

Cardiovascular outcomes in breast cancer survivors: a systematic review and meta-analysis

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Abstract

Background: It is unclear whether the future risk of cardiovascular events in breast cancer survivors is greater than in the general population.

Objectives: This meta-analysis reports the incidence of cardiovascular events in patients with breast cancer, before quantifying the risk of cardiovascular disease development in breast cancer patients, compared to the risk in a general matched cancer-free population.

Methods: We searched PubMed, Scopus, and Web of Science databases (up to March 23, 2022) for observational studies and post-hoc analyses of RCTs. Cardiovascular death, heart failure (HF), atrial fibrillation (AF), coronary artery disease (CAD), myocardial infarction (MI), stroke were the individual endpoints for our meta-analysis. We pooled incidence rates (IRs) and risk in hazard ratios (HRs), using random-effects meta-analyses. Heterogeneity was reported through the I^2 statistic, and publication bias was examined using funnel plots and Egger's test in the meta-analysis of risk.

Results: 142 studies were identified in total, 116 (2,111,882 patients) relevant to incidence rate, and 26 (836,301 patients) relevant to risk. The pooled IR for cardiovascular death was 1.73 (95% CI 1.18, 2.53), 4.44 (95% CI 3.33, 5.92) for HF, 4.29 (95% CI 3.09, 5.94) for CAD, 1.98 (95% CI 1.24, 3.16) for MI, 4.33 (95% CI 2.97, 6.30) for stroke of any type, and 2.64 (95% CI 2.97, 6.30) for ischemic stroke. Compared to matched cancer-free controls, breast cancer patients had higher risk for cardiovascular death within five years of cancer diagnosis (HR=1.09; 95% CI: 1.07, 1.11), HF within ten years (HR=1.21; 95% CI: 1.1, 1.33), and AF within three years (HR=1.13; 95% CI: 1.05, 1.21).

Conclusion: Breast cancer exposure was associated with the increased risk for cardiovascular death, HF and AF. The pooled incidence for cardiovascular endpoints varied depending on population characteristics and endpoint studied.

Lay Abstract

This work investigated the absolute and relative risk of cardiovascular outcomes in breast cancer survivors.

- The incidence for cardiovascular death, heart failure (HF), and coronary artery disease were 1.73, 4.44, and 4.29 per 1000 person-years, respectively.
- Breast cancer was associated with a higher risk of cardiovascular death, HF, and atrial fibrillation when compared to the general population.
- Clinicians should carefully assess breast cancer survivors for their cardiovascular risk factor profile and monitor their cardiovascular function.

Keywords: Breast Cancer, Cardiovascular Diseases, Heart Disease Risk Factors, Epidemiology, Incidence, Systematic Review.

Registration: CRD42022298741

Introduction

Breast cancer (BC) accounts for approximately one in four of all incident cancers in women and represents the most common cause of cancer related mortality in women,¹ with a lifetime probability of developing BC of one in eight.² Advances in the treatment of BC, as well as earlier diagnosis has meant that the 5-year survival of BC patients has risen to over 90%² with close to 3 million BC survivors in the United States.³ As patients with BC survive to older age, cardiovascular diseases (CVD) are increasingly recognised as an important cause of morbidity and mortality⁴ in this population, with older women diagnosed with early-stage BC more likely to die from CVD than cancer.⁵ This increased risk relates to shared risk factors,⁶ common pathophysiological pathways and cardiovascular toxicity of many therapies used to treat BC including conventional chemotherapies,^{7,8,9} targeted therapies,⁸ immunotherapies¹⁰ and radiotherapy.

Whilst several studies have reported cardiovascular outcomes in case-only studies amongst BC survivors,^{5,11–15} increasingly literature has compared cardiovascular outcomes in this group of patients to the general cancer-free population. The cardiovascular outcomes reported vary according to the length of follow-up following BC diagnosis, nature of CVD event and cardiotoxic BC treatments received.^{16–18} The relationships between BC and future risk of cause-specific CVD are complex with inconsistent data published, with reported increases in future heart failure (HF) risk,^{19,20} increases,²¹ decreases¹⁹ and no effects²² on future coronary heart disease risk and both increases²³ and no significant changes in future stroke risk.¹⁹

There is a need to quantify the future cardiovascular risk associated with BC for appropriate risk stratification and for informing service planning and provision in this population of patients. We therefore conducted this meta-analysis to evaluate the risk for the development of cause specific CVD in BC patients compared to those in the general matched

cancer-free population, how it varies in time and investigate the incidence of cardiovascular events in patients with BC.

Materials and methods

The systematic review was conducted according to the prospectively registered protocol ([CRD42022298741](#)). The methods are described in detail in Supplementary Materials. Briefly, PubMed, Web of Science, Scopus were the principal sources for the systematic search. The predetermined endpoints were cardiovascular mortality, HF, coronary artery disease (CAD), myocardial infarction (MI), any stroke, ischemic or hemorrhagic stroke, and atrial fibrillation (AF, Central Illustration). We conducted data extraction and risk of bias evaluation within the Systematic Review Database Repository Plus web platform.²⁴ The Newcastle-Ottawa scale was applied for risk of bias assessment.²⁵

We pooled incidence rates (IRs) using a generalized linear mixed model based on a Poisson-Normal assumption, with maximum likelihood estimation and inverse-variance weighting.²⁶ The relative risk was pooled using pairwise random-effects meta-analyses, with hazard ratios (HRs) as effect estimates. Publication bias for the risk meta-analyses was assessed using Egger's test and through the visual inspection of funnel plots.

We also conducted leave-one-out sensitivity analyses for meta-analyses of HRs and IRs with significant results. The between-study heterogeneity was estimated with the I^2 statistic. The potential reasons for heterogeneity were investigated within subgroup and meta-regression analyses if possible. All statistical analyses were conducted with R programming language.

Results

We identified 142 studies in total, with 26 articles (836,301 patients, Central Illustration)^{16,17,21–23,27–27} relevant to the first aim and 116 reports (2,111,882 patients) for the second aim only (Supplementary References). The flow diagram is described in Figure 1 and Supplementary Table S1-S2. The baseline characteristics for the studies are presented in Table 1 and Supplementary Table S3. The majority of studies included in the meta-analysis of HRs were of retrospective design. Thirteen were derived from North America while 4 studies were conducted in Asia and the remaining 9 studies were of European origin. The reported follow-up time ranged from 1 to 11.8 years. The studies included patients with mean age from 47.7 to 77 years old. Baseline clinical characteristics was heterogeneous with a prevalence of diabetes mellitus (DM) ranging from 2.2 to 29.9%, hypertension from 5.4 to 72%, dyslipidemia from 3.8 to 65.5. The studies varied in terms of BC stage (ductal carcinoma in situ ranged from 0 to 100%). In addition, reported treatment of BC varied across the studies (radiotherapy, 38.9-100%; chemotherapy, 20-53.2%; any endocrine therapy, 32-80%; tamoxifen, 9.9-53%; other aromatase inhibitors, 19.3-46.3%; anthracycline, 32.9-62.5%; trastuzumab, 7.5-12.7%).

For studies with IRs, 77 out of 116 reports were retrospective cohort studies, 14 were prospective cohort studies, and 23 were post hoc analyses of randomized controlled trials. The studies varied widely with respect to mean age (46-76.8 years), prevalence of cardiovascular risk factors (DM, 2-69%; hypertension, 0.6-85%; dyslipidemia, 0.9-46.7), BC stage (ductal carcinoma in situ, 0-100%), and treatment (surgery, 45.9-100%; chemotherapy, 0-100%; any endocrine treatment, 1.5-100%; tamoxifen use, 0.9-87.4%; other aromatase inhibitor use, 8.3-100%; anthracycline, 0-100%; trastuzumab, 0-100%; radiotherapy, 4.5-100%).

Regarding the risk of bias assessment (Table 2), the majority of studies for the relative risk of CVD were based on large administrative electronic health record systems,

therefore, we rated them as low risk of bias due to representativeness of the exposed cohort and selection of non-exposed cohorts. The BC diagnosis was mainly based on international codes of diseases retrieved from medical records, hence the studies were unlikely to be biased due to ascertainment of exposure. Some studies did not provide data on the prevalence of outcome of interest before follow-up commencement. Consequently, we rated these studies as with uncertain or high risk of bias. Since outcomes definitions were mainly based on record linkage through administrative health databases, the studies were of low risk of bias due to ascertainment of outcome. All studies reported sufficient follow-up duration. The follow-up rate was unclear in some investigations, so were rated with uncertain risk of bias due to adequacy of follow-up. The details of quality assessment of studies for the second aim could be found in Supplementary Table S4.

3.1. The risk of cardiovascular outcomes in BC patients as compared to the general matched cancer-free population.

Patients with BC were more likely to die from CVD as compared to matched healthy cancer-free counterparts (HR 1.09, 95% CI 1.07-1.11) during the first 5 years following BC diagnosis (Figure 2). Leave-one-out sensitivity analyses further support these findings (Supplementary Table S5). However, the difference in cardiovascular death risk between BC and the general matched cancer-free population was not statistically significant in the period between 8 to 11 years following BC diagnosis (HR 1.23, 95% CI 0.99-1.52).

Furthermore, individuals with BC demonstrated a higher risk of HF as compared to matched healthy non-cancer controls in a period from 1 to 2 years (HR 1.21, 95% CI 1.1-1.33), 2 to 5 years (HR 1.22, 95% CI 1.11-1.33), and 5 to 10 years (HR 1.19, 95% CI 1.1-1.29) of follow-up (Figure 3). The results were robust after the use of Knapp and Hartung adjustment and leave-one-out sensitivity (Supplementary Table S5). In contrast, the results

for the HF risk during the 1st year from index diagnosis were less persistent (HR 1.29, 95% CI 1.03-1.63), with statistical significance lost after the Knapp and Hartung adjustment (HR 1.29, 95% CI 0.87-1.91) and sensitivity analyses (Figure 3, Supplementary Table S5).

BC patients experienced higher rates of AF compared to cancer-free controls for the first three years of follow-up after index diagnosis (up to 3 months: HR 1.64, 95% CI 1.18-2.26; from 3 months to 3 years: HR 1.13, 95% CI 1.05-1.21, Figure 4). The statistical significance remained after the use of the Knapp and Hartung adjustment and leave-one-out sensitivity analyses (Supplementary Table S5). The risk of AF beyond three years could not be assessed due to the lack of published reports.

Meta-analysis showed a comparable risk of CAD in both cohort from the index date to 5 years and from 5 years to 8 years of follow-up (HR 0.97, 95% CI 0.90-1.02; HR 1.01, 95% CI 0.92-1.10, respectively, Supplementary Figure S1). The analyses demonstrated some trends for the reduced risk of MI in BC cohorts in comparison with that of cancer-free controls for the first 2 years of follow-up, however, these results were derived only from maximum likelihood estimation (Supplementary Figure S2). Moreover, these results were not robust during leave-one-out sensitivity analyses (Supplementary Table S5).

There was also no significant association between BC and the risk of any stroke during 8 years from the index date (HR 0.99, 95% CI 0.83-1.19, Supplementary Figure S3). Similarly, we did not find any significant relationship between BC and the risk of ischemic stroke (HR 1.19, 95% CI 0.94-1.51, Supplementary Figure S4). For hemorrhagic stroke, meta-analyses were not conducted, as only two studies reported effect estimates. Overall, the certainty of evidence for the first aim of our meta-analysis was graded as moderate.

3.2. The incidence of cardiovascular outcomes in BC patients.

We conducted separate meta-analyses for regional and nationwide studies that were part of the Surveillance, Epidemiology, and End Results (SEER) Program to prevent the

situation when the same cohort of patients contributes several times to overall results. If recruitment periods of nationwide SEER-based studies coincide, we include them consequently one after another.

The pooled IR for cardiovascular death was 1.73 per 1000 person-years (95% CI 1.18-2.53) when only regional SEER-based studies were included (Figure 5). The findings were similar (IR 1.53, 95% CI 0.97-2.39, Supplementary Figure S5) with a nationwide SEER-based study. Leave-one-out sensitivity analyses and analyses with other studies on the same cohorts provided similar results (Supplementary Tables S6,7). The cardiovascular mortality was substantially higher in the study by Wildiers et al (IR 21.74, 95%CI 7.01-67.4) that can be related to unique inclusion criteria (metastatic BC patients treated with trastuzumab). Exclusion of this study did not impact on overall results (IR 1.65, 95% CI 1.13-2.41, Supplementary Figure S6).

The mean incidence of HF was 4.44 per 1000 person-years (95% CI 3.33-5.92, Supplementary Figure S7) with regional SEER-based studies. Incorporation of the nationwide SEER-based study with the longest follow-up did not alternate these results (IR 4.52, 95% CI 3.35-6.1, Supplementary Figure S8). All types of sensitivity analyses provided similar data (Supplementary Tables S6,7). The analysis without the study by Wildiers et al gave a pooled estimate of 4.32 per 1000 person-years (95% CI 3.24-5.74). The rank correlation test for funnel plot asymmetry was not significant ($p = 0.39$, Supplementary Figure S6).

The pooled IR for CAD was 4.29 per 1000 person-years of follow-up (95% CI 3.09-5.94, Supplementary Figure S9). The rank correlation test for funnel plot asymmetry did not indicate any significant publication bias ($p=0.21$). Sensitivity analyses provided similar results (Supplementary Table 6,7).

The average IR for MI was 1.98 per 1000 person-years (95%CI 1.24-3.16, Supplementary Figure S10). The incidence was 2.16 (95% CI 1.23-3.79, Supplementary

Figure S11) with the nationwide SEER-based cohort. Sensitivity analyses were consistent with the main analysis with no evidence for publication bias (Supplementary Figure S6).

The overall IR for stroke of any type was 4.33 per 1000 person-years (95% CI 2.97-6.30, Supplementary Figure S12). Sensitivity analyses provided approximately the same mean IRs (Supplementary Table S6,7).

The pooled incidence for ischemic stroke was 2.64 per 1000 person-years of follow-up (95% CI 1.79-3.92, Supplementary Figure S13). The mean IR for AF was 12.95 per 1000 person-years (95% CI 12.60-13.31, Supplementary Figure S14) with only 2 studies included. Due to the low number of studies, we could not estimate the average incidence for hemorrhagic stroke.

In summary, the pooled IRs for cardiovascular death, HF, CAD, MI, stroke, ischemic stroke, and AF were 1.73 (95% CI 1.18-2.53), 4.44 (95% CI 3.33-5.92), 4.29 (95% CI 3.09-5.94), 1.98 (95% CI 1.24-3.16), 4.33 (95% CI 2.97-6.30), 2.64 (95% CI 1.79-3.92), and 12.95 (95% CI 12.60-13.31), respectively. A high heterogeneity was observed for all analyses (Supplementary Table S8-9). Mean age, proportion of patients with DM, hypertension, tumour size more than 5 cm, stage 4 of BC, surgery, and chemotherapy were found to be statistically significant for at least 2 outcomes, however, the residual heterogeneity was still high. The incidence of cardiovascular death and MI was higher in studies with a more elderly population. The studies with a greater proportion of patients with DM demonstrated higher rates for HF, CAD, and MI. Also, the pooled IRs for CAD and MI were positively associated with a prevalence of hypertension. Paradoxically, death from cardiovascular causes occurred more often in studies with a lower proportion of subjects with tumour size more than 5 cm. However, the opposite trend was observed for HF. The average incidences for cardiovascular death and HF were also positively correlated with a percentage of patients with stage 4 BC. Patients were more likely to die from cardiovascular causes or develop CAD in studies with

more frequent use of surgery or chemotherapy. Surgery was also associated with a lower incidence for HF.

The incidences of cardiovascular death, HF, and MI were higher in observational studies rather than in randomized controlled trials. Also, the pooled IRs of cardiovascular death and stroke were higher in non-Asian countries compared to those from Asian countries (p value for subgroup differences 0.02, 0.05, respectively).

Discussion

Our meta-analysis is the first to evaluate the future risk of cause-specific CVD development in BC patients in comparison to those in general matched non-cancer populations, how this risk varies over time and to investigate the cause-specific incidence of cardiovascular events in patients with BC. We report that compared to the general matched non-cancer population, BC was associated with an increased risk for cardiovascular death, HF and AF, but not CAD, MI, or ischemic stroke. Furthermore, using data derived from 116 studies including 2,111,882 patients we estimate a pooled IR for cardiovascular death of 1.73 per 1000 person-years, for HF 4.44 per 1000 person-years, for CAD and MI 4.29 and 1.98, per 1000 person-years, and for stroke and AF 4.33 and 12.95 per 1000 person-years, respectively. Finally we report that there was a significant association between the IRs for many of the cardiovascular outcomes assessed and tumour size, advanced tumour stage (stage 4), and chemotherapy.

Our analysis suggests that BC is associated with an increased relative risk of 20% of HF within the first year of diagnosis and persists for at least 10 years thereafter. Interestingly, meta-regression did not show an association between oestrogen receptor positivity, tumour grade or HER2 positivity with incident HF rates, although there was a significant association with stage 4 cancer. Anthracyclines and trastuzumab that are used to treat patients with BC

are cardiotoxic, contributing to an increased risk of HF in BC survivors^{9,41} with the risk increasing with increasing cumulative doses of anthracyclines. Doxorubicin interacts with DNA, binding to topoisomerase II β and disrupting DNA repair, causing myocyte cell death.⁴⁸ Anthracyclines also form complexes with intracellular iron, generating oxygen radicals which damage DNA, proteins, and the mitochondrial membrane.⁴⁹ Trastuzumab, pertuzumab and T-DMI are monoclonal antibodies that inhibit the signalling of HER2 (human epidermal growth factor receptor 2). Trastuzumab binds to the extracellular domain of the ErbB2 tyrosine kinase receptor leading to inhibition of ErbB2 signalling. Cardiac dysfunction associated with trastuzumab is a direct consequence of ErbB2 inhibition in cardiac myocytes.⁵⁰ HF associated with these cancer therapies may have a different trajectory / prognosis than that influence through interaction with pre-existing CVD and traditional cardiovascular risk factors.

In an analysis of administrative data from Ontario, Canada, women diagnosed with HF after receiving anthracyclines or trastuzumab were matched on age and important HF prognostic factors to cancer-free HF controls.⁵¹ Women developing HF following chemotherapy for BC had fewer comorbidities such as ischemic heart disease, DM, chronic kidney disease or hypertension compared to cancer-free controls. The prognosis of HF related to the chemotherapeutic agent used, women developing HF after trastuzumab-based chemotherapy had a lower risk of HF hospitalisations than cancer-free HF controls, although the anthracycline-HF cohort had similar risk to matched controls. Trastuzumab related HF may have better outcomes compared to the cancer free HF control because it is often reversible, in contrast to the less-reversible cardiotoxicity associated with anthracyclines.⁵²

We also report a time dependent increase in the risk of AF in patients with BC. The increased risk of AF associated with BC was greatest in the first 3 months following BC diagnosis (HR 1.64, 95% CI 1.18-2.26) but is lower in the longer term (from 3 months to 3 years: HR 1.13, 95% CI 1.05-1.21). Similarly, a population-based, retrospective, matched

cohort study conducted in Toronto, Ontario, Canada, of 68 113 women diagnosed with EBC who were matched 1:3 to a cancer-free control group showed that the greatest risk of AF was greatest in the first year but persisted in periods of follow up of greater than 5 years.⁴⁰ This increased risk may be multifactorial. The increased risk of HF observed in this population may predispose patients to an increase in the risk of AF. The stress of BC diagnosis, surgery, cardiotoxic cancer therapies and electrolyte disturbances triggered by cytotoxic chemotherapeutic agents may all predispose to AF, although the study highlighted above suggested that the relative rate of AF was higher in patients with stage III disease and chemotherapy exposure but was not specifically increased by treatment with cardiotoxic agents.⁴⁰

Our analysis suggests that patients with BC are not at increased relative risk of CAD development or future MI. Nevertheless, we were unable to assess whether this risk was modified by use of chemotherapy, radiotherapy to the left chest or prevalent CVD, although in our meta-regression analysis there was a significant association between prevalent CVD and incident rate of CAD, and DM and MI. Nearly two-thirds of BCs are hormone-receptor positive. Older postmenopausal women are at higher baseline risk of CAD, making them more susceptible to agents that CAD risk. Aromatase inhibitors are often used in postmenopausal women with hormone-receptor positive BC for up to 10 years depending BC risk.⁵³ Aromatase inhibitors are associated with worse hypertension control, dyslipidemia, and endothelial dysfunction that may lead to a higher risk of MI and cardiovascular mortality compared to estrogen receptor modulators such as tamoxifen.⁵⁴ Radiotherapy can damage vascular endothelial and smooth muscle cells, leading to impaired vascular tone, inflammatory activation, fibrosis and vascular calcification contributing to the development of CAD, the risk of which increases with radiation dose.^{55,56}

There are a number of emerging strategies that may mitigate the risk of cardiotoxicity in patients with BC. Dexrazoxane has been used as a primary prevention treatment to protect against anthracycline cardiotoxicity. Its mode of action is complex, including prevention of doxorubicin binding to topoisomerase II β and cardiotoxicity. A meta-analysis of 7 trials estimated a 65% (RR, 0.35; 95% CI, 0.27–0.45) reduction in cardiac events with dexrazoxane versus placebo,^{57,58} and it is now recommended for high risk patients in the recent ESC 2022 guideline for cardio-oncology.⁵⁹ Administration of doxorubicin via infusion as opposed to bolus administration is associated with a significant decrease in the risk of symptomatic cardiotoxicity (OR, 4.13; 95% CI, 1.75–9.72 for bolus administration versus infusion) without loss of efficacy.⁶⁰

The increased risk of cardiovascular death may be reduced by aggressive treatment of traditional cardiovascular risk factors in this population such as hypertension, DM, dyslipidemia, and lifestyle. Management of blood pressure, glucose, and hypercholesterolemia and treatment of tobacco abuse should follow current international guidelines and use of statins in patients with BC includes the same indications as in primary and secondary prevention of CVD.^{61,62} Baseline risk assessment, primary and secondary prevention and new surveillance pathways and early detection are now recommended in the 2022 ESC guidelines for cardio-oncology.⁵⁹

Several limitations should be considered when interpreting our meta-analysis. We were unable to perform meta-regression and subgroup analyses for the first aim of our meta-analysis due to the small number of included reports. The definitions of cardiovascular outcomes differed widely across the primary studies, explaining some of the substantial heterogeneity of the observed results. Furthermore, the majority of investigations were retrospective with inadequate reporting of baseline patient information. This prevented us

from investigating the relationship between cardiovascular outcomes and a variety of relevant variables (type of surgery, used therapeutic agents, for example).

Conclusion

BC was related with a higher risk of cardiovascular death, HF, and AF when compared to the general population, but not CAD, MI, or ischemic stroke. Furthermore, using data from 116 studies involving 2,111,882 patients, we estimate a pooled IR of 1.73 per 1000 person-years for cardiovascular death, 4.44 per 1000 person-years for HF, 4.29 and 1.98 per 1000 person-years for CAD and MI, and 4.33 and 12.95 per 1000 person-years for stroke and AF, respectively. BC survivors should have careful assessment of their cardiovascular risk factor profile and future CVD risk, with guideline recommended treatment to target risk factors, and careful longer-term monitoring of cardiovascular function.

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Conflict of interest

None

Authors' Contributions

MAM is an author of the idea and conceptualised the study design. AG, SI, HNT, MA, MK, ET, MAM designed the study and wrote the study protocol. AG, SI, HNT, BO conducted systematic search, study selection, extraction and risk of bias assessment. AG performed statistical analyses. MAM, MP, EK supervised statistical analyses. AG and MAM drafted the manuscript. MAM, MA, BK, ARL, MK, ET, MP, EK, HAQ supervised the writing. All authors had full access to the data. All authors participated in the interpretation of the results, review and approval of the paper, and the decision to submit it for publication. The corresponding author attests that all listed authors meet authorship criteria and that no others meeting the criteria have been omitted.

Data availability statement

Data and programming codes related to this article can be obtained from the GitHub profile.

References

- 1 Sung H, Ferlay J, Siegel RL, *et al.* Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. *CA Cancer J Clin* 2021;71:209–49.
- 2 Siegel RL, Miller KD, Fuchs HE, *et al.* Cancer statistics, 2022. *CA Cancer J Clin* 2022;72:7–33.
- 3 de Moor JS, Mariotto AB, Parry C, *et al.* Cancer survivors in the United States: prevalence across the survivorship trajectory and implications for care. *Cancer Epidemiol Biomark Prev Publ Am Assoc Cancer Res Cosponsored Am Soc Prev Oncol* 2013;22:561–70.
- 4 Raisi-Estabragh Z, Kobo O, Freeman P, *et al.* Temporal trends in disease-specific causes of cardiovascular mortality amongst patients with cancer in the USA between 1999 to 2019. *Eur Heart J Qual Care Clin Outcomes* 2022;;qcac016.
- 5 Abdel-Qadir H, Austin PC, Lee DS, *et al.* A population-based study of cardiovascular mortality following early-stage breast cancer. *JAMA Cardiol* 2017;2:88–93.
- 6 Koene RJ, Prizment AE, Blaes A, *et al.* Shared Risk Factors in Cardiovascular Disease and Cancer. *Circulation* 2016;133:1104–14.
- 7 Hamid A, Anker MS, Ruckdeschel JC, *et al.* Cardiovascular Safety Reporting in Contemporary Breast Cancer Clinical Trials. *J Am Heart Assoc* 2022;;e025206.
- 8 Moslehi JJ. Cardiovascular Toxic Effects of Targeted Cancer Therapies. *N Engl J Med* 2016;375:1457–67.
- 9 Kastora SL, Pana TA, Sarwar Y, *et al.* Biomarker Determinants of Early Anthracycline-Induced Left Ventricular Dysfunction in Breast Cancer: A Systematic Review and Meta-Analysis. *Mol Diagn Ther* 2022;26:369–82.
- 10 Curigliano G, Cardinale D, Suter T, *et al.* Cardiovascular toxicity induced by chemotherapy, targeted agents and radiotherapy: ESMO Clinical Practice Guidelines. *Ann*

Oncol Off J Eur Soc Med Oncol 2012;23 Suppl 7:vii155-166.

- 11 Chapman J-AW, Meng D, Shepherd L, *et al.* Competing causes of death from a randomized trial of extended adjuvant endocrine therapy for breast cancer. *J Natl Cancer Inst* 2008;100:252–60.
- 12 Colzani E, Liljegren A, Johansson ALV, *et al.* Prognosis of patients with breast cancer: causes of death and effects of time since diagnosis, age, and tumor characteristics. *J Clin Oncol Off J Am Soc Clin Oncol* 2011;29:4014–21.
- 13 Du XL, Fox EE, Lai D. Competing causes of death for women with breast cancer and change over time from 1975 to 2003. *Am J Clin Oncol* 2008;31:105–16.
- 14 Hanrahan EO, Gonzalez-Angulo AM, Giordano SH, *et al.* Overall survival and cause-specific mortality of patients with stage T1a,bN0M0 breast carcinoma. *J Clin Oncol Off J Am Soc Clin Oncol* 2007;25:4952–60.
- 15 Roychoudhuri R, Robinson D, Putcha V, *et al.* Increased cardiovascular mortality more than fifteen years after radiotherapy for breast cancer: a population-based study. *BMC Cancer* 2007;7:9.
- 16 Ramin C, Schaeffer ML, Zheng Z, *et al.* All-Cause and Cardiovascular Disease Mortality Among Breast Cancer Survivors in CLUE II, a Long-Standing Community-Based Cohort. *J Natl Cancer Inst* 2021;113:137–45.
- 17 Bradshaw PT, Stevens J, Khankari N, *et al.* Cardiovascular Disease Mortality Among Breast Cancer Survivors. *Epidemiol Camb Mass* 2016;27:6–13.
- 18 Florido R, Daya NR, Ndumele CE, *et al.* Cardiovascular Disease Risk Among Cancer Survivors: The Atherosclerosis Risk In Communities (ARIC) Study. *J Am Coll Cardiol* 2022;80:22–32.
- 19 Strongman H, Gadd S, Matthews A, *et al.* Medium and long-term risks of specific cardiovascular diseases in survivors of 20 adult cancers: a population-based cohort study

- using multiple linked UK electronic health records databases. *Lancet Lond Engl* 2019;394:1041–54.
- 20 Thavendiranathan P, Abdel-Qadir H, Fischer HD, *et al.* Breast Cancer Therapy-Related Cardiac Dysfunction in Adult Women Treated in Routine Clinical Practice: A Population-Based Cohort Study. *J Clin Oncol Off J Am Soc Clin Oncol* 2016;34:2239–46.
- 21 Ng HS, Vitry A, Koczwara B, *et al.* Patterns of comorbidities in women with breast cancer: a Canadian population-based study. *Cancer Causes Control* 2019;30:931–41.
- 22 Chang JS, Shin J, Park E-C, *et al.* Risk of cardiac disease after adjuvant radiation therapy among breast cancer survivors. *Breast* 2019;43:48–54.
- 23 Navi BB, Reiner AS, Kamel H, *et al.* Association between incident cancer and subsequent stroke. *Ann Neurol* 2015;77:291–300.
- 24 Galimzhanov A, Sedralmontaha I, Tun HN, *et al.* Breast cancer and cardiovascular outcomes. Syst. Rev. Data Repos. <https://sdr.ahrq.gov/> (accessed 27 May 2022).
- 25 Wells GA, Wells G, Shea B, *et al.* The Newcastle-Ottawa Scale (NOS) for Assessing the Quality of Nonrandomised Studies in Meta-Analyses. 2014.
- 26 Stijnen T, Hamza TH, Özdemir P. Random effects meta-analysis of event outcome in the framework of the generalized linear mixed model with applications in sparse data. *Stat Med* 2010;29:3046–67.
- 27 D’Souza M, Smedegaard L, Madelaire C, *et al.* Incidence of atrial fibrillation in conjunction with breast cancer. *Heart Rhythm* 2019;16:343–8.
- 28 Riihimäki M, Thomsen H, Brandt A, *et al.* Death causes in breast cancer patients. *Ann Oncol Off J Eur Soc Med Oncol* 2012;23:604–10.
- 29 Staszewsky L, Robusto F, Lepore V, *et al.* Cardiovascular mortality and morbidity burden in successive and age pre-stratified case-control cohorts of breast cancer women. A population-based study. *Breast Cancer Res Treat* 2020;183:177–88.

- 30 Lamont EB, Christakis NA, Lauderdale DS. Favorable cardiac risk among elderly breast carcinoma survivors. *Cancer* 2003;98:2–10.
- 31 van Herk-Sukel MPP, Shantakumar S, Kamphuisen PW, *et al.* Myocardial infarction, ischaemic stroke and pulmonary embolism before and after breast cancer hospitalisation. A population-based study. *Thromb Haemost* 2011;106:149–55.
- 32 Khan NF, Mant D, Carpenter L, *et al.* Long-term health outcomes in a British cohort of breast, colorectal and prostate cancer survivors: a database study. *Br J Cancer* 2011;105 Suppl 1:S29-37.
- 33 Ligibel JA, James O'Malley A, Fisher M, *et al.* Risk of myocardial infarction, stroke, and fracture in a cohort of community-based breast cancer patients. *Breast Cancer Res Treat* 2012;131:589–97.
- 34 Lash TL, Thwin SS, Yood MU, *et al.* Comprehensive evaluation of the incidence of late effects in 5-year survivors of breast cancer. *Breast Cancer Res Treat* 2014;144:643–63.
- 35 Park N-J, Chang Y, Bender C, *et al.* Cardiovascular disease and mortality after breast cancer in postmenopausal women: Results from the Women's Health Initiative. *PLoS One* 2017;12:e0184174.
- 36 Reiner AS, Navi BB, DeAngelis LM, *et al.* Increased risk of arterial thromboembolism in older men with breast cancer. *Breast Cancer Res Treat* 2017;166:903–10.
- 37 Saliba W, Rennert HS, Gronich N, *et al.* Association of atrial fibrillation and cancer: Analysis from two large population-based case-control studies. *PloS One* 2018;13:e0190324.
- 38 Andersen KK, Olsen TS. Risk of Ischemic and Hemorrhagic Strokes in Occult and Manifest Cancers. *Stroke* 2018;49:1585–92.
- 39 Wadsten C, Wennstig A-K, Garmo H, *et al.* Risk of ischemic heart disease after radiotherapy for ductal carcinoma in situ. *Breast Cancer Res Treat* 2018;171:95–101.

- 40 Abdel-Qadir H, Thavendiranathan P, Fung K, *et al.* Association of early-stage breast cancer and subsequent chemotherapy with risk of atrial fibrillation. *JAMA Netw Open* 2019;2:e1911838.
- 41 Abdel-Qadir H, Thavendiranathan P, Austin PC, *et al.* The risk of heart failure and other cardiovascular hospitalizations after early stage breast cancer: A matched cohort study. *J Natl Cancer Inst* 2019;111:854–62.
- 42 Lee J, Hur H, Lee JW, *et al.* Long-term risk of congestive heart failure in younger breast cancer survivors: A nationwide study by the SMARTSHIP group. *Cancer* 2020;126:181–8.
- 43 Wennstig A-K, Wadsten C, Garmo H, *et al.* Long-term risk of ischemic heart disease after adjuvant radiotherapy in breast cancer: results from a large population-based cohort. *Breast Cancer Res* 2020;22:10.
- 44 Yoo T-K, Park SH, Do Han K, *et al.* Cardiovascular events and mortality in a population-based cohort initially diagnosed with ductal carcinoma in situ. *BMC Cancer* 2021;21:735.
- 45 Guha A, Fradley MG, Dent SF, *et al.* Incidence, risk factors, and mortality of atrial fibrillation in breast cancer: a SEER-Medicare analysis. *Eur Heart J* 2022;43:300–12.
- 46 Paterson DI, Wiebe N, Cheung WY, *et al.* Incident Cardiovascular Disease Among Adults With Cancer: A Population-Based Cohort Study. *JACC CardioOncology* 2022;4:85–94.
- 47 Yang H, Bhoo-Pathy N, Brand JS, *et al.* Risk of heart disease following treatment for breast cancer - results from a population-based cohort study. *eLife* 2022;11:e71562.
- 48 Lenneman CG, Sawyer DB. Cardio-Oncology: An Update on Cardiotoxicity of Cancer-Related Treatment. *Circ Res* 2016;118:1008–20.
- 49 Childs AC, Phaneuf SL, Dirks AJ, *et al.* Doxorubicin treatment in vivo causes cytochrome C release and cardiomyocyte apoptosis, as well as increased mitochondrial efficiency, superoxide dismutase activity, and Bcl-2:Bax ratio. *Cancer Res* 2002;62:4592–8.
- 50 Hahn VS, Lenihan DJ, Ky B. Cancer therapy-induced cardiotoxicity: basic mechanisms

- and potential cardioprotective therapies. *J Am Heart Assoc* 2014;3:e000665.
- 51 Abdel-Qadir H, Tai F, Croxford R, *et al*. Characteristics and Outcomes of Women Developing Heart Failure After Early Stage Breast Cancer Chemotherapy: A Population-Based Matched Cohort Study. *Circ Heart Fail* 2021;14:e008110.
- 52 Nathan PC, Amir E, Abdel-Qadir H. Cardiac Outcomes in Survivors of Pediatric and Adult Cancers. *Can J Cardiol* 2016;32:871–80.
- 53 Mayer EL, Burstein HJ. Postmenopausal breast cancer: a best endocrine strategy? *Lancet Lond Engl* 2015;386:1317–9.
- 54 Khosrow-Khavar F, Filion KB, Bouganim N, *et al*. Aromatase Inhibitors and the Risk of Cardiovascular Outcomes in Women With Breast Cancer: A Population-Based Cohort Study. *Circulation* 2020;141:549–59.
- 55 Darby SC, Ewertz M, McGale P, *et al*. Risk of ischemic heart disease in women after radiotherapy for breast cancer. *N Engl J Med* 2013;368:987–98.
- 56 Abdel-Qadir H, Amir E, Fischer HD, *et al*. The risk of myocardial infarction with aromatase inhibitors relative to tamoxifen in post-menopausal women with early stage breast cancer. *Eur J Cancer*. 2016 Nov;68:11-21.
- 57 Kalam K, Marwick TH. Role of cardioprotective therapy for prevention of cardiotoxicity with chemotherapy: a systematic review and meta-analysis. *Eur J Cancer Oxf Engl* 1990 2013;49:2900–9.
- 58 Abdel-Qadir H, Ong G, Fazelzad R, Amir E, Lee DS, Thavendiranathan P, Tomlinson G. Interventions for preventing cardiomyopathy due to anthracyclines: a Bayesian network meta-analysis. *Ann Oncol*. 2017 Mar 1;28(3):628-633.
- 59 Lyon AR, López-Fernández T, Couch LS, Asteggiano R, Aznar MC, Bergler-Klein J, *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): Developed by the task force on cardio-oncology of the European Society of Cardiology (ESC), *Eur Heart J*, 2022; ehac244.

60 Smith LA, Cornelius VR, Plummer CJ, *et al.* Cardiotoxicity of anthracycline agents for the treatment of cancer: systematic review and meta-analysis of randomised controlled trials. *BMC Cancer* 2010;10:337.

61 Arnett DK, Blumenthal RS, Albert MA, *et al.* 2019 ACC/AHA Guideline on the Primary Prevention of Cardiovascular Disease: A Report of the American College of Cardiology/American Heart Association Task Force on Clinical Practice Guidelines. *Circulation* 2019;140:e596–646.

62 Visseren FLJ, Mach F, Smulders YM, *et al.* 2021 ESC Guidelines on cardiovascular disease prevention in clinical practice. *Eur Heart J* 2021;42:3227–337.

Figure legends

Figure 1. Flow-diagram of the meta-analysis.

Figure 2. The risk of cardiovascular death in patients with breast cancer compared to those in the general population. PMID, PubMed identification number; CI, confidence interval; RE, random-effects model; REML, restricted maximum likelihood; ML, maximum likelihood; KNHA, Knapp and Hartung adjustment.

Figure 3. The risk of heart failure in patients with breast cancer compared to those in the general population. A. during the first year after breast cancer diagnosis; B. 1-2 years after breast cancer diagnosis; C. 2-5 years after breast cancer diagnosis; D. 5-10 years after breast cancer diagnosis.

PMID, PubMed identification number; CI, confidence interval; RE, random-effects model; REML, restricted maximum likelihood; ML, maximum likelihood; KNHA, Knapp and Hartung adjustment.

Figure 4. The risk of atrial fibrillation in patients with breast cancer compared to those in the general population. PMID, PubMed identification number; CI, confidence interval; RE, random-effects model; REML, restricted maximum likelihood; ML, maximum likelihood; KNHA, Knapp and Hartung adjustment.

Figure 5. The incidence rate of cardiovascular death in breast cancer patients per 1000 person-years of follow-up. In this analysis, regional SEER-based studies were included. PMID, PubMed identification number; FU, follow-up (person-years); CI, confidence interval; RE, random effects; REML, restricted maximum likelihood.

Graphical abstract. Main findings. AF, atrial fibrillation; CAD, coronary artery disease; CV, cardiovascular; HF, heart failure; MI, myocardial infarction. Parts of the figure were drawn by using pictures from Servier Medical Art. Servier Medical Art by Servier is

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