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ORIGINAL RESEARCH

# Risk of Cancer After Diagnosis of Cardiovascular Disease

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## ABSTRACT

**BACKGROUND** Cardiovascular disease (CVD) and cancer share several risk factors. Although preclinical models show that various types of CVD can accelerate cancer progression, clinical studies have not determined the impact of atherosclerosis on cancer risk.

**OBJECTIVES** The objective of this study was to determine whether CVD, especially atherosclerotic CVD, is independently associated with incident cancer.

**METHODS** Using IBM MarketScan claims data from over 130 million individuals, 27 million cancer-free subjects with a minimum of 36 months of follow-up data were identified. Individuals were stratified by presence or absence of CVD, time-varying analysis with multivariable adjustment for cardiovascular risk factors was performed, and cumulative risk of cancer was calculated. Additional analyses were performed according to CVD type (atherosclerotic vs nonatherosclerotic) and cancer subtype.

**RESULTS** Among 27,195,088 individuals, those with CVD were 13% more likely to develop cancer than those without CVD (HR: 1.13; 95% CI: 1.12-1.13). Results were more pronounced for individuals with atherosclerotic CVD (aCVD), who had a higher risk of cancer than those without CVD (HR: 1.20; 95% CI: 1.19-1.21). aCVD also conferred a higher risk of cancer compared with those with nonatherosclerotic CVD (HR: 1.11; 95% CI: 1.11-1.12). Cancer subtype analyses showed specific associations of aCVD with several malignancies, including lung, bladder, liver, colon, and other hematologic cancers.

**CONCLUSIONS** Individuals with CVD have an increased risk of developing cancer compared with those without CVD. This association may be driven in part by the relationship of atherosclerosis with specific cancer subtypes, which persists after controlling for conventional risk factors. (J Am Coll Cardiol CardioOnc 2023;5:431-440) © 2023 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 authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the Author Center.

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**ABBREVIATIONS AND ACRONYMS**

**aCVD** = atherosclerotic cardiovascular disease

**BMI** = body mass index

**CHIP** = clonal hematopoiesis of indeterminate potential

**CV** = cardiovascular

**CVD** = cardiovascular disease

**naCVD** = nonatherosclerotic cardiovascular disease

**HRA** = health risk assessment

**PH** = proportional hazards

**TDPS** = time-dependent propensity score

Cardiovascular (CV) disease (CVD) and cancer continue to represent the 2 leading causes of death in the United States.[1,2] These diseases share a multitude of risk factors, underscored by the reduction in mortality from both conditions when patients adhere to CV risk reduction guidelines.[3-5] However, it is becoming increasingly clear that the 2 diseases may have a more complicated relationship, including shared pathophysiological mechanisms that extend beyond traditional risk factors.

Recent preclinical studies using murine models of heart failure, cardiac remodeling, or myocardial infarction have each demonstrated that solid tumors grow more quickly in the presence of CV abnormalities.[6-8] In addition, several epidemiologic studies have shown that various forms of CVD may be associated with increased cancer progression and reduced survival.[6-9] However, these retrospective cohort studies have been unable to determine which forms of CVD are associated with increased risk and, more importantly, if this relationship is simply driven by shared risk factors. Further, it remains unclear whether there is increased risk across all cancer types or if it is specific for certain cancers.[5,10,11]

The current study aimed to investigate the association of CVD, both atherosclerotic and nonatherosclerotic, with the development of cancer. Looking at both atherosclerotic and nonatherosclerotic disease facilitates potential delineation of unique relationships with cancer based on underlying disease processes. An understanding of this relationship has the potential to better inform cancer risk stratification and screening.[12,13] In addition, improved characterization of the interaction between cancer and CVD could ultimately guide further mechanistic efforts to investigate pathophysiology mediating their interaction.

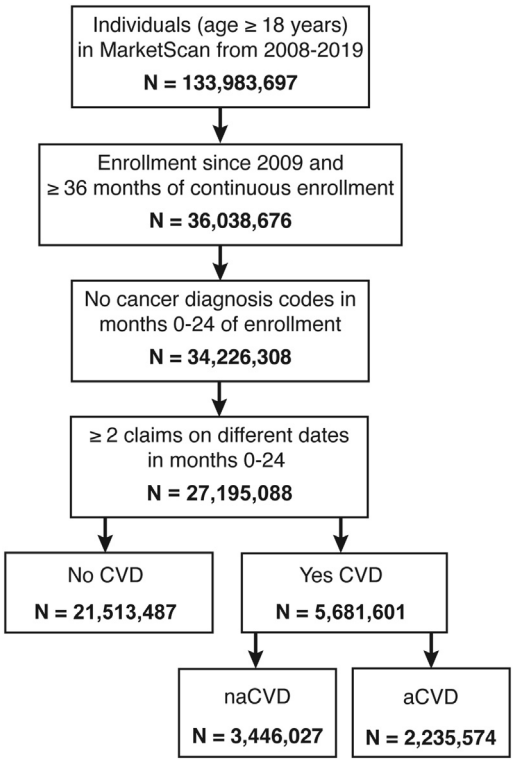
## METHODS

**DATA SOURCES.** We performed a retrospective cohort study using data from the 2009-2019 IBM MarketScan Research Databases, which contains deidentified data for approximately 161 million patients, including enrollment records and health insurance claims from inpatient services, outpatient visits, and outpatient prescription drugs. Mortality data are not available in the MarketScan data set. This study followed the Strengthening the Reporting of Observational Studies in Epidemiology (STROBE) reporting guidelines for cohort studies and was exempted by the University of Texas MD Anderson Cancer Center Institutional Review Board because of its use of deidentified data.

We additionally linked individuals who responded to the health risk assessment (HRA) survey in the 2009-2019 MarketScan Databases through unique enrollee identifiers. The HRA data contain biometric and behavioral information collected from risk assessment questionnaires administrated by the U.S. corporations and health plans that contributed data to MarketScan. Specifically, it provided self-reported information on health indicators such as body mass index (BMI) and smoking status. It has been shown that the prevalence estimates of both variables are comparable to national estimates.[14-16]

**STUDY DESIGN.** In this retrospective cohort study, we included patients 18 years of age or older enrolled since 2009 and with at least 36 months of continuous enrollment, and no cancer diagnosis codes in the first 24 months of enrollment. This yielded a cohort of over 27 million individuals. All individuals had a 24-month run-in period from the time of cohort entry. During the run-in period, individuals were classified into 2 groups depending on the presence or absence of CVD. Those with CVD were then subclassified into atherosclerotic (aCVD) or nonatherosclerotic (naCVD) disease subtypes. Presence of CVD was defined during the run-in period as 2 or more separate International Classification of Disease (ICD), 9th (ICD-9) or 10th (ICD-10) edition diagnosis or Current Procedural Terminology (CPT) codes indicating either aCVD or naCVD, in either the inpatient or outpatient setting (Supplemental Table 1). After the start of follow-up, an individual's CVD status was adjusted on a time-dependent basis with individuals able to move from no CVD to CVD (including naCVD or aCVD) and from naCVD to aCVD based on a relevant ICD or CPT code. Codes were selected from previously validated and utilized algorithms demonstrating a >95% specificity of single code use for coronary artery disease, peripheral arterial disease, cerebrovascular disease, heart failure, valvular disease, and congenital heart disease,[17-28] and >85% specificity of single code use for atrial fibrillation.[29] Those with only a single CVD code during the run-in period were excluded, and those meeting diagnostic criteria for both aCVD and naCVD were assigned to the aCVD cohort. Time-dependent propensity scores (TDPS) were derived from a Cox proportional hazards (PH) model where the independent variable was time to CVD and the

**FIGURE 1** Cohort Selection From MarketScan Databases




Flow diagram demonstrates sequential inclusion criteria for the study and group separation. aCVD = atherosclerotic cardiovascular disease; CVD = cardiovascular disease; naCVD = nonatherosclerotic cardiovascular disease.

covariates included age, sex, diabetes, hypertension, chronic kidney disease, and hyperlipidemia. The primary outcome of interest was incident cancer, defined as 2 or more separate cancer ICD-9/ICD-10 codes after the 24-month run-in period, either in the inpatient or outpatient setting (Supplemental Table 1). The start of follow-up (index date) was defined as 24 months after the date of first enrollment. Nonmelanoma skin cancers were not included in either enrollment or outcome metrics. We included a latency period where individuals with a cancer detected in the 3 months following a change in CVD status were excluded. As a separate sensitivity analysis, we excluded heart failure codes from the definition of CVD, given data supporting an epidemiologic association between heart failure and incident cancer.[10]

As a secondary analysis, we utilized the same analytic approach among individuals with HRA-linked data additionally adjusting our models for self-reported BMI and smoking status (n = 1,257,493). HRA-linked cohort characteristics are summarized in Supplemental Table 2.

**STATISTICAL ANALYSIS.** Baseline age was compared using a *t*-test (mean) and Wilcoxon rank sum test (median). All other baseline characteristics were compared using a chi-square test (categorical). The primary outcome was defined as the time from index date to the diagnosis date of any incident cancer (event) or the last follow-up date (censor, end of enrollment, or end of study December 31, 2019). Secondary outcomes included time from index date to the diagnosis date of each of the top 20 most frequent organ-specific cancers (event) or last follow-up date (censor). We used inverse probability treatment weighted Cox PH regression based on the patient's TDPS with the weights being TDPS/(1 − TDPS) for CVD adjusted for age, sex, diabetes, hypertension, chronic kidney disease, hyperlipidemia, statin use, health care contacts, region, and insurance type. Participants were censored in the individual cancer analyses when they developed other organ-specific cancers. We checked the PH assumption using Schoenfeld residuals. Cox model results are presented as the HR with 95% CI.

We considered a 2-sided *P* value <0.05 statistically significant unless otherwise indicated. Individuals with missing data for each variable were treated as a separate unknown category with no imputation. All statistical analyses were performed using SAS Enterprise Guide version 9.4 (SAS Institute) and R 4.0.5 (R Foundation for Statistical Computing).

## RESULTS

**RISK OF ALL CVD.** A total of 27,195,088 individuals with or without CVD underwent time-dependent analysis with Cox PH modeling for multivariable adjustment (**Figure 1**). The mean age was 43.3 ± 15.7 years, and 55.7% were female. The median follow-up time was 33 (IQR: 20-52) months. **Table 1** summarizes cohort baseline characteristics before multivariable adjustment.

An unadjusted estimate of cumulative incidence of cancer diagnosis was generated as a Kaplan-Meier representation (**Figure 2A**), suggesting those with CVD have higher cumulative incidence of cancer than those without CVD. Time-dependent analysis with multivariable adjusted Cox PH modeling revealed that individuals with CVD were in fact at significantly higher risk of developing incident cancer (HR: 1.13; 95% CI: 1.12-1.13) (**Table 2**).

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**TABLE 1 Baseline Characteristics of Cohorts by CVD Group (N = 27,195,088)**

| | No CVD (n = 21,513,487) | CVD (n = 5,681,601) |
|---|---|---|
| Age at first enrollment, y | | |
| Mean ± SD | 40.1 ± 14.1 | 55.2 ± 15.6 |
| Median (IQR) | 40 (29-51) | 55 (46-55) |
| 18-39 | 10,347,588 (48.1) | 863,543 (15.2) |
| 40-49 | 5,069,643 (23.6) | 1,061,920 (18.7) |
| 45-59 | 4,442,217 (20.6) | 1,718,394 (30.2) |
| 60-64 | 971,359 (4.5) | 580,828 (10.2) |
| 65-69 | 313,813 (1.5) | 388,933 (6.8) |
| 70-79 | 282,009 (1.3) | 649,727 (11.4) |
| ≥80 | 86,858 (0.4) | 418,256 (7.4) |
| Female | 12,217,110 (56.8) | 2,936,883 (51.7) |
| Diabetes | 1,495,805 (7.0) | 1,151,571 (20.3) |
| Hypertension | 4,326,092 (20.1) | 2,880,691 (50.7) |
| CKD | 63,297 (0.3) | 142,430 (2.5) |
| Hyperlipidemia | 5,209,744 (24.2) | 2,788,120 (49.1) |
| Region | | |
| Northeast | 4,143,494 (19.3) | 1,356,807 (23.9) |
| North Central | 4,791,035 (22.3) | 1,324,658 (23.3) |
| South | 7,954,907 (37.0) | 2,053,350 (36.1) |
| West | 4,135,964 (19.2) | 817,753 (14.4) |
| Unknown | 488,087 (2.3) | 129,033 (2.3) |
| Insurance | | |
| PPO | 12,835,259 (59.7) | 3,175,803 (55.9) |
| HMO | 2,965,998 (13.8) | 763,661 (13.4) |
| Other | 4,500,888 (20.9) | 1,449,536 (25.5) |
| Unknown | 1,211,342 (5.6) | 292,601 (5.1) |
| Statin use | 1,270,860 (5.9) | 1,350,904 (23.8) |
| Health care visits, per y | | |
| 0-1 | 5,304,611 (24.7) | 478,554 (8.4) |
| 2-5 | 6,864,776 (31.9) | 951,813 (16.8) |
| 5-10 | 5,255,804 (24.4) | 1,560,786 (27.5) |
| >10 | 4,088,296 (19.0) | 2,690,448 (47.4) |

Values are mean ± SD, median (IQR), or n (%). All *P* values <0.001 for characteristics between the 2 cohorts.

CKD = chronic kidney disease; CVD = cardiovascular disease; HMO = health maintenance organization; PPO = preferred provider organization.

**RISK OF NONATHEROSCLEROTIC AND ATHEROSCLEROTIC CVD.** The CVD group was then split into aCVD and naCVD. The aCVD cohort was older with a higher proportion of men and medical comorbidities compared with the naCVD cohort (Supplemental Table 3). An unadjusted estimate of cumulative incidence of cancer diagnosis was generated as a Kaplan-Meier representation (**Figure 2B**), suggesting those with aCVD have higher cumulative incidence of cancer than both those without CVD and individuals with naCVD. The naCVD group also had a higher cumulative incidence of cancer than the no CVD group. To control for imbalances in age, sex, and other comorbidities between those with atherosclerotic vs nonatherosclerotic forms of CVD, time-dependent analysis with multivariable adjusted Cox PH modeling was performed. These studies revealed that those with aCVD (HR: 1.20; 95% CI: 1.19-1.21) and naCVD (HR: 1.08; 95% CI: 1.07-1.08) were both at significantly increased risk of incident cancer compared with individuals without CVD (**Figure 2B**, **Table 2**). In addition, the risk of incident cancer remained significantly higher in the aCVD group when directly compared with the naCVD group (HR: 1.11; 95% CI: 1.11-1.12).

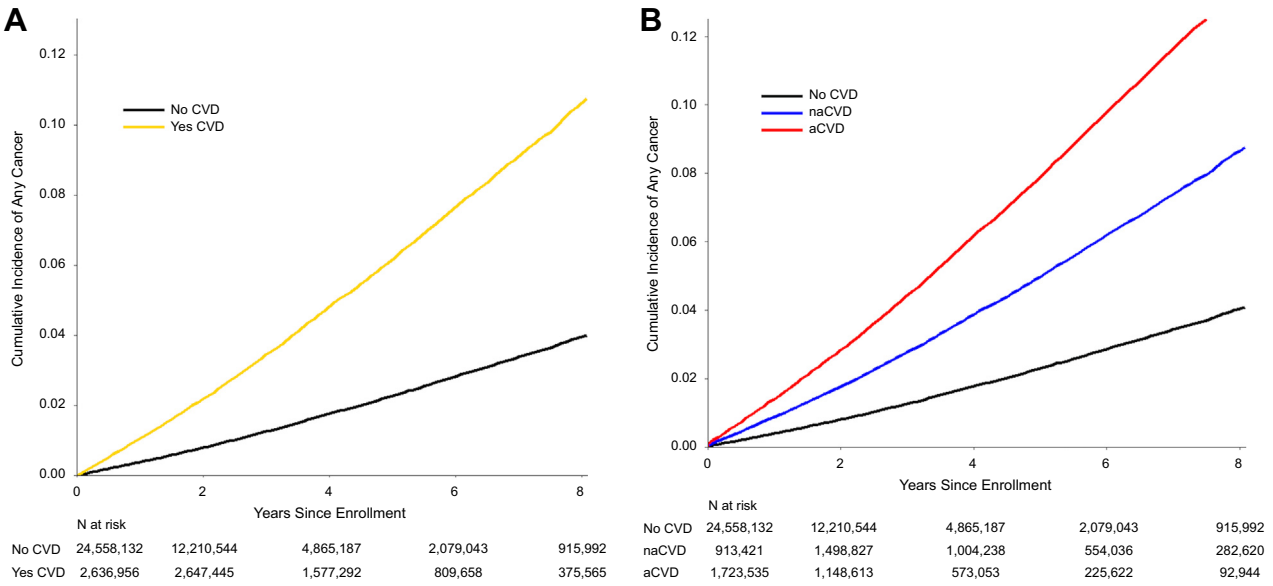
To determine whether our results were being driven by an association of heart failure and cancer, we conducted a sensitivity analysis excluding all individuals with heart failure diagnosis codes. This censored a total of 877,928 individuals from the original cohort. Results were consistent with our primary analysis demonstrating an increased risk of cancer among those with CVD (HR: 1.11; 95% CI: 1.11-1.12), and specifically, aCVD (HR: 1.19; 95% CI: 1.18-1.20) and naCVD (HR: 1.07; 95% CI: 1.06-1.08), compared with those without CVD after multivariable adjustment to control for available CV comorbidities. aCVD also continued to have an increased risk of cancer compared with naCVD (HR: 1.11; 95% CI: 1.10-1.12).

Individuals with HRA data (n = 1,257,493) provided the opportunity to adjust for additional CV risk factors of smoking status and BMI[14-16] (Supplemental Table 2). Compared with the primary analysis cohort, these patients on average are younger with lower rates of comorbidities; the HRA survey is employer-sponsored, disproportionately selecting for a younger working population.

Compared with individuals without CVD, those with CVD were at significantly increased risk of developing cancer (HR: 1.24; 95% CI: 1.20-1.27) (Supplemental Table 4). When those without CVD were compared with CVD subgroups, both aCVD (HR: 1.35; 95% CI: 1.30-1.41) and naCVD (HR: 1.19; 95% CI: 1.15-1.23) had increased risk of incident cancer. The difference between aCVD and naCVD in this data set was also consistent with our primary analysis, with aCVD conferring increased risk of incident cancer (HR: 1.14; 95% CI: 1.14-1.20).

**CANCER SUBTYPE ANALYSIS.** The association of aCVD and naCVD with the 20 most frequently diagnosed cancers in our data set were examined (**Figure 3**). Both aCVD and naCVD had significantly increased risk of multiple cancer subtypes compared with those without CVD. When directly compared, aCVD had a significantly higher risk than naCVD for cancers of the lung, bladder, colon, head and neck, liver, prostate, pancreas, and kidney, as well as lymphoma, leukemia, and other hematologic

**FIGURE 2** **Cumulative Incidence of Cancer According to CVD Group**




Kaplan-Meier estimates of time from index date to any cancer diagnosis among cohorts (N = 27,195,088 ) according to CVD group: CVD vs no CVD **(A)** and aCVD vs naCVD or no CVD **(B)**. Index date was set at 24 months after the date of first enrollment. Estimates by group are before time-varying analysis with multivariable adjustment. Number at risk reflects time-varying exposure variable. Abbreviations as in **Figure 1**.

malignancies (Supplemental Figure 1). Notably, aCVD also had a significantly lower risk for breast, ovarian, and uterine cancers. The overall number of cancers by subtype included in the analyses, as well as *P* values for different comparisons, are listed in Supplemental Table 5.

Because several of the examined cancer subtypes have known associations with tobacco use, we utilized our HRA-linked data set to further control for smoking status and BMI in a multivariable analysis (Supplemental Figure 2). This analysis continued to observe an increased association for bladder (HR: 1.58; 95% CI: 1.24-2.01), colon (HR: 1.53; 95% CI: 1.16-2.01), and lung (HR: 1.43; 95% CI: 1.17-1.74) cancers, lymphoma (HR: 1.42; 95% CI: 1.19-1.71), leukemia (HR: 1.40; 95% CI: 1.06-1.85), and other hematologic malignancies (HR: 1.42; 95% CI: 1.11-1.82) in the aCVD group compared with the naCVD group. The overall number of cancers by subtype in the HRA analysis, as well as *P* values for different comparisons, are listed in Supplemental Table 6.

**TABLE 2** **Adjusted HRs for the Association of CVD With Incident Cancer (N = 27,195,088)**

| | HR | 95% CI | *P* Value |
|---|---|---|---|
| No CVD vs | | | |
| CVD | 1.129 | 1.123-1.134 | <0.001 |
| No CVD vs | | | |
| naCVD | 1.076 | 1.069-1.082 | <0.001 |
| aCVD | 1.199 | 1.191-1.207 | <0.001 |
| naCVD vs | | | |
| No CVD | 0.930 | 0.924-0.935 | <0.001 |
| aCVD | 1.114 | 1.106-1.123 | <0.001 |

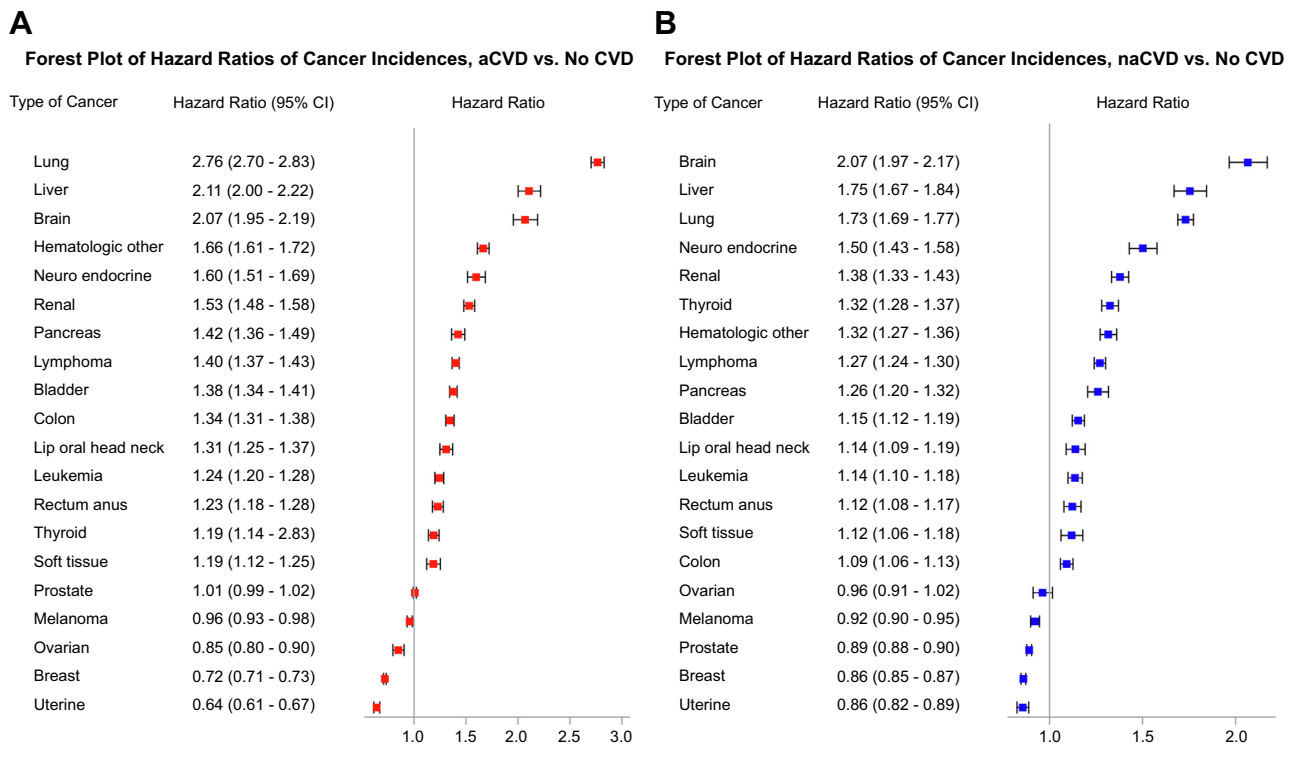
Model used inverse probability treatment weighted Cox proportional hazards regression based on the patient's time-dependent propensity score (TDPS) with the weights being TDPS/(1 − TDPS) for cardiovascular disease (CVD) adjusted for age, sex, diabetes, hypertension, chronic kidney disease, hyperlipidemia, statin use, health care contacts, region, and insurance type.

aCVD = atherosclerotic cardiovascular disease; naCVD = nonatherosclerotic cardiovascular disease.

## DISCUSSION

Our retrospective cohort study demonstrates that individuals with CVD have a significantly increased risk of incident cancer compared with those without CVD. We found that this risk was most pronounced among individuals with aCVD, even after adjusting for all available CV comorbidities and degree of health care contacts (**Central Illustration**). With data from over 27 million individuals, this is the largest study to explore this relationship. Importantly, our findings were consistent in secondary analyses that controlled for self-reported smoking status and BMI, as well as

**FIGURE 3 Forest Plots of the Association of CVD With Cancer Incidences**



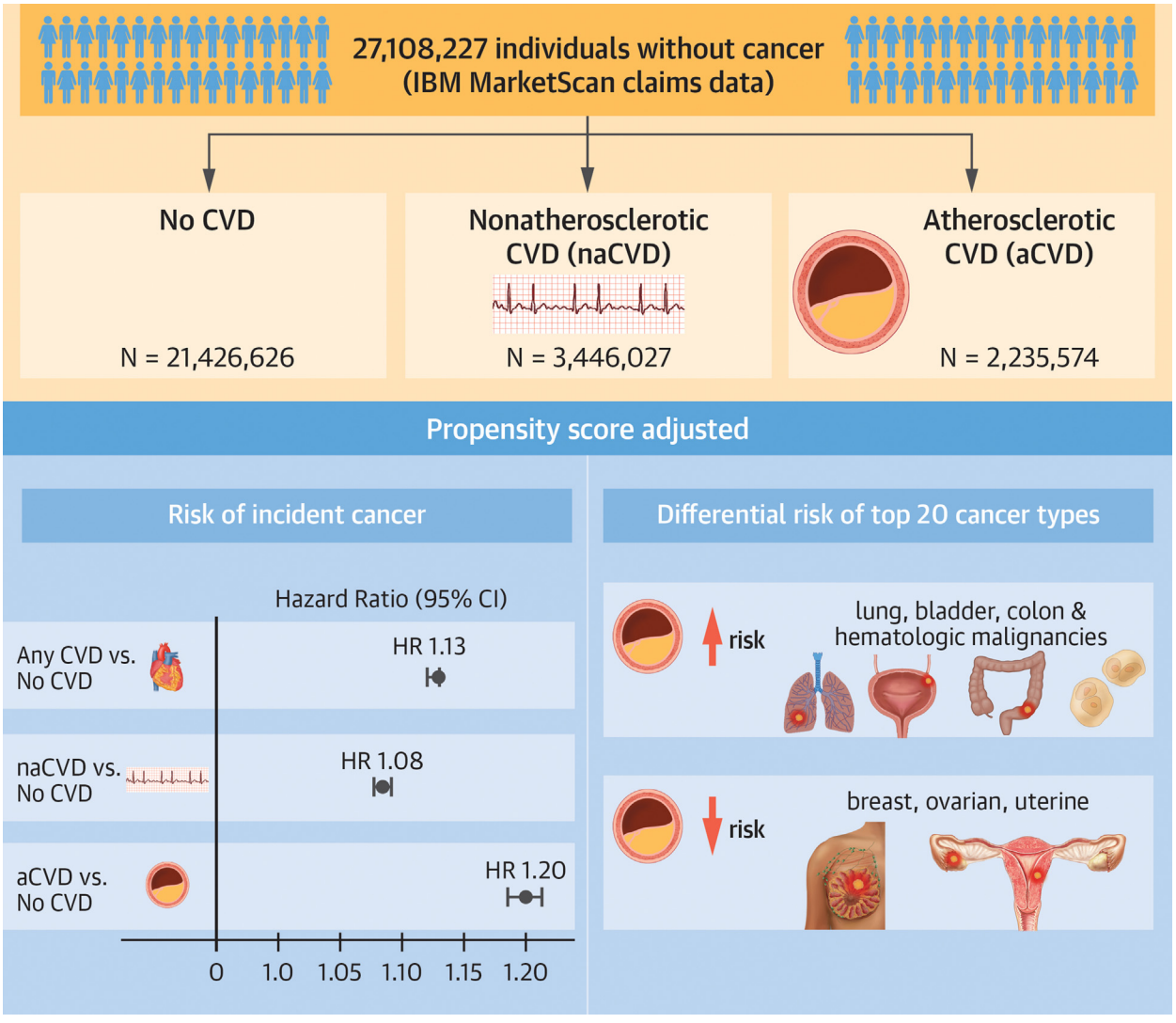

Forest plots of HRs based on inverse probability treatment weighted Cox proportional hazards regression from the patient's time-dependent propensity score (TDPS) with the weights being TDPS/(1 − TDPS) for CVD adjusted for age, sex, diabetes, hypertension, chronic kidney disease, hyperlipidemia, statin use, health care contacts, region, and insurance type (N = 27,195,088). **(A)** aCVD vs no CVD, and **(B)** naCVD vs no CVD. Abbreviations as in Figure 1.

when heart failure diagnoses were excluded, suggesting that the presence of heart failure or traditional CV risk factors may not fully account for the observed associations. Finally, cancer subtype analyses demonstrated specific associations between aCVD and a range of individual cancers, highlighting areas for future mechanistic research.

Our findings build upon prior studies. A study of 32,095 individuals from the Sakakibara Heart Institute in Japan comparing cancer incidence between those with atherosclerotic and those with nonatherosclerotic forms of CVD found the presence of atherosclerosis to be an independent risk factor for cancer diagnosis.[11] Generalizability of these results, however, was limited by the absence of a healthy control group, limited study size to explore cancer subtypes, and a homogenous sample with a single ancestry of participants from a tertiary-care center. Our results build upon these findings by incorporating a healthy control group, increased power to determine cancer subtypes, and use of a more diverse patient population. Another analysis that utilized data from 20,305 Framingham Heart Study and PREVEND (Prevention of Renal and Vascular End-Stage Disease) study participants found that traditional CV risk factors are associated with increased cancer incidence.[5] This study, like the ARIC (Atherosclerosis Risk In Communities) and MESA (Multi-Ethnic Study of Atherosclerosis) studies, showed that measures taken to improve CV health also decrease cancer risk.[3,4] Analysis of this cohort, however, did not ultimately demonstrate an increased risk of cancer diagnosis associated with CV events or CV prevalence, and was unable to determine whether the link was driven by underlying shared risk factors or the existence CVD itself.[5,30]

Two previous retrospective cohort studies found a connection between heart failure and cancer incidence.[6,10] These studies, however, did not distinguish between atherosclerotic and nonatherosclerotic etiologies of heart failure and were unable to control for smoking. Our sensitivity analysis excluding heart failure diagnoses entirely from the data set did not alter findings of our primary analysis; both the

**CENTRAL ILLUSTRATION** **Risk of Cancer After Diagnosis of Cardiovascular Disease**




**Bell CF, et al. J Am Coll Cardiol CardioOnc. 2023;5(4):431–440.**

In this population-based cohort of over 27 million individuals, we determined that cardiovascular disease (CVD) was associated with higher risk of incident cancer. This association was most pronounced for atherosclerotic CVD (aCVD), which appeared to be specifically associated with bladder, colon, lung, and hematologic malignancies, even after accounting for traditional risk factors. naCVD = nonatherosclerotic cardiovascular disease.

atherosclerotic and nonatherosclerotic groups continued to have increased cancer incidence compared with those without CVD. Therefore, our results do not appear to be driven by a specific association between heart failure and cancer.

The individual cancer analyses demonstrate that many cancer subtypes occur at higher rates in patients with CVD. The risk differed, however, according to the presence or absence of atherosclerosis. For example, in both the primary analysis and the secondary HRA-based analysis (which adjusted for BMI and smoking, in addition to each of the covariates listed in Table 1), individuals with aCVD had an increased risk of bladder, colon, and lung cancers, as well as lymphoma, leukemia, and hematologic malignancies, relative to those with naCVD

and those without CVD. Interestingly, traditionally hormone-driven cancers, including breast and ovarian cancer, demonstrated an inverse association, with aCVD conferring a protective effect. Although mechanisms underlying this association are unclear, it is interesting to note that estrogen impacts vasodilation and vascular remodeling, and has been shown to have a net antiatherosclerotic effect.[31] Additionally, aromatase inhibitors, which cause systemic estradiol depletion, have been associated with a modest increase in CV events in placebo-controlled randomized clinical trials.[32,33] There is also increasing recognition of several known shared pathways in sterol/oxysterol and hormone metabolism that influence plaque progression and hormone-sensitive malignancies.[34]

It is enticing to hypothesize that these links between CVD and specific cancer subtypes are mediated through shared biological processes (eg, inflammation, metabolic adaptations, etc). Indeed, recent mouse studies have sought to explore the pathologic crosstalk between cancer and CVD. Two studies of heart failure models have found increased rates of cancer formation mediated by secreted factors.[6,7] Another using a murine model of acute myocardial infarction showed increased cancer progression mediated through innate immune system reprogramming.[8] One study employing a mouse model of obesity/metabolic syndrome found that tumor growth was enhanced via alterations in T cells within the tumor microenvironment.[35] Although no preclinical studies have yet modeled the impact of atherosclerosis on tumorigenesis, these prior publications suggest that perturbations of CV homeostasis may promote tumorigenesis.

Human studies also suggest pathophysiological overlap between cancer and CVD independent of shared traditional risk factors. For example, genome-wide association studies have shown that the most important commonly inherited genetic variant associated with atherosclerosis resides in a well-known cancer locus at chromosome 9p21, rather than in a gene that regulates traditional CV risk factors.[36-40] Inflammation and immune cell activation have also been linked to both conditions. The CANTOS (Canakinumab Anti-inflammatory Thrombosis Outcomes) trial, designed to test the hypothesis that an anti-interleukin-1ß antibody could reduce adverse CV outcomes, surprisingly found a concomitant reduction in lung cancer and lung cancer mortality.[41-44] Similarly, macrophage checkpoint inhibitors designed to reactivate anticancer immune surveillance machinery in subjects with lymphoma were recently found to simultaneously reduce vascular inflammation in those same individuals.[45] A final area of overlap relates to the phenomenon of clonal hematopoiesis of indeterminate potential (CHIP), which refers to the clonal expansion of mutated myeloid cells that can precede hematological malignancies. This process is also associated with risk for coronary disease, causing investigators to revisit the clonal hypothesis of atherosclerosis and its overlap with the clonally expanding cancer stem cell. Although the precise molecular mechanism linking CHIP mutations to heart disease remains undefined, inflammasome activation is thought to be central to this process.[46-49] Interestingly, patients in the CANTOS trial with CHIP mutations benefited more from canakinumab than those without a CHIP mutation.[49]

**STUDY LIMITATIONS.** First, our study design was observational in nature, meaning causality cannot be demonstrated. Second, there is potential misclassification of diagnoses within the ICD coding system, though codes were chosen based on rigorous review of validated claims-based algorithms.[17-29] Third, because mortality data were not available in the MarketScan data set, we were unable to conduct an analysis incorporating the competing risk of death, and it is possible that our incidence estimates may be overestimated. Fourth, our results may be subject to residual confounding from unknown covariates. We are unable to account for over-the-counter medication use, such as aspirin, in this data set. Although our secondary analysis using HRA data was able to control for BMI and smoking as covariates,[14-16] this data set was not able to account for cumulative pack-years. It also had fewer patients and was restricted to individuals between 18 to 65 years of age upon enrollment. Additionally, we were unable to control for certain other potential risk factors, such as physical activity, environmental exposures, alcohol consumption, and other sociodemographic variables. Finally, because our data set does not include information on race or ethnicity, it is impossible to discern whether these factors influence the relationship between CVD and cancer.

## CONCLUSIONS

This study found that the presence of CVD is associated with an increased incidence of cancer, particularly among individuals with atherosclerotic CVD.

Further work to understand the interaction between CVD and cancer could have significant implications. Initiation of actual long-term randomized clinical trials to explore things such as aggressive cancer subtype screening based on CV diagnosis would improve delineation of associated risks, or even elucidate circulating biomarkers that could alter prevention and screening approaches in a more accurate and personalized manner. More broadly considering the concept of interdependence, another area for clinical investigation could be whether increasingly stringent cardiac risk factor modification has a benefit in certain individuals with cancer (or cancer subtypes) compared with routine care. Insight into shared mechanisms could provide an avenue to explore therapies that address humanity's 2 leading killers at the same time.[50]

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## PERSPECTIVES

**COMPETENCY IN PATIENT CARE AND PROCEDURAL SKILLS:** Patients with CVD have disproportionately higher rates of incident cancer compared with those without CVD, irrespective of shared traditional risk factors. The risk for certain types of malignancies varies depending on whether the patient has atherosclerotic CVD or nonatherosclerotic CVD.

**TRANSLATIONAL OUTLOOK:** Further basic work is needed to understand the biological interactions of different CVD types with cancer, in addition to prospective studies considering whether patients with different types of CVD could benefit from adjusted cancer prevention or screening protocols.

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**KEY WORDS** atherosclerosis, cardiovascular disease, epidemiology, medical claims, risk prediction

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