (16.7)	–
Targeted therapy	13,756 (15.0)	–
Protein kinase inhibitors	648 (0.7)	–
Antiangiogenic therapy	852 (0.9)	–
Immunomodulatory	691 (0.8)	–
Other targeted therapy	12,516 (13.7)	–
Hormonal/antihormonal treatment[c]	46,540 (50.9)	
Prior comorbidities		
Venous thromboembolism	4,836 (5.3)	12,255 (2.7)
Ischemic heart disease	9,615 (10.5)	46,196 (10.1)
Atrial fibrillation or flutter	6,633 (7.3)	27,450 (6.0)
Stroke	4,543 (5.0)	22,547 (4.9)
Hypertension or use of antihypertensive agents	53,164 (58.2)	243,505 (53.3)
Diabetes mellitus	6,897 (7.5)	27,891 (6.1)
Congestive heart failure or cardiomyopathy	3,561 (3.9)	14,800 (3.2)
Pericarditis, endocarditis, or myocarditis	725 (0.8)	2,463 (0.5)
Aorta aneurysm or dissection	1,157 (1.3)	3,943 (0.9)
Chronic obstructive pulmonary disease	8,679 (9.5)	34,209 (7.5)
Kidney failure	2574 (2.8)	8,640 (1.9)
Lipid-lowering therapy	28,923 (31.6)	144,646 (31.6)

Values are n (%) or median (Q1-Q3). [a]For solid cancers and lymphoma. [b]Treatments received within the first 12 months after cancer diagnosis; categories are not mutually exclusive. [c]For breast and prostate cancer.

FIGURE 1 Flow Chart



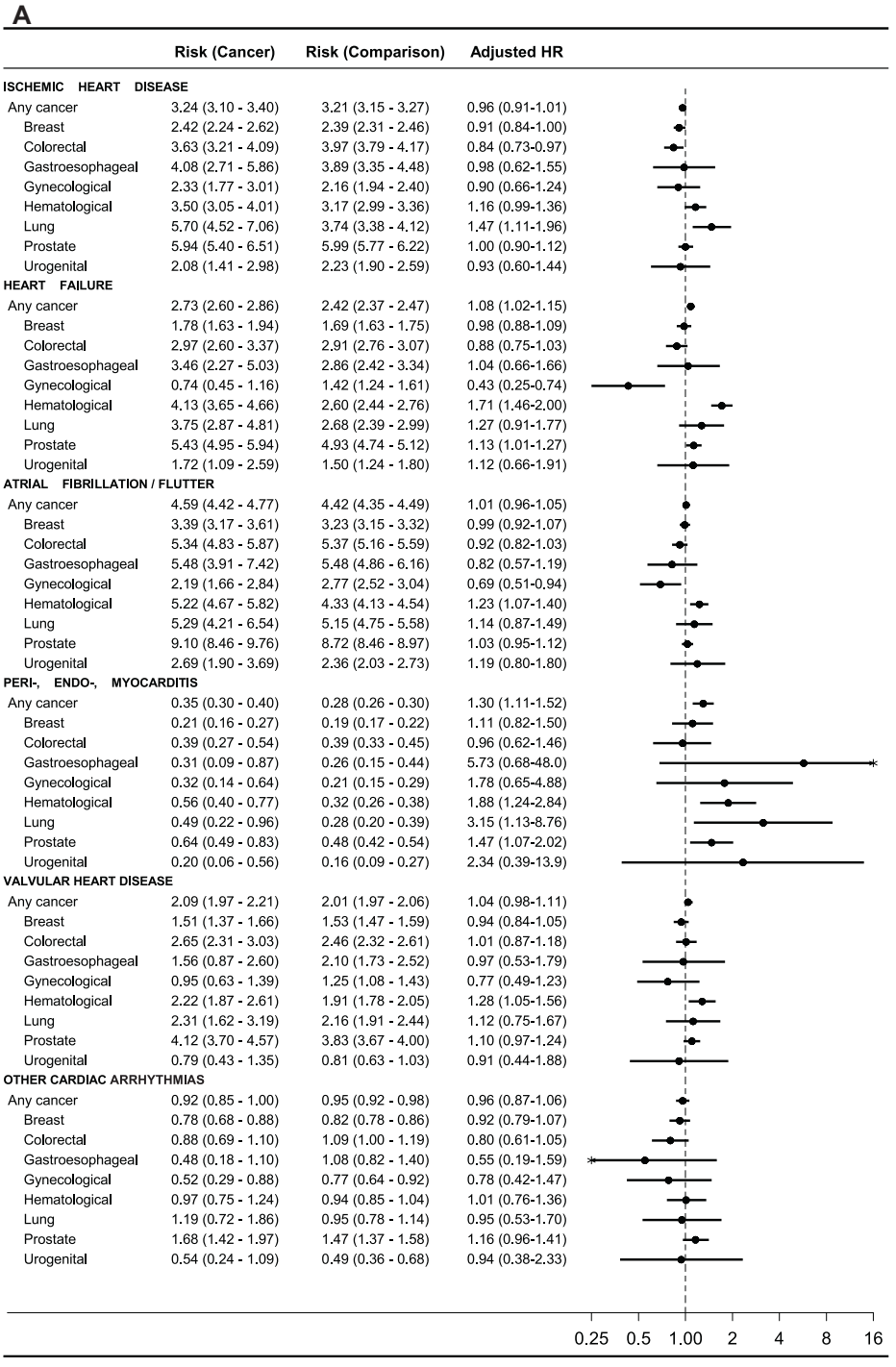
Among 471,569 cancer patients identified between 2004 and 2019, 206,452 received systemic cancer treatment within 12 months of diagnosis. Of these, 91,407 were alive 3 years later (the index date) and had no evidence of recent cancer treatment or relapse. At index date, each survivor was matched to 5 cancer-free individuals from the general population and followed for up to 5 years for study outcomes or censoring. *For breast and prostate cancer, systemic treatment included (anti)hormonal agents.

and prostate cancer had a higher risk compared with their matched counterparts (HR: 1.71; 95% CI: 1.46-2.00 and HR: 1.13; 95% CI: 1.01-1.27, respectively).

Compared with their matched comparators, cancer survivors who had received chemotherapy or targeted therapy were at increased risk of heart failure or cardiomyopathy (HR: 1.15; 95% CI: 1.06-1.25 and HR: 1.59; 95% CI: 1.35-1.86, respectively). Among chemotherapy recipients, elevated risks were observed for those treated with alkylating agents (HR: 1.49; 95% CI: 1.26-1.77), nitrogen mustard analogues (HR: 1.50; 95% CI: 1.26-1.79), cytotoxic antibiotics (HR: 1.60; 95% CI: 1.34-1.91), anthracyclines (HR: 1.64; 95% CI: 1.38-1.95), plant alkaloids (HR: 1.37; 95% CI: 1.17-1.61), vinca alkaloids (HR: 1.72; 95% CI: 1.37-2.16), and podophyllotoxin derivatives (HR: 1.97; 95% CI: 1.24-3.11) (Figure 3). The risk was increased for the overall group of targeted therapies (HR: 1.59; 95% CI: 1.35-1.86), but not for any of its subgroups or for recipients of hormonal therapies.

Stroke. The 5-year cumulative incidence of stroke was 2.90% (95% CI: 2.77%-3.04%) in the cancer survivor cohort and 2.82% (95% CI: 2.77%-2.88%) in the comparison cohort (HR: 1.01; 95% CI: 0.96-1.06). An increased risk was observed only for survivors of prostate cancer (HR: 1.12; 95% CI: 1.00-1.25) and recipients of platinum-based chemotherapy (HR: 1.19; 95% CI: 1.04-1.36) (Figures 2 and 3).

FIGURE 2 **Outcomes in Cancer Survivors and Comparison Individuals, by Cancer Type**



Cardiovascular outcomes in cancer survivors and their matched cancer-free comparators during 5-year follow-up. Risks are shown as cumulative incidences and adjusted HRs with 95% CIs. Outcomes are stratified by cancer type at first cancer diagnosis. Results indicate that cardiovascular risk is increased in cancer survivors, with variations across cancer types. These include ischemic heart disease, heart failure, atrial fibrillation/flutter, peri-/endo-/ myocarditis, valvular heart disease, and other cardiac arrhythmias, as well as aortic aneurysm and dissection, stroke, venous thromboembolism, kidney failure, and hypertension.

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FIGURE 2 Continued

B

	Risk (Cancer)	Risk (Comparison)	Adjusted HR
AORTIC ANEURYSM AND DISSECTION			
Any cancer	0.76 (0.69 - 0.83)	0.75 (0.72 - 0.77)	1.05 (0.94-1.16)
Breast	0.37 (0.31 - 0.45)	0.36 (0.34 - 0.39)	0.97 (0.78-1.20)
Colorectal	1.01 (0.81 - 1.25)	1.07 (0.98 - 1.17)	0.97 (0.76-1.24)
Gastroesophageal	1.44 (0.76 - 2.48)	1.13 (0.87 - 1.46)	1.54 (0.76-3.14)
Gynecological	0.23 (0.10 - 0.49)	0.34 (0.26 - 0.44)	1.33 (0.51-3.44)
Hematological	0.73 (0.55 - 0.97)	0.78 (0.70 - 0.88)	1.02 (0.74-1.41)
Lung	1.45 (0.93 - 2.17)	0.87 (0.71 - 1.05)	1.66 (0.98-2.82)
Prostate	1.82 (1.55 - 2.12)	1.76 (1.65 - 1.88)	1.04 (0.87-1.24)
Urogenital	0.27 (0.09 - 0.66)	0.51 (0.37 - 0.69)	0.75 (0.23-2.48)
STROKE			
Any cancer	2.90 (2.77 - 3.04)	2.82 (2.77 - 2.88)	1.01 (0.96-1.06)
Breast	2.13 (1.96 - 2.31)	2.31 (2.23 - 2.38)	0.87 (0.80-0.96)
Colorectal	3.45 (3.05 - 3.88)	3.23 (3.07 - 3.40)	1.02 (0.89-1.17)
Gastroesophageal	3.87 (2.62 - 5.50)	3.04 (2.59 - 3.56)	1.13 (0.73-1.75)
Gynecological	1.83 (1.35 - 2.43)	1.83 (1.63 - 2.06)	1.05 (0.75-1.47)
Hematological	2.82 (2.42 - 3.27)	2.75 (2.59 - 2.92)	1.03 (0.87-1.23)
Lung	3.84 (2.93 - 4.92)	3.29 (2.97 - 3.64)	1.23 (0.91-1.67)
Prostate	5.18 (4.71 - 5.69)	4.80 (4.61 - 4.99)	1.12 (1.00-1.25)
Urogenital	1.11 (0.65 - 1.80)	1.80 (1.51 - 2.13)	0.56 (0.32-1.00)
VENOUS THROMBOEMBOLISM			
Any cancer	2.02 (1.91 - 2.14)	1.43 (1.39 - 1.47)	1.50 (1.41-1.61)
Breast	1.59 (1.45 - 1.75)	1.26 (1.20 - 1.31)	1.30 (1.17-1.45)
Colorectal	2.19 (1.88 - 2.54)	1.54 (1.43 - 1.66)	1.48 (1.23-1.77)
Gastroesophageal	1.50 (0.78 - 2.63)	2.06 (1.69 - 2.48)	0.60 (0.30-1.18)
Gynecological	1.69 (1.23 - 2.26)	1.31 (1.14 - 1.50)	1.53 (1.06-2.19)
Hematological	2.33 (1.97 - 2.73)	1.40 (1.28 - 1.52)	1.77 (1.45-2.16)
Lung	3.73 (2.86 - 4.77)	1.62 (1.39 - 1.86)	2.87 (2.02-4.06)
Prostate	2.96 (2.61 - 3.33)	1.98 (1.86 - 2.10)	1.69 (1.46-1.96)
Urogenital	1.63 (1.04 - 2.43)	0.95 (0.75 - 1.19)	2.23 (1.26-3.95)
KIDNEY FAILURE			
Any cancer	2.36 (2.24 - 2.48)	1.92 (1.88 - 1.97)	1.17 (1.10-1.25)
Breast	1.41 (1.27 - 1.55)	1.27 (1.22 - 1.33)	0.93 (0.82-1.05)
Colorectal	2.78 (2.42 - 3.17)	2.33 (2.20 - 2.48)	1.06 (0.90-1.25)
Gastroesophageal	3.06 (1.94 - 4.57)	2.53 (2.12 - 3.00)	1.18 (0.67-2.06)
Gynecological	1.85 (1.37 - 2.44)	1.21 (1.05 - 1.39)	1.46 (0.97-2.20)
Hematological	2.29 (1.94 - 2.69)	1.83 (1.70 - 1.97)	1.38 (1.12-1.69)
Lung	3.09 (2.32 - 4.03)	2.09 (1.84 - 2.37)	1.67 (1.15-2.43)
Prostate	5.36 (4.89 - 5.87)	4.19 (4.02 - 4.36)	1.32 (1.18-1.48)
Urogenital	2.17 (1.48 - 3.09)	1.01 (0.80 - 1.25)	2.75 (1.59-4.78)
HYPERTENSION			
Any cancer	8.24 (7.99 - 8.50)	8.68 (8.58 - 8.78)	0.95 (0.91-0.98)
Breast	7.69 (7.33 - 8.05)	7.93 (7.79 - 8.07)	0.94 (0.88-0.99)
Colorectal	8.62 (7.89 - 9.38)	9.99 (9.69 - 10.30)	0.94 (0.84-1.05)
Gastroesophageal	6.80 (4.82 - 9.22)	9.97 (9.07 - 10.91)	0.59 (0.40-0.87)
Gynecological	5.60 (4.63 - 6.69)	6.83 (6.42 - 7.26)	0.85 (0.68-1.07)
Hematological	6.19 (5.56 - 6.86)	8.11 (7.82 - 8.41)	0.77 (0.68-0.88)
Lung	10.2 (8.55 - 12.0)	9.83 (9.24 - 10.45)	1.04 (0.84-1.29)
Prostate	14.1 (13.2 - 14.9)	12.54 (12.22 - 12.87)	1.09 (1.01-1.18)
Urogenital	3.70 (2.72 - 4.89)	3.93 (3.49 - 4.41)	1.05 (0.73-1.51)

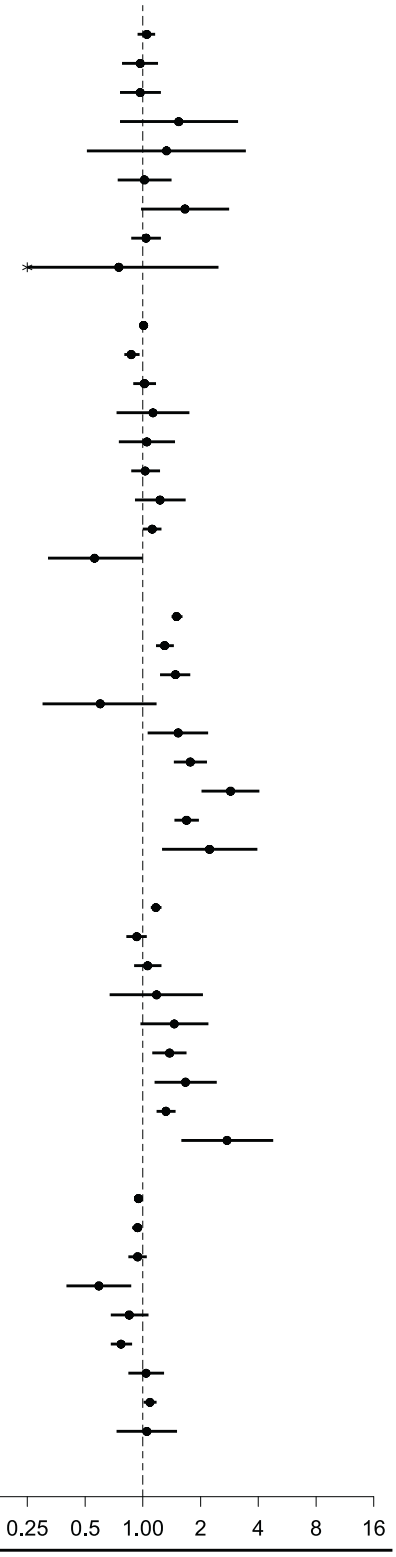
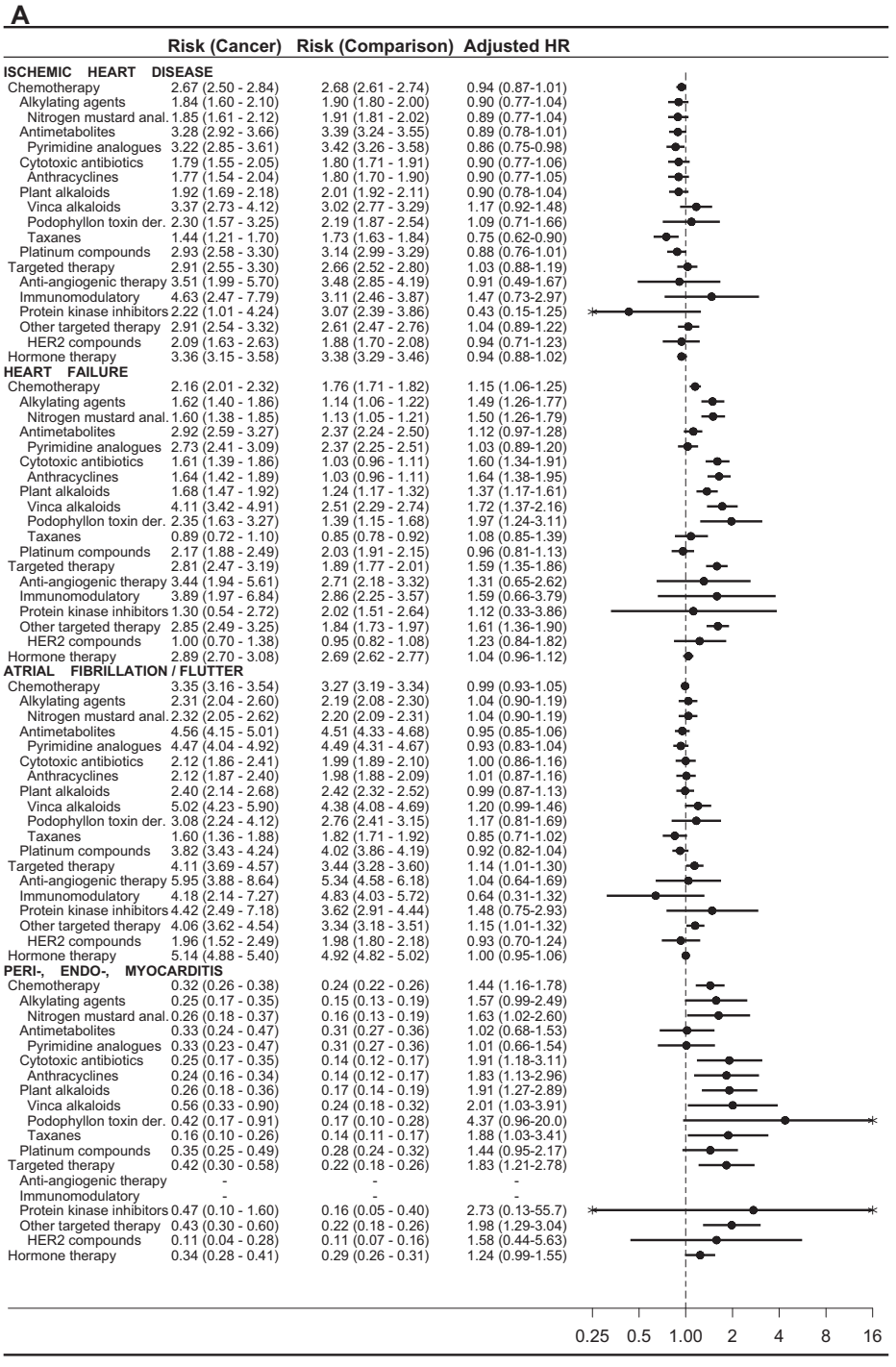


FIGURE 3 **Outcomes in Cancer Survivors and Comparison Individuals, by Treatment Group**



Cardiovascular outcomes in cancer survivors and their matched cancer-free comparators during 5-year follow-up. Risks are shown as cumulative incidences and adjusted HRs with 95% CIs. Outcomes are stratified by cancer treatment received within the first 12 months after initial diagnosis. Results indicate that cardiovascular risk is increased in cancer survivors and varies by treatment type. (A) includes ischemic heart disease, heart failure, atrial fibrillation/flutter, and peri-/endo-/myocarditis. (B) includes stroke, venous thromboembolism, kidney failure, and hypertension. (C) includes valvular heart disease, other cardiac arrhythmias, aortic aneurysm/dissection. *Hormonal treatment was evaluated only in survivors of breast and prostate cancer. HER2 = human epidermal growth factor receptor 2.

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FIGURE 3 Continued

B

	Risk (Cancer)	Risk (Comparison)	Adjusted HR
STROKE			
Chemotherapy	2.28 (2.13 - 2.43)	2.19 (2.13 - 2.25)	1.02 (0.95-1.11)
Alkylating agents	1.36 (1.16 - 1.58)	1.64 (1.55 - 1.74)	0.80 (0.68-0.95)
Nitrogen mustard anal.	1.34 (1.14 - 1.57)	1.66 (1.57 - 1.75)	0.78 (0.65-0.93)
Antimetabolites	2.82 (2.50 - 3.17)	2.93 (2.79 - 3.07)	0.93 (0.81-1.07)
Pyrimidine analogues	2.82 (2.49 - 3.17)	2.93 (2.79 - 3.08)	0.93 (0.81-1.07)
Cytotoxic antibiotics	1.29 (1.09 - 1.52)	1.56 (1.47 - 1.65)	0.77 (0.65-0.93)
Anthracyclines	1.28 (1.08 - 1.50)	1.54 (1.45 - 1.64)	0.78 (0.65-0.93)
Plant alkaloids	1.56 (1.35 - 1.79)	1.78 (1.69 - 1.87)	0.88 (0.75-1.02)
Vinca alkaloids	2.81 (2.24 - 3.47)	3.01 (2.76 - 3.27)	0.94 (0.74-1.19)
Podophyllon toxin der.	1.85 (1.19 - 2.74)	1.86 (1.57 - 2.19)	1.15 (0.71-1.86)
Taxanes	1.12 (0.92 - 1.35)	1.40 (1.31 - 1.50)	0.80 (0.65-0.99)
Platinum compounds	2.98 (2.63 - 3.35)	2.51 (2.38 - 2.64)	1.19 (1.04-1.36)
Targeted therapy	2.33 (2.02 - 2.68)	2.33 (2.21 - 2.47)	1.00 (0.85-1.18)
Anti-angiogenic therapy	3.64 (2.09 - 5.86)	3.10 (2.53 - 3.77)	1.05 (0.55-1.99)
Immunomodulatory	5.36 (2.90 - 8.90)	2.69 (2.11 - 3.38)	1.55 (0.72-3.31)
Protein kinase inhibitors	3.51 (1.81 - 6.09)	2.29 (1.74 - 2.95)	1.18 (0.54-2.62)
Other targeted therapy	2.25 (1.93 - 2.60)	2.29 (2.16 - 2.43)	0.99 (0.83-1.17)
HER2 compounds	0.91 (0.63 - 1.27)	1.52 (1.36 - 1.69)	0.61 (0.42-0.90)
Hormone therapy	3.12 (2.92 - 3.32)	3.13 (3.05 - 3.21)	0.97 (0.90-1.04)
VENOUS THROMBOEMBOLISM			
Chemotherapy	1.79 (1.66 - 1.93)	1.22 (1.18 - 1.27)	1.57 (1.44-1.72)
Alkylating agents	1.50 (1.29 - 1.73)	1.02 (0.95 - 1.10)	1.57 (1.33-1.87)
Nitrogen mustard anal.	1.48 (1.27 - 1.71)	1.03 (0.96 - 1.11)	1.55 (1.30-1.84)
Antimetabolites	1.97 (1.70 - 2.26)	1.51 (1.41 - 1.62)	1.37 (1.16-1.61)
Pyrimidine analogues	1.95 (1.68 - 2.25)	1.51 (1.41 - 1.61)	1.36 (1.15-1.62)
Cytotoxic antibiotics	1.35 (1.14 - 1.57)	0.99 (0.92 - 1.07)	1.39 (1.16-1.67)
Anthracyclines	1.37 (1.17 - 1.59)	0.99 (0.92 - 1.06)	1.42 (1.19-1.70)
Plant alkaloids	1.65 (1.44 - 1.88)	1.09 (1.02 - 1.16)	1.65 (1.41-1.93)
Vinca alkaloids	2.61 (2.08 - 3.23)	1.48 (1.31 - 1.66)	1.94 (1.48-2.53)
Podophyllon toxin der.	0.76 (0.40 - 1.33)	1.10 (0.88 - 1.35)	0.94 (0.44-2.01)
Taxanes	1.43 (1.20 - 1.68)	0.97 (0.89 - 1.05)	1.61 (1.32-1.96)
Platinum compounds	2.16 (1.87 - 2.47)	1.49 (1.39 - 1.59)	1.60 (1.35-1.89)
Targeted therapy	1.92 (1.64 - 2.24)	1.28 (1.18 - 1.38)	1.66 (1.38-1.99)
Anti-angiogenic therapy	1.44 (0.65 - 2.80)	1.47 (1.09 - 1.94)	1.41 (0.55-3.59)
Immunomodulatory	1.74 (0.72 - 3.59)	1.17 (0.80 - 1.65)	1.74 (0.61-4.92)
Protein kinase inhibitors	1.42 (0.51 - 3.21)	1.13 (0.77 - 1.62)	1.92 (0.59-6.27)
Other targeted therapy	1.93 (1.63 - 2.26)	1.29 (1.19 - 1.40)	1.62 (1.34-1.96)
HER2 compounds	1.22 (0.89 - 1.64)	1.04 (0.91 - 1.19)	1.18 (0.82-1.69)
Hormone therapy	2.06 (1.91 - 2.23)	1.51 (1.46 - 1.57)	1.45 (1.32-1.59)
KIDNEY FAILURE			
Chemotherapy	1.79 (1.66 - 1.93)	1.42 (1.37 - 1.47)	1.20 (1.09-1.32)
Alkylating agents	1.03 (0.86 - 1.23)	0.94 (0.88 - 1.01)	0.99 (0.80-1.24)
Nitrogen mustard anal.	1.05 (0.87 - 1.25)	0.94 (0.87 - 1.01)	1.00 (0.80-1.24)
Antimetabolites	2.49 (2.19 - 2.82)	1.90 (1.79 - 2.01)	1.17 (1.00-1.38)
Pyrimidine analogues	2.50 (2.20 - 2.84)	1.90 (1.79 - 2.02)	1.20 (1.02-1.41)
Cytotoxic antibiotics	1.02 (0.84 - 1.23)	0.87 (0.80 - 0.94)	1.03 (0.83-1.30)
Anthracyclines	1.01 (0.84 - 1.21)	0.87 (0.81 - 0.94)	1.03 (0.82-1.29)
Plant alkaloids	1.20 (1.02 - 1.40)	1.09 (1.02 - 1.16)	1.02 (0.84-1.23)
Vinca alkaloids	2.17 (1.68 - 2.75)	1.93 (1.73 - 2.13)	0.98 (0.72-1.32)
Podophyllon toxin der.	1.49 (0.93 - 2.26)	1.04 (0.83 - 1.29)	1.46 (0.74-2.87)
Taxanes	0.88 (0.70 - 1.09)	0.82 (0.75 - 0.89)	1.01 (0.77-1.32)
Platinum compounds	2.07 (1.79 - 2.38)	1.70 (1.60 - 1.81)	1.11 (0.93-1.33)
Targeted therapy	1.58 (1.33 - 1.87)	1.45 (1.35 - 1.55)	1.14 (0.92-1.41)
Anti-angiogenic therapy	2.76 (1.39 - 4.90)	1.85 (1.42 - 2.36)	0.84 (0.32-2.19)
Immunomodulatory	2.36 (1.13 - 4.36)	2.14 (1.64 - 2.75)	1.17 (0.40-3.42)
Protein kinase inhibitors	2.67 (1.21 - 5.11)	2.07 (1.55 - 2.71)	1.44 (0.58-3.56)
Other targeted therapy	1.47 (1.22 - 1.77)	1.42 (1.31 - 1.52)	1.09 (0.87-1.37)
HER2 compounds	0.61 (0.38 - 0.92)	0.85 (0.73 - 0.98)	0.66 (0.38-1.14)
Hormone therapy	2.58 (2.40 - 2.76)	2.15 (2.09 - 2.22)	1.13 (1.03-1.23)
HYPERTENSION			
Chemotherapy	6.04 (5.78 - 6.32)	7.08 (6.97 - 7.19)	0.87 (0.82-0.92)
Alkylating agents	4.64 (4.24 - 5.07)	5.47 (5.30 - 5.64)	0.78 (0.71-0.87)
Nitrogen mustard anal.	4.65 (4.24 - 5.09)	5.52 (5.34 - 5.69)	0.78 (0.70-0.87)
Antimetabolites	7.00 (6.42 - 7.61)	8.63 (8.38 - 8.88)	0.89 (0.80-0.98)
Pyrimidine analogues	7.05 (6.46 - 7.67)	8.67 (8.41 - 8.93)	0.89 (0.80-0.99)
Cytotoxic antibiotics	4.30 (3.90 - 4.72)	5.28 (5.11 - 5.46)	0.74 (0.66-0.83)
Anthracyclines	4.30 (3.91 - 4.72)	5.24 (5.07 - 5.41)	0.74 (0.67-0.83)
Plant alkaloids	4.95 (4.55 - 5.37)	5.83 (5.67 - 6.00)	0.80 (0.73-0.88)
Vinca alkaloids	6.23 (5.30 - 7.26)	8.14 (7.72 - 8.58)	0.78 (0.64-0.93)
Podophyllon toxin der.	3.72 (2.74 - 4.92)	5.20 (4.70 - 5.74)	0.75 (0.53-1.07)
Taxanes	4.63 (4.18 - 5.12)	5.27 (5.08 - 5.46)	0.80 (0.71-0.90)
Platinum compounds	6.40 (5.84 - 6.99)	7.78 (7.54 - 8.02)	0.91 (0.81-1.01)
Targeted therapy	5.97 (5.42 - 6.55)	7.39 (7.16 - 7.64)	0.78 (0.69-0.87)
Anti-angiogenic therapy	7.93 (5.23 - 11.34)	9.04 (7.98 - 10.19)	0.91 (0.57-1.46)
Immunomodulatory	7.05 (4.25 - 10.77)	8.60 (7.45 - 9.84)	0.77 (0.42-1.40)
Protein kinase inhibitors	6.12 (3.53 - 9.70)	7.97 (6.84 - 9.20)	0.81 (0.43-1.54)
Other targeted therapy	5.83 (5.27 - 6.43)	7.26 (7.01 - 7.52)	0.77 (0.68-0.86)
HER2 compounds	5.09 (4.31 - 5.96)	5.91 (5.57 - 6.25)	0.78 (0.64-0.94)
Hormone therapy	9.76 (9.38 - 10.15)	9.45 (9.31 - 9.60)	0.99 (0.94-1.04)

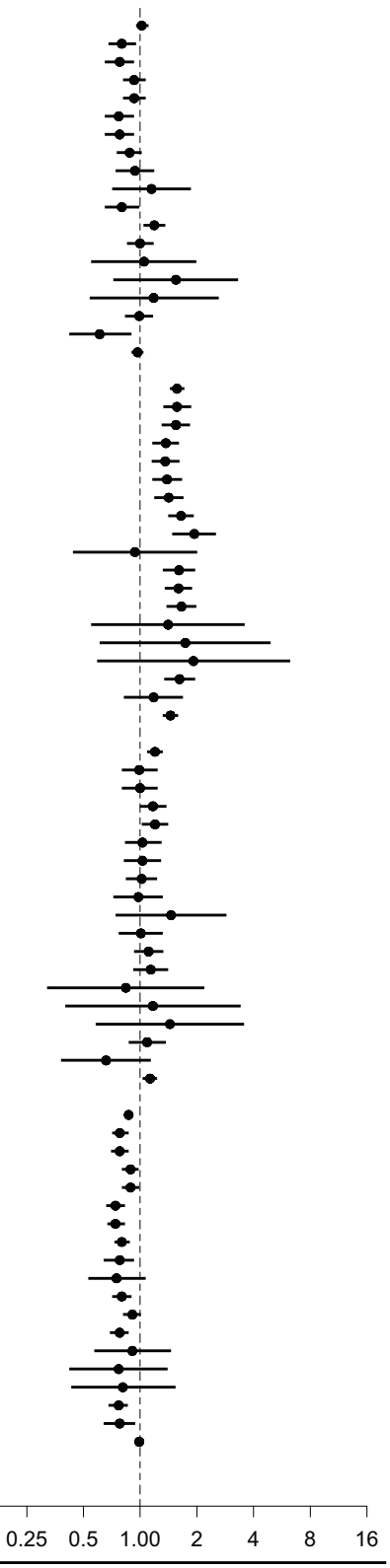


FIGURE 3 Continued

C

	Risk (Cancer)	Risk (Comparison)	Adjusted HR
VALVULAR HEART DISEASE			
Chemotherapy	1.59 (1.47 - 1.73)	1.51 (1.46 - 1.56)	1.08 (0.99-1.19)
Alkylating agents	1.13 (0.95 - 1.33)	1.08 (1.01 - 1.16)	1.10 (0.91-1.33)
Nitrogen mustard anal.	1.10 (0.92 - 1.31)	1.08 (1.00 - 1.15)	1.10 (0.90-1.33)
Antimetabolites	2.33 (2.04 - 2.65)	2.10 (1.99 - 2.22)	1.08 (0.93-1.26)
Pyrimidine analogues	2.36 (2.06 - 2.68)	2.12 (2.00 - 2.25)	1.07 (0.92-1.25)
Cytotoxic antibiotics	1.04 (0.87 - 1.24)	0.96 (0.89 - 1.03)	1.12 (0.91-1.37)
Anthracyclines	1.06 (0.89 - 1.27)	0.96 (0.89 - 1.03)	1.14 (0.93-1.39)
Plant alkaloids	1.24 (1.06 - 1.45)	1.17 (1.10 - 1.24)	1.09 (0.91-1.30)
Vinca alkaloids	2.49 (1.95 - 3.14)	1.92 (1.73 - 2.13)	1.23 (0.93-1.62)
Podophyllon toxin der.	1.42 (0.89 - 2.17)	1.10 (0.89 - 1.36)	1.49 (0.84-2.62)
Taxanes	0.82 (0.65 - 1.02)	0.94 (0.86 - 1.02)	0.95 (0.74-1.21)
Platinum compounds	1.73 (1.47 - 2.02)	1.80 (1.70 - 1.92)	0.95 (0.80-1.13)
Targeted therapy	1.68 (1.42 - 1.97)	1.53 (1.43 - 1.64)	1.19 (0.99-1.44)
Anti-angiogenic therapy	1.94 (0.89 - 3.69)	2.37 (1.88 - 2.95)	1.19 (0.55-2.60)
Immunomodulatory	1.95 (0.80 - 4.03)	2.16 (1.64 - 2.79)	1.78 (0.69-4.57)
Protein kinase inhibitors	0.71 (0.20 - 1.99)	1.15 (0.78 - 1.63)	1.14 (0.23-5.65)
Other targeted therapy	1.69 (1.42 - 2.00)	1.52 (1.42 - 1.64)	1.18 (0.97-1.44)
HER2 compounds	0.85 (0.58 - 1.21)	0.85 (0.73 - 0.98)	1.07 (0.71-1.61)
Hormone therapy	2.30 (2.14 - 2.48)	2.26 (2.19 - 2.33)	1.00 (0.92-1.09)
OTHER CARDIAC ARRHYTHMIAS			
Chemotherapy	0.72 (0.64 - 0.81)	0.79 (0.76 - 0.83)	0.90 (0.78-1.02)
Alkylating agents	0.66 (0.53 - 0.83)	0.66 (0.61 - 0.72)	0.88 (0.68-1.13)
Nitrogen mustard anal.	0.68 (0.54 - 0.84)	0.67 (0.61 - 0.73)	0.90 (0.70-1.15)
Antimetabolites	0.74 (0.59 - 0.93)	0.97 (0.90 - 1.06)	0.78 (0.61-1.01)
Pyrimidine analogues	0.72 (0.57 - 0.91)	0.98 (0.90 - 1.06)	0.79 (0.60-1.02)
Cytotoxic antibiotics	0.66 (0.52 - 0.83)	0.66 (0.60 - 0.72)	0.90 (0.69-1.16)
Anthracyclines	0.65 (0.52 - 0.82)	0.65 (0.60 - 0.72)	0.89 (0.69-1.15)
Plant alkaloids	0.74 (0.60 - 0.90)	0.68 (0.63 - 0.74)	0.96 (0.76-1.20)
Vinca alkaloids	1.06 (0.73 - 1.50)	0.90 (0.77 - 1.04)	0.94 (0.62-1.41)
Podophyllon toxin der.	0.98 (0.55 - 1.62)	0.59 (0.44 - 0.78)	1.74 (0.83-3.68)
Taxanes	0.62 (0.47 - 0.80)	0.62 (0.56 - 0.69)	0.94 (0.71-1.26)
Platinum compounds	0.83 (0.66 - 1.03)	0.82 (0.75 - 0.90)	1.02 (0.79-1.32)
Targeted therapy	0.88 (0.69 - 1.10)	0.85 (0.78 - 0.93)	0.96 (0.74-1.25)
Anti-angiogenic therapy	1.10 (0.35 - 2.74)	0.83 (0.56 - 1.20)	1.60 (0.43-5.93)
Immunomodulatory	0.86 (0.17 - 2.84)	0.84 (0.54 - 1.25)	0.14 (0.01-2.95)
Protein kinase inhibitors	-	-	-
Other targeted therapy	0.91 (0.71 - 1.15)	0.86 (0.78 - 0.95)	0.97 (0.74-1.27)
HER2 compounds	0.56 (0.34 - 0.87)	0.68 (0.57 - 0.79)	0.71 (0.42-1.20)
Hormone therapy	1.05 (0.94 - 1.17)	1.03 (0.99 - 1.08)	1.00 (0.88-1.13)
AORTIC ANEURYSM AND DISSECTION			
Chemotherapy	0.60 (0.53 - 0.68)	0.60 (0.57 - 0.63)	1.06 (0.92-1.23)
Alkylating agents	0.42 (0.31 - 0.55)	0.36 (0.32 - 0.41)	1.19 (0.87-1.64)
Nitrogen mustard anal.	0.42 (0.32 - 0.56)	0.35 (0.31 - 0.39)	1.25 (0.90-1.73)
Antimetabolites	0.90 (0.73 - 1.10)	0.92 (0.84 - 1.00)	1.06 (0.84-1.34)
Pyrimidine analogues	0.90 (0.73 - 1.11)	0.92 (0.84 - 1.00)	1.05 (0.83-1.34)
Cytotoxic antibiotics	0.37 (0.27 - 0.50)	0.32 (0.28 - 0.36)	1.13 (0.80-1.61)
Anthracyclines	0.37 (0.27 - 0.50)	0.33 (0.29 - 0.38)	1.09 (0.77-1.54)
Plant alkaloids	0.40 (0.30 - 0.53)	0.42 (0.38 - 0.47)	0.97 (0.71-1.32)
Vinca alkaloids	0.96 (0.65 - 1.37)	0.94 (0.80 - 1.08)	1.07 (0.70-1.62)
Podophyllon toxin der.	0.51 (0.21 - 1.08)	0.48 (0.35 - 0.66)	1.15 (0.41-3.28)
Taxanes	0.21 (0.13 - 0.32)	0.26 (0.23 - 0.31)	0.79 (0.48-1.31)
Platinum compounds	0.88 (0.70 - 1.08)	0.79 (0.72 - 0.86)	1.23 (0.96-1.58)
Targeted therapy	0.57 (0.43 - 0.75)	0.62 (0.56 - 0.69)	1.02 (0.75-1.39)
Anti-angiogenic therapy	0.53 (0.14 - 1.54)	1.08 (0.77 - 1.50)	0.84 (0.23-3.00)
Immunomodulatory	1.16 (0.39 - 2.78)	0.62 (0.38 - 0.98)	5.43 (0.92-32.2)
Protein kinase inhibitors	0.71 (0.24 - 1.73)	0.84 (0.53 - 1.28)	1.27 (0.30-5.43)
Other targeted therapy	0.53 (0.39 - 0.72)	0.60 (0.53 - 0.67)	0.93 (0.66-1.30)
HER2 compounds	0.25 (0.12 - 0.47)	0.31 (0.24 - 0.39)	0.71 (0.32-1.56)
Hormone therapy	0.81 (0.71 - 0.92)	0.76 (0.72 - 0.80)	1.04 (0.90-1.20)

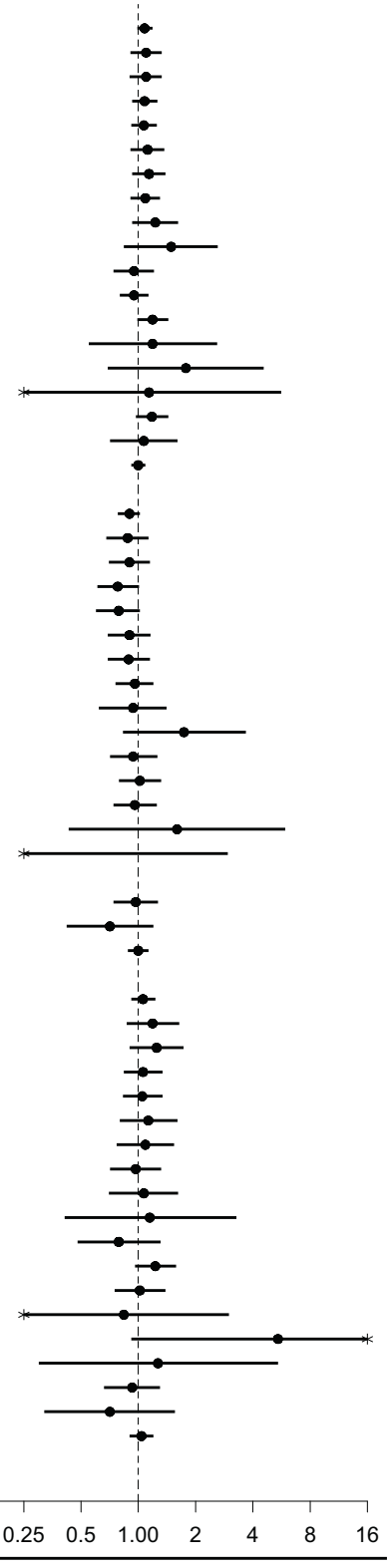
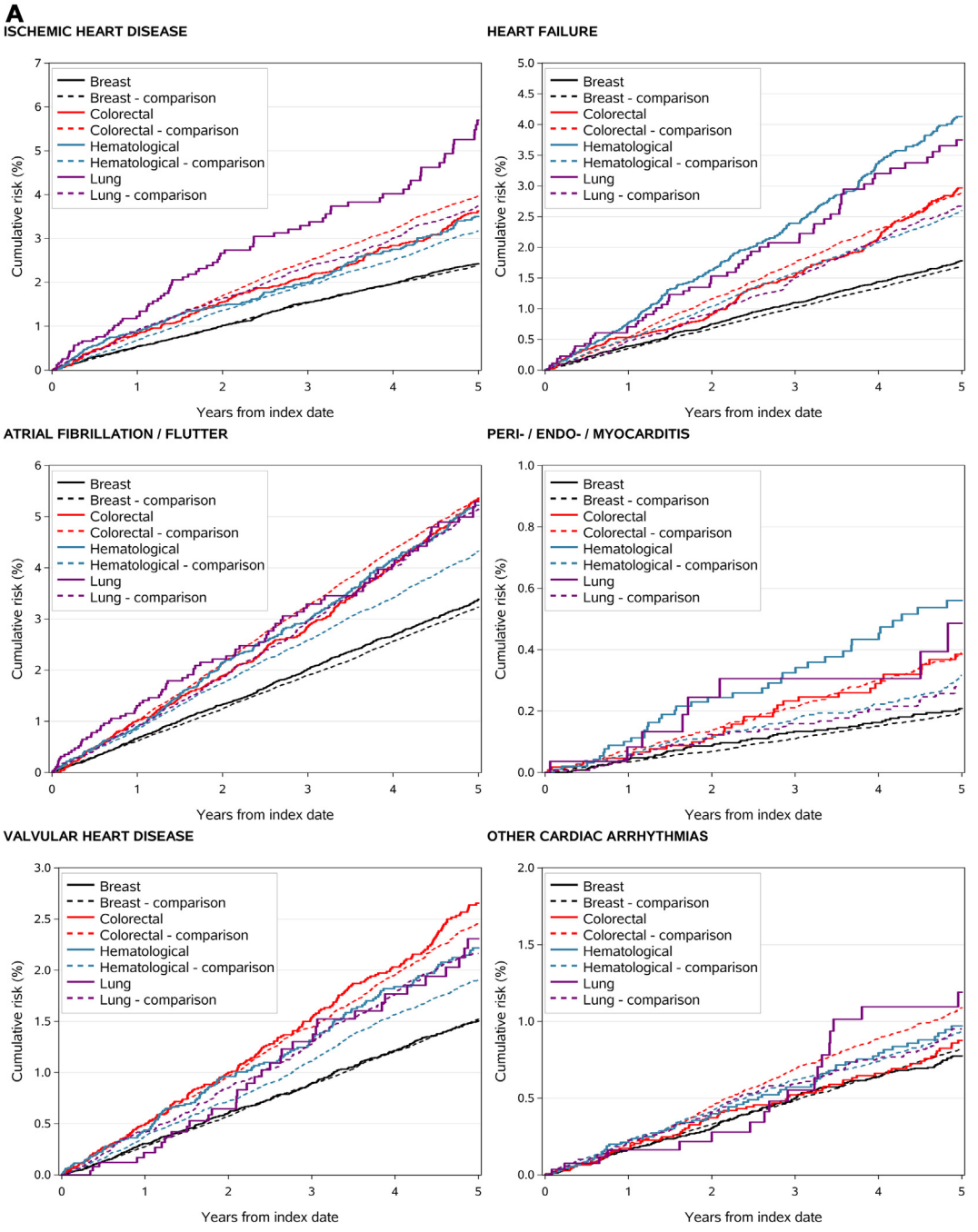


FIGURE 4 **Cumulative Incidence Curves for Selected Cancer Types**



Cumulative incidence curves for cardiovascular outcomes in cancer survivors and their matched cancer-free comparators during 5-year follow-up, stratified by 4 cancer types: breast cancer, colorectal cancer, hematological malignancies, and lung cancer. Results indicate that cardiovascular risk is increased in cancer survivors and varies by cancer types. These include ischemic heart disease, heart failure, atrial fibrillation/flutter, peri-/endo-/myocarditis, valvular heart disease, and other cardiac arrhythmias, as well as aortic aneurysm and dissection, stroke, venous thromboembolism, kidney failure, and hypertension.

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FIGURE 4 Continued

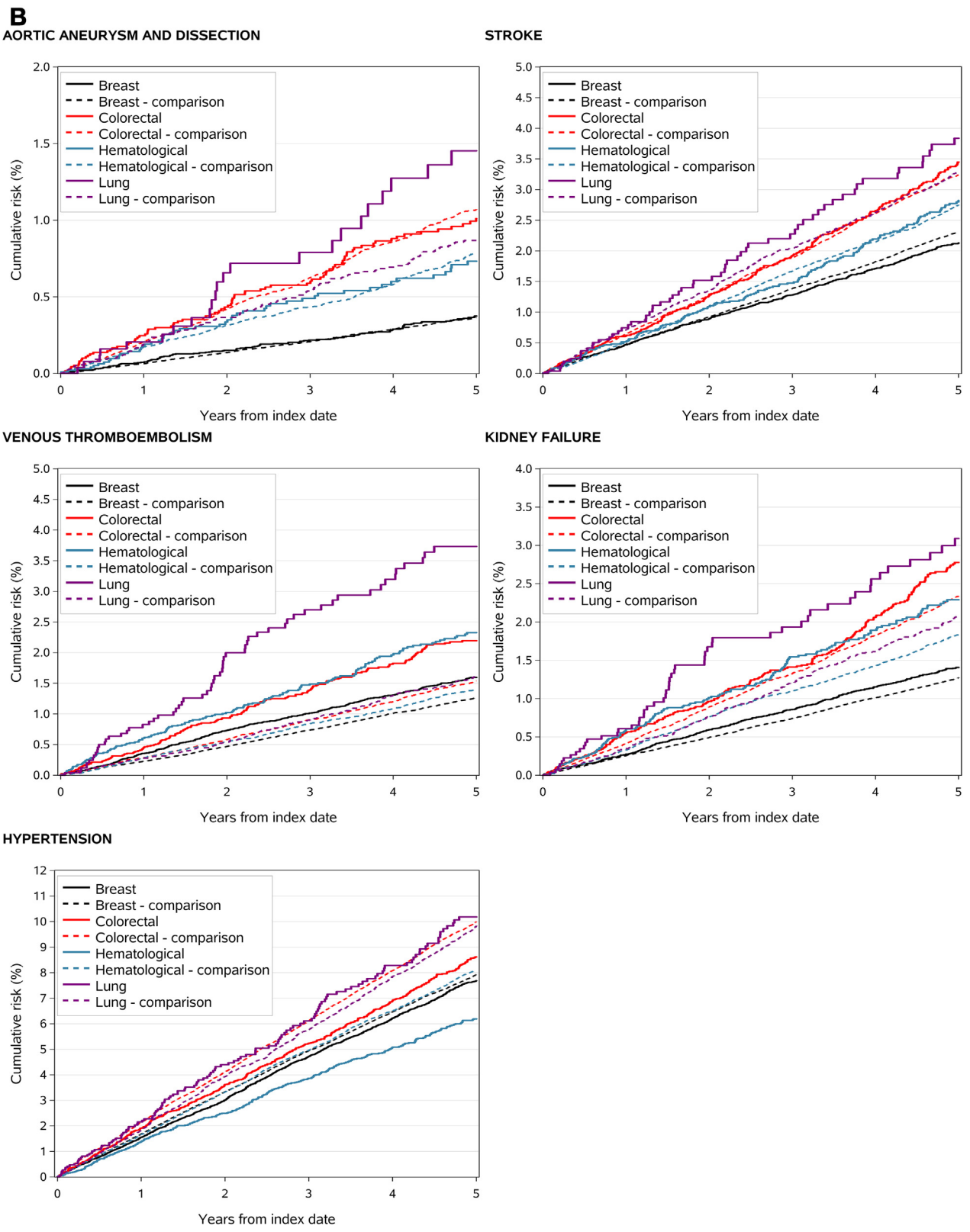
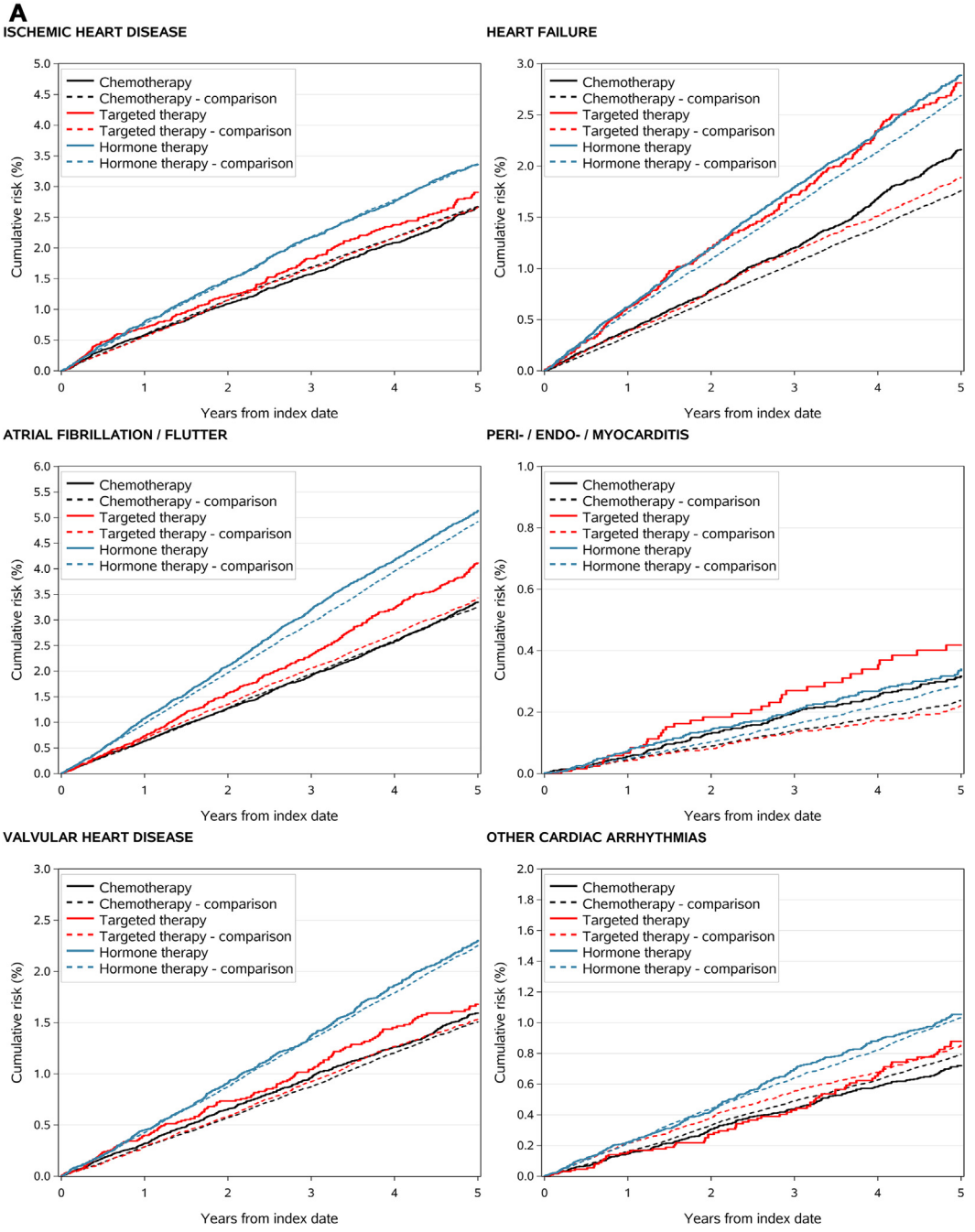


FIGURE 5 Cumulative Incidence Curves for Selected Treatment Groups



Cumulative incidence curves for cardiovascular outcomes in cancer survivors and their matched cancer-free comparators during 5-year follow-up, stratified by treatment groups: chemotherapy, targeted therapy, and hormonal therapy. These include ischemic heart disease, heart failure, atrial fibrillation/flutter, peri-/endo-/myocarditis, valvular heart disease, and other cardiac arrhythmias, as well as aortic aneurysm/dissection, stroke, venous thromboembolism, kidney failure, and hypertension. *Hormonal treatment was evaluated only in survivors of breast and prostate cancer.

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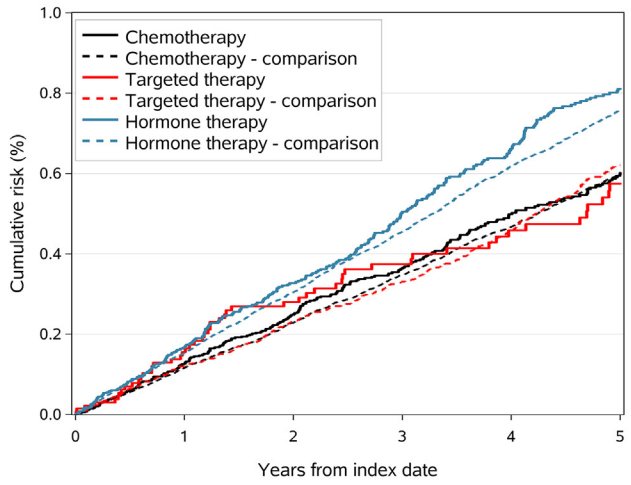
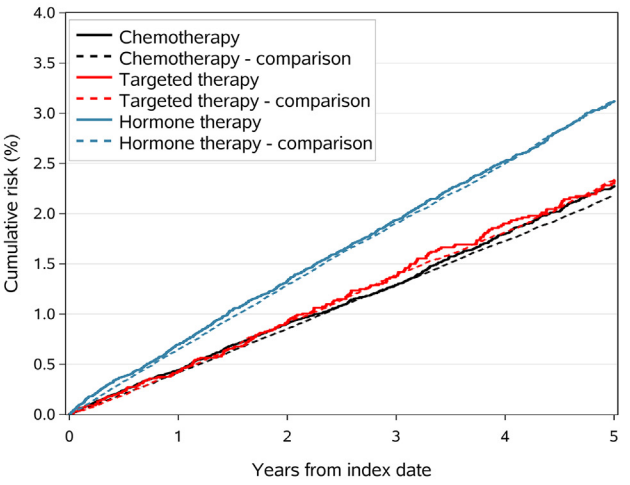
FIGURE 5 Continued

B

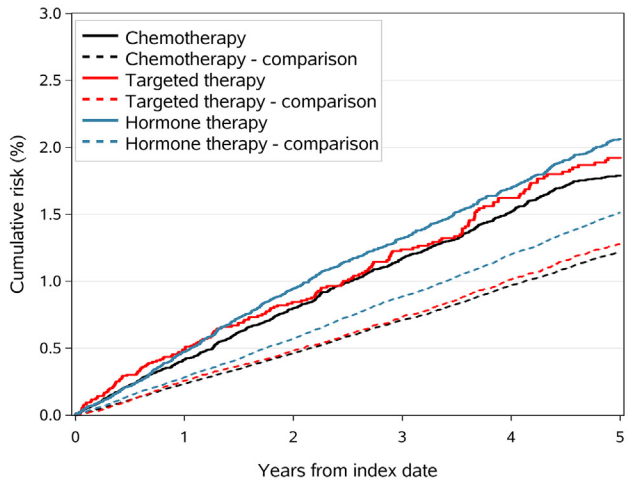
AORTIC ANEURYSM AND DISSECTION



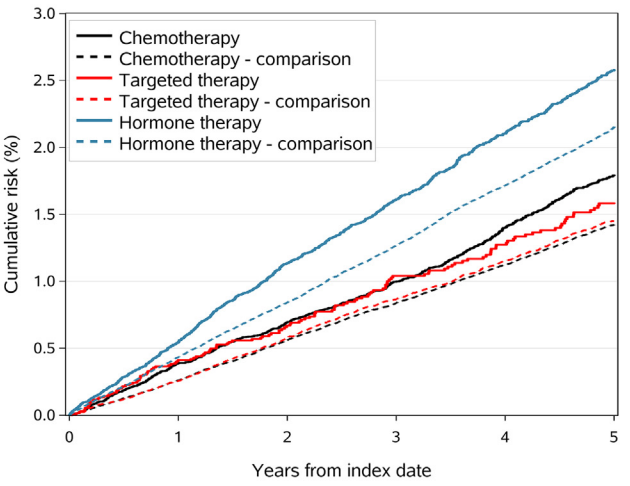
STROKE



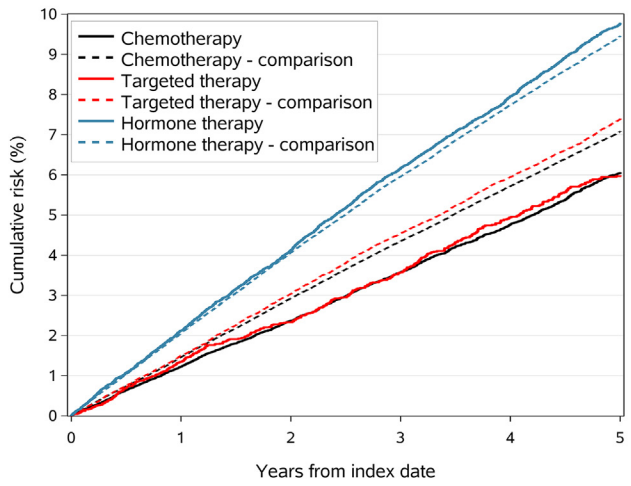
VENOUS THROMBOEMBOLISM



KIDNEY FAILURE



HYPERTENSION



Kidney failure. The 5-year cumulative incidence of the composite outcome of acute or chronic kidney failure was 2.36% (95% CI: 2.24-2.48) in the cancer survivor cohort and 1.92% (95% CI: 1.88-1.97) in the comparison cohort (HR: 1.17; 95% CI: 1.10-1.25) (**Figure 2**). Compared with their matched comparators, cancer survivors with a previous diagnosis of hematological cancer (HR: 1.38; 95% CI: 1.12-1.69), lung cancer (HR: 1.67; 95% CI: 1.15-2.43), urogenital cancer (HR: 2.75; 95% CI: 1.59-4.78), or prostate cancer (HR: 1.32; 95% CI: 1.18-1.48) were at higher risk of kidney failure. An increased risk was also observed among cancer survivors who had previously received chemotherapy (HR: 1.20; 95% CI: 1.09-1.32) or hormonal therapy (HR: 1.13; 95% CI: 1.03-1.23), but not targeted therapy (HR: 1.14; 95% CI: 0.92-1.41) (**Figure 3**).

Venous thromboembolism. Venous thromboembolism was more common in the cancer survivor cohort, with a five-year cumulative incidence of 2.02% (95% CI: 1.91-2.14), compared with 1.43% (95% CI 1.39-1.47) in the comparison cohort (HR: 1.50; 95% CI: 1.41-1.61) (**Figure 2**). The risk was elevated across nearly all treatment groups (**Figure 3**) and all cancer types, except for gastroesophageal cancer (HR: 0.60; 95% CI: 0.30-1.18).

Atrial fibrillation or flutter. The 5-year cumulative incidence of atrial fibrillation or flutter was 4.59% (95% CI: 4.42%-4.77%) in the cancer survivor cohort and 4.42% (95% CI: 4.35%-4.49%) in the matched comparator cohort (HR: 1.01; 95% CI: 0.96-1.05). An increased risk was observed among survivors of hematological cancer (HR: 1.23; 95% CI: 1.07-1.40) and recipients of targeted therapy (HR: 1.14; 95% CI: 1.01-1.30).

Other cardiovascular outcomes. The cumulative incidences and associated HRs for additional cardiovascular outcomes are shown in **Figures 2 and 3**. Compared with their matched comparators, cancer survivors had a higher risk of the composite outcome of pericarditis, endocarditis, or myocarditis (HR: 1.30; 95% CI: 1.11-1.52). However, there was no evidence of increased risk for aortic aneurysm or dissection (HR: 1.05; 95% CI: 0.94-1.16), hypertension (HR: 0.95; 95% CI: 0.91-0.98), valvular heart disease (HR: 1.04; 95% CI: 0.98-1.11), or other cardiac arrhythmias (HR: 0.96; 95% CI: 0.87-1.06) (**Figure 2**).

SECONDARY AND SENSITIVITY ANALYSES. Results from the secondary analysis—where individuals with a history of the outcome were not excluded—were consistent with the main findings (Supplemental Figures 1 and 2). Similarly, results from the analysis that did not censor individuals at the time of a new cancer diagnosis or relapse are shown in Supplemental Figures 3 and 4. For several cardiovascular outcomes, findings remained comparable to the main analysis, including ischemic heart disease (HR: 0.96; 95% CI: 0.92-1.01) and heart failure or cardiomyopathy (HR: 1.10; 95% CI: 1.04-1.16). However, risks of atrial fibrillation or flutter (HR: 1.08; 95% CI: 1.04-1.13), venous thromboembolism (HR: 1.85; 95% CI: 1.76-1.95), and kidney failure (HR: 1.67; 95% CI: 1.56-1.80) were substantially higher in the analysis that included patients with new or relapsed cancer.

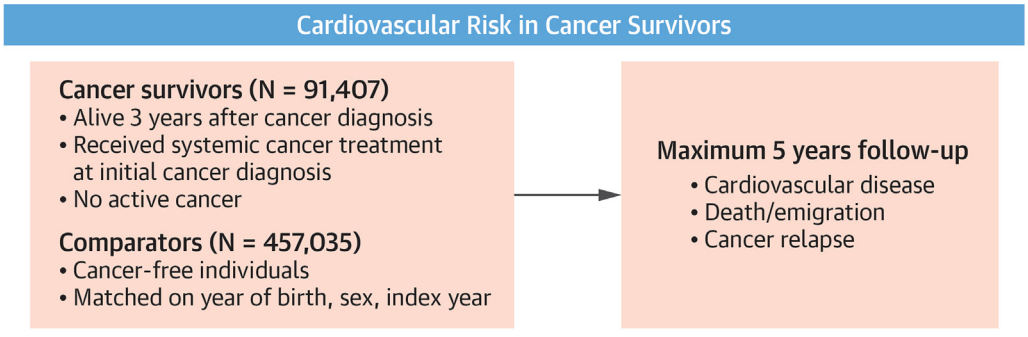
CANCER (RELAPSE) FOLLOWING STUDY OUTCOMES. Among cancer survivors who experienced acute ischemic heart disease during follow-up, 2.2% had a new cancer diagnosis or relapse within 30 days of the event. Similar proportions were observed following other outcomes: 2.4% after heart failure or cardiomyopathy, 3.1% after atrial fibrillation or flutter, 2.0% after valvular heart disease, 2.3% after stroke, 5.5% after venous thromboembolism, 3.9% after kidney failure, and 3.0% after a diagnosis of hypertension (Supplemental Table 3).

DISCUSSION

In this nationwide cohort study, cancer survivors who were free of cancer and/or treatment 3 years after diagnosis had an increased risk of heart failure, venous thromboembolism, kidney failure, and the composite outcome of pericarditis, endocarditis, or myocarditis (**Central Illustration**). By contrast, there was no evidence of increased risk for stroke and ischemic heart disease in the overall survivor group. However, increased risks emerged for specific cancer types and treatment agents. For instance, venous thromboembolism risk was consistently elevated across nearly all cancer types. Ischemic heart disease was more common among lung cancer survivors, and atrial fibrillation or flutter was more frequent among hematological cancer survivors and recipients of targeted therapy. Notably, cardiovascular events were often followed by cancer relapse or a new primary cancer diagnosis.

International cardiology and oncology associations increasingly recognize the clinical importance of cardiovascular disease in cancer survivors—a field known as cardio-oncology. Current guidance primarily focuses on preventive strategies and monitoring for long-term cardiotoxicity.[3,19-22] However, data on cardiovascular outcomes in cancer survivors remain limited, and existing guidelines emphasize the need for more real-world observational evidence.[3,7,20,23,24] In the current study, we aimed to address that gap by estimating absolute and relative risks in a

CENTRAL ILLUSTRATION **Cardiovascular Risk in Cancer Survivors**



Risk of cardiovascular disease in cancer survivors strongly dependent on cancer type and prior systemic treatment

Select Study Outcomes	Hazard Ratio (95% CI) Cancer Survivors Relative to Comparators
Atrial fibrillation	1.01 (0.96-1.05)
Prior hematological malignancy	1.23 (1.07-1.40)
Prior targeted therapy	1.14 (1.01-1.30)
Ischemic heart disease	0.96 (0.91-1.01)
Prior lung cancer	1.47 (1.11-1.96)
Heart failure or cardiomyopathy	1.08 (1.02-1.15)
Prior hematological malignancy	1.71 (1.46-2.00)
Prior anthracyclines	1.64 (1.38-1.95)
Kidney failure	1.17 (1.10-1.25)
Prior urogenital cancer	2.75 (1.59-4.78)
Pericarditis, endocarditis or myocarditis	1.30 (1.11-1.52)
Venous thromboembolism	1.50 (1.41-1.61)

Mulder FI, et al. JACC CardioOncol. 2025;7(4):360–378.

A total of 91,407 cancer survivors with no signs of active disease were matched to 457,035 cancer-free individuals from the general population. During the 5-year of follow-up, cancer survivors had increased risk of several cardiovascular diseases, with substantial variation by cancer type and prior cancer treatment.

well-defined survivor cohort with strict follow-up and detailed information on cancer treatments.

The increased risk of heart failure or cardiomyopathy among recipients of anthracyclines, alkylating agents, and HER-2 targeting agents is well established.[3,19-22] Consistent with prior evidence, our study also identified increased risks in these groups. In addition, we observed increased risks after treatment with plant alkaloids, podophyllotoxin derivatives, and protein kinase inhibitors—agents less commonly emphasized in existing guidelines.

The risk of other cardiovascular complications, such as hypertension, stroke, and aortic aneurysm or dissection, was not higher in cancer survivors compared with the general population, which may be reassuring for clinicians and patients. As a result, routine screening for these complications in the overall cancer survivor population may not be

justified. For certain outcomes, risk was even lower among survivors than among their matched comparators—for example, hypertension in breast cancer survivors (HR: 0.95; 95% CI: 0.91-0.98). This finding contrasts with previous reports suggesting that hypertension risk is often increased in patients with cancer.[25] One possible explanation is socioeconomic status: higher socioeconomic status is associated with increased breast cancer risk but lower cardiovascular risk.[26] Another explanation is that many cases of hypertension may not have been identified around the time of diagnosis, when patients are closely monitored—before the start of follow-up in this study. This is supported by the higher prevalence of hypertension among breast cancer survivors at baseline (22%) compared with their matched comparators (16%).

Two other population-based studies have previously reported on cardiovascular risk in cancer survivors. The first, by Strongman et al,[8] matched 108,215 cancer survivors in the United Kingdom to 523,541 cancer-free individuals in an observational cohort study conducted between 1990 and 2015. They reported increased risks of several outcomes—including venous thromboembolism, heart failure or cardiomyopathy, arrhythmias, pericarditis, coronary artery disease, stroke, and valvular heart disease—across multiple cancer types. By contrast, our study did not find an increased risk of valvular heart disease or stroke for any cancer type. The second study, by Kjaer et al,[7] matched 458,646 Danish cancer survivors to 2,121,567 cancer-free comparators using Danish health care registries.[7] Risk estimates were reported for broad diagnostic categories (eg, diseases of the cardiovascular system) and consistently favored cancer-free comparators over cancer survivors.

Unlike our study, neither the Strongman nor the Kjaer analysis could determine whether participants were cancer-free status at study entry, experienced cancer relapse during follow-up, or received specific cancer treatments. Both studies defined cancer survivors simply as all patients alive 1 year after cancer diagnosis, without accounting for active cancer status.

Our study builds on previous research by providing more up-to-date estimates that are likely more relevant to cancer survivors who have completed systemic treatment and no longer have active cancer or ongoing therapy. This stricter definition of cancer survivorship resulted in substantially lower risk estimates. For example, in our main analysis—with censoring at cancer relapse—the HR for kidney failure was 1.17 (95% CI: 1.10-1.25) (**Figure 2**), compared with 1.30 (95% CI: 1.23-1.37) in the secondary analysis without censoring (Supplemental Figure 3).

Importantly, 32,149 individuals who were alive 3 years after their cancer diagnosis were not included in the survivor cohort because they likely still had active cancer under our definitions (eg, receipt of systemic treatment in the prior 12 months). Excluding this group was critical, as their risk estimates were substantially higher than those observed in the defined survivor cohort for several outcomes, including atrial fibrillation or flutter (5.10% vs 4.59%), venous thromboembolism (5.25% vs 2.02%), and kidney failure (3.80% vs 2.36%; data not shown).

A key strength of this study is the use of real-world clinical data from Danish healthcare registries, which are known for their high predictive value for cardiovascular disease diagnoses.[9] These nationwide registries capture all Danish cancer patients, regardless of race, socioeconomic background, or insurance status. Unlike previous population-based studies,[7,8] we aimed to restrict the analysis to individuals who were cancer-free by incorporating data on cancer relapse codes, systemic treatment, cancer-related surgery, and radiotherapy. In addition, the use of national prescription data allowed us to examine associations between specific cancer treatment groups and cardiovascular outcomes.

This population-based cohort study provides detailed insights into the long-term risk of cardiovascular complications in cancer survivors. Our findings may help raise awareness, support the identification of high-risk groups, and inform future guideline development. Given the considerable variation in risk across subgroups, monitoring strategies should follow a personalized, risk-based approach.

STUDY LIMITATIONS. Because cancer treatments were not mutually exclusive, associations between specific treatments and cardiovascular or kidney outcomes may have been influenced by other agents administered as part of multidrug regimens. Additionally, treatment data were captured only during the first 12 months after cancer diagnosis, limiting our ability to assess the effects of therapies given thereafter. Detailed treatment information was also available only from 2004 onward. Some subgroups included relatively few patients, resulting in wide confidence intervals and limiting the granularity of our findings by specific agents or cancer types. Finally, we were unable to assess cumulative doses of cancer treatments or (thoracic) radiotherapy, which may have provided further insight into treatment-related risks.

In addition, the observational nature of the study limits our ability to draw causal conclusions.

Associations between cancer treatments and study outcomes may be subject to confounding by indication, as treatment choices are influenced by comorbidities, cancer type, and stage. It remains unclear whether observed associations between specific cancer types and cardiovascular outcomes are driven by the treatment itself or by unmeasured confounders such as smoking, socioeconomic status, or elevated body mass index. However, we attempted to partially account for this by adjusting for obesity and chronic obstructive pulmonary diseases.

Survivors included in this study may represent a healthier subgroup, as frail patients at higher risk of severe cardiovascular disease or kidney failure may have died before entering follow-up. This could have contributed to some of the null findings. Although the quality of Danish medical registries in considered high, missing diagnosis codes may have reduced the sensitivity of outcome detection and led to underestimation of event rates in both cohorts. Finally, closer clinical monitoring of cancer survivors may have introduced surveillance bias, potentially inflating outcome rates in the survivor cohort.

DATA STATEMENT

Data can be requested from the Danish Health Data Authority- Sundhedsdatastyrelsen, which manages Danish health care registries.

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PERSPECTIVES

COMPETENCY IN MEDICAL KNOWLEDGE: Cancer survivors, as a group, are at increased risk of several cardiovascular diseases compared with individuals who have never had cancer. These risks vary by cancer type and by the systemic treatments received. Clinicians should inform survivors of these risks on an individualized basis and ensure appropriate monitoring.

TRANSLATIONAL OUTLOOK: Future population-based cohort studies should aim to replicate these findings in cancer survivors without active disease. Data from this study and future cohorts should be integrated to support personalized risk prediction—ideally through online risk calculators tailored to cancer survivors.

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KEY WORDS **acute coronary syndrome, arrhythmia, cancer survivorship, cancer, cohort study, epidemiology, kidney failure, myocardial infarction, neoplasm, stroke, venous thromboembolism**

APPENDIX **For supplemental figures and tables, please see the online version of this paper.**