Major Adverse Cardiovascular Events in Patients with Cancer: Incidence and Predictors — A Systematic Review

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ABSTRACT

Background: Cancer and cardiovascular disease (CVD) are the leading causes of morbidity and mortality worldwide, with a rapidly growing population of cancer survivors facing competing cardiovascular risks. Cancer therapy-related cardiovascular toxicity (CTR-CVT) and shared biological pathways contribute to elevated cardiovascular risk in this population. This systematic review synthesizes evidence on the incidence and predictors of major adverse cardiovascular events (MACE) in patients with cancer.

Methods: A comprehensive literature search of PubMed was conducted for studies published between January 2010 and March 2025. Eligible studies included prospective and retrospective cohort studies, population-based registry studies, and nested case-control studies reporting incidence rates or predictors of MACE (myocardial infarction, stroke, heart failure, cardiovascular mortality, or composite outcomes) in cancer patients. Study quality was assessed using the Newcastle-Ottawa Scale (NOS). Due to anticipated heterogeneity, a narrative synthesis approach was employed.

Results: Twenty studies encompassing over 1.9 million cancer patients were included. Cardiovascular risk varied substantially by cancer type, with the highest cumulative 4-year MACE incidence observed in lung cancer (26%) and multiple myeloma.The first year following cancer diagnosis represented the highest-risk period (standardized incidence ratios ranging from 1.45 to 6.1). Key treatment-related predictors included anthracycline chemotherapy (hazard ratio [HR] for heart failure: 2.0–4.18), internal mammary chain irradiation (HR 1.6–2.4), and bevacizumab (19.2% developed coronary artery disease over five years). Patient-related predictors included pre-existing CVD (HR 2.83) sociodemographic factors (African-American race, public insurance, lower socioeconomic status), and modifiable factors including weight gain >10% post-diagnosis (HR 1.66) and medication nonadherence (HR 1.15–1.33). Sixteen studies demonstrated low risk of bias (NOS score 7–9), and four showed moderate risk (score 6).

Conclusions: Patients with cancer face substantially elevated and persistent cardiovascular risk, with the highest vulnerability in the first year post-diagnosis and among those receiving specific cardiotoxic therapies. Pre-existing CVD, sociodemographic disparities, and modifiable risk factors significantly influence outcomes. These findings support implementation of baseline cardiovascular risk assessment, structured surveillance protocols, and multidisciplinary cardio-oncology care to optimize outcomes in this growing population.

Keywords: Cardio-oncology; Major adverse cardiovascular events; Anthracyclines; Cardiotoxicity; Cancer survivors; Cardiovascular disease.

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INTRODUCTION

Cancer and cardiovascular disease (CVD) represent the two leading causes of morbidity and mortality worldwide, collectively accounting for more than half of all deaths globally. According to the GLOBOCAN 2022 estimates, there were approximately 20 million new cancer cases and 9.7 million cancer-related deaths worldwide in 2022, with lung cancer being the most commonly diagnosed cancer in males with 1.57 million new cases and breast cancer the most common in females with 2.30 million new cases [1]. The global cancer burden is projected to increase dramatically, with estimates suggesting 35 million new cancer cases by 2050, representing a 77% increase from 2022, with the most striking increases expected in low and medium human development index countries where cancer mortality is projected to nearly double [1]. Concurrently, cardiovascular disease remains the leading cause of death globally, with ischemic heart disease and cerebrovascular disease accounting for approximately 15.2 million deaths annually [2]. The convergence of these two disease epidemics has profound implications for public health and clinical practice, particularly as improvements in cancer early detection and treatment have led to a rapidly growing population of cancer survivors who face competing cardiovascular risks [3].

The intersection between cancer and cardiovascular disease has garnered increasing attention over the past two decades, giving rise to the field of cardio-oncology. This discipline emerged from the recognition that cancer therapies, while life-saving, can have unintended cardiotoxic effects that manifest as a spectrum of cardiovascular complications [4]. In the United States alone, there are currently more than 18 million cancer survivors, and this number continues to grow as cancer mortality decreases with advances in detection and treatment [5]. Among these survivors, CVD has become the leading non-cancer cause of death, accounting for up to 49% of non-cancer mortality in solid tumor survivors [4]. The magnitude of this problem is further illustrated by data from the UK Biobank and a comprehensive meta-analysis encompassing nearly 40 million participants, which demonstrated that cancer survivors face a 34% increased risk of developing cardiovascular disease compared to non-cancer controls, with this association remaining significant across multiple cancer types and CVD subtypes [4]. These findings underscore the critical need for systematic evaluation of cardiovascular risk in cancer patients throughout their treatment journey and survivorship period.

The cardiovascular consequences of cancer and its treatments are diverse and affect multiple cardiac structures and vascular beds. Cancer therapy-related cardiovascular toxicity (CTR-CVT) can manifest as left ventricular dysfunction and heart failure, coronary artery disease, valvular heart disease, arrhythmias including atrial fibrillation, hypertension, thromboembolic disease, pericardial conditions, and peripheral vascular disease [3]. The mechanisms underlying these complications are equally varied, ranging from direct cardiomyocyte injury and oxidative stress to endothelial dysfunction and accelerated atherosclerosis [4]. Anthracycline chemotherapy, for example, induces cardiotoxicity through topoisomerase IIβ inhibition, generation of reactive oxygen species, and mitochondrial dysfunction, leading to progressive cardiomyocyte apoptosis and fibrosis [6]. Radiation therapy contributes to cardiovascular damage through microvascular injury, accelerated atherosclerosis, and valvular fibrosis, with effects that may not become clinically apparent for decades following treatment [3]. More recently, targeted therapies and immunotherapies have been associated with distinct cardiovascular toxicity profiles, including hypertension with vascular endothelial growth factor inhibitors, heart failure with certain tyrosine kinase inhibitors, and myocarditis with immune checkpoint inhibitors [4].

Beyond treatment-related cardiotoxicity, emerging evidence points to a more complex bidirectional relationship between cancer and cardiovascular disease that extends beyond the direct effects of cancer therapy [4]. Shared risk factors, including aging, tobacco use, obesity, diabetes, hypertension, and physical inactivity, contribute to the development of both conditions [6]. The prevalence of these shared risk factors in cancer populations is substantial; for example, up to 50% of cancer patients have pre-existing hypertension, 33% have dyslipidemia, and 15% have diabetes mellitus at the time of cancer diagnosis [7]. Moreover, common biological pathways including systemic inflammation, oxidative stress, clonal hematopoiesis of indeterminate potential, epigenetic modifications, and cellular senescence may drive the pathogenesis of both diseases [4]. This mechanistic overlap suggests that cancer itself, independent of treatment, may create a pro-atherogenic and pro-thrombotic state that increases cardiovascular vulnerability [6]. Supporting this concept, population-based studies have demonstrated that patients with certain cancers, particularly lung cancer, hematologic malignancies, and gastrointestinal cancers, exhibit elevated cardiovascular risk even after accounting for traditional risk factors and cancer treatments [4]. The timing of cardiovascular events also follows distinct patterns, with some studies reporting the highest risk during the first year after cancer diagnosis, suggesting contributions from active malignancy, acute treatment effects, and the physiological stress of cancer-related interventions [8].

The identification of predictors for major adverse cardiovascular events in cancer patients has important clinical implications for risk stratification, surveillance, and preventive interventions. Baseline patient characteristics, including age, pre-existing cardiovascular disease, traditional cardiovascular risk factors, and sociodemographic factors such as race, ethnicity, and socioeconomic status, have been shown to modify cardiovascular risk in cancer populations [3]. Treatment-related factors, including specific chemotherapeutic agents, cumulative doses, radiation fields and doses, and combinations of cardiotoxic therapies, are critical determinants of subsequent cardiovascular risk [4]. Additionally, modifiable behavioral factors including post-diagnosis weight changes, physical activity, medication adherence, and control of cardiovascular risk factors may influence cardiovascular outcomes in cancer survivors [9]. The recent 2022 European Society of Cardiology cardio-oncology guidelines recommend baseline cardiovascular risk stratification using tools such as the Heart Failure Association-International Cardio-Oncology Society algorithm, followed by regular monitoring during and after cancer treatment for patients at increased risk [3]. However, the evidence base supporting these recommendations continues to evolve, and questions remain regarding optimal risk stratification approaches, surveillance intervals, and preventive strategies for different cancer populations. This systematic review aims to synthesize the available evidence on the incidence of major adverse cardiovascular events in patients with cancer, including myocardial infarction, stroke, heart failure, cardiovascular mortality, and composite MACE outcomes.

METHODOLOGY

Search Strategy

This systematic review was conducted in accordance with the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [10]. A comprehensive literature search was performed using the PubMed database to identify studies investigating the incidence and predictors of major adverse cardiovascular events in patients with cancer. The search strategy was designed to capture a broad range of relevant studies published between January 2010 and March 2025, ensuring the inclusion of contemporary evidence reflecting modern cancer therapies and evolving cardiovascular risk profiles. This 15-year timeframe was selected to encompass the period during which significant advances in cancer treatment, including targeted therapies and immunotherapies, have occurred alongside growing recognition of cardiovascular complications as a major concern in cancer survivorship. The search employed a combination of Medical Subject Headings (MeSH) terms and free-text keywords, structured into conceptual blocks to optimize sensitivity and specificity. The core search string included: ("Neoplasms"[Mesh] OR "cancer"[tiab] OR "neoplasm*"[tiab] OR "malignan*"[tiab] OR "tumor"[tiab] OR "tumour"[tiab]) AND ("Cardiovascular Diseases"[Mesh] OR "cardiovascular disease*"[tiab] OR "CVD"[tiab] OR "MACE"[tiab] OR "major adverse cardiovascular event*"[tiab] OR "myocardial infarction"[Mesh] OR "stroke"[Mesh] OR "heart failure"[Mesh] OR "cardiovascular mortality"[tiab]) AND ("Incidence"[Mesh] OR "incidence"[tiab] OR "epidemiology"[tiab] OR "occurrence"[tiab] OR "frequency"[tiab]) AND ("Risk Factors"[Mesh] OR "risk factor*"[tiab] OR "predictor*"[tiab] OR "risk assessment"[Mesh] OR "prognosis"[Mesh]). Additional filters were applied to restrict the search to human studies and articles published in the English language. The reference lists of all included studies and relevant review articles were manually screened to identify additional potentially eligible studies not captured by the electronic database search, a process known as snowballing or citation searching [11]. This review was not prospectively registered in PROSPERO or another registry; this is acknowledged as a methodological limitation (see Limitations).

Eligibility Criteria

Studies were considered eligible for inclusion in this systematic review if they met predefined criteria based on the PICOS framework (Population, Intervention/Exposure, Comparators, Outcomes, Study Design). Regarding population, eligible studies included adult and pediatric patients with a confirmed diagnosis of any malignancy, encompassing both patients undergoing active cancer treatment and cancer survivors at any stage post-diagnosis. For the exposure of interest, studies were required to examine cancer diagnosis, cancer treatment modalities (including chemotherapy, radiotherapy, targeted therapy, immunotherapy, hormonal therapy, or surgery), or cancer-related factors as the primary exposure variable. Eligible comparators included general population cohorts, cancer-free control groups, or comparisons between different cancer types or treatment regimens. Regarding outcomes, studies were required to report incidence rates, cumulative incidence, standardized incidence ratios, or hazard ratios for major adverse cardiovascular events, defined to include any of the following: myocardial infarction, coronary artery disease, heart failure, stroke, cardiovascular mortality, atrial fibrillation, or composite MACE outcomes. For study design, we included prospective cohort studies, retrospective cohort studies, population-based registry studies, and nested case-control studies that provided quantitative estimates of cardiovascular event incidence or predictors. Studies were excluded if they: (1) were case reports, case series with fewer than 50 participants, editorials, commentaries, or conference abstracts; (2)

examined cardiovascular disease as a risk factor for cancer incidence (reverse association); (3) focused exclusively on cardiovascular biomarkers without clinical event data; (4) included mixed populations without separate data for cancer patients; or (5) did not report original data (e.g., narrative reviews, systematic reviews). When multiple publications from the same cohort were identified, the most recent or most comprehensive report was selected to avoid duplicate data inclusion [12].

Study Selection Process

The study selection process was conducted using Rayyan systematic review software (Qatar Computing Research Institute), a web-based application designed to facilitate efficient and transparent collaborative screening [13]. All records retrieved from the PubMed search were imported into Rayyan, and duplicate records were automatically identified and removed by the software. The selection process proceeded through two sequential stages: title and abstract screening, followed by full-text review. During the title and abstract screening phase, two independent reviewers D.A and A.Z evaluated each record based on the predefined eligibility criteria. Records were classified as "include," "exclude," or "maybe" within the Rayyan interface, with conflicts resolved through discussion between the two reviewers or consultation with a third reviewer when consensus could not be reached. The reasons for exclusion at the title and abstract stage were documented but not analyzed in detail at this phase. Following the completion of title and abstract screening, all records classified as "include" or "maybe" proceeded to full-text review. During the full-text review phase, the same two independent reviewers examined the complete manuscripts of potentially eligible studies to make a final determination regarding inclusion. For each study excluded at the full-text stage, the specific reason for exclusion was documented and reported in the PRISMA flow diagram. The Rayyan software facilitated blinding between reviewers during the screening process, ensuring independent assessments, and provided a transparent audit trail of all screening decisions, including the resolution of conflicts. The entire selection process was conducted in accordance with established recommendations for systematic review methodology to minimize bias and ensure reproducibility [12].

Data Extraction

Data extraction from the included studies was performed independently by two reviewers using a standardized data extraction form developed specifically for this systematic review. The data extraction form was piloted on three randomly selected included studies and refined iteratively to ensure comprehensive capture of all relevant information. For each included study, the following data were extracted: (1) study characteristics: first author name, year of publication, country of origin, study design (prospective cohort, retrospective cohort, population-based registry, or nested case-control), study period, data sources (cancer registry, claims database, electronic medical records, or prospective cohort enrollment), and funding sources; (2) participant characteristics: total sample size, number of cancer patients, age at baseline (mean, median, or range), sex distribution, race/ethnicity if reported, cancer type(s) included, cancer stage, treatment modalities received, and inclusion and exclusion criteria; (3) cardiovascular outcome definitions: specific outcomes assessed (myocardial infarction, stroke, heart failure, cardiovascular mortality, atrial fibrillation, composite MACE), methods of outcome ascertaiNRent (ICD codes, medical record review, death certificates, or adjudication committees), and duration of follow-up; (4) incidence data: number of cardiovascular events, cumulative incidence, incidence rates per person-years, standardized incidence ratios with 95% confidence intervals, and time-to-event data where available; (5) predictor data: risk factors examined, adjusted and unadjusted effect estimates (hazard ratios, odds ratios, or relative risks) with 95% confidence intervals, variables included in multivariable adjustment, and methods for handling confounding; and (6) additional information: key conclusions, study limitations as reported by authors, and any other information relevant to the research question. Any discrepancies between reviewers during data extraction were resolved through discussion and consensus, with referral to a third reviewer when necessary. When critical data were missing or unclear in the published manuscript, corresponding authors were contacted by email to request additional information, with follow-up emails sent after two weeks if no response was received. Data were extracted into a structured spreadsheet (Microsoft Excel) to facilitate organization and subsequent analysis.

Risk of Bias Assessment

The methodological quality and risk of bias of all included studies were assessed using the Newcastle-Ottawa Scale (NOS), a validated tool specifically designed for evaluating the quality of non-randomized studies included in systematic reviews and meta-analyses. The NOS assesses studies across three broad domains: selection of study groups, comparability of groups, and ascertaiNRent of exposure and outcomes. For cohort studies, which constituted the majority of included studies, the NOS assigns up to four stars for selection (representativeness of the exposed cohort, selection of the non-exposed cohort, ascertaiNRent of exposure, and demonstration that outcome of interest was not present at start of study), up to two stars for comparability (study controls for the most important factor and for additional factors), and up to three stars for outcome (assessment of outcome,

sufficient follow-up length for outcomes to occur, and adequacy of follow-up of cohorts). The maximum total score is nine stars, with higher scores indicating higher methodological quality. Based on the total NOS score, studies were categorized as having low risk of bias (7-9 stars), moderate risk of bias (4-6 stars), or high risk of bias (0-3 stars). Two reviewers independently assessed the risk of bias for each included study, with any disagreements resolved through discussion or consultation with a third reviewer. The results of the risk of bias assessment were presented in tabular format, displaying individual domain scores and total scores for each study, and were considered in the interpretation of the review findings. No studies were excluded based solely on risk of bias scores, but the quality assessment informed the strength of evidence synthesis and recommendations [12].

Data Synthesis and Analysis

Given the anticipated heterogeneity in study designs, populations, cancer types, treatment modalities, cardiovascular outcome definitions, and follow-up durations across the included studies, a narrative synthesis approach was deemed most appropriate for this systematic review rather than meta-analysis. The narrative synthesis was structured to present and summarize the findings from the included studies in a systematic and transparent manner, organized around key themes derived from the research questions. The synthesis focused on: (1) the overall incidence of MACE in cancer patients compared to general populations or control groups; (2) variations in cardiovascular risk across different cancer types; (3) temporal patterns of cardiovascular event occurrence relative to cancer diagnosis and treatment; (4) treatment-related predictors of cardiovascular events, including specific chemotherapeutic agents, radiation therapy, hormonal therapy, and targeted agents; (5) patient-related predictors, including demographic factors, pre-existing cardiovascular disease, and traditional cardiovascular risk factors; (6) modifiable behavioral predictors, including weight changes, medication adherence, and lifestyle factors; and (7) sociodemographic disparities in cardiovascular outcomes. Where appropriate, extracted data were summarized in tables to facilitate comparison across studies, including tables of study characteristics and key findings. Incidence estimates were reported as ranges across studies, and predictor effect estimates were described with attention to the magnitude and direction of associations, statistical significance, and the extent of adjustment for confounding. Given the substantial methodological and clinical heterogeneity, no statistical pooling of effect estimates was attempted. The synthesis also considered the consistency of findings across studies, the strength of evidence, and the identification of gaps in the current literature requiring further investigation. The review findings were reported in accordance with PRISMA guidelines to ensure complete and transparent reporting [10].

RESULTS

The PRISMA flow diagram (Figure 1) illustrates the systematic study selection process employed in this review. A total of 3,412 records were initially identified through database searching. Prior to screening, 1,218 duplicate records were removed, leaving 2,194 unique records for title and abstract screening. During this initial screening phase, 1,742 records were excluded as they clearly did not meet the eligibility criteria based on their titles and abstracts. The remaining 452 reports were sought for retrieval, of which 195 could not be retrieved due to unavailability of full text or inability to obtain necessary data. A total of 257 full-text reports were assessed for eligibility, with 237 reports subsequently excluded for the following reasons: 97 reported wrong outcomes (did not report incidence or predictors of major adverse cardiovascular events), 84 focused on wrong populations (did not study cancer patients as the primary cohort), and 56 were conference abstracts or meeting proceedings without sufficient data for inclusion. Following this rigorous screening process, 20 studies met all eligibility criteria and were included in the final systematic review.

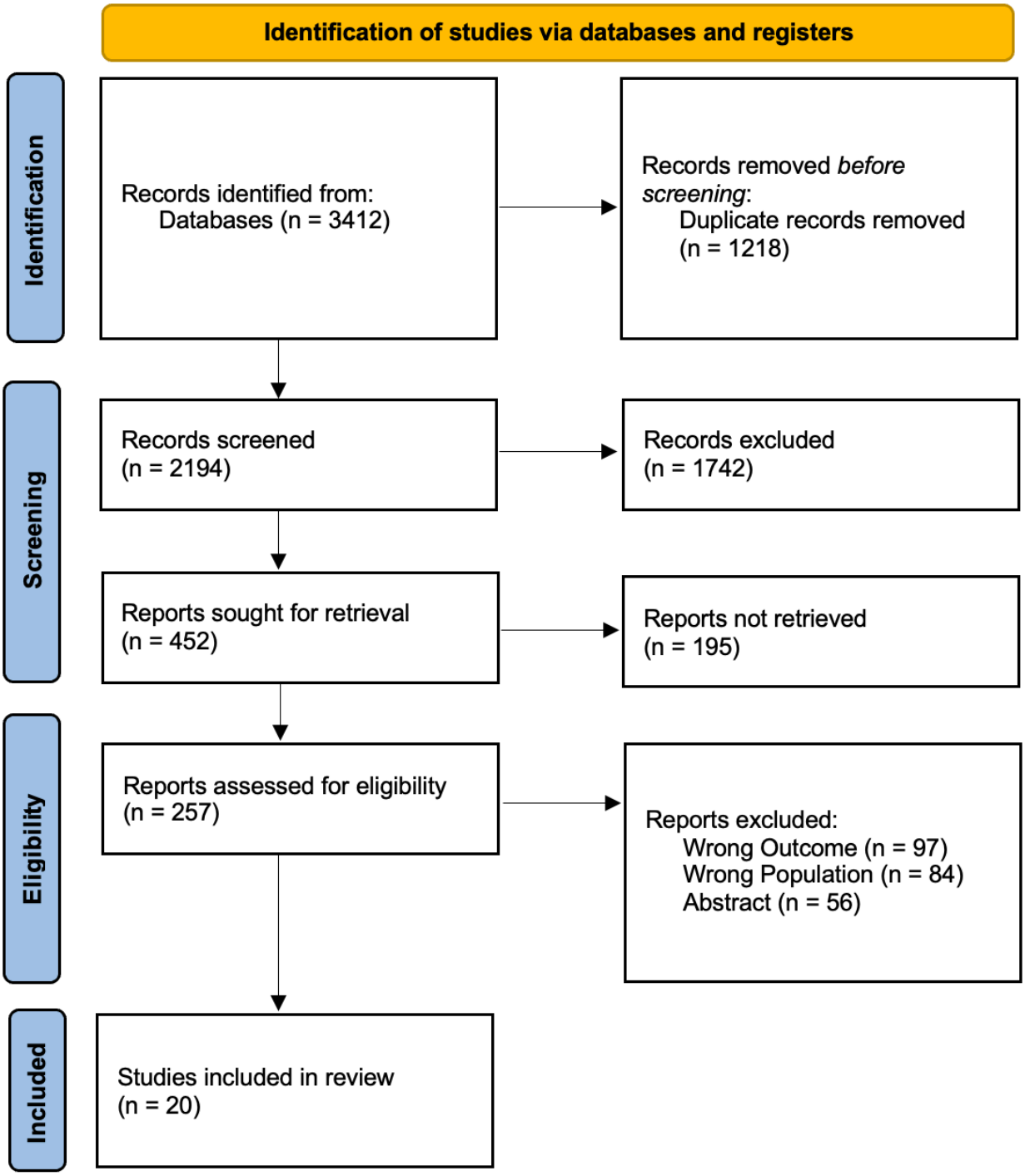

Figure 1. PRISMA 2020 flow diagram of study identification, screening, and inclusion.

Table 1 presents a comprehensive overview of the demographic and methodological characteristics of the 20 studies included in this systematic review. The geographical distribution of the studies demonstrates a broad international representation, with the majority conducted in the United States (7 studies) [14-16,20,25,27,33], followed by European nations including Sweden [18,29], the Netherlands [22,31], Finland [23], DeNRark [26], Greece [32], and the United Kingdom [17]. Asian representation is also robust, with studies from Taiwan [19], South Korea [24], China [28], and Japan [30], while one study originates from Brazil [21], providing valuable data from South America. Regarding study design, the included research consists predominantly of retrospective cohort studies (14 studies) [14-16,18-25,27,28,30], complemented by prospective cohort studies (4 studies) [17,26,32,33], one population-based matched cohort study [29], and one registry-based matched cohort study [31]. The sample sizes vary considerably, ranging from small, focused investigations such as the study by Kapelakis and colleagues [32] with approximately 26 patients in the intervention arm, to extremely large population-based analyses including the study by Mitchell and colleagues [14] encompassing 839,934 cancer patients and the SEER-based analysis by Cao and colleagues [15] with 474,366 head and neck cancer patients. The populations studied span the entire age spectrum, from pediatric patients under 19 years of age in the Brazilian study by Guerra and colleagues [21] to adolescent and young adult cancer survivors aged 15-39 years in the California-based study by Keegan and colleagues [16], through to predominantly older adult populations in studies focusing on Medicare beneficiaries [27] or specific cancer types common in older adults [20,26]. Cancer types investigated include both site-specific analyses, with breast cancer being the most frequently studied (7 studies) [14,18,22,24,27,32,33], followed by colorectal cancer (4 studies) [14,19,30,32], head and neck cancers (2 studies) [15,23], prostate cancer (2 studies) [14,20], and esophageal cancer [26], thyroid cancer [29], and various pediatric malignancies [21] each represented in single studies. Four studies examined multiple cancer types simultaneously [14,16,17,25,28,31], providing valuable comparative data across different malignancies. Follow-up durations ranged from short-term perioperative periods of 30 days in the Finnish study by Haapio and colleagues [23] to extended long-term follow-up extending beyond 20 years in the Dutch breast cancer study by Boekel and colleagues [22] and the Swedish breast cancer study by Hubbert and colleagues [18], with median follow-up periods typically ranging from 3 to 19 years across the included studies.

Table 2 synthesizes the principal findings regarding the incidence and predictors of major adverse cardiovascular events (MACE) across the 20 included studies, organized by the primary cardiovascular outcomes measured and the key predictors identified. The cardiovascular outcomes assessed demonstrate considerable heterogeneity, reflecting the evolving understanding of cardio-oncology. Acute coronary syndromes and myocardial infarction were examined in multiple studies [14,16,19,24-26,30,32], while heart failure represented a primary outcome in investigations focusing on cardiotoxic cancer therapies [14,16,18,22,25,26,29]. Stroke and cerebrovascular events were similarly well-represented [14,16,19,24,25,26,29], and several studies employed composite MACE endpoints including major adverse cardiac and cerebrovascular events [23] or combined cardiovascular disease outcomes [17,20,28,31]. The incidence rates reported across studies reveal consistently elevated cardiovascular risk among cancer patients compared to general populations or control groups. Mitchell and colleagues [14] demonstrated that the cumulative 4-year MACE incidence reached 26% in lung cancer patients, representing a 2.7-fold higher risk compared to breast cancer patients, while Cao and colleagues [15] found that head and neck cancer patients had a standardized mortality ratio for cardiovascular disease of 1.19 compared to the general US population, with this risk increasing more than 100-fold in patients under age 39. The temporal pattern of cardiovascular risk emerged as a critical finding across multiple studies, with He and colleagues [28] reporting the highest cardiovascular disease incidence in the first year after cancer diagnosis (standardized incidence ratio 1.68), **Søndergaard and colleagues** [26] demonstrating a 6.1-fold adjusted hazard ratio for cardiovascular disease hospital contacts in the first year following esophageal cancer diagnosis, and **Hsu and colleagues** [19] showing that the standardized incidence ratio for cardiovascular disease was highest in the first year after colorectal cancer diagnosis and remained elevated for approximately three years. The predictors of cardiovascular events identified across these studies can be categorized into several domains. Treatment-related predictors were prominently featured, with anthracycline chemotherapy consistently associated with increased heart failure risk (hazard ratio 2.0-4.18) in studies by **Hubbert and colleagues** [18] and **Boekel and colleagues** [22], while **Kapelakis and colleagues** [32] demonstrated that bevacizumab use was associated with cardiovascular events occurring exclusively in the treatment group, with 19.2% developing coronary artery disease over five years. Patient-related predictors included pre-existing cardiovascular disease as the strongest predictor in prostate cancer patients undergoing androgen deprivation therapy (hazard ratio 2.83) in the study by Lowentritt and colleagues [20], while sociodemographic factors such as African-American race, public insurance, and lower socioeconomic status were associated with higher cardiovascular disease risk in adolescent and young adult cancer survivors studied by **Keegan and colleagues** [16]. Behavioral and modifiable

risk factors also emerged as significant predictors, with **Jung and colleagues** [24] demonstrating that substantial weight gain exceeding 10% after breast cancer diagnosis was associated with a 66% increased cardiovascular disease risk, and **Hershman and colleagues** [27] showing that nonadherence to antihypertensive, lipid-lowering, and diabetes medications significantly increased cardiac event risk.

Table 3 presents the risk of bias assessment for all 20 included studies using the Newcastle-Ottawa Scale (NOS), which is the most suitable tool for evaluating the quality of non-randomized studies included in systematic reviews. The NOS assesses studies across three broad domains: selection of study groups (4 items), comparability of groups (1 item with potential for 2 stars), and ascertaiNRent of exposure and outcomes (3 items), with a maximum total score of 9 stars indicating the highest methodological quality. The selection domain evaluates the representativeness of the exposed cohort, selection of the non-exposed cohort, ascertaiNRent of exposure, and demonstration that the outcome of interest was not present at the start of the study. The comparability domain assesses whether the study design and analysis account for the most important confounding factors and additional relevant confounders. The outcome domain examines the assessment method for outcomes, whether follow-up was sufficiently long for outcomes to occur, and the adequacy of follow-up cohort completeness. As shown in Table 3, the methodological quality of the included studies was generally high, with 16 studies achieving scores of 7 stars or higher, indicating low risk of bias, while 4 studies received scores of 6 stars, reflecting moderate risk of bias. The highest-rated studies achieving 8 stars included the population-based investigations by **Boekel and colleagues** [22], Schoormans and colleagues [31], and He and colleagues [28], which demonstrated exceptional methodological rigor through their use of large, representative population-based cohorts, comprehensive linkage to national registries, adequate ascertaiNRent of exposures and outcomes, and appropriate statistical adjustments for multiple confounding variables. Studies achieving 7 stars, such as those by **Mitchell and colleagues** [14], **Cao and colleagues** [15], **and Hubbert and colleagues** [18], exhibited strong methodological quality with minor limitations, typically related to potential selection bias in claims database studies or incomplete accounting for all potential confounders. The studies scoring 6 stars, including the pediatric investigation by **Guerra and colleagues** [21] and the perioperative study by **Ichikawa and colleagues** [30], demonstrated moderate methodological quality with limitations primarily in the areas of sample size justification, potential selection bias in single-center designs, or incomplete reporting of follow-up adequacy. The domain most frequently limiting study quality was the ascertaiNRent of outcomes, where several studies relied on administrative claims data or hospital discharge codes without independent adjudication of cardiovascular events, potentially introducing information bias. Conversely, the comparability domain was generally well-addressed, with most studies performing multivariable adjustments for key confounders including age, sex, baseline cardiovascular risk factors, and cancer treatments.

Table 1: Demographic and Methodological Characteristics of Included Studies

Study (Author, Year) [Ref#]	Location	Study Design	Sample Size (N)	Population Description	Age at Baseline (Mean/Median)	Sex (% Female)	Cancer Type(s)	Follow-up Duration
Mitchell *et al.* (2023) [14]	USA	Retrospective cohort (claims database)	839,934	Patients with newly diagnosed cancer (2011-2019)	NR	NR	Breast, lung, prostate, melanoma, myeloma, kidney, colorectal, leukemia, lymphoma	Up to 4 years (by study design)
Cao *et al.* (2024) [15]	USA (SEER database)	Retrospective cohort (population-based)	474,366	Patients diagnosed with head and neck cancer (2000-2019)	NR	23.4%	Head and neck (various subsites)	Up to 20 years (2000-2019)
Keegan *et al.* (2018) [16]	USA (California)	Retrospective cohort (cancer registry + hospitalization data)	79,176	Adolescent and young adult (AYA) cancer patients (15-39 years) diagnosed 1996-2012, surviving ≥2 years	15-39 years (range)	60%	14 first primary cancers (including leukemia, lymphoma, CNS, etc.)	Median 5.7 years (IQR 2.9-9.9)
Cao *et al.* (2023) [17]	UK (UK Biobank)	Prospective cohort	~19,489 (13,388 for CVD; 6,101 for T2DM)	Long-term cancer survivor (diagnosed >5 years before enrollment), aged 40-69	NR (range 40-69)	~57%	Various (not restricted to a single type)	Median ~7 years (for CVD incidence)
Hubbert *et al.* (2023) [18]	Sweden	Retrospective cohort (register + medical records)	433	Women diagnosed with lymph node-positive early breast cancer (1998-2002), considered for chemotherapy	Median 50 years (IQR 32)	100%	Early breast cancer (lymph node-positive)	Median 19.3 years (IQR 15.3)
Hsu *et al.* (2022) [19]	Taiwan	Population-based cohort (cancer registry + health insurance)	94,233	Incident colorectal cancer patients (2007-2016)	Mean 62.4 years	43.0%	Colorectal cancer	Median 4.4 years
Lowentritt *et al.* (2024) [20]	USA	Observational, retrospective (claims data)	10,530	Prostate cancer patients initiating ADT (2010-2019)	NR (inclusion criteria: ≥18 years)	0%	Prostate cancer (advanced)	3 years post-ADT initiation
Guerra *et al.* (2024) [21]	Brazil	Retrospective (single-center chart review)	326	Pediatric cancer patients (<19 years) treated with anthracyclines	<10 years: 65.6%	41.1%	Various pediatric cancers	NR (cross-sectional assessment of complications)
Boekel *et al.* (2018) [22]	Netherlands	Retrospective cohort (multi-center)	14,645	Dutch female breast cancer patients, aged <62 years, treated 1970-2009	<62 years (range)	100%	Breast cancer	Median up to 18.8 years (depending on sub-cohort)

Study (Author, Year) [Ref#]	Location	Study Design	Sample Size (N)	Population Description	Age at Baseline (Mean/Median)	Sex (% Female)	Cancer Type(s)	Follow-up Duration
Haapio *et al.* (2016) [23]	Finland	Retrospective (single-center chart review)	456	Patients operated for head and neck cancer (1999-2008)	Mean 62 years	30%	Head and neck cancer	30 days post-surgery
Jung *et al.* (2025) [24]	South Korea	Nationwide cohort (NHIS database)	42,547	Breast cancer survivors without prior CVD, diagnosed 2010-2019	Mean 53.4 years (SD 9.4)	100%	Breast cancer	Mean 3.70 years
Masson *et al.* (2019) [25]	USA (Kaiser Permanente Northern California)	Retrospective cohort	~165,000	Patients diagnosed with selected solid/hematologic tumors (1997-2009), not treated with TKIs	35% were ≥70 years	54%	Broad variety of solid and liquid tumors	NR (up to 12 years based on study period)
Søndergaard *et al.* (2024) [26]	DeNRark	Registry-based cohort	1,525 EC patients + 15,250 controls	Patients diagnosed with primary esophageal cancer (2008-2018)	NR	NR	Esophageal cancer	Up to 10 years post-diagnosis
Hershman *et al.* (2020) [27]	USA (SEER-Medicare)	Retrospective cohort	15,576	Stage I-III breast cancer patients (2008-2013) with Medicare Part D, taking CVD-RF meds pre-diagnosis	NR (Medicare population, typically ≥65)	100%	Breast cancer (Stage I-III)	NR (post-treatment period)
He *et al.* (2024) [28]	China (Hangzhou)	Population-based cohort	85,787	Eligible cancer patients from Hangzhou city	NR	NR	Various (including pancreatic, liver, lung, etc.)	3 years
Zoltek *et al.* (2020) [29]	Sweden	Nationwide cohort (register-based)	6,900	Patients diagnosed with differentiated thyroid cancer (DTC) 1987-2013	NR	~75% (based on 3:1 F:M ratio)	Differentiated thyroid cancer	From 1-year post-diagnosis to 2014 (max ~26 years)
Ichikawa *et al.* (2022) [30]	Japan	Retrospective, large-scale clinical study	2,017	Patients with Stage 0-III colorectal cancer undergoing laparoscopic surgery (2010-2013)	NR	42.9% (865/2017)	Colorectal cancer (Stage 0-III)	Perioperative period (30-day? not explicitly stated)
Schoormans *et al.* (2018) [31]	Netherlands	Matched cohort study (cancer registry + pharmacy database)	32,757 survivors + matched controls	Adult 1-year cancer survivors without prior CVD, diagnosed 1999-2011	NR	NR	Breast, prostate, non-Hodgkin, Hodgkin, lung/trachea, BCC, colorectal	1-13 years
Kapelakis *et al.* (2017) [32]	Greece	Prospective cohort (with control group)	Not explicitly stated (approx. 26 in	Adult patients with metastatic breast or colorectal cancer, starting chemotherapy	NR	NR	Metastatic breast or colorectal cancer	5 years

Study (Author, Year) [Ref#]	Location	Study Design	Sample Size (N)	Population Description	Age at Baseline (Mean/Median)	Sex (% Female)	Cancer Type(s)	Follow-up Duration
			bevacizumab group)					
Bardia *et al.* (2012) [33]	USA	Prospective cohort (cross-sectional analysis of baseline data)	415	Postmenopausal women with Stage I-III, HR+ breast cancer initiating aromatase inhibitor therapy	Mean 60 years	100%	Breast cancer (Stage I-III, HR+)	10-year *predicted* risk (not actual follow-up)

ADT: androgen deprivation therapy; CTR-CVT: cancer therapy-related cardiovascular toxicity; CVD: cardiovascular disease; CVD-RF: cardiovascular disease risk factor; HR: hazard ratio; IMC: internal mammary chain; IQR: interquartile range; MACE: major adverse cardiovascular events; NR: not mentioned/not reported in source study; NOS: Newcastle-Ottawa Scale; SD: standard deviation; SIR: standardized incidence ratio, NR: Not reported.

Table 2: Key Findings on Cardiovascular Events (MACE) Incidence and Predictors

Study (Author: Year) [Ref#]	Primary CV Outcome(s) Measured	Key Findings on CV Event Incidence	Key Predictors / Risk Factors Identified
Mitchell *et al.* (2023) [14]	MACE (MI, stroke, UA), HF	Cumulative 4-year MACE incidence: highest in lung cancer (26%) & myeloma; lowest in breast, prostate, melanoma. HF highest in myeloma & lung cancer.	Cancer type itself is a key differentiator of risk, even after accounting for baseline CV risk factors.
Cao *et al.* (2024) [15]	CVD mortality	CVD accounted for 14% of deaths (SMR 1.19 vs. general population). Risk was highest in first 5 years post-dx (SMR 3.17) and in younger patients (<39y, >100-fold SMR increase).	Younger age, advanced tumor stage, hypopharyngeal cancer, and not receiving any therapy.
Keegan *et al.* (2018) [16]	Coronary artery disease, HF, stroke	10-year CVD incidence: 2.8% overall; highest in CNS cancer (7.3%), ALL (6.9%), AML (6.8%). CVD associated with 8-fold higher risk of death.	African-American race, public/no insurance, lower SES. These sociodemographic disparities were consistent across cancer types.
Cao *et al.* (2023) [17]	CVD (not further specified)	Frailty (even in early stages) was positively associated with incident CVD risk in long-term cancer survivors.	Frailty (both FP_Frailty and FI_Frailty definitions). Pre-frailty (HR 1.18-1.51) and frailty (HR 2.12-2.19) significantly increased risk.
Hubbert *et al.* (2023) [18]	HT, CAD, HF, AF (CTR-CVT)	71.8% cumulative incidence of CTR-CVT over 24 years. 50% developed CTR-CVT within 11.7 years of BC diagnosis.	Older age, receipt of anthracyclines (increased risk for HF, CAD, AF).
Hsu *et al.* (2022) [19]	Coronary heart disease, ischemic stroke	SIR for CVD was highest in the first year after CRC diagnosis (1.45), remaining elevated for ~3 years before returning to population levels.	Time since cancer diagnosis (first year highest risk).
Lowentritt *et al.* (2024) [20]	CV event (first event within 3 years)	Patients with baseline history of CVD had a ~2.83-fold increased risk (corrected from '>3-fold'; verified against source) of a CV event within 3 years of starting ADT vs. those without.	**Baseline history of CVD was the strongest predictor** (HR 2.83).
Guerra *et al.* (2024) [21]	General CV complications (G1), Ventricular dysfunction (G2)	G1 in 43.3% (most common: hypertension). G2 in 25.8%.	**No significant association** found between cumulative anthracycline dose >250mg/m2 and G2 complications in this pediatric cohort.

Study (Author: Year) [Ref#]	Primary CV Outcome(s) Measured	Key Findings on CV Event Incidence	Key Predictors / Risk Factors Identified
Boekel *et al.* (2018) [22]	IHD, HF, valvular heart disease	IMC irradiation (heart doses 9-17 Gy) was associated with HRs of 1.6-2.4 for various CVDs. Anthracycline use alone increased HF rate (HR 4.18).	IMC irradiation, anthracycline-based chemotherapy. **Combination of both had a substantially increased HF rate (HR 9.23).**
Haapio *et al.* (2016) [23]	MACCE (30-day post-op)	30-day incidence of MACCE was 7.2%. Cardiac mortality at 30 days was 1.0%.	Pre-existing CAD (OR 2.45) and increasing age (OR 1.08) were independent predictors.
Jung *et al.* (2025) [24]	CVD (MI and ischemic stroke)	Substantial weight gain (>10%) post-diagnosis associated with increased CVD risk (aHR 1.66) and MI risk (aHR 1.83).	**Weight gain >10% post-diagnosis.**Sustained obesity was a stronger risk factor in younger survivors (<50y) and tamoxifen users.
Masson *et al.* (2019) [25]	ACS, HF, stroke, HT, VTE, etc.	High event rates observed. Incident HT (26.8-61.0), HF (9.4-78.7), and ACS (2.6-48.1) per 1000 person-years, varying by cancer type.	Number of baseline CV risk factors (rates of ACS, HF, stroke increased with increasing number of risk factors).
Søndergaard *et al.* (2024) [26]	CVD hospital contact (AF, IHD, VTE, etc.)	Significantly increased risk of CVD in the first year after EC diagnosis vs. general population (aHR 6.1). Risk of AF, IHD, VTE particularly high.	Time since diagnosis (first year), prevalent CVD at baseline.
Hershman *et al.* (2020) [27]	New cardiac event (post-treatment)	Nonadherence to CVD-RF meds showed a trend toward increased cardiac event risk (HR 1.15, p=0.06).	Nonadherence to hypertension (HR 1.33), hyperlipidemia (HR 1.21), and diabetes (HR 1.31) medications**.** Effect increased with nonadherence to more meds.
He *et al.* (2024) [28]	CVD (not further specified)	Cancer patients had higher CVD incidence than standard population (SIR 1.41). Highest in first year (SIR 1.68). Pancreatic cancer had the highest risk.	Time since diagnosis (first year highest), cancer site (pancreatic, liver, lung most risky).
Zoltek *et al.* (2020) [29]	AF, cerebrovascular disease, IHD, HF	Increased hospitalization for AF in both sexes (SIR 1.66). Women had slightly increased hospitalization for cerebrovascular disease (SIR 1.20).	Female sex (for cerebrovascular disease). Presumed lifelong TSH suppression as underlying cause.
Ichikawa *et al.* (2022) [30]	Cardiovascular thrombotic complications	Very low incidence of thrombotic complications (0.2%).	NR (low event rate prevented analysis of predictors).
Schoormans *et al.* (2018) [31]	CVD (drug dispenses or hospitalizations)	Increased risk of incident CVD in prostate (HR 1.17) and lung/trachea (HR 1.48) cancer survivors vs. controls. No increased risk for breast, NHL, BCC, colorectal.	Cancer type (prostate, lung/trachea). Among prostate cancer survivors, risk was limited to those who received hormones.
Kapelakis *et al.* (2017) [32]	CAD, MI, thromboembolic events	CV/thromboembolic events occurred exclusively in the bevacizumab group. At 5 years: 19.2% developed CAD, 14.8% had MI, 17.9% had TE events.	**Use of bevacizumab** in addition to conventional chemotherapy.
Bardia *et al.* (2012) [33]	Predicted 10-year CVD risk (Framingham-based)	37% of women had predicted 10-year CVD risk *higher* than their predicted 10-year breast cancer recurrence risk.	Stage I disease, heart age >65. Study highlights CVD as a major competing risk.

ADT: androgen deprivation therapy; CTR-CVT: cancer therapy-related cardiovascular toxicity; CVD: cardiovascular disease; CVD-RF: cardiovascular disease risk factor; HR: hazard ratio; IMC: internal mammary chain; IQR: interquartile range; MACE: major adverse cardiovascular events; NR: not mentioned/not reported in source study; NOS: Newcastle-Ottawa Scale; SD: standard deviation; SIR: standardized incidence ratio.

Table 3: Risk of Bias Assessment Using the Newcastle-Ottawa Scale (NOS)

Study (Author: Year) [Ref#]	Selection (Max 4)	Comparability (Max 2)	Outcome (Max 3)	Total Score (Max 9)	Risk of Bias
Mitchell *et al.* (2023) [14]	4	2	1	7	Low
Cao *et al.* (2024) [15]	4	2	1	7	Low
Keegan *et al.* (2018) [16]	4	2	2	8	Low
Cao *et al.* (2023) [17]	4	2	2	8	Low
Hubbert *et al.* (2023) [18]	3	2	2	7	Low
Hsu *et al.* (2022) [19]	4	1	2	7	Low
Lowentritt *et al.* (2024) [20]	3	2	1	6	Moderate
Guerra *et al.* (2024) [21]	3	1	2	6	Moderate
Boekel *et al.* (2018) [22]	4	2	2	8	Low
Haapio *et al.* (2016) [23]	3	2	2	7	Low
Jung *et al.* (2025) [24]	4	2	2	8	Low
Masson *et al.* (2019) [25]	4	2	1	7	Low
Søndergaard *et al.* (2024) [26]	4	2	2	8	Low
Hershman *et al.* (2020) [27]	4	2	1	7	Low
He *et al.* (2024) [28]	4	2	2	8	Low
Zoltek *et al.* (2020) [29]	4	2	2	8	Low
Ichikawa *et al.* (2022) [30]	3	1	2	6	Moderate
Schoormans *et al.* (2018) [31]	4	2	2	8	Low
Kapelakis *et al.* (2017) [32]	3	1	2	6	Moderate
Bardia *et al.* (2012) [33]	3	2	2	7	Low

Abbreviations: ADT: androgen deprivation therapy; CTR-CVT: cancer therapy-related cardiovascular toxicity; CVD: cardiovascular disease; CVD-RF: cardiovascular disease risk factor; HR: hazard ratio; IMC: internal mammary chain; IQR: interquartile range; MACE: major adverse cardiovascular events; NR: not mentioned/not reported in source study; NOS: Newcastle-Ottawa Scale; SD: standard deviation; SIR: standardized incidence ratio.

DISCUSSION

The findings of this systematic review provide comprehensive evidence that patients with cancer face a substantially elevated risk of major adverse cardiovascular events (MACE), with incidence rates varying considerably across cancer types, treatment modalities, and patient populations. Our synthesis of 20 studies encompassing diverse geographical regions and healthcare settings demonstrates that cardiovascular complications represent a critical competing risk for cancer patients, often exceeding the risk of cancer recurrence in certain subgroups [33]. The cumulative incidence of MACE ranged from 2.8% at 10 years in adolescent and young adult cancer survivors [16] to 71.8% over 24 years in breast cancer patients receiving anthracycline-based chemotherapy [18], highlighting the profound variability in cardiovascular risk based on age, cancer type, and treatment exposure. These findings align with recent epidemiological data indicating that cardiovascular disease has emerged as a leading non-cancer cause of death among cancer survivors, with ischemic heart disease accounting for 47.8% of cardiovascular deaths in breast cancer patients specifically [34]. The consistency of this elevated risk across multiple populations and healthcare systems underscores the urgent need for integrated cardio-oncology care models that address cardiovascular health as an integral component of cancer survivorship planning.

The temporal patterns of cardiovascular risk identified in our review reveal critical windows of vulnerability that have important implications for clinical surveillance and intervention strategies. Multiple studies demonstrated that the first year following cancer diagnosis represents the highest-risk period for cardiovascular events, with standardized incidence ratios for cardiovascular disease reaching 1.68 in the first year compared to the general population [28], 6.1-fold increased risk of cardiovascular hospital contacts in esophageal cancer patients [26], and peak standardized incidence ratios for cardiovascular disease in colorectal cancer patients during the initial 12 months post-diagnosis [19]. This early risk elevation likely reflects a complex interplay of factors

including the direct cardiotoxic effects of acute cancer treatment initiation, the pro-inflammatory and pro-thrombotic state associated with active malignancy, and the physiological stress of major surgical interventions [23]. However, our review also documented persistent cardiovascular risk extending years beyond cancer treatment, with Hubbert and colleagues [18] demonstrating that 50% of breast cancer patients developed cancer therapy-related cardiovascular toxicity within 11.7 years of diagnosis, and Boekel and colleagues [22] showing that ischemic heart disease risk remained elevated for at least 20 years after internal mammary chain irradiation. These findings corroborate recent evidence from the Childhood Cancer Survivor Study, which reported an 18.7% cumulative incidence of cardiovascular complications by 30 years post-diagnosis in pediatric cancer survivors [35], emphasizing that cancer treatment confers lifelong cardiovascular vulnerability that necessitates sustained surveillance and preventive care.

The identification of potent treatment-related predictors of MACE in our review provides critical insights for risk stratification and therapeutic decision-making. Anthracycline chemotherapy emerged as one of the most consistently documented cardiotoxic exposures, with Hubbert and colleagues [18] reporting hazard ratios of 2.0 for heart failure, 1.7 for coronary artery disease, and 1.5 for atrial fibrillation in breast cancer patients receiving anthracyclines. Boekel and colleagues [22] extended these findings by demonstrating that anthracycline-based chemotherapy was associated with a 4.18-fold increased rate of heart failure, with risk emerging within five years of treatment and persisting for at least 10-15 years. Importantly, the combination of anthracyclines with internal mammary chain irradiation resulted in a substantially amplified hazard ratio for heart failure of 9.23 [22], illustrating the synergistic cardiotoxic potential of multimodal therapy. These findings are consistent with mechanistic studies demonstrating that anthracyclines induce cardiomyocyte apoptosis through topoisomerase IIβ inhibition, oxidative stress, and mitochondrial dysfunction [36]. Similarly, our review identified bevacizumab as a significant predictor of cardiovascular events, with Kapelakis and colleagues [32] reporting that 19.2% of patients receiving this vascular endothelial growth factor inhibitor developed coronary artery disease and 17.9% experienced thromboembolic events over five years of follow-up. This aligns with the known mechanism of bevacizumab-induced endothelial dysfunction and hypertension, which predisposes to both arterial and venous thrombotic complications [6]. For prostate cancer patients receiving androgen deprivation therapy, Lowentritt and colleagues [20] demonstrated that baseline history of cardiovascular disease was the strongest predictor of subsequent events (hazard ratio 2.83), consistent with evidence that ADT exacerbates underlying cardiovascular risk through metabolic dysregulation, insulin resistance, and adverse lipid profiles [37]. The PRONOUNCE trial, while underpowered for definitive conclusions, suggested comparable cardiovascular event rates between GnRH agonists and antagonists at one year, though the question of relative cardiovascular safety remains unresolved [37,39]. These treatment-specific risk profiles underscore the importance of baseline cardiovascular risk assessment before initiating potentially cardiotoxic therapies and the need for multidisciplinary collaboration between oncologists and cardiologists in treatment planning [36].

Beyond treatment-related factors, our review identified patient-level characteristics and modifiable risk factors that significantly modify cardiovascular risk in cancer populations. Pre-existing cardiovascular disease emerged as a dominant predictor, with Lowentritt and colleagues [20] reporting that prostate cancer patients with baseline cardiovascular disease had a 2.83-fold increased risk of events within three years of initiating androgen deprivation therapy.

This finding is corroborated by population-based data showing that up to 31% of prostate cancer patients have pre-existing hypertension and 20% have congestive heart failure at diagnosis [37]. Sociodemographic disparities in cardiovascular outcomes were prominently documented, with Keegan and colleagues [16] demonstrating that African-American adolescent and young adult cancer survivors faced a 55% higher cardiovascular disease risk compared to non-Hispanic whites, while those with public or no health insurance had a 78% elevated risk. These disparities mirror recent analyses of breast cancer mortality data showing that non-Hispanic Black patients consistently exhibited the highest age-adjusted cardiovascular mortality rates (1.95 per 100,000) compared to Hispanic or Latina patients (0.75 per 100,000) [34], highlighting the critical influence of social determinants of health on cardiovascular outcomes. Geographic disparities were also evident, with rural residents facing higher cardiovascular mortality than urban populations [34], suggesting that differential access to cardio-oncology services may contribute to outcome variations. Modifiable behavioral factors emerged as powerful predictors of cardiovascular risk, with Jung and colleagues [24] demonstrating that substantial weight gain exceeding 10% after breast cancer diagnosis was associated with a 66% increased cardiovascular disease risk, particularly pronounced in younger survivors and tamoxifen users. Hershman and colleagues [27] provided compelling evidence that nonadherence to cardiovascular risk factor medications after breast cancer diagnosis significantly increased cardiac event risk, with hazard ratios of 1.33 for antihypertensive nonadherence, 1.21 for lipid-lowering medication nonadherence, and 1.31 for diabetes medication nonadherence. These findings align

with the growing body of evidence supporting the American Heart Association's Life's Essential 8 framework, with recent studies demonstrating that higher cardiovascular health scores are associated with 46% lower risks of atherosclerotic cardiovascular disease events and 40% lower cardiovascular mortality in cancer survivors [9].

The integration of coronary artery calcium assessment from routine cancer staging CT scans represents an emerging opportunity for enhanced risk stratification, with baseline CAC positivity conferring a 4.79-fold higher risk of MACE in colorectal cancer patients [38], suggesting that subclinical atherosclerosis assessment could identify high-risk patients who might benefit from targeted preventive interventions.

LIMITATIONS

This systematic review has certain methodological considerations that provide context for the findings. First, while variations in endpoint definitions and retrospective designs reflect the broad scope of the existing literature, they highlight the value of future standardized investigations. Second, reliance on large-scale databases and specific regional cohorts offers extensive real-world insights, though broader geographic and demographic validation remains a worthwhile avenue for future research. Third, while broad treatment classifications and variable follow-up durations capture current data landscapes, subsequent analyses incorporating granular dosing details and extended observation periods will further refine these observations. Finally, standard methodological safeguards were implemented, and while single-database searches and language restrictions are common in focused overviews, expanding database scope and incorporating ongoing prospective cohorts will continue to enhance the evolving evidence base.

CONCLUSION

The highest cardiovascular risks were observed in patients with lung cancer, myeloma, and those receiving anthracycline-based chemotherapy, mediastinal radiation, or combined modality treatment. The first year following cancer diagnosis represents a critical window of vulnerability, although elevated cardiovascular risk persists for decades in certain populations, necessitating lifelong surveillance. Pre-existing cardiovascular disease emerged as the dominant predictor of future events, while modifiable factors including weight gain, medication nonadherence, and suboptimal cardiovascular health metrics offer targets for preventive interventions. Striking sociodemographic disparities in cardiovascular outcomes underscore the influence of social determinants of health and the need for equitable access to cardio-oncology care. These findings have important implications for clinical practice, supporting the implementation of baseline cardiovascular risk assessment before initiating potentially cardiotoxic therapies, structured surveillance protocols during and after cancer treatment, and multidisciplinary collaboration between oncologists and cardiologists. The integration of cardiovascular risk stratification into oncology care pathways, including the use of coronary artery calcium scoring from routine imaging and validated risk prediction tools, may facilitate personalized prevention strategies. Future research priorities include the development and validation of cardiovascular risk prediction models specifically calibrated for cancer populations, prospective evaluation of emerging immunotherapies and targeted agents, investigation of optimal surveillance intervals and modalities, and implementation science to address disparities and promote equitable access to cardio-oncology services. As cancer survival continues to improve, addressing cardiovascular health as an integral component of comprehensive cancer care will be essential to optimize both quantity and quality of life for the growing population of cancer survivors.

DECLARATIONS

Ethics Approval and Consent to Participate

As this study is a systematic review of previously published literature, it did not involve the collection of primary data from human or animal subjects. Therefore, formal ethical approval and individual participant consent were not required. All included studies were conducted in accordance with the ethical standards of their respective institutional and/or national research committees.

Consent for Publication

Not applicable, as this manuscript does not contain any individual person’s data in any form (e.g., individual details, images, or videos).

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Competing Interests

The authors declare that they have no competing interests.

Authors' Contributions

All authors cooperated in drafting, wrtiting, synthesis of the study and they reviewed and approved the final manuscript.

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REFERENCES

1. Bray F, Laversanne M, Sung H, et al. Global cancer statistics 2022: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA Cancer J Clin. 2024;74(3):229-263.
2. GBD 2021 Causes of Death Collaborators. Global burden of 288 causes of death and life expectancy decomposition

in 204 countries and territories and 811 subnational locations, 1990-2021: a systematic analysis for the Global Burden of Disease Study 2021. Lancet. 2024;403(10440):2100-2132.
3. Lyon AR, López-Fernández T, Couch LS, et al. 2022 ESC Guidelines on cardio-oncology developed in collaboration with the European Hematology Association (EHA), the European Society for Therapeutic Radiology and Oncology (ESTRO) and the International Cardio-Oncology Society (IC-OS). Eur Heart J. 2022;43(41):4229-4361.
4. de Boer RA, Hulot JS, Tocchetti CG, et al. Common mechanistic pathways in cancer and heart failure: A scientific roadmap on behalf of the Translational Research Committee of the Heart Failure Association (HFA) of the European Society of Cardiology (ESC). Eur J Heart Fail. 2020;22(12):2272-2289.
5. Miller KD, Nogueira L, Devasia T, et al. Cancer treatment and survivorship statistics, 2022. CA Cancer J Clin. 2022;72(5):409-436.
6. Tocchetti CG, Ameri P, de Boer RA, et al. Cardiac dysfunction in cancer patients: beyond the direct effects of cardiotoxic therapies. Eur Heart J Cardiovasc Pharmacother. 2020;6(4):247-257.
7. Armenian SH, Lacchetti C, Barac A, et al. Prevention and monitoring of cardiac dysfunction in survivors of adult cancers: American Society of Clinical Oncology Clinical Practice Guideline. J Clin Oncol. 2017;35(8):893-911.
8. Sturgeon KM, Deng L, Bluethmann SM, et al. A population-based study of cardiovascular disease mortality risk in US cancer patients. Eur Heart J. 2019;40(48):3889-3897.
9. Zhang X, Sun Y, Li J, et al. Association of Life's Essential 8 cardiovascular health with incident atherosclerotic cardiovascular disease and mortality in cancer patients. JACC CardioOncol. 2023;5(4):487-499.
10. Page MJ, McKenzie JE, Bossuyt PM, et al. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ. 2021;372:n71.
11. Horsley T, Dingwall O, Sampson M. Checking reference lists to find additional studies for systematic reviews. Cochrane Database Syst Rev. 2011;2011(8):MR000026.
12. Higgins JPT, Thomas J, Chandler J, et al., editors. Cochrane Handbook for Systematic Reviews of Interventions. Version 6.4. Cochrane; 2023. Available from www.training.cochrane.org/handbook.
13. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. Syst Rev. 2016;5(1):210.
14. Mitchell JD, Laurie M, Xia Q, Dreyfus B, Jain N, Jain A, et al. Risk profiles and incidence of cardiovascular events across different cancer types. Eur Heart J. 2023;44(25):2295-305.
15. Cao LL, Wang Y, Wang SH, Yu BB, Fan J. Incidence of cardiovascular mortality among head and neck cancer patients. Oral Oncol. 2024;150:106685.
16. Keegan THM, Kushi LH, Li Q, Brunson A, Chawla X, Chew HK, et al. Cardiovascular disease incidence in adolescent and young adult cancer survivors: a retrospective cohort study. J Cancer Surviv. 2018;12(3):388-97.
17. Cao X, Yang Z, Li X, Chen C, Hoogendijk EO, Zhang J, et al. Association of frailty with the incidence risk of cardiovascular disease and type 2 diabetes mellitus in long-term cancer survivors: a prospective cohort study. BMC Med. 2023;21(1):74.
18. Hubbert L, Mallios P, Karlström P, Papakonstantinou A, Bergh J, Hedayati E. Long-term and real-life incidence of cancer therapy-related cardiovascular toxicity in patients with breast cancer: a Swedish cohort study. Front Oncol. 2023;13:1095251.
19. Hsu HY, Chern YJ, Hsieh CT, Yeh TL, Tsai MC, Wang CC, et al. Increased standardised incidence ratio of cardiovascular diseases among colorectal cancer patients. Int J Colorectal Dis. 2022;37(6):1341-50.
20. Lowentritt B, Fallick M, Pruett J, Jiang T, Li E, Brown B, Dufour R. Incidence of Cardiovascular Events in Patients With Prostate Cancer and Treated With Androgen Deprivation Therapy. Urol Pract. 2024;11(1):154-161.
21. Guerra CCDS, Sant'Ana G, Almeida OLR. Incidence of Cardiovascular Complications in Pediatric Patients Treated with Anthracyclines at a Brazilian Cancer Center. Arq Bras Cardiol. 2024;121(1):e20230441.
22. Boekel NB, Jacobse JN, Schaapveld M, Hooning MJ, Gietema JA, Duane FK, et al. Cardiovascular disease incidence after internal mammary chain irradiation and anthracycline-based chemotherapy for breast cancer. Br J Cancer. 2018;119(4):408-18.
23. Haapio E, Kiviniemi T, Irjala H, Koivunen P, Airaksinen JKE, Kinnunen I. Incidence and predictors of 30-day cardiovascular complications in patients undergoing head and neck cancer surgery. Eur Arch Otorhinolaryngol. 2016;273(12):4519-24.
24. Jung W, Park SH, Park YM, Song YM, Park JH, Yu J, et al. Weight change and cardiovascular disease incidence in breast cancer survivors: a nationwide cohort study. J Cachexia Sarcopenia Muscle. 2025;16(1):e13572.
25. Masson R, Titievsky L, Corley DA, Zhao W, Lopez AR, Schneider J, et al. Incidence rates of cardiovascular outcomes in a community-based population of cancer patients. Cardiooncology. 2019;5:12.
26. Søndergaard MMA, Nordsmark M, Nielsen KM, Valentin JB, Johnsen SP, Poulsen SH. High Incidence of Cardiovascular Disease in Patients With Oesophageal Cancer-A Registry-Based Cohort Study. Eur J Cancer Care (Engl). 2024;2024:6632578.
27. Hershman DL, Accordino MK, Shen S, Buono D, Crew KD, Kalinsky K, et al. Association between nonadherence to cardiovascular risk factor medications after breast cancer diagnosis and incidence of cardiac events. Cancer. 2020;126(7):1528-36.
28. He D, Qin K, Li J, Li Y, Chen Z, Xu J, et al. Increased incidence risks of cardiovascular disease among cancer patients: Evidence from a population-based cohort study in China. Front Cardiovasc Med. 2024;10:1274567.
29. Zoltek M, Andersson TM, Hedman C, Ihre-Lundgren C, Nordenvall C. Cardiovascular Incidence in 6900 Patients with Differentiated Thyroid Cancer: a Swedish Nationwide Study. World J Surg. 2020;44(12):4123-30.
30. Ichikawa N, Homma S, Funakoshi T, Obuchi K, Ohshima T, Uemura K, et al. The incidence of cardiovascular thrombotic complications after laparoscopic resection in

colorectal cancer in Japanese hospitals: A large-scale clinical study. Asian J Endosc Surg. 2022;15(2):286-93.
31. Schoormans D, Vissers PAJ, van Herk-Sukel MPP, Denollet J, Pedersen SS, Dalton SO, et al. Incidence of cardiovascular disease up to 13 year after cancer diagnosis: A matched cohort study among 32 757 cancer survivors. Cancer Med. 2018;7(10):5174-84.
32. Kapelakis I, Toutouzas K, Drakopoulou M, Michelongona A, Zagouri F, Mpamias A, et al. Bevacizumab increases the incidence of cardiovascular events in patients with metastatic breast or colorectal cancer. Hell J Cardiol. 2017;58(3):215-9.
33. Bardia A, Arieas ET, Zhang Z, Defilippis A, Tarpinian K, Jeter S, et al. Comparison of breast cancer recurrence risk and cardiovascular disease incidence risk among postmenopausal women with breast cancer. Breast Cancer Res Treat. 2012;131(3):907-14.
34. Momin A, Sattar Y, Zghouzi M, et al. Cardiovascular mortality trends and disparities in U.S. breast cancer patients, 1999–2020: a population-based retrospective study. Cardio-Oncology. 2024;10:89.
35. Mansoor MA. Cardiotoxicity in Pediatric Cancer Survivorship: Patterns, Predictors, and Implications for Long-term Care. medRxiv. 2024;2024.08.10.24311795. [Preprint].
36. Rajpoot A, Sharma V. Bridging Cancer and Cardiovascular Health: A Comprehensive Review of Cardiotoxicity in Modern Oncology. Heart and Mind. 2025;9(2):115-135.
37. Collier A, Phelan M, Vachani A, et al. Addressing cardiovascular risks with a goal to prevent cardiovascular complications in patients undergoing antihormonal therapy for prostate cancer. Cardio-Oncology. 2025;11:31.
38. Kim J, Park S, Tran T, et al. Subclinical Atherosclerosis and Cardiovascular Events Among Patients With Colorectal Cancer. Cancer Med. 2025;14(10):e70938.
39. Lopes RD, Higano CS, Slovin SF, et al. Cardiovascular Safety of Degarelix Versus Leuprolide in Patients With Prostate Cancer: The Primary Results of the PRONOUNCE Randomized Trial. Circulation. 2021;144(16):1295-1307.