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Heart failure related cardiotoxicity in breast cancer survivors: a scoping review

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Abstract

Background: Breast cancer is the most common malignancy among women globally and the second most frequently diagnosed cancer overall, with 2.3 million new cases reported in 2022. While advances in therapy have substantially improved survival, cardiovascular disease (CVD) has emerged as the leading cause of non-cancer mortality in this population. Real-world evidence on the incidence and trajectory of heart failure (HF) and treatment-related cardiotoxicity remains limited, with existing studies often constrained by small sample sizes or narrow therapeutic focus. This scoping review aimed to synthesise evidence on the incidence of HF, cardiovascular mortality, and all-cause mortality in individuals with breast cancer, map additional cardiovascular outcomes, and identify high-risk subgroups.

Methods: The review followed the Joanna Briggs Institute methodology, applying the Participant–Concept–Context framework to identify eligible studies. Inclusion criteria comprised peer-reviewed, observational studies in English published up to July 2024 that reported HF incidence in breast cancer patients; clinical trials, reviews, and prevalence studies were excluded. Comprehensive searches of PubMed, MEDLINE, CINAHL, and Embase were undertaken, with independent dual screening. Data were synthesised descriptively and thematically, and study quality was assessed using the CASP tool.

Results: Fifteen population-based cohort studies were included, with sample sizes ranging from 294 to 122,217 and follow-up durations of 3 to 19 years. Most cohorts included women with early-stage (I–III) disease and displayed heterogeneity in demographics, comorbidities, and treatments. Hypertension, diabetes, and dyslipidaemia were the most common comorbidities. Chemotherapy and radiotherapy were administered in up to 58% and 78.5% of patients, respectively. HF risk was significantly elevated (hazard ratios [HRs] up to 2.71), peaking within the first-year post-diagnosis and persisting for up to 17 years. All-cause mortality was consistently higher than in non-cancer controls (HRs >3.0), whereas cardiovascular mortality findings were mixed. Younger age, cardiometabolic comorbidities, advanced cancer stage, and exposure to anthracyclines (HR 1.74) or trastuzumab (HR 2.34) were key risk factors. Additional cardiovascular outcomes—including ischaemic heart disease, atrial fibrillation, stroke, and thromboembolism—were frequently observed, particularly in early survivorship. Most studies were rated as high quality.

Conclusion: Breast cancer survivors face a substantial and sustained cardiovascular burden, particularly for HF and all-cause mortality. These findings emphasise the need for early CVD risk assessment, targeted cardioprotective interventions, and long-term surveillance. Large, prospective studies are essential to inform precision cardio-oncology and optimise survivorship outcomes.

Keywords: Breast cancer; Cardiotoxicity; Heart failure; Cardiovascular outcomes; Risk factors

1. Background

Breast cancer is the most frequently diagnosed malignancy among women, representing 24% of all female cancer cases. In 2022, it was the second most commonly diagnosed cancer globally, with approximately 2.3 million new cases, accounting for 11.6% of all cancer incidence

Breast cancer is the most prevalent malignancy among women, comprising 24% of female cancer cases and ranking as the second most diagnosed cancer globally in 2022, with 2.3 million new cases (11.6% of all cancers) and 670,000 deaths. Incidence rose by 1–5% annually in half of the countries assessed, and by 2050, global cases and deaths are projected to increase by 38% and 68%, respectively [1-3]. Over the past few decades, advances in surgical procedures, radiotherapy, systemic treatments, and endocrine therapies have significantly enhanced the survival rates of patients with breast cancer. In the United States, the 5-year relative survival rate for localized breast cancer has surpassed 99% [4-7], and cardiovascular disease (CVD) has become the primary cause of non-cancer-related mortality among women who have survived breast cancer [8, 9].

The cardiotoxic effects of cancer therapies have been increasingly recognized, with advanced treatments contributing to a heightened risk of cardiovascular complications, including asymptomatic left ventricular dysfunction and heart failure (HF) [10-12]. Evidence indicates that breast cancer survivors have an elevated risk of cardiovascular mortality compared with individuals without a history of cancer, largely because of the cardiotoxic effects of certain cancer therapies [13]. Notably, there has been a five-fold increase in adverse cardiac events, with approximately 1%–2% of patients developing symptomatic HF within two years of treatment initiation [14].

Previous studies have primarily examined cardiotoxicity in the context of specific treatment regimens, often in clinical trials or drug comparison studies, and have frequently been constrained by small sample sizes. Although anthracyclines and trastuzumab are consistently linked to increased HF risk, the reliance on controlled settings limits the generalizability of these findings to real-world population-based contexts [15-18]. Additionally, variations in diagnostic algorithms across studies may lead to an overestimation of HF incidence, complicating direct comparisons between populations [19, 20]. Moreover, HF and breast cancer share common risk factors, highlighting the importance of risk stratification and promotion of optimal cardiovascular health to prevent cardiotoxicity in this population [21].

Extensive research has investigated HF outcomes in patients with breast cancer compared with cancer-free cohorts. However, the reported incidence of HF varies significantly owing to heterogeneity in post-diagnosis follow-up duration, cancer treatment regimens, and preexisting risk factors. Although numerous studies have compared CVD-related mortality between breast cancer survivors and non-cancer controls, a critical gap remains in understanding the specific impact of CVD on mortality following breast cancer diagnosis. In particular, limited evidence exists regarding the contribution of distinct cardiovascular outcomes (such as ischemic, hypertensive, and pulmonary heart disease; cardiomyopathy; and HF) to overall mortality in this population [22, 23]. This knowledge gap is crucial because a nuanced understanding of

which specific cardiovascular events contribute most significantly to overall and cardiovascular mortality is essential for developing targeted preventative, surveillance, and management strategies tailored to breast cancer survivors.

Despite increasing awareness of cardiovascular complications among breast cancer survivors, real-world evidence on the incidence, trajectory, and clinical outcomes of heart failure (HF) in this population remains limited. In light of this, the present scoping review was conducted to: (1) examine the reported risk of HF, cardiovascular mortality, and all-cause mortality in individuals diagnosed with breast cancer; (2) identify risk factors associated with the development of HF within this population; and (3) explore additional cardiovascular outcomes relevant to breast cancer survivorship. In alignment with the core objectives of a scoping review, this study also aimed to systematically map the breadth and scope of existing literature and to identify key research gaps that warrant further investigation.

To achieve these aims, the review adopted an incidence-based, population-level synthesis of cohort studies, enabling a comprehensive characterization of cardiovascular risk and outcomes across diverse clinical settings. Rather than generating pooled effect estimates, this approach was intended to provide a descriptive overview of available evidence, summarize trends in study designs and outcome measures, and support the formulation of future research priorities. This framework facilitates a multidimensional understanding of cardiovascular risk in breast cancer survivorship and informs strategies for risk stratification, early detection, and targeted prevention in clinical and research contexts.

2. Methods

This review was conducted in accordance with the Joanna Briggs Institute framework, which expands the methodological principles established by Arksey and O'Malley. This approach includes defining a clear research question, setting explicit inclusion and exclusion criteria, and systematically analyzing the literature [24, 25]. Scoping reviews are particularly useful for synthesizing evidence in emerging fields because they incorporate studies with diverse designs and methodologies [26].

A structured protocol was developed prior to the scoping review to ensure methodological rigor, enhance transparency, and support the reproducibility of the findings. The protocol delineated all key components of the review methodology, including research objectives, review questions, eligibility criteria, sources of evidence, a comprehensive search strategy, data extraction procedures, an analytical framework, and predefined plans for managing methodological deviations [27]. Although the protocol was not prospectively registered in a public repository, it was rigorously adhered to throughout the review process and served as an internal benchmark to maintain consistency and validity. This review adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses extension for Scoping Reviews (PRISMA-ScR) to ensure comprehensive, transparent, and methodologically robust reporting in alignment with established best practices for scoping reviews.

Eligibility criteria

The eligibility criteria for this review were established using the Population–Concept–Context.

Population:

Eligible studies included individuals diagnosed with breast cancer, irrespective of histological subtype, disease stage (I–IV), age, or treatment status. The review specifically targeted populations in which the incidence of newly diagnosed heart failure (HF) was reported as an outcome. Studies incorporating a comparison group without breast cancer were also included, as they allowed for the assessment of relative cardiovascular risk between cancer and non-cancer cohorts.

Concept:

The central concept of interest was the occurrence of incident HF in the context of breast cancer. Accordingly, studies were included if they reported newly diagnosed HF events, rather than prevalence data or outcomes related to preexisting cardiovascular disease. Investigations exploring the cardiotoxic effects of breast cancer treatments—such as chemotherapy, radiotherapy, targeted therapies (e.g., HER2-directed agents), or endocrine therapy—were included, provided they focused on the development of HF during or after treatment.

Context:

All healthcare settings and geographical regions were considered, provided that the studies met minimum standards for methodological rigor and reporting quality. To ensure consistency in interpretation, only peer-reviewed articles published in English up to August 2024 were included.

Eligible study designs were limited to analytical observational studies, including prospective and retrospective cohort studies, case-control studies, and analytical cross-sectional studies that reported on incident HF outcomes. Studies were excluded if they (1) focused on HF prevalence or preexisting cardiac conditions, (2) assessed the efficacy of pharmacological interventions or were designed as clinical trials, (3) were published as systematic reviews, meta-analyses, or narrative reviews, or (4) were non-peer-reviewed publications (e.g., editorials, commentaries, conference abstracts), animal studies, or articles published in languages other than English.

This comprehensive set of inclusion and exclusion criteria was designed to capture high-quality primary evidence on the incidence and risk factors of treatment-related HF among individuals with breast cancer, while minimizing bias related to existing cardiovascular comorbidities and ensuring relevance to real-world clinical practice.

Search strategy

The search strategy was designed to comprehensively identify relevant studies through an initial exploratory search of the PubMed, MEDLINE, Cumulative Index to Nursing and Allied Health Literature (CINAHL), and Embase databases using keywords, index terms, and controlled vocabulary extracted from titles, abstracts, and subject headings. The following databases were selected for broad coverage: PubMed and MEDLINE for biomedical and clinical research, CINAHL for nursing and allied health literature, and EMBASE for pharmacological and international biomedical studies. This approach ensured a thorough and unbiased search, capturing diverse perspectives on cardiovascular outcomes and HF in patients with breast cancer. The preliminary search guided the refinement of a systematic search strategy tailored to each database (Additional File 1: Table A1). In addition, the reference lists of the included studies were screened for relevant studies. The search was conducted until October 11, 2024.

Data selection and extraction

All records retrieved from the systematic literature search were imported into EndNote (version X9), and duplicate entries were thoroughly removed. Study selection was conducted in two sequential stages: (1) an initial screening of titles and abstracts based on predefined eligibility criteria, followed by (2) a comprehensive full-text review of potentially relevant articles.

To uphold methodological rigor and enhance transparency, the screening process was independently performed by two reviewers (PA and KM). Both investigators assessed titles, abstracts, and full-text articles. Discrepancies at any stage were resolved through discussion. Where consensus could not be achieved, a third reviewer (AR) was consulted to

adjudicate and ensure uniform application of the inclusion criteria. The overall selection process is illustrated using a PRISMA-compliant flow diagram (Figure X).

Data extraction was also conducted independently by PA and KM using a standardized, pre-tested extraction form developed in Microsoft Excel. This form was designed to ensure consistency, accuracy, and completeness in capturing variables aligned with the review's objectives. No automated software or online platforms were utilized during this process. Disagreements in extracted data were resolved through consensus, with AR serving as a third-party adjudicator when necessary. In cases of missing, ambiguous, or unclear data, corresponding study authors were contacted to obtain clarification.

Extracted variables included study design, setting, sample size, participant demographics, baseline comorbidities, cancer treatment modalities (e.g., chemotherapy, radiotherapy, trastuzumab), cardiovascular outcomes (e.g., incident heart failure, cardiovascular mortality), effect estimates (e.g., hazard ratios), duration of follow-up, and key methodological limitations. A summary of study characteristics and extracted data is presented in Table 1.

Data analysis and presentation

The extracted data were systematically categorized into three key domains to ensure a structured synthesis. General study characteristics, including study design, sample size, patient demographics (e.g., age, sex, and comorbidities), and follow-up duration, were analyzed to assess study heterogeneity and contextualize the findings. Cardiovascular outcomes related to HF in patients with breast cancer were examined based on the incidence, progression, severity, left ventricular ejection fraction, biomarkers, imaging findings, and clinical manifestations. Additionally, data on HF treatment outcomes were synthesized, focusing on the risk, incidence, and effectiveness of therapeutic interventions, including the impact of chemotherapy regimens, cardiotoxicity risk factors, and patient comorbidities. A descriptive synthesis approach was employed, with quantitative data summarized in tables and statistical measures, such as frequencies, percentages, and medians, where applicable. Qualitative findings were analyzed thematically to identify key patterns, and the results were systematically presented in structured tables and narrative summaries to facilitate clarity and cross-study comparisons.

Quality assessment of articles

All included studies underwent formal quality assessment using validated tools appropriate for their study designs to ensure methodological rigor and enhance the credibility of the findings of the review. The Critical Appraisal Skills Programme (CASP) checklist and the National Institutes of Health Quality Assessment Tool for Observational Cohort and Cross-Sectional Studies were employed to evaluate core methodological domains, including clarity of objectives, study design, participant selection, data collection methods, ethical considerations, analytical strategies, and overall contribution to the evidence base [28].

Each study was classified into one of the following four categories: A (high quality; minimal risk of bias), B (moderate quality; minor limitations), C (methodological concerns with potential impact on validity), or D (significant methodological weaknesses or high risk of bias). All 16 included studies received ratings of A, B, or C, reflecting an overall acceptable level of methodological quality. Frequently observed limitations included the incomplete adjustment for confounding variables, reliance on administrative data for outcome classification, and potential misclassification bias.

A detailed summary of the quality assessment outcomes is provided in Additional File 2: Table A2, which supports the reliability of the synthesized evidence and the robustness of the conclusions of the review.

3. Literature search results

The study selection process, as outlined in the PRISMA flow diagram (Figure 1), involved multiple stages of screening and exclusion to ensure the inclusion of relevant studies for the scoping review. Of the 1,429 records identified, 286 duplicates were removed, and 851 studies were excluded after title and abstract screening. Among the 292 full-text articles assessed for eligibility, 276 were excluded because of insufficient data on HF incidence (n = 198), non-relevant study designs (n = 55), or lack of specific data on breast cancer populations (n = 23). Fifteen studies met the inclusion criteria and were thus included.

Characteristics of included studies

The included studies showed substantial variability in demographic characteristics, comorbidities, and treatment patterns among breast cancer populations across diverse geographic regions. Most studies employed large, population-based cohort designs or retrospective analyses utilizing data from national cancer registries and health databases.

The included studies, published between 2007 and 2024, enrolled sample sizes ranging from 294 to 122,000 individuals. Most cohorts comprised women with non-metastatic breast cancer (stages I–III), with follow-up durations of 3 to 19 years. Mean age varied across studies, reflecting demographic heterogeneity. Common comorbidities included dyslipidemia, hypertension, and diabetes. Treatment regimens also varied, with chemotherapy administered in up to 58% and radiotherapy in up to 78.5% of cases. Surgical intervention was the most consistently reported modality, with rates approaching 100% in studies that provided this information (Table 1).

[Insert Table 1 here]

Outcome definitions for incident heart failure (HF) and mortality varied across studies, as detailed in Supplementary Table S1. Most studies identified incident HF using ICD-9 or ICD-10 codes from hospital discharge records, administrative claims, or national registries, with some requiring hospitalization or physician-confirmed diagnoses. Cardiovascular mortality was commonly defined as death due to CV causes based on ICD-coded death certificates or registry data. All-cause mortality was typically obtained from national death records. Despite this variability, all studies estimated hazard ratios using Cox proportional hazards models. These methodological differences may influence the comparability of results across studies.

[Insert Table S1 here]

Of the 15 studies appraised using the CASP tool, 14 were rated as high quality (Grade A) and two as moderate quality (Grade B), with no studies classified as low quality. All the studies adequately addressed the key methodological domains, supporting the overall credibility and robustness of the evidence (Additional File 2: Table A2).

Primary Outcomes: Risk of HF, cardiovascular mortality, and all-cause mortality in breast cancer and non-cancer populations

This review summarized the current evidence on the risk of HF, cardiovascular mortality, and all-cause mortality among individuals with breast cancer compared with non-cancer populations (Table 2).

[Insert Table 2 here]

In most studies, breast cancer survivors exhibited a significantly elevated risk of HF. The reported hazard ratios (HRs) ranged from 0.80 to 2.28. The highest risk was noted by Lam et al. (HR: 2.28; 95% confidence interval [CI]: 1.31–3.95), followed by Lee et al [29]. (HR: 1.40; 95% CI: 1.27–1.54) and Liang et al. [30], who reported a particularly heightened risk within the first year post-diagnosis (HR: 2.71; 95% CI: 1.70–4.33) [29, 30]. Long-term follow-up by Yang et al [15]. demonstrated persistent risk up to 17 years (HR: 1.28; 95% CI: 1.03–1.59) [27]. Similarly, studies by Paterson et al. (2022) and Gue et al. reported a significantly elevated risk of heart failure among breast cancer survivors, with hazard ratios (HRs) of 1.26 (95% CI: 1.20–1.33) and 1.08 (95% CI: 1.04–1.11) [31, 32], respectively. In contrast, only one study—conducted by Hedayati et al. —did not observe an increased risk, reporting an HR of 0.80 (95% CI: 0.34–1.90) [33].

Consistent evidence indicates that all-cause mortality is significantly elevated among breast cancer populations compared to non-cancer controls. Paterson et al. (and Gue et al. (2022) reported notably high hazard ratios of 3.48 (95% CI: 3.38–3.59) and 3.55 (95% CI: 3.47–3.64) [31, 32], respectively. In contrast, findings for cardiovascular mortality were more variable. Paterson et al. (2022) observed a modest but statistically significant increase in cardiovascular mortality risk (HR: 1.14; 95% CI: 1.05–1.23), whereas both Gue et al. (2022) and Hedayati et al. (2020) reported no significant association, with HRs of 0.94 (95% CI: 0.88–1.00) and 0.94 (95% CI: 0.71–1.24), respectively [31-33].. Notably, Koric et al. identified an elevated risk of cardiovascular mortality among long-term survivors beyond 10–15 years post-diagnosis (HR: 1.32; 95% CI: 1.00–1.75), suggesting a potential delayed onset of cardiovascular risk in this population [34].

Secondary outcomes: Risk factors, HF, and other cardiac outcomes in patients with breast cancer

Table 3 presents the adjusted HRs with 95% CIs for HF among patients with breast cancer stratified by demographic factors, comorbidities, cancer stage, and treatment exposure. Age emerged as a significant predictor of HF among patients with breast cancer, with younger and middle-aged individuals exhibiting higher adjusted HRs than older adults. Liang et al. reported HRs of 2.21 for patients aged <50 years, 1.38 for those aged 50–59 years, and 1.03 for those aged ≥60 years. Similarly, Staszewsky et al [35]. observed a pronounced risk in the 50–69 years age group (HR 7.96) relative to patients ≥70 years (HR 1.17), while Lee et al. found elevated risks in individuals aged 51–65 (HR 1.58) and ≥66 years (HR 4.46) [30, 35]. These age-stratified hazard ratios reflect the relative risk of incident heart failure (HF) in breast cancer patients compared to non-cancer controls within each age category, rather than the effect of age within the breast cancer cohort. The findings suggest that the relative impact of breast cancer and its treatments on HF risk is more pronounced in younger individuals, though this does not indicate a higher absolute risk of HF in younger patients. In contrast, Matthews et al [36]. identified only modest associations in older age groups, while Lam et al. [37] reported a small but statistically significant increase (HR 1.1). Comorbidities were independently associated with cardiac events, with diabetes mellitus (HR 2.32, 95% CI: 2.07–2.61), hypertension (HR 1.41, 95% CI: 1.28–1.56), and elevated body mass index (BMI) (HR 1.04, 95% CI: 1.03–1.05) contributing significantly to risk [37].

Cancer stage and systemic therapy were strongly associated with HF. Patients with stage 2 disease (HR 1.18, 95% CI: 1.14–1.21), stage 3 disease (HR 1.56, 95% CI: 1.49–1.64), and advanced or metastatic disease (HR 1.33, 95% CI: 1.07–1.66) had progressively higher risks, while stage 1 was associated with a modestly protective effect (HR 0.95, 95% CI: 0.93–0.97)[36]. Among the treatment modalities, trastuzumab was associated with the greatest increase in risk (HR 2.34, 95% CI: 1.05–5.22), followed by anthracycline-based chemotherapy (HR 1.74, 95% CI: 1.20–2.52) and general

chemotherapy (HR 1.37, 95% CI: 1.23–1.52) [15, 29]. Radiation therapy demonstrated heterogeneous associations across studies, with reported HRs ranging from 0.73 (95% CI: 0.65–0.83) to 1.75 (95% CI: 0.63–4.85), reflecting variability in patient populations and treatment protocols [15, 16, 29, 38].

[Insert Table 3 here]

Table 4 presents adjusted hazard ratios (HRs) and 95% confidence intervals (CIs) for various cardiovascular outcomes among patients with breast cancer, as reported across the included studies. All studies utilized population-based control groups without a history of breast cancer, typically matched or adjusted for age. Covariates included in the multivariable adjustment models are detailed in the final column. While most studies adjusted for age and key cardiovascular risk factors, few explicitly reported adjustment for the competing risk of death, limiting comparability and potentially influencing the accuracy of risk estimates. The incidence of ischemic heart disease was highest during the first year following breast cancer diagnosis (HR: 1.45; 95% CI: 1.03–2.04), with a subsequent decline over time (HR: 1.12; 95% CI: 0.79–1.61 at 1–2 years; HR: 0.79; 95% CI: 0.61–1.03 at 10–17 years) [15]. Atrial fibrillation and other arrhythmias demonstrated the greatest relative risk within the initial year (HR: 2.14; 95% CI: 1.63–2.81), with persistently elevated risk observed up to 17 years post-diagnosis (HR: 1.42; 95% CI: 1.21–1.67). Similarly, stroke and other cerebrovascular events showed a sustained increase in risk (HR: 1.24; 95% CI: 1.00–1.53) [34]. Thromboembolic events, including pulmonary embolism, exhibited some of the strongest associations (HR: 2.65; 95% CI: 2.53–2.77). The risk of ventricular tachycardia or fibrillation approached statistical significance (HR: 1.28; 95% CI: 0.79–2.01) [31, 34]. In addition, elevated risks for coronary artery disease and other heart diseases were reported by Riihimäki et al. (2012) and Khan et al. (2011), with HRs of 1.33 (95% CI: 1.23–1.45) and 1.27 (95% CI: 1.11–1.44), respectively, further highlighting the cardiovascular vulnerability in this population [39, 40].

[Insert Table 4 here]

4. Discussion

This scoping review adds to the expanding corpus of literature elucidating the intersection between breast cancer survivorship and cardiovascular morbidity, particularly heart failure (HF). The findings reinforce robust associations between breast cancer and elevated risks of HF-related, cardiovascular, and all-cause mortality, thereby substantiating prior epidemiological and clinical observations. The pronounced risk of HF-related mortality observed during the early post-diagnosis period underscores the significant influence of oncologic therapies, preexisting comorbidities, and disease-related pathophysiological mechanisms on adverse cardiovascular outcomes [31, 32].

While the overall directionality of cardiovascular risk was consistent across the included studies, the magnitude of effect varied considerably. Reported hazard ratios (HRs) for HF ranged from 0.80 to 2.71, reflecting underlying heterogeneity in study design, population characteristics, therapeutic exposures, and outcome definitions. Particularly salient are the temporally stratified findings by Yang et al.[15], which demonstrated a sharply increased risk of HF within the first year following diagnosis—a period corresponding to intensive treatment exposure—followed by a relative decline in risk over time. These temporal patterns suggest an acute window of heightened vulnerability, likely attributable to the cardiotoxic effects of anthracyclines, HER2-targeted therapies, and thoracic irradiation. Similarly, Paterson et al. and Gue

et al. reported substantially elevated all-cause mortality (HRs >3.4), underscoring the multifaceted burden borne by breast cancer survivors. Conversely, Khan et al. (2011) reported a decreased risk of cardiovascular mortality (HR 0.57), which may reflect survivor bias, differential baseline risk profiles, or competing mortality risks unrelated to cardiovascular disease [31, 32, 40].

The early peak in cardiovascular mortality following diagnosis aligns with the mechanistic trajectory of treatment-related cardiotoxicity. Direct myocardial injury, compounded by systemic inflammation, oxidative stress, and exacerbation of subclinical cardiovascular disease, is well-documented in association with anthracyclines and HER2-targeted agents [41, 42]. While some degree of risk attenuation may occur over time due to therapeutic de-escalation, initiation of cardioprotective interventions, or partial myocardial recovery, the first year following diagnosis emerges as a critical window for cardiovascular surveillance and preventive care.

The excess all-cause mortality observed in breast cancer patients further illustrates the complex interplay between malignancy-related pathophysiology, immunologic dysregulation, and cumulative treatment-related toxicities. Although cardiovascular sequelae constitute a major contributor to excess mortality, the additive effects of tumor progression, treatment complications, and systemic illness are also significant. These findings reaffirm the necessity of a multidisciplinary approach to survivorship care that includes comprehensive cardiovascular risk assessment, particularly as survivors transition beyond the acute treatment phase [43].

This review highlights several key determinants of heart failure (HF) risk among patients with breast cancer, including age, treatment-related exposures, preexisting comorbidities, and cancer stage. The age-stratified hazard ratios reported across studies reflect the relative risk of HF in breast cancer patients compared to non-cancer controls within each age group, rather than the effect of age on HF risk within the breast cancer cohort itself. Notably, the relative risk was highest among younger patients, particularly those under 50 years of age) (e.g., Liang et al., 2024: HR 2.21) [30], suggesting that breast cancer treatments may exert a disproportionately greater cardiotoxic impact in this subgroup. However, older age remains a key determinant of absolute HF risk, as evidenced by studies reporting higher overall HF incidence among older patients (e.g., Lee et al., 2020: HR 4.46 for age ≥66 years) [29],. These findings underscore the multifactorial nature of cardiovascular vulnerability in this population, shaped by both baseline risk and treatment-related effects.

In line with existing evidence, exposure to anthracyclines (HR 1.74) and trastuzumab (HR 2.34) was consistently associated with increased HF risk, reinforcing their well-established cardiotoxic profiles [15-18]. Traditional cardiovascular risk factors, including diabetes mellitus (HR 2.32), hypertension (HR 1.41), and elevated body mass index (HR 1.04), were independently associated with HF, highlighting the cumulative burden of cardiometabolic dysfunction [37, 38]. Moreover, advancing cancer stage was associated with a stepwise increase in HF risk (HR 1.18 for stage 2; HR 1.56 for stage 3), likely reflecting greater exposure to systemic therapies and disease burden [36]. Collectively, these findings emphasize the need for personalized cardiovascular risk assessment and surveillance throughout the cancer continuum. Younger patients, those exposed to high-risk therapies, and individuals with underlying cardiometabolic conditions represent particularly vulnerable subgroups who may benefit from targeted prevention and early intervention strategies.

The findings synthesized in this review highlight the substantial and multifaceted cardiovascular burden experienced by breast cancer survivors, extending well beyond the commonly recognized risk of heart failure. The incidence of ischemic heart disease was most pronounced during the first year following diagnosis, suggesting an acute period of heightened vulnerability likely attributable to the direct cardiotoxic effects of systemic cancer therapies, pro-

inflammatory states, and vascular endothelial injury. In contrast, the sustained elevation in the risk of arrhythmias—particularly atrial fibrillation—indicates potential long-term electrophysiological remodeling and cardiovascular sequelae. However, the observed heterogeneity in cardiovascular mortality estimates across studies may reflect differences in study design, treatment exposure, comparator selection, and methods of outcome ascertainment. Importantly, these findings underscore the imperative for a comprehensive, multidisciplinary approach to survivorship care that proactively incorporates cardiovascular risk stratification, longitudinal monitoring, and preventive strategies. Initiating such efforts during the early phases of treatment and maintaining them throughout long-term follow-up is essential. As survival outcomes in breast cancer continue to improve, the integration of cardio-oncology frameworks into standard clinical care will be critical for mitigating late cardiovascular morbidity and mortality in this growing population.

Strengths and Limitations

This scoping review makes a substantive contribution to the existing literature by synthesizing data from 16 large, population-based cohort studies, thereby enhancing the generalizability of findings across diverse demographic groups. By focusing exclusively on primary research, the review offers a comprehensive mapping of current evidence while minimizing redundancy and the overrepresentation of previously synthesized data. This approach facilitates the identification of emerging trends, research gaps, and underexplored areas, providing a more nuanced understanding of cardiovascular risks in breast cancer survivors.

Key strengths of this review include the large cohort sizes, the racial and ethnic diversity of study populations, and the inclusion of matched non-cancer control groups—all of which enhance the generalizability and external validity of the findings. The incorporation of longitudinal follow-up facilitates a more robust evaluation of long-term cardiovascular risk trajectories and disease progression. Moreover, the emphasis on primary observational and clinical data minimizes the risk of bias associated with secondary analyses, thereby improving the reliability and real-world relevance of the results. Notably, most included studies employed comparable definitions for incident heart failure based on standardized ICD coding systems, and all utilized Cox proportional hazards models to estimate effect sizes—promoting methodological consistency and enabling meaningful cross-study comparisons. While the exclusion of systematic reviews and meta-analyses limited the ability to derive pooled risk estimates or quantitatively assess temporal trends, this deliberate focus on original research reinforces the methodological rigor and applicability of the synthesis.

Despite notable strengths, some limitations merit consideration. Most prominently, substantial methodological heterogeneity across studies may compromise the consistency and comparability of findings. Differences in study populations, follow-up durations, outcome definitions, and statistical approaches limit conclusions about the magnitude and direction of cardiovascular risk. Cardiotoxicity definitions varied widely—from subclinical markers like reduced left ventricular ejection fraction (LVEF) to clinical outcomes such as heart failure, cardiovascular mortality, and hospitalization—affecting both sensitivity and clinical relevance.

Cardiac monitoring protocols and assessment timing were also inconsistent, ranging from systematic echocardiographic surveillance to reliance on administrative or retrospective data. Follow-up durations spanned from two years to nearly two decades, complicating cross-study comparisons. Few studies reported multiple cardiotoxicity endpoints, limiting insights into outcome trajectories or interactions. Additionally, many used retrospective designs, had small sample sizes, and lacked adequate adjustment for confounders, introducing selection bias and reducing internal validity.

Younger individuals and racially minoritized populations were consistently underrepresented, highlighting the need for more inclusive research to improve generalizability. Methodologically, most studies used population-based controls without breast cancer, typically matched or adjusted for age and/or sex. However, only a subset accounted for competing risks from non-cardiovascular death, which may influence the accuracy of cause-specific cardiovascular risk estimates, particularly in long-term survivorship. Variability in cardiovascular mortality estimates likely reflects differences in study design, treatment exposure, comparator selection, and outcome ascertainment.

Together, these limitations underscore the need for standardized cardiotoxicity definitions, harmonized monitoring protocols, robust adjustment strategies—including for competing risks—and consistent comparator frameworks to support meaningful synthesis and guide evidence-based practice in cardio-oncology.

Clinical implications and future directions

Cardiovascular disease remains the leading cause of non-cancer mortality among breast cancer survivors, underscoring the urgent need for a paradigm shift toward integrated cardio-oncology care. While this scoping review did not undertake a meta-analytic synthesis, several studies suggest a possible decline in heart failure (HF) incidence in recent years, potentially reflecting heightened clinical awareness, enhanced surveillance practices, and the adoption of cardioprotective strategies. Pharmacologic agents such as beta-blockers and angiotensin-converting enzyme (ACE) inhibitors have shown efficacy in high-risk populations; however, additional randomized trials are required to determine the optimal timing, dosing, and patient selection to maximize therapeutic benefit while minimizing unnecessary exposure [41, 42, 44].

Multidisciplinary cardio-oncology services—incorporating cardiovascular risk assessment, biomarker surveillance, advanced imaging, and individualized lifestyle interventions—represent a promising model for early detection and risk mitigation. These frameworks are especially critical for patients receiving anthracyclines, trastuzumab, and other known cardiotoxic therapies. Nevertheless, implementation remains variable across institutions, and robust real-world evaluations are needed to assess clinical effectiveness and scalability [45, 46].

To address current evidence gaps and improve long-term outcomes, future research should prioritize the harmonization of outcome definitions, the inclusion of racially and ethnically diverse populations, and the systematic collection of long-term cardiovascular endpoints. Prospective cohort studies and collaborative consortia will be essential to enable pooled analyses, improve statistical power, refine risk prediction tools, and guide the development of evidence-based clinical guidelines for cardioprotective care.

Emerging areas of investigation include the use of novel biomarkers, advanced cardiac imaging modalities, and digital health technologies to facilitate personalized risk stratification and longitudinal monitoring. There is also increasing interest in developing precision medicine tools that integrate genomic, proteomic, and imaging data to enable real-time cardiovascular risk assessment and inform individualized intervention strategies.

In conclusion, this review highlights the persistent fragmentation within the current evidence base while delineating key priorities for both clinical practice and future research. A coordinated and inclusive research agenda—centered on population diversity, therapy-specific cardiotoxicity, and the integration of multidisciplinary care models—will be critical to advancing cardio-oncology and improving cardiovascular outcomes in breast cancer survivorship.

5. Conclusions

Breast cancer survivors face a substantially increased risk of heart failure and all-cause mortality, with additional cardiovascular complications such as ischemic heart disease, atrial fibrillation, and thromboembolism emerging early in survivorship and persisting long-term. These risks are exacerbated by cardiotoxic therapies, advanced cancer stage, and preexisting cardiometabolic conditions. The findings underscore the urgent need for integrated cardio-oncology strategies, including early risk stratification, personalized surveillance, and preventive interventions, to mitigate long-term cardiovascular morbidity and mortality in this growing population.

Abbreviations

BMI: body mass index

CASP: Critical Appraisal Skills Programme

CI: confidence interval

CINAHL: Cumulative Index to Nursing and Allied Health Literature

CVD: cardiovascular disease

HER2: human epidermal growth factor receptor 2

HF: heart failure

HRs: hazard ratios

PRISMA: Preferred Reporting Items for Systematic reviews and Meta-Analyses

Declarations

Ethics approval and consent to participate

Not applicable.

Consent for publication

Not applicable.

Availability of data and materials

The data analyzed in this scoping review were obtained exclusively from publicly accessible, previously published studies identified through a comprehensive literature search. Relevant summary data extracted from the included studies are presented in the Additional Files to enhance transparency and reproducibility. No individual-level participants or proprietary datasets were used in this study. Additional details and data can be provided by the corresponding author upon request.

Competing interests

The authors declare that they have no competing interests.

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Authors' Contributions

PV and AR conceived the original idea for this study. PV, FG, and KJM designed the study. PV and SA performed the article screening, data extraction, and data analysis, whereas AR resolved discrepancies during the article selection process. PV and AR interpreted data and results. All the authors contributed to the intellectual content of the manuscript, critically revised the manuscript, and approved the final version.

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Not applicable.

Additional Files

Additional File 1: Search strategy

.docx

Table A1

Additional File 2: Quality assessment checklist: CASP Tool

.docx

Table A2

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615

616 **Table 1: Baseline characteristics of the studies**

Author	Year	Country (database)	Study design	Data source(s)	Population	Control	Study (year)	Sample size	Comparison group (N)	Mean age (year)	Diabetes (%)	Hypertension (%)	Other underlying diseases	Chemotherapy (%)	Radiotherapy (%)	Surgery (%)
Liang et al. [30]	2024	UK	A large, population-based cohort study	The UK Biobank	Women with breast cancer	Healthy (Non–Breast Cancer) Control	12 (2006-2018)	16241	235036	58.9 ± 7.3	4.9	53.2	Obesity (24.2%)			
Yang et al. [15]	2022	Sweden	A large, population-based cohort study	The Stockholm-Gotland Breast Cancer Registry	All patients diagnosed with non-metastatic breast cancer (Stages I–III)	Healthy (Non–Breast Cancer) Control	7 (2001-2008)	8015	8015					41.5	78.5	99
Paterson et al. [31]	2022	Canada	A large, population-based cohort study	The Alberta Cancer Registry	Women with breast cancer	Healthy (Non–Breast Cancer) Control	11 (2007-2018)	29407	4295227							
Koric et al. [34]	2022	USA	A large, population-based cohort study	The Utah Population Database (UPDB)	Women with breast cancer	Healthy (Non–Breast Cancer) Control	12 (1997- 2009)	6641	36612					43.9%	55.7%	99.5 %
Gue et al. [32]	2021	France	A retrospective longitudinal cohort study	Utilizing the national hospitalization database covering hospital care	Women with breast cancer	Healthy (Non–Breast Cancer) Control	6 (2013-2019)	64480	1424286	63.0 ±13.7	9.1	27.7	Dyslipidemia (10.3%), thyroid diseases (8.2%), obesity (10.1), anemia (10%)			
Matthews et al. [36]	2021	USA	A large, population-based cohort	The Surveillance, Epidemiology, and End Results (SEER)-Medicare Database	All women with an incident stage I–III breast cancer diagnosis	Healthy (Non–Breast Cancer) Control	9 (2004-2013)	91473	454197	75(70–81) *	20.2	48.9	Rheumatoid diseases (2.3%), chronic kidney disease (3.3%)			
Staszewsky et al. [35]	2020	Italy	A population-based retrospective cohort study	Puglia Region	Women with breast cancer	Healthy (Non–Breast Cancer) Control	7 (2007-2014)	18165	18165	61.0±14.3	11.5	45.8	Dyslipidemia (15.2%), arrhythmia (4.0%), heart diseases (1.4%)			
Lee et al. [29]	2020	Korea	A population-based retrospective cohort study	National Health Information Database	Women with breast cancer	Healthy (Non–Breast Cancer) Control	8 (2005-2013)	91227	273 681	49.1±10.1	6.6	19.3	Dyslipidemia (12.2%)			
Lam et al. [37]	2020	USA	A large, population-based cohort	The WHI National Health Study	Postmenopausal women (ages 50 to 79 years)	Healthy (Non–Breast Cancer)	5 (1993-1998)	2188	44174	63±7	38	50	Dyslipidemia (14%), stroke (2%), peripheral artery disease (25%)			

						Control										
Hedayati et al. [33]	2020	Sweden	A large, population-based cohort	The SwedeHF	Heart failure diagnosis population	Healthy (Non–Breast Cancer) Control	5 (2008-2013)	294	1470	77(68–85)*	15.6	52	Heart failure			
Ng et al. [47]	2018	Canada	A retrospective cohort study	The provincial linked administrative health datasets from British Columbia, Canada	Women with breast cancer	Healthy (Non–Breast Cancer) Control	13 (2000-2013)	12127	23102				Any cardiovascular conditions (39%), pain/inflammation (34.8%), gastric acid disorders (18.4%), hyperlipidemia (16.2%)			
Abdel-Qadir et al. [48]	2019	Canada	A population-based, retrospective cohort study	The Ontario Health Insurance Plan (OHIP)	Early-stage breast cancer	Healthy (Non–Breast Cancer) Control	10 (2005-2015)	78318	234954	61(51–72)*	16.6	47	CKD (3%), COPD (4.9%), cerebrovascular disease (2.7%), IHD (8.0%)			
Riihimaki et al. [39]	2011	Sweden	A large, population-based cohort	The Swedish Family-Cancer Database	Women with breast cancer	Healthy (Non–Breast Cancer) Control	19 (1987-2006)	122 217	3554 255							
Khan et al. [40]	2011	UK	A matched cohort analysis of longitudinal primary care records comparing cancer survivors and controls	The UK General Practice Research Database (GPRD)	Patients who survived at least five years after a diagnosis of breast, colorectal, or prostate cancer	Healthy (Non–Breast Cancer) Control	3 (2003-2006)	16938	67649	66.9±12.3						
Hooning et al. [38]	2007	Netherland	a Large, Population-Based Cohort	The Netherlands Cancer Institute (NKI) or the Erasmus Medical Centre, Daniel den Hoed Cancer Centre (DDHK)	Female breast cancer survivors diagnosed before the age of 71 years and treated for Stage I, II, or IIIA disease.	Healthy (Non–Breast Cancer) Control	16 (1970-1986)	942	4414	49	9	26	Hypercholesterolemia (10%).	58		12

CKD, chronic kidney disease; COPD, chronic obstructive pulmonary disease; IHD, ischemic heart disease

* Median (interquartile range).

620 **Table 2: Primary outcomes: Risk of heart failure, cardiovascular mortality, and all-cause mortality in breast cancer populations**

Author	Heart Failure (HR [95% CI])	CV Mortality (HR [95% CI])	All-Cause Mortality (HR [95% CI])	Incident HF / Rate (per 100 PY) [95% CI]	Mean Follow-up (years)	Adjustment Variables used in analyses
Liang et al. [30]	1.20 (1.09–1.33)				12.8	Age, ethnicity, education, smoking, alcohol use, obesity, physical activity, LDL cholesterol, depressed mood, hypertension, diabetes, and use of antihypertensives, antidiabetics, and statins.
Yang et al. [15]	<1 year: 2.71 (1.70–4.33) 1–2 years: 2.07 (1.27–3.37) 10–17 years: 1.28 (1.03–1.59)				10.8	Age and year of diagnosis, menopausal status, Charlson comorbidity index, clinical stage, tumor size, surgery type, history of hypertension, chronic pulmonary disease, tobacco use, and all treatment variables.
Paterson et al. [31]	1.26 (1.20-1.33)	1.14 (1.05-1.23)	3.48 (3.38-3.59)		11.8	Baseline age, sex, neighborhood deprivation, rural/urban residence, distance to cancer center and family doctor, and 31 comorbidities (including heart failure, diabetes, hypertension, depression, chronic pulmonary disease, stroke/TIA, and others).
Koric et al. [34]	>10-15 years: 0.96 (0.71-1.31)	>10-15 years: 1.32 (1.00-1.75)			12	Baseline Charlson Comorbidity Index (CCI), BMI, tobacco use, race, ethnicity, birth year, and birth state.
Gue et al. [32]	1.079 (1.04–1.11)	0.94 (0.88–1.00)	3.554 (3.47– 3.64)		5.1	Age and cardiovascular risk factors using multivariable adjustment and propensity score–matched analysis.
Matthews et al. [36]	1.07 (1.06 -1.09)	0.96(0.95 - 0.98)			4	Age, region, time since index, calendar year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and prior cardiovascular disease (excluding the outcome of interest).
Staszewsky et al. [35]	3 years: 1.47 (1.14–1.90)				4	Unadjusted analysis
Lee et al. [29]	1.396 (1.27–1.54)				3.1	Age, income, prior diabetes, hypertension, and dyslipidemia.
Lam et al. [37]	2.28 (1.31–3.95)				14	Age-adjusted analysis
Hedayati et al. [33]	0.80 (0.34–1.90)	0.94 (0.71–1.24)	1.04 (0.83–1.29)		2	Age-adjusted analysis
Ng et al. [47]	1.23 (1.14–1.32)			1.45 (1.36–1.54)	13	Age, Diabetes, hypertension, hyperlipidemia, ischemic heart disease, TIA, cerebrovascular disease, renal failure, atrial fibrillation, and COPD.
Abdel-Qadir et al. [48]	1.21 (1.14–1.29)				5.7	Age, income, and history of diabetes, hypertension, and dyslipidemia.
Riihimaki et al. [39]	1.38 (1.31–1.46)				10	Age-adjusted analysis
Khan et al. [40]	1.95 (1.27–3.01)			0.57 (0.50 – 0.65)	5	Smoking and BMI to account for potential confounding effects.
Hooning et al. [38]				0.95 (0.85 – 1.04)	18	Age, race, cancer stage, year of diagnosis, pre-existing heart disease, and comorbidities.

621 CI, confidence interval; HF, heart failure

Table Legend:Hazard ratios (HRs) reflect the relative risk of each outcome among breast cancer survivors compared to either non-cancer control populations or the lowest exposure group within the respective study, unless otherwise specified. ‘Incident HF Cases / Incidence Rate’ denotes the number of newly diagnosed heart failure cases and the corresponding incidence rate per 100 person-years. Incidence rates were not calculable in studies where relevant data were unavailable. Mean follow-up duration is presented as reported in each study.

Table 3: Adjusted Hazard Ratios (HRs) for Risk Factors and Underlying Associations with Heart Failure in Patients with breast cancer (95% CI)

Author (Year)	Age	Treatment with anthracyclines	Treatment with trastuzumab	Chemotherapy	Radiation	Hormonal treatment	BMI	Hypertension	DM	Cancer staging
Liang et al. [30]	<50 years: 2.21 (1.55–3.17) 50–59 years: 1.38 (1.13–1.69) ≥60 years: 1.03 (0.90–1.19)									
Yang et al. [15]		1.74 (1.20–2.52)	2.34 (1.05–5.22)		1.75 (0.63–4.85)					
Matthews et al. [36]	66–75 years: 1.24 (1.21–1.28)									Stage 1: 0.95 (0.93–0.97)
	75–85 years: 1.02 (1.00–1.04)									Stage 2: 1.18 (1.14–1.21)
	>85 years: 1.01 (0.98–1.04)									Stage 3: 1.56 (1.49–1.64)
Staszewsky et al. [35]	< 50 years: 6.18 (0.74–51.31) 50–69 years: 7.96 (2.81–22.55) ≥ 70 years: 1.17 (0.88–1.55)									
Lee et al. [29]	Age (51-65 years): 1.578 (1.351–1.843) Age (≥66 y): 4.455 (3.699–5.366)	1.24 (1.07–1.44)	1.225 (1.03–1.464)		0.73 (0.65–0.83)					
Lam et al. [37]	1.1 (1.09-1.1)						1.04 (1.03–1.05)	1.41 (1.28–1.56)	2.32 (2.07–2.61)	
Hooning et al. [38]				0.78 (0.45–1.37)	1.47 (1.04–2.08)	1.60 (1.16–2.20)		1.35 (1.03–1.76)	1.13 (0.78–1.63)	

BMI, body mass index;
DM, diabetes mellitus

Table 4. Adjusted Hazard Ratios (HRs) for Risk of Other Cardiovascular Outcomes in Patients with Breast Cancer Compared to Population-Based Controls (95% CI)

Author (Year)	Ischemic heart disease/myocardial infraction*	Atrial fibrillation/cardiac arrhythmia	Cerebrovascular incidence/stroke	Thrombosis/ pulmonary embolism	Coronary artery disease/other heart disease	Ventricular tachycardia or fibrillation	Bleeding	Adjustment Variables used in analyses
Yang et al. [15]	<1 year: 1.45 (1.03–2.04)	<1 year: 2.14 (1.63–2.81)						Age and year of diagnosis, menopausal status, Charlson comorbidity index, clinical stage, tumor size, surgery type, hypertension, chronic pulmonary disease, tobacco use, and all treatment variables.
	1–2 years years: 1.12 (0.79–1.61)	1-2 years: 1.08 (0.76–1.53)						
	10–17 years: 0.79 (0.61–1.03)	10–17 years: 1.42 (1.21–1.67)						
Paterson et al. [31]	0.98 (0.87–1.10)		1.16 (1.10–1.22)	2.65 (2.53–2.77)				Baseline age, sex, neighborhood deprivation, rural/urban status, distance to cancer center and family doctor, and 31 comorbidities including heart failure, diabetes, hypertension, atrial fibrillation, COPD, depression, stroke/TIA, and others.
Koric et al.[34]	1.02 (0.62–1.68)	0.96 (0.76–1.22)	1.24 (1.00–1.53)	0.65 (0.19–2.20)		1.28 (0.79–2.01)		Baseline Charlson Comorborbidity Index (CCI), BMI, tobacco use, race, ethnicity, birth year, and birth state.
Gue et al. [32]	0.811 (0.746– 0.881)		0.849 (0.792– 0.910)				1.425 (1.362–1.491)	Age and cardiovascular risk factors using multivariable adjustment and propensity score–matched analysis.
Matthews et al.[36]	0.97 (0.94 to 1.00)	1.09 (1.07–1.10)	0.98 (0.97–1.00)	1.61 (1.55–1.66)				Age, race/ethnicity, SEER region, time since index, calendar year, rheumatoid arthritis, chronic kidney disease, hypertension, diabetes, and prior cardiovascular disease
Staszewsky et al. [35]	1.01 (0.74– 1.38)	0.82 (0.50–1.33)				1.24 (0.38– 4.05)		**Unadjusted analysis**
Ng et al. [47]	1.09 (1.03–1.16)		1.05 (0.92–1.21)					Diabetes, hypertension, hyperlipidemia, ischemic heart disease, heart failure, transient ischemic attack, renal failure, and atrial fibrillation.
Abdel-Qadir et al. [48]	0.99 (0.94–1.05)	1.31 (1.23–1.39)	1.10 (1.04–1.17)					Age, income, and history of diabetes, hypertension, and dyslipidemia.
Riihimaki et al. [39]	1.02 (0.95–1.09)		1.09 (1.03–1.16)		1.33 (1.23–1.45)			Age-adjusted analysis
Khan et al. [40]					1.27 (1.11–1.44)			Smoking and BMI to account for potential confounding.
Hooning et al. [38]	1.23 (1.08–1.39)							Age, race, cancer stage, year of diagnosis, pre-existing heart disease, and comorbidities.

CI: confidence interval

Footnote: The incidence of cardiac outcomes was assessed over different follow-up durations across the studies. Yang et al. [14]: 10.8 years; Paterson et al. [30]: 11.8 years; Koric et al. [34]: 12 years; Gue et al. [31]: 5.1 years; Matthews et al. [36]: 4 years; Staszewsky et al. [35]: 4 years; Ng et al. [47]: 13 years; Abdel-Qadir et al. [48]: 5.7 years: Riihimaki et al. [49]: 10 years; Khan et al. [50]: 5 years; and Hooning et al. [38]: 18 years.

***Ischemic heart disease (IHD) and coronary artery disease (CAD) are reported according to the terminology used in the original studies. While frequently used interchangeably, IHD may refer to a broader spectrum of myocardial ischemia beyond anatomically defined obstructive coronary artery disease.**

Table Supplementary 1. Outcome Definitions and Statistical Methods for Incident HF and Mortality Across Included Studies

Author (Year)	Outcome Definition	**Statistical Method**
Liang et al. [30]	**Incident Heart Failure (HF):** Defined as the first diagnosis of HF (ICD-10) based on UK Biobank first occurrence data. **Mortality:** Defined as death with a primary or contributing cause coded under ICD-10, obtained from linked national death registry records	Hazard ratios were calculated using Cox proportional hazards models.
Yang et al. [15]	**Incident Heart Failure (HF):** First recorded diagnosis of heart failure (ICD-10), identified from hospital records or national health registries; the event date reflects the earliest documented occurrence. **Cardiovascular Mortality:** Death with a primary or contributing cause coded under ICD-10, obtained from linked national death registry data.	Hazard ratios were calculated using Cox proportional hazards models.
Paterson et al. [31]	**Incident Heart Failure (HF):** First recorded diagnosis of heart failure during follow-up, identified using registry data. **Cardiovascular (CV) Mortality:** Defined as death attributed to cardiovascular causes, classified using ICD-10 codes.	Hazard ratios were calculated using Cox proportional hazards models.
Koric et al. [34]	**Incident Heart Failure (HF) and Mortality Outcomes:** Identified using **ICD-9/10 codes** from **Utah statewide hospital and ambulatory surgery databases**.	Hazard ratios were calculated using Cox proportional hazards models.
Gue et al. [32]	**Incident Heart Failure (HF):** First recorded diagnosis of heart failure during follow-up, identified using registry data. **Cardiovascular (CV) Mortality:** Defined as death attributed to cardiovascular causes, classified using ICD-10 codes.	Hazard ratios were calculated using Cox proportional hazards models.
Matthews et al. [36]	**Incident HF and Mortality Outcomes:** Identified using **ICD-9 and HCPCS codes** from claims data; both **composite and individual cardiovascular outcomes** were evaluated.	Hazard ratios were calculated using Cox proportional hazards models.
Staszewsky et al. [35]	**Incident HF:** New diagnosis identified from hospital discharge records using ICD-9/10-CM codes. **Mortality:** All-cause and cardiovascular mortality based on death certificates; CV death defined if listed among the first seven contributing causes.	Hazard ratios were calculated using Cox proportional hazards models.
Lee et al. [29]	**Incident HF:** New diagnosis of congestive heart failure (ICD-10) accompanied by a hospitalization claim. **Mortality:** All-cause mortality identified from death records.	Hazard ratios were calculated using Cox proportional hazards models.
Lam et al. [37]	**Incident HF:** First hospitalization for definite or possible acute decompensated heart failure; women with chronic HF at baseline were excluded.	Hazard ratios were calculated using Cox proportional hazards models.

	Mortality: Cause of death centrally adjudicated and classified as cardiovascular, cancer-related, other, or unknown, supported by National Death Index data.	
Hedayati et al. [33]	**Incident HF and Mortality Outcomes:** Diagnoses identified using ICD-9/10 codes from national health registers. **Mortality:** All-cause and cause-specific (cardiovascular and HF-related) mortality determined via linkage with the Swedish Cause of Death Register.	Hazard ratios were calculated using Cox proportional hazards models.
Ng et al. [47]	**Incident HF:** Identified using ICD-9/10 codes from linked provincial health databases, including the BC Cancer Registry and Medical Services data. **Mortality:** All-cause mortality determined from death records or inferred from lack of subsequent healthcare data; follow-up ended at death or last recorded encounter.	Hazard ratios were calculated using Cox proportional hazards models.
Abdel-Qadir et al. [48]	**Incident HF:** Defined as hospitalization for heart failure, identified via linked Canadian administrative databases, including the Discharge Abstract Database and the National Ambulatory Care Reporting System. **Mortality:** Defined using ICD-9 and ICD-10 codes	Hazard ratios were calculated using Cox proportional hazards models.
Riihimaki et al. [39]	**Incident HF:** Identified using ICD-9 and ICD-10 codes from national health registers. **Mortality:** Defined using ICD-9 and ICD-10 codes from the Swedish Cause of Death Register, based on both underlying and multiple contributing causes of death.	Hazard ratios were calculated using Cox proportional hazards models.
Khan et al. [40]	**Incident HF:** New diagnosis of heart failure during the study period, identified using ICD-9/10 codes. **Mortality:** Determined from death records using ICD-9/10 codes.	Hazard ratios were calculated using Cox proportional hazards models.
Hooning et al. [38]	**Incident HF:** First diagnosis of congestive heart failure (CHF) during follow-up, identified using ICD-9 codes. **Mortality:** Determined from ICD-9-coded cause of death and analyzed using Cox models, stratified by treatment type and period.	Hazard ratios were calculated using Cox proportional hazards models.

Figure Legend

Figure 1: PRISMA Flow Chart Outlining Selection of Sources of Evidence