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FULL RESEARCH PAPER
Cancer

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

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Aims It is unclear whether the future risk of cardiovascular events in breast cancer (BC) survivors is greater than in the general population. This meta-analysis quantifies the risk of cardiovascular disease development in BC patients, compared to the risk in a general matched cancer-free population, and reports the incidence of cardiovascular events in patients with BC.

Methods and results We searched PubMed, Scopus, and Web of Science databases (up to 23 March 2022) for observational studies and *post hoc* analyses of randomized controlled trials. Cardiovascular death, heart failure (HF), atrial fibrillation (AF), coronary artery disease (CAD), myocardial infarction (MI), and 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. One hundred and forty-two studies were identified in total, 26 (836 301 patients) relevant to the relative risk and 116 (2 111 882 patients) relevant to IRs. Compared to matched cancer-free controls, BC patients had higher risk for cardiovascular death within 5 years of cancer diagnosis [HR = 1.09; 95% confidence interval (CI): 1.07, 1.11], HF within 10 years (HR = 1.21; 95% CI: 1.1, 1.33), and AF within 3 years (HR = 1.13; 95% CI: 1.05, 1.21). 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 ischaemic stroke.

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.

Registration CRD42022298741.

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

- Breast cancer was associated with a higher risk of cardiovascular death, heart failure (HF), and atrial fibrillation when compared to the general population.

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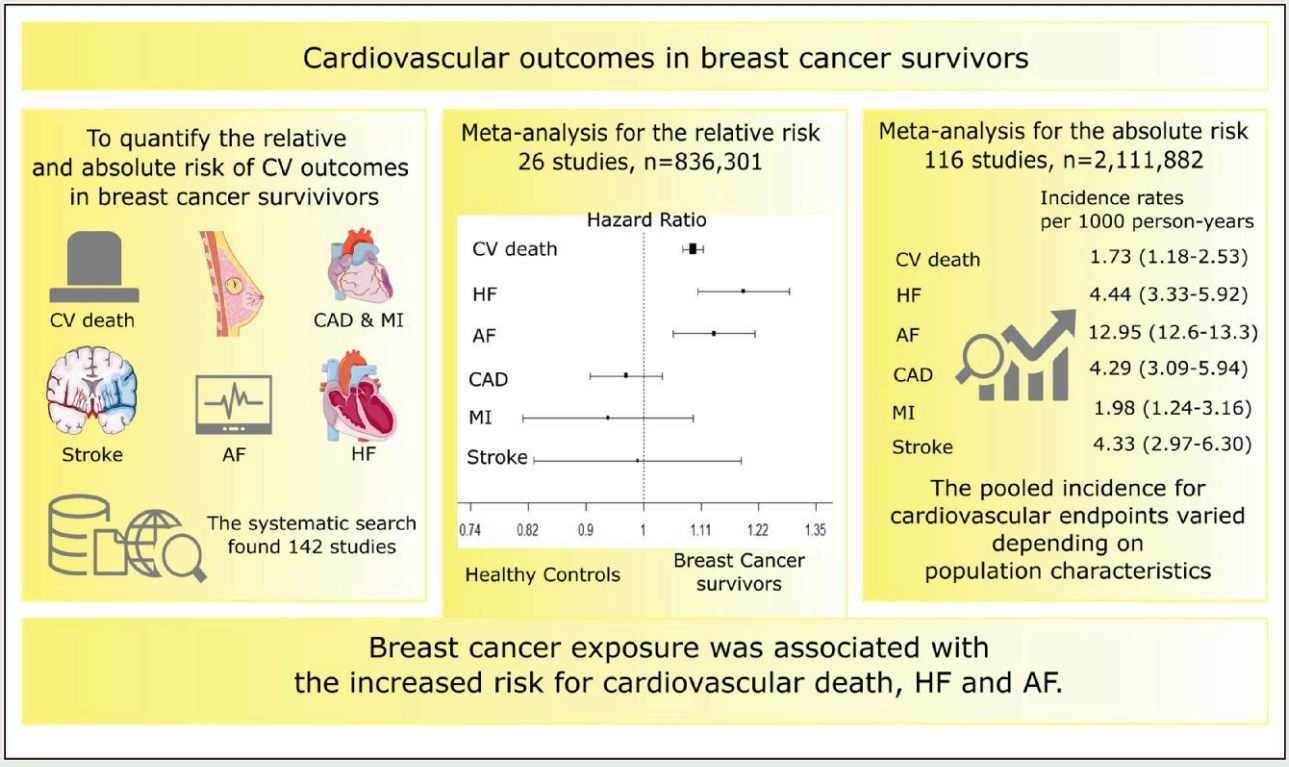
- The incidence for cardiovascular death, HF, and coronary artery disease were 1.73, 4.44, and 4.29 per 1000 person-years, respectively.
- Clinicians should carefully assess breast cancer survivors for their cardiovascular risk factor profile and monitor their cardiovascular function.

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 licensed under a Creative Commons Attribution 3.0 Unported License (https://creativecommons.org/licenses/by/3.0/).

Keywords Breast cancer • Cardiovascular diseases • Heart disease risk factors • Epidemiology • Incidence • Systematic review

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, have meant that the 5-year survival of BC patients has risen to over 90%[2] with close to 3 million BC survivors in the USA.[3] As patients with BC survive to older age, cardiovascular diseases (CVD) are increasingly recognized as an important cause of morbidity and mortality[4] 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] immunotherapies,[10] and radiotherapy.

While several studies have reported cardiovascular outcomes in case-only studies among 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] decreases,[19] and no effects[22] on future coronary heart disease risk, and both increases[23] 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.

Methods

The systematic review was conducted according to the prospectively registered protocol (CRD42022298741). We followed the principles described in the Preferred Reporting Items for Systematic Reviews and Meta-Analyses

statement.[24] Both a traditional keyword-based and citation-based systematic search were performed. PubMed, Web of Science, and Scopus were the principal sources for the systematic search. The search in the main databases was relaunched before the statistical analyses (up to 23 March 2022). We also explored study registries, journal websites, BioMed Explorer, Dimensions, and international meeting proceedings to retrieve additional publications.[25]

The citation-based search was conducted on CoCites, Connected Papers, and SnowGlobe.[26,27] We did not apply any filters based on language or dates of publications. The flowchart for the search strategy was created with a ShinyApp web tool.[28]

Aims of the meta-analysis

We conducted this meta-analysis in order to address two main goals:

(1) To compare the risk of cardiovascular outcomes in BC population and those in a general matched cancer-free population.
(2) To estimate the incidence rates (IRs) of cardiovascular endpoints in patients with BC.

Screening

For the first aim of our systematic review, the publications were selected if they reported the risk of cardiovascular outcomes in patients with BC at different stages as compared to those in the general matched cancer-free population. Given the heterogeneity of the meta-analysis, the matching criteria were different across the included studies. For the second aim, we retrieved studies that provided original data on the incidence of cardiovascular outcomes in BC patients. Since treatment strategy was changed dramatically after 1990,[29] we excluded studies with a study population enroled predominantly before 1990.

The predetermined endpoints were cardiovascular mortality, HF, coronary artery disease (CAD), myocardial infarction (MI), any stroke, ischaemic or haemorrhagic stroke, and atrial fibrillation (AF; Graphical Abstract). We used outcome definitions utilized in primary studies. Academic correspondences, editorials, case reports, systematic and narrative reviews were excluded. The research team used the Rayyan platform for collaboration during the screening phase.[30]

Data extraction and risk of bias evaluation

We conducted data extraction and risk of bias evaluation within the Systematic Review Database Repository Plus web platform.[31] The following data were collected during the extraction phase if available: study design, key inclusion and exclusion criteria, recruitment period, sample characteristics (age, race, postmenopausal status, history of comorbid conditions, diabetes mellitus (DM), hypertension, dyslipidaemia, smoking, alcohol intake, chronic kidney disease, body mass index, BC stages, grades and types, side and size of breast tumour, and details on received treatment), reported outcomes, outcome measurement details, and main results.

Unreported means were derived with formulae from Wan *et al.* and the Cochrane group.[32,33] If the number of person-years of follow-up was not provided, we calculated it by multiplying the sample size by the median/mean follow-up time. Therefore, for the second aim of our meta-analysis, we removed publications that did not report median follow-up time and event numbers.

The Newcastle-Ottawa Scale was applied for risk of bias assessment.[34] Any disagreements were discussed within the research team until consensus was reached.

Statistical analyses

The relative risk was pooled using pairwise random-effects meta-analyses, with hazard ratios (HRs) as effect estimates. The studies that reported other effect estimates were excluded. Since assumption for hazard proportionality was not fulfiled in some original studies, we analysed evidence separately for different periods of time from BC diagnosis. The analysed time periods varied across the specified outcomes, since we selected them depending on the availability of data from the original reports. For the studies by D'Souza *et al.*, Riihimäki *et al.*, and Staszewsky *et al.*, the study HR was derived by synthesizing original HRs for different groups by fixed-effects meta-analyses.[35–37] Ninety-five per cent confidence intervals (CIs) were calculated with Wald-type statistics and Knapp and Hartung adjustment.[38] We used a restricted maximum likelihood random effects (REML) model, with inverse variance weighting. Publication bias for the risk meta-analyses was assessed using Egger's test and through the visual inspection of funnel plots, if 10 or more studies were available to ensure adequate power.[39]

We pooled IRs using a generalized linear mixed model based on a Poisson–normal assumption, with maximum likelihood estimation and inverse variance weighting.[40] We also conducted leave-one-out sensitivity analyses for meta-analyses of HRs and IRs with significant results. As some reports were based on the same cohort of patients, we incorporated them one after another during sensitivity analyses in order to prevent a situation when individual cohorts contribute to each individual endpoint more than once. 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. Following a general rule of thumb, we performed meta-regression analyses for analyses with more than 10 included studies.[39] All statistical analyses were conducted with the use of metafor and lme4 R packages.[41,42] All presented results could be obtained by running an R code based on a data set provided in Supplementary material online. The related R code could also be found on the Github platform. The certainty of evidence was graded according to the Grading of Recommendations, Assessment, Development and Evaluation Working Group guidelines.[43]

Results

We identified 142 studies in total, with 26 articles (836 301 patients, Graphical Abstract)[16,17,21–23,35–37,44–61] relevant to the first aim and 116 reports (2 111 882 patients) for the second aim only (see Supplementary material online, *References*). The flow diagram is described in *Figure 1* and Supplementary material online, *Tables S1 and S2*. The baseline characteristics of the studies are presented in *Table 1* for the meta-analysis of the relative risk and Supplementary material online, *Table S3* for studies that reported only IRs. The majority of studies that compared BC patients to cancer-free controls were of retrospective design. Thirteen were derived from North America while four studies were conducted in Asia and the remaining nine 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 were heterogeneous with a prevalence of DM ranging from 2.2 to 29.9%, hypertension from 5.4 to 72%, and dyslipidaemia 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%; and trastuzumab, 7.5–12.7%; *Table 1*). Unfortunately, many studies missed information on baseline characteristics (risk factors and treatment options), which made it impossible to conduct meta-regression analyses on these parameters. As can be seen from *Table 1*, the original investigations varied greatly regarding matching criteria used; however, all studies were matched for age, and in the majority of reports, study arms were matched or statistical analyses were adjusted for race, socioeconomic status, comorbidities, and some common cardiovascular risk factors. In a total of 15 out of 26 studies, approaches to competing risk assessments were clearly reported (*Table 1*).

For studies with IRs (see Supplementary material online, *Table S3*), 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%; and dyslipidaemia, 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%; and radiotherapy, 4.5–100%).

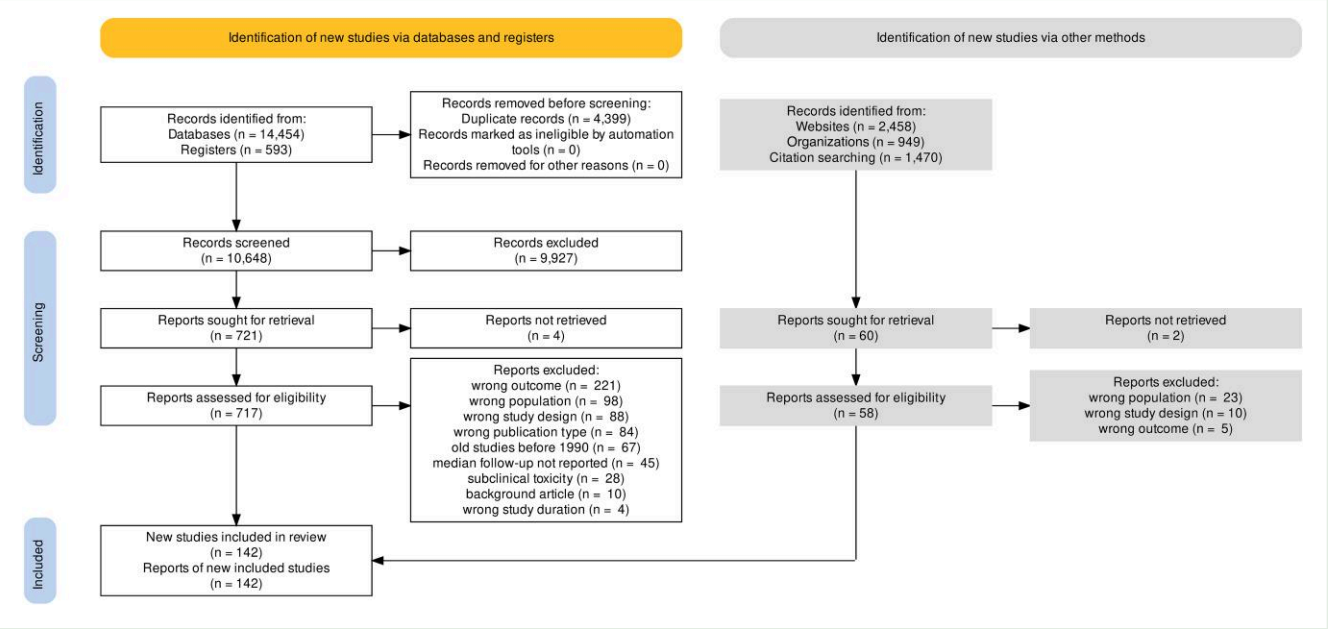


Figure 1 Flow diagram of the meta-analysis.

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. The follow-up rate was unclear in some investigations that compared the risks of cardiovascular outcomes in BC patients to those of cancer-free controls, so were rated with uncertain risk of bias due to adequacy of follow-up. The details of quality assessment of studies that reported incidence data could be found in Supplementary material online, *Table S4*.

The risk of cardiovascular outcomes in breast cancer 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 (see Supplementary material online, *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 and 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 (see Supplementary material online, *Table S5*). In contrast, the results for the HF risk during the first 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 material online, *Table S5*).

Breast cancer patients experienced higher rates of AF compared to cancer-free controls for the first 3 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 (see Supplementary material online, *Table S5*). The risk of AF beyond 3 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 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 material online, *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 (see Supplementary material online, *Figure S2*). Moreover, these results were not robust during leave-one-out sensitivity analyses (see Supplementary material online, *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 material online, *Figure S3*). Similarly, we did not find any significant relationship between BC and the risk of ischaemic stroke (HR 1.19, 95% CI 0.94–1.51; Supplementary material online, *Figure S4*). For haemorrhagic 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.

The incidence of cardiovascular outcomes in breast cancer patients

We conducted separate meta-analyses for regional and nationwide studies that were part of the Surveillance, Epidemiology, and End

Table 1 Baseline features of the studies that compared the risk of cardiovascular outcomes in breast cancer population and those in a general matched cancer-free population

Author	Year	PMID	Country	FU, y	Study design	Sample size	Mean age, y	DM, %	Hypertension, %	Dyslipidaemia, %	DCIS, %	Surgery, %	Chemotherapy, %	Radiotherapy, %	Competing risk analysis	Matching and adjusted variables
Lamont	2003	12 833 448	USA		Retrospective cohort	5980	67.5	15			17				NM	Age, race, socioeconomic status, geographic location, cohort entry year, and CCI
van Herk-Sukel	2011	21 614 410	The Netherlands	3.7 (mean)	Retrospective cohort	11 473	59	7	34	11		92	20		NM	Age, prior use of antithrombotic drugs, lipid-lowering drugs, antihypertensive drugs, and other cardiovascular drugs
Khan	2011	22 048 030	UK		Retrospective cohort	16 938	66.9								NM	Age, gender, primary care practice, smoking, BMI
Ligibel	2012	21 881 937	USA	2.5 (median)	Retrospective cohort	44 463	67			21.2					NM	Age, socioeconomic status, race, urban/rural residence, CCI, number of unique drug classes, statin use, proton pump inhibitor use
Riihimäki	2012	21 586 686	Sweden		Retrospective cohort	122 000									Yes	Age, socioeconomic index, and geographical region of residence
Lash	2014	24 584 822	USA		Retrospective cohort	1361		15							Semi-Bayes shrinkage	Age, care setting, calendar time, CCI and its components
Navi	2015	25 472 885	USA	4.3 (median)	Retrospective cohort	69 234	76		72		15				Yes	Age, sex, race, registry, CCI, HTN, AF
Bradshaw	2016	26 414 938	USA		Retrospective cohort	1413	59	9.1	34	30			42	61	Yes	Age, menopausal status, previous use of hormone replacement therapy, smoking, BMI, alcohol, history of DM, dyslipidaemia, MI, HTN, or stroke
Park	2017	28 934 233	USA	10.4 (median)	Retrospective cohort	4518	68.03	4.3	29.9	11.3					NM	Age (other variables were not clearly reported)
Reiner	2017	28 836 029	USA		Retrospective cohort	881	77				7				Yes	Age, sex, race, registry, and CCI
Saliba	2018	29 324 747	Israel		Retrospective cohort	11 220	63.6								NM	Age, sex, ethnicity and residence, smoking, alcohol, physical activity, education, use of aspirin,

Continued

Table 1 *Continued*

Author	Year	PMID	Country	FU, y	Study design	Sample size	Mean age, y	DM, %	Hypertension, %	Dyslipidaemia, %	DCIS, %	Surgery, %	Chemotherapy, %	Radiotherapy, %	Competing risk analysis	Matching and adjusted variables
																statins, and anticoagulants, HTN, DM, HF, and cardiovascular disease
Andersen	2018	29 866 752	Denmark	1 (mean/ median)	Retrospective cohort										Yes	Age, sex, income, education, calendar year, MI, HF, PAD, CKD, COPD, DM, HTN, and AF
Wadsten	2018	29 730 730	Sweden	8.8 (median)	Retrospective cohort	6270					100	99.5		38.9	Yes	Age, education, CCI, and previous IHD
D'Souza	2019	30 709 772	Denmark	3	Retrospective cohort	74 155	62	4.4	19.1	11.5					Yes	Age, sex, HTN, IHD, HF, DM, thyroid disease, CKD, PAD, COPD, chronic liver disease
Chang	2019	30 447 482	Korea	6.1 (mean)	Retrospective cohort	1015			36.4			100		100	Yes	Age, smoking, CCI, calendar year, HTN, BMI, cholesterol, exercise, residential area, income, and disabled status
Abdel-Qadir	2019	31 539 076	Canada	5.7 (mean)	Retrospective cohort	68 113	60	15.9	43.4		0		53.2	71.7	Yes	Age, breast imaging, year of cohort entry, rural residence, IHD, HF, DM, HTN, PAD, stroke, COPD, and CKD
Ng	2019	31 280 456	Canada	5	Retrospective cohort	12 127				16.2					Yes	Age, comorbidity score, income, DM, HTN, hyperlipidaemia, HF, transient ischaemic attack, cerebrovascular disease, CKD, AF, COPD
Abdel-Qadir	2019	30 715 404	Canada, Ontario	5.7 (mean)	Retrospective cohort	78 318	61	16.6	47		0			65.3	Yes	Age, rural residence, IHD, HF, DM, HTN, PAD, stroke, COPD, AF, and CKD
Lee	2020	31 454 422	Korea	3.1 (median)	Retrospective cohort	91 227	49.1	6.6	19.3	12.2		100		72.6	NM	Age, sex, income, DM, HTN, and dyslipidaemia
Wennstig	2020	31 969 169	Sweden	8.1 (mean)	Retrospective cohort	60 217					14.3	96.1	27.5	62.2	NM	Age, the number of previous IHD events, time since last IHD event, CCI, and education
Staszewsky	2020	32 588 164	Italy		Retrospective cohort	18 165	61	11.5	45.8	15.2					NM	Age, drug-derived complexity index, history of DM, COPD, HTN, CKD,

Continued

Table 1 *Continued*

Author	Year	PMID	Country	FU, y	Study design	Sample size	Mean age, y	DM, %	Hypertension, %	Dyslipidaemia, %	DCIS, %	Surgery, %	Chemotherapy, %	Radiotherapy, %	Competing risk analysis	Matching and adjusted variables
																arrhythmias, IHD, cerebrovascular disease, PAD, peripheral venous disease, pulmonary thrombo embolism, arterial thrombo embolism, dyslipidaemia
Yoo	2021	34 174 850	Korea	5.4 (median)	Retrospective cohort	13 740	47.68	5.04	15.86	10.76					NM	Age, year, income, DM, HTN, and dyslipidaemia
Ramin	2021	32 634 223	USA, Washington County, MD	10.4 (median)	Prospective cohort	628	64.5	2.2	18.6	3.8	0				Yes	Age, menopausal status, education, smoking, alcohol intake, BMI, and history of oral hormone use
Guha	2022	34 791 123	USA	1 (total)	Retrospective cohort	85 423		29.9	70	65.5		88.9		48.9	Yes	Age, race, Hispanic ethnicity, calendar year, registry, CCI, marital status, urban residence, income, obesity, smoking, HTN, stroke
Paterson	2022	35 492 824	Canada, Alberta	11.8 (median)	Retrospective cohort	29 407					10.6				Yes	Age, sex, neighbourhood material deprivation quintile, rural residence, distance to closest cancer centre, distance to closest family doctor, and the 31 comorbidities
Yang	2022	35 293 856	Sweden	10.8 (median)	Retrospective cohort	8015	59		5.4		0	99		77.5	Yes	Age (other variables were not clearly reported)

AF, atrial fibrillation; BMI, body mass index; CCI, Charlson Comorbidity Index; CKD, chronic kidney disease; COPD, chronic obstructive lung disease; DCIS, ductal carcinoma *in situ*; DM, diabetes mellitus; FU, follow-up time; HF, heart failure; HTN, hypertension; IHD, ischaemic heart disease; MI, myocardial infarction; NM, not mentioned; PAD, peripheral artery disease; PMID, PubMed identification number; y, years.

Table 2 Risk of bias assessment of the studies that compared the risk of cardiovascular outcomes in breast cancer population and those in a general matched cancer-free population

Author	Year	PMID	1. Representativeness of the exposed cohort	2. Selection of the non-exposed cohort	3. Ascertainment of exposure	4. Demonstration that outcome of interest was not present at the start of the study	5. Comparability of cohorts on the basis of the design or analysis	6. Assessment of outcome	7. Was follow-up long enough for outcomes to occur	8. Adequacy of follow up of cohorts
Lamont	2003	12 833 448	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain or high risk
van Herk-Sukel	2011	21 614 410	Low risk	Low risk	Low risk	Uncertain or high risk	Low risk	Low risk	Low risk	Uncertain or high risk
Khan	2011	22 048 030	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain or high risk
Ligibel	2012	21 881 937	Low risk	Low risk	Low risk	Uncertain or high risk	Low risk	Low risk	Low risk	Low risk
Riihimäki	2012	21 586 686	Low risk	Low risk	Low risk	Low risk	Uncertain risk	Low risk	Low risk	Low risk
Lash	2014	24 584 822	Low risk	Low risk	Low risk	Uncertain or high risk	Low risk	Low risk	Low risk	Low risk
Navi	2015	25 472 885	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain or high risk
Bradshaw	2016	26 414 938	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Park	2017	28 934 233	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain or high risk
Reiner	2017	28 836 029	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Saliba	2018	29 324 747	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain or high risk
Andersen	2018	29 866 752	Low risk	Low risk	Low risk	Uncertain or high risk	Low risk	Low risk	Low risk	Low risk
Wadsten	2018	29 730 730	Low risk	Low risk	Low risk	Uncertain or high risk	Low risk	Low risk	Low risk	Uncertain or high risk
D'Souza	2019	30 709 772	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Chang	2019	30 447 482	Low risk	Low risk	Low risk	Uncertain or high risk	Low risk	Low risk	Low risk	Low risk
Abdel-Qadir	2019	31 539 076	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain or high risk
Ng	2019	31 280 456	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Uncertain or high risk
Abdel-Qadir	2019	30 715 404	Low risk	Low risk	Low risk	Uncertain or high risk	Low risk	Low risk	Low risk	Low risk
Lee	2020	31 454 422	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Wennstig	2020	31 969 169	Low risk	Low risk	Low risk	Uncertain or high risk	Low risk	Low risk	Low risk	Uncertain or high risk
Staszewsky	2020	32 588 164	Low risk	Low risk	Low risk	Uncertain or high risk	Low risk	Low risk	Low risk	Uncertain or high risk
Yoo	2021	34 174 850	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Ramin	2021	32 634 223	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

Continued

Table 2 *Continued*

Author	Year	PMID	1. Representativeness of the exposed cohort	2. Selection of the non-exposed cohort	3. Ascertainment of exposure	4. Demonstration that outcome of interest was not present at the start of the study	5. Comparability of cohorts on the basis of the design or analysis	6. Assessment of outcome	7. Was follow-up long enough for outcomes to occur	8. Adequacy of follow up of cohorts
Guha	2022	34 791 123	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk
Paterson	2022	35 492 824	Low risk	Low risk	Low risk	Uncertain or high risk	Low risk	Low risk	Low risk	Low risk
Yang	2022	35 293 856	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk	Low risk

PMID, PubMed identification number.

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 material online, *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 (see Supplementary material online, *Tables S6 and S7*). 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).[62] Exclusion of this study did not impact on overall results (IR 1.65, 95% CI 1.13–2.41; Supplementary material online, *Figure S6*).

The mean incidence of HF was 4.44 per 1000 person-years (95% CI 3.33–5.92; Supplementary material online, *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 material online, *Figure S8*). All types of sensitivity analyses provided similar data (see Supplementary material online, *Tables S6 and S7*). 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 material online, *Figure S6*).

The pooled IR for CAD was 4.29 per 1000 person-years of follow-up (95% CI 3.09–5.94; Supplementary material online, *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 (see Supplementary material online, *Tables S6 and S7*).

The average IR for MI was 1.98 per 1000 person-years (95% CI 1.24–3.16; Supplementary material online, *Figure S10*). The incidence was 2.16 (95% CI 1.23–3.79; Supplementary material online, *Figure S11*) with the nationwide SEER-based cohort. Sensitivity analyses were consistent with the main analysis with no evidence for publication bias (see Supplementary material online, *Figure S6*).

The overall IR for stroke of any type was 4.33 per 1000 person-years (95% CI 2.97–6.30, Supplementary material online, *Figure S12*). Sensitivity analyses provided approximately the same mean IRs (see Supplementary material online, *Tables S6 and S7*).

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

In summary, the pooled IRs for cardiovascular death, HF, CAD, MI, stroke, ischaemic 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 (see Supplementary material online, *Tables S8 and S9*). Mean age, proportion of patients with DM, hypertension, tumour size more than 5 cm, stage 4 BC, surgery, and chemotherapy were found to be statistically significant for at least two 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

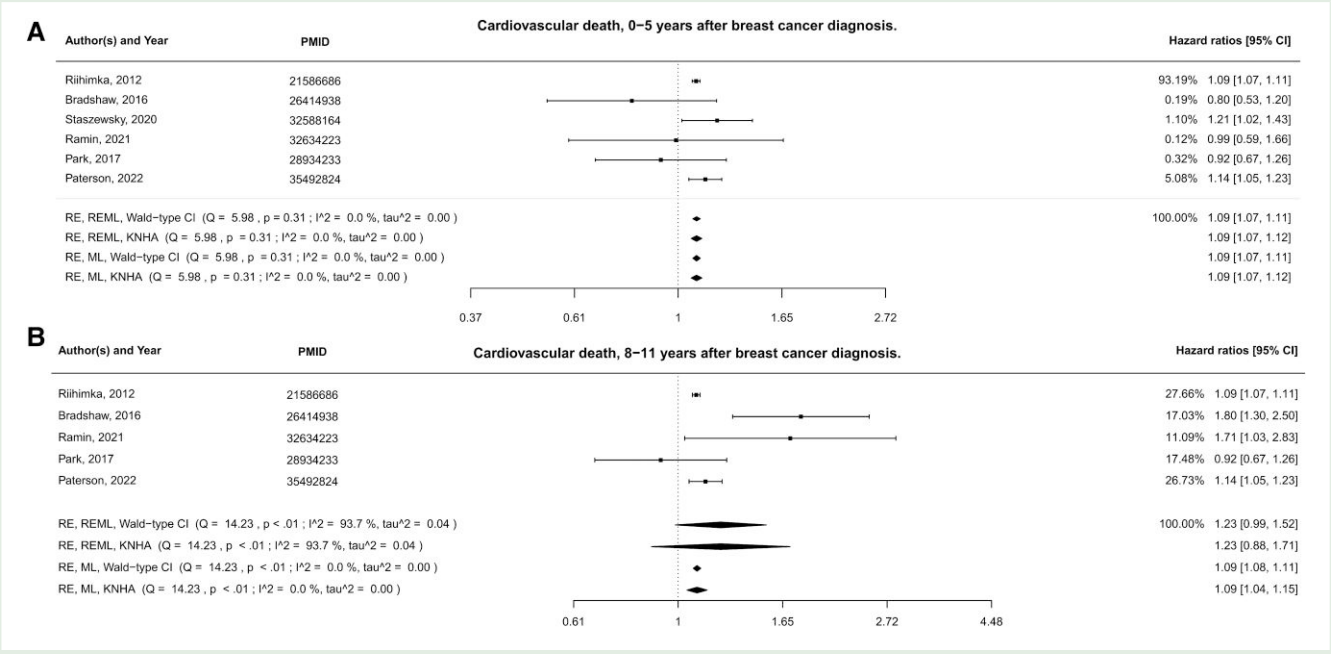


Figure 2 The risk of cardiovascular death in patients with breast cancer compared to those in the general population. PMID, PubMed identification number; CI, confidence interval; RE, random-effects model; REML, restricted maximum likelihood; ML, maximum likelihood; KNHA, Knapp and Hartung adjustment.

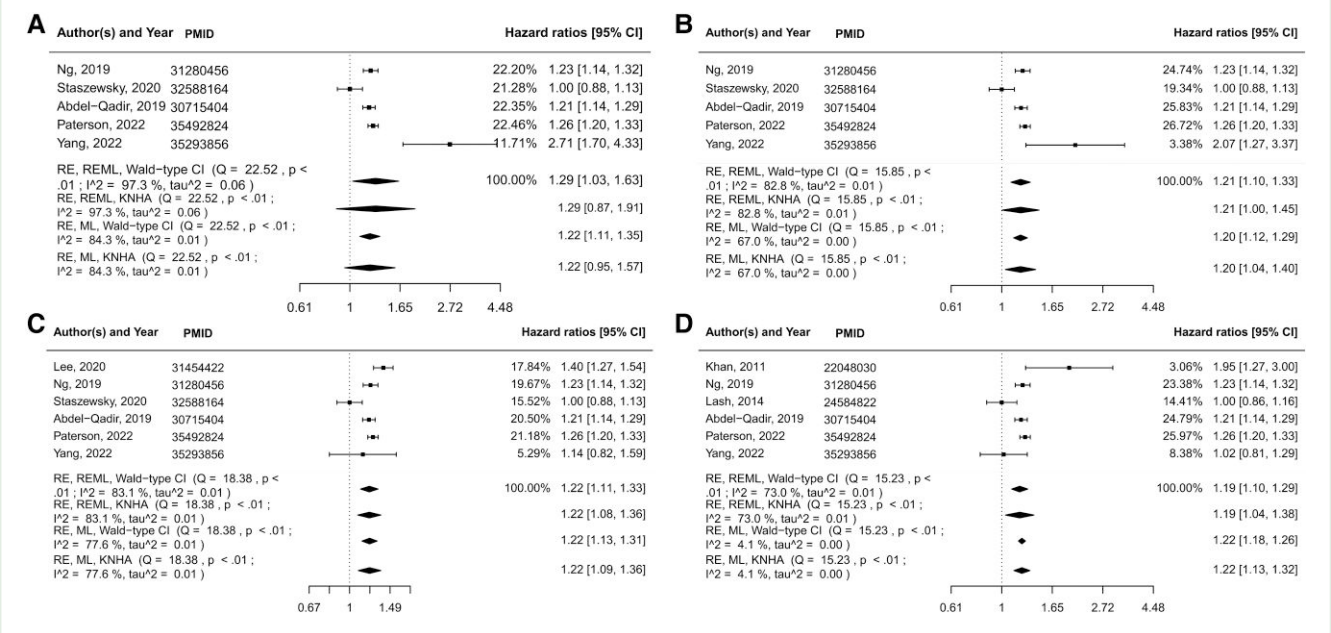


Figure 3 The risk of heart failure in patients with breast cancer compared to those in the general population. (*A*) During the first year after breast cancer diagnosis; (*B*) 1–2 years after breast cancer diagnosis; (*C*) 2–5 years after breast cancer diagnosis; and (*D*) 5–10 years after breast cancer diagnosis. PMID, PubMed identification number; CI, confidence interval; RE, random-effects model; REML, restricted maximum likelihood; ML, maximum likelihood; KNHA, Knapp and Hartung adjustment.

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 with those from Asian

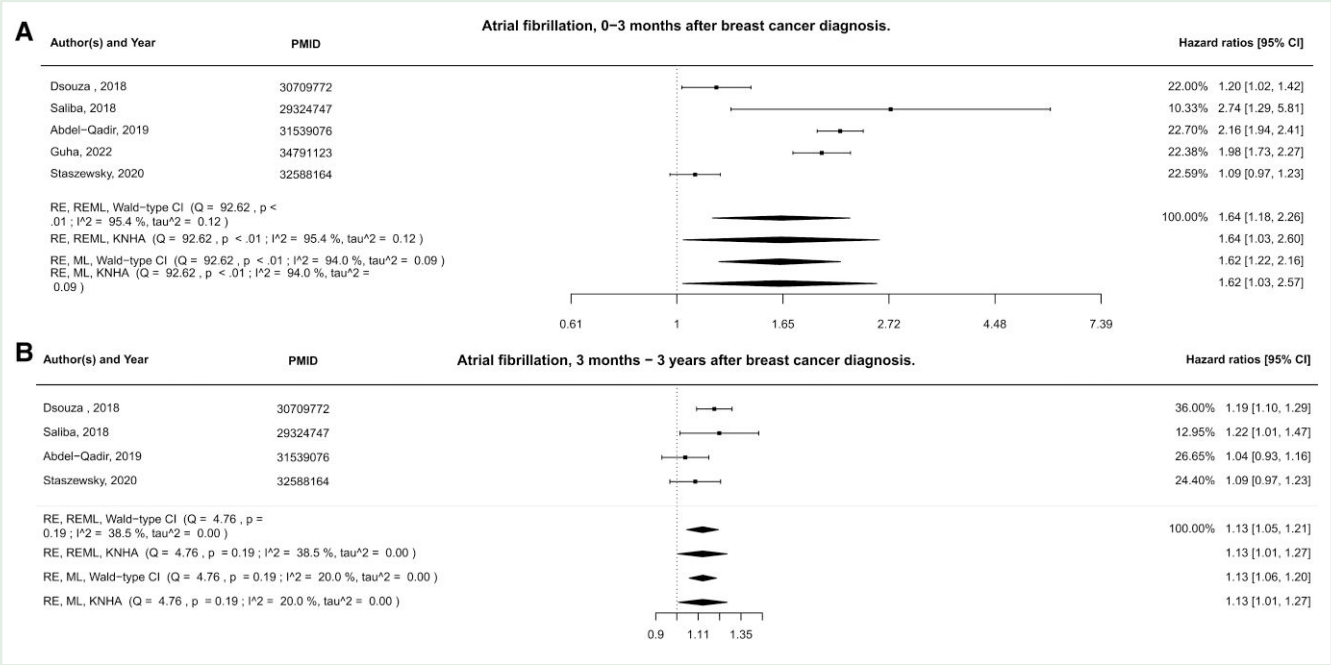


Figure 4 The risk of atrial fibrillation in patients with breast cancer compared to those in the general population. PMID, PubMed identification number; CI, confidence interval; RE, random-effects model; REML, restricted maximum likelihood; ML, maximum likelihood; KNHA, Knapp and Hartung adjustment.

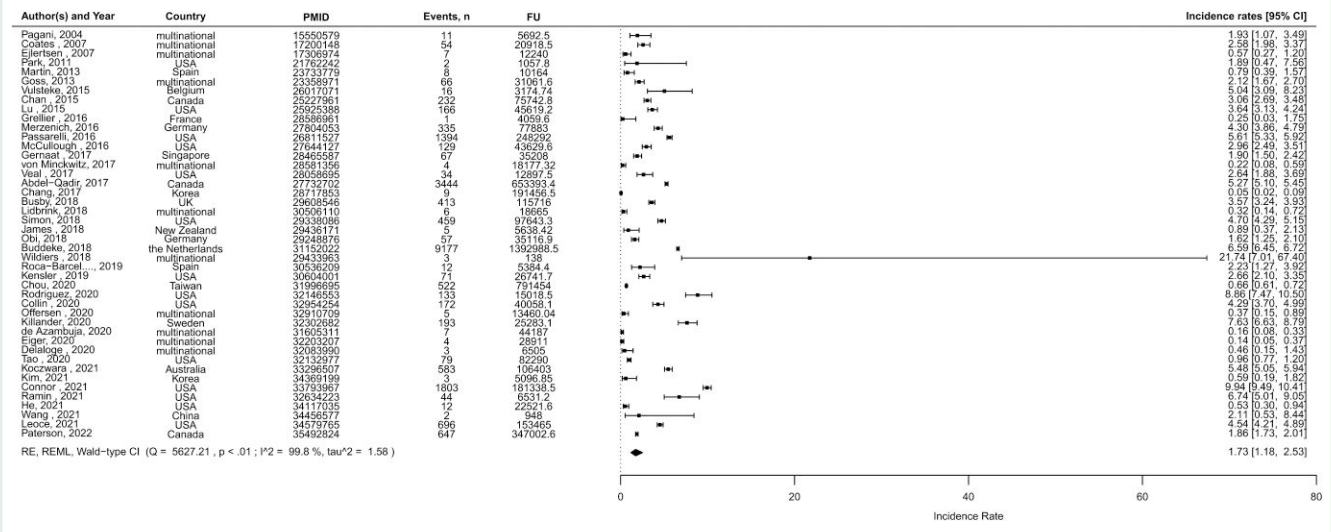


Figure 5 The incidence rate of cardiovascular death in breast cancer patients per 1000 person-years of follow-up. In this analysis, regional Surveillance, Epidemiology, and End Results–based studies were included. PMID, PubMed identification number; FU, follow-up (person-years); CI, confidence interval;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

countries (*P* value for subgroup differences 0.02 and 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 ischaemic stroke. Furthermore, using data derived from 116 studies including 2 111 882 patients, we estimate a pooled IR for cardiovascular death of 1.73

(95% CI 1.18, 2.53) per 1000 person-years, for HF 4.44 (95% CI 3.33, 5.92) per 1000 person-years, for CAD and MI 4.29 (95% CI 3.09, 5.94) and 1.98 (95% CI 1.24, 3.16) per 1000 person-years, and for stroke and AF 4.33 (95% CI 2.97, 6.30) and 12.95 (95% CI 12.60–13.31) 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 (human epidermal growth factor receptor 2) 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[9,55] with the risk increasing with increasing cumulative doses of anthracyclines. Doxorubicin interacts with DNA, binding to topoisomerase IIβ and disrupting DNA repair, causing myocyte cell death.[63] Anthracyclines also form complexes with intracellular iron, generating oxygen radicals which damage DNA, proteins, and the mitochondrial membrane.[64] Trastuzumab, pertuzumab, and T-DMI are monoclonal antibodies that inhibit the signalling of HER2/ErbB2. Trastuzumab binds to the extracellular domain of the ErbB2 tyrosine kinase receptor leading to the inhibition of ErbB2 signalling. Cardiac dysfunction associated with trastuzumab is a direct consequence of ErbB2 inhibition in cardiac myocytes.[65] Heart failure associated with these cancer therapies may have a different trajectory/prognosis than that influenced through interaction with pre-existing CVD and traditional cardiovascular risk factors.

Given the limited data, we were unable to estimate the impact of anthracycline or trastuzumab-based therapy on the relative risk of HF in BC survivors compared to those in cancer-free controls. 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 controls.[66] Women developing HF following chemotherapy for BC had fewer comorbidities such as ischaemic heart disease, DM, chronic kidney disease, or hypertension compared to cancer-free controls. The prognosis of HF is related to the chemotherapeutic agent used, and women developing HF after trastuzumab-based therapy had a lower risk of HF hospitalizations 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.[67]

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 early BC 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.[54] 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.[54]

Our analysis suggests that patients with BC are not at increased relative risk of CAD development or future MI. Nevertheless, we could not exclude the association between BC and the future risk of CAD given the limited number of the included studies and the heterogeneity of the study population. Furthermore, we were unable to assess whether this risk was modified by the 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 increase CAD risk. Aromatase inhibitors are often used in postmenopausal women with hormone receptor–positive BC for up to 10 years depending on BC risk.[68] Aromatase inhibitors are associated with worse hypertension control, dyslipidaemia, and endothelial dysfunction that may lead to a higher risk of MI and cardiovascular mortality compared with oestrogen receptor modulators such as tamoxifen.[69] 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.[70,71]

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 IIβ and cardiotoxicity. A meta-analysis of seven trials estimated a 65% (relative risk 0.35, 95% CI 0.27–0.45) reduction in cardiac events with dexrazoxane vs. placebo,[72,73] and it is now recommended for high-risk patients in the recent European Society of Cardiology (ESC) 2022 guideline for cardio-oncology.[74]

The increased risk of cardiovascular death may be reduced by aggressive treatment of traditional cardiovascular risk factors in this population such as hypertension, DM, dyslipidaemia, and lifestyle. Management of blood pressure, glucose, and hypercholesterolaemia 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.[75,76] 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.[74]

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 and used therapeutic agents, for example). Given the predominantly retrospective design of original studies, the possibility of selection bias should be considered. Furthermore, the meta-analyses and meta-regression analyses were performed on aggregated statistics, while calculations on individual patient data could provide more accurate estimates. Since the risk estimates for some outcomes were based only on a handful of available studies, we believe that our meta-analysis needs to be updated as new evidence accumulates. Due to limited data, we were not also able to conduct subgroup analyses to estimate the relative risk of cardiovascular outcomes in patients with different stages of BC and different treatment strategies compared to those in cancer-free controls.

Conclusion

Breast cancer was related with a higher risk of cardiovascular death, HF, and AF when compared to the general population, but not CAD, MI, or

ischaemic 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. Breast cancer 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.

Supplementary material

Supplementary material is available at *European Journal of Preventive Cardiology*.

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Author contributions

M.A.M. is an author of the idea and conceptualized the study design. A.G., S.I., H.N.T., M.A., M.K., E.T., and M.A.M. designed the study and wrote the study protocol. A.G., S.I., H.N.T., and B.O. conducted systematic search, study selection, extraction, and risk of bias assessment. A.G. performed statistical analyses. M.A.M., M.P., and E.K. supervised statistical analyses. A.G. and M.A.M. drafted the manuscript. M.A.M., M.A., B.K., A.R.L., M.K., E.T., M.P., E.K., and H.A.-Q. 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.

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Data availability

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

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