Outcome and presentation of heart failure in breast cancer patients: findings from a Swedish register-based study

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Aims

Heart failure (HF) patients diagnosed with breast cancer (BC) may have a higher risk of death, and different HF presentation and treatment than patients without BC.

Methods and results

A total of 14 998 women with incident HF (iHF) or prevalent HF (pHF) enrolled in the Swedish HF Registry within and after 1 month since HF diagnosis, respectively, between 2008 and 2013. Patients were linked with the National Patient-, Cancer-, and Cause-of-Death Registry. Two hundred and ninety-four iHF and 338 pHF patients with BC were age-matched to 1470 iHF and 1690 pHF patients without BC. Comorbidity and treatment characteristics were compared using the χ^2 tests for categories. Cox proportional hazard models assessed the hazard ratio (HR) and 95% confidence intervals (95% CIs) of all-cause and cardiovascular mortality among HF patients with and without BC. In the pHF group, BC patients had less often myocardial infarction (21.6% vs. 28.6%, $P < 0.01$) and received less often aspirin (47.6% vs. 55.1%, $P = 0.01$), coronary revascularization (11.8% vs. 16.2%, $P < 0.01$), or device therapy (0.9% vs. 3.0%, $P = 0.03$). After median follow-up of 2 years, risk of all-cause mortality (iHF: HR = 1.04, 95% CI = 0.83–1.29 and pHF: HR = 0.94, 95% CI = 0.79–1.12), cardiovascular mortality (iHF: HR = 0.94, 95% CI = 0.71–1.24 and pHF: HR = 0.89, 95% CI = 0.71–1.10), and HF mortality (iHF: HR = 0.80, 95% CI = 0.34–1.90 and pHF: HR = 0.75, 95% CI = 0.43–1.29) were similar for patients with and without BC in the iHF and pHF groups.

Conclusion

Risk of all-cause and cardiovascular mortality in HF patients did not differ by BC status. Differences in pre-existing myocardial infarction and HF treatment among pHF patients with and without BC may suggest differences in pathogenesis of HF.

Keywords

Breast cancer • Heart failure • Clinical presentation • Mortality • Epidemiology

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Introduction

Heart failure (HF) is a common disease with poor prognosis and increasing prevalence with age.^{1–3} Breast cancer (BC) incidence has increased during the past decades.^{4,5} Earlier disease detection and advances in treatment resulted in improved long-term survival in BC patients.⁶ However, the risk of cardiovascular disease (CVD), including HF, is increased among BC patients exposed to cardiotoxic treatments such as anthracycline-based chemotherapy and trastuzumab.^{7,8} Death from CVD occurs among one in four older BC patients.⁹ Therefore, the number of HF patients with a history of BC will be increasing. Data about the effect of BC on survival and treatment of HF is, however, limited.

Conventional chemotherapy, immunotherapy, radiotherapy, and targeted therapies can decrease left ventricular function either by direct damage to cardiomyocytes and/or ischaemia related to accelerated atherosclerosis, and lead to asymptomatic subclinical cardiac injury detectable with circulating biomarkers or strain echocardiography as well as clinically overt HF.^{7,8,10} Heart failure in BC patients is mostly defined as a reduction of left ventricular ejection fraction by >10 percentage points and below the lower limit of normality.¹¹ Data are limited on outcome, presentation and management of clinically overt HF in patients with BC than on incidence of HF secondary to the cancer-treatment, which are necessary to better understand the impact of HF on BC survivors.¹²

Using the Swedish Heart Failure Register (SwedeHF) and additional other National registries, we aimed to evaluate the risk factors, clinical presentations, HF treatments, and outcomes of HF patients with BC compared to HF patients without a cancer diagnosis.

Methods

Study cohort

We analysed data of 17 540 women with HF diagnosis, enrolled in the SwedeHF between 1 January 2008 and 31 December 2013 (Figure 1,

Supplementary material online, Table S2). SwedeHF was linked with the Swedish National Patient Register (NPR) to identify the date of HF diagnosis. The index date is the inclusion date into the SwedeHF after HF diagnosis. The date of HF diagnosis was used to estimate time between HF diagnosis and index date to classify HF patients as incident (iHF) or prevalent (pHF). Incident HF patients were those enrolled in SwedeHF within 1 month after HF diagnosis, and pHF patients were those enrolled after 1 month after their HF diagnosis. This classification is needed as the HF management differs between the two groups: up-titration of HF medication aiming for specified target doses and device therapy decision is common during the first month after HF diagnosis.

SwedeHF was linked with the Swedish Cancer Register to identify patients diagnosed with BC before HF diagnosis. Subsequently, 2539 patients were excluded due to cancer diagnosis other than BC and three patients were excluded as the registered death date was before the index date. As such, 14 998 HF patients were eligible for this study of which 632 patients had a history of BC. For the present study, every patient with BC was matched by age to five patients without a BC diagnosis. This resulted in 1764 iHF patients of whom 294 were diagnosed with BC and 2028 pHF patients of which 338 were diagnosed with BC.

This study complied with the Declaration of Helsinki and was approved by regional ethics review board in Linköping University Hospital (Dnr 2012/172-31). According to Swedish legislation, patients registered in national quality registers do not need to provide written informed consent but are informed that their data will be entered the registers and that they can opt-out at any time.

Clinical registers

SwedeHF is a nationwide and voluntary quality reporting registry founded in 2000 with around 10 000 registrations added every year. The majority of Swedish hospitals (70 out of 80) enroll patients without financial compensation, and record approximately 80 variables from adult inpatient wards and outpatient clinics. Hospitalizations are registered as they occur and outpatient visits annually. In contrast, a minority of Swedish outpatient primary care clinics enrolls patients: 100 out of 1000. The inclusion criterion is clinician-judged HF.

Coverage of pHF in the inpatient setting is 54%. Coverage of pHF in primary care is much lower, but few patients are seen exclusively in

Figure 1 Sample selection in a study of 3972 women enrolled in the Swedish Heart Failure Register between 2008 and 2013, with and without breast cancer.

primary care and thus are eventually registered in cardiology or internal medicine departments. Coverage of iHF is around 10%, because the first contact with HF usually occurs at a caregiver that does not report to the registry, such as in the emergency department or primary care facility.^{1,13} The date of HF diagnosis and entry in SwedeHF may differ, because the first contact of HF can occur at a caregiver that does not immediately report to SwedeHF.

All patients with HF were linked by their unique personal identity numbers to the NPR, the Swedish Cancer Register, Swedish Cause-of-Death Register and Prescribed Drug Register. NPR has had nationwide coverage since 1987 and includes all inpatient hospitalizations in Sweden.¹⁴ Since 2001, Swedish counties are also obliged to report hospital-based outpatient physician visits to the register. The Cancer Register, established in 1958, covers the entire population, as health care providers must report newly detected cancer cases.¹⁵ Information on cause-specific mortality was obtained from the Cause-of-Death Register, which has been updated annually since 1961.¹⁶ Cohort data were also linked with the Prescribed Drug Register, which contains data on all drugs dispensed from Swedish pharmacies since July 2005 to determine HF treatment at enrolment into SwedeHF.¹⁷

The diagnostic codes used in all registers are those of International Classification of Diseases (ICD-10) Version 9 or 10. The pharmaceutical codes used in the Prescribed Drug Register are those of the Anatomical Therapeutic Chemical (ATC) Classification System.

Characteristics, treatment, and comorbidities

SwedeHF provides detailed information on clinical presentation of HF, comorbidities, demographic characteristics, results of clinical and laboratory tests, and HF treatment.¹ The severity of HF is coded according to the New York Heart Association (NYHA) functional classification. It classifies patients in one of four categories based on their limitations during physical activity; the limitations/symptoms are in regards to normal breathing and varying degrees in shortness of breath and or angina pain.¹⁸ The Prescribed Drug Register was used to identify fulfilled prescriptions for drugs related to CVD using the Anatomical Therapeutic Chemical classification codes (Supplementary material online, Table S1).

Pre-existing comorbidities were defined as a diagnosis in the NPR before or at the time of HF diagnosis using the ICD 9 or 10 codes (Supplementary material online, Table S2).

Statistical methods

Baseline characteristics were compared between iHF patients with and without BC, and between pHF patients with and without BC. Medians [interquartile range (IQR)] were used to describe continuous variables without normally distributed data. Differences in characteristics were tested using the χ^2 tests and *t*-tests for categorical and continuous data, respectively.

Kaplan–Meier plots survival estimates were visualized using the Kaplan–Meier method. Cox proportional hazard models¹⁹ were used to estimate age-adjusted hazard ratios (HRs) and 95% confidence intervals (95% CIs), comparing iHF patients with BC to those without BC, and comparing pHF patients with BC to those without BC. All-cause and cause-specific (CVD and HF) relative risk of death was estimated with Cox proportional hazard models analyses. The proportional hazards assumptions were tested by evaluation of the scaled Schoenfeld residuals over time. In all models, follow-up time started at index date and ended at date of death, date of new primary BC, date of metastatic disease after HF diagnosis, or 31 December 2013; whichever came first. The Cox proportional alpha was set at 0.05, and all tests were two-tailed. Statistical analyses were conducted using the R version 3.2.3.

Results

Median age at HF diagnosis was 77 (IQR = 68–85) years for iHF patients and 79 (IQR = 73–86) years for pHF patients (Table 1). In the iHF group, 68.2% (*n* = 1003) patients without BC and 60.2% (*n* = 177) patients with BC were diagnosed in the inpatient department. In the pHF group, 53.8% (*n* = 909) patients without BC and 52.1% (*n* = 176) patients with BC were diagnosed in the inpatient department. Over half of patients with and without BC in the iHF and pHF groups were hospitalized at time of enrolment in SwedeHF. All patients with iHF were enrolled in SwedeHF immediately, median time 0.0 (IQR = 0.0–0.0) years. In the pHF group, patients with BC were enrolled after median of 1.8 (IQR = 0.4–5.5) years after HF diagnosis, and patients without BC were enrolled after a median of 2.1 (IQR = 0.4–5.0) years after HF diagnosis. Median time between BC diagnosis and HF diagnosis was 6.2 (IQR = 3.3–8.4) years in the iHF group and 6.2 (IQR = 2.8–8.4) years in the pHF group. Median follow-up was 2.2 (IQR = 0.9–2.8) years for iHF patients without BC and 2.0 (IQR = 0.8–4.0) years for iHF patients with BC. Median follow-up was 1.8 (IQR = 0.7–3.4) years for pHF patients without BC and 2.1 (IQR = 0.7–3.5) years for pHF patients with BC.

Cardiovascular risk factors and treatments

Over half of patients had hypertension, regardless of BC and HF group (Table 2). Prevalent HF patients with BC had less often pre-existing myocardial infarction than pHF patients with BC [21.6% (*n* = 73) vs. 28.6% (*n* = 484), *P* < 0.01]. Also, pHF patients without BC were more often treated with implantable cardioverter-defibrillators and cardiac resynchronization therapy than pHF patients with BC [1.6% (*n* = 27) vs. 0.6% (*n* = 2) and 3.0% (*n* = 50) vs. 0.9% (*n* = 3), respectively, *P* = 0.03]. Prevalent HF patients with BC received less often aspirin [47.6% (*n* = 161) vs. 55.1% (*n* = 932), *P* = 0.01] and underwent less often coronary revascularization than pHF patient without BC [11.8% (*n* = 40) vs. 16.2% (*n* = 274), *P* = 0.05] (Table 2).

Mortality

Total person years for iHF patients with and without BC was 704 and 3571, respectively (Table 3). Total person years for pHF patients with and without BC was 785 and 3652, respectively. The cumulative incidence of death from any cause, CVD, and HF was higher among pHF patients than iHF patients (Figure 2, Table 3). Overall, the cumulative incidence of patients with BC did not differ from patients without BC until approximately 4 years after SwedeHF registry enrolment. Thereafter, the difference in cumulative incidence of patients without BC and patients with BC became larger, with a higher incidence of CVD and HF among patients without BC.

In the iHF and pHF groups, comparing patients with and without BC, the age-adjusted risk of death from any-cause (HR = 1.04, 95% CI = 0.83–1.29 and HR = 0.94, 95% CI = 0.79–1.12, respectively), CVD (HR = 0.94, 95% CI = 0.71–1.24 and HR = 0.89, 95% CI = 0.71–1.10, respectively), and HF (HR = 0.80, 95% CI = 0.34–1.90 and HR = 0.75, 95% CI = 0.43–1.29, respectively) (Table 3).

Table 1 Baseline characteristics at enrolment in SwedeHF of 294 women with incident HF and BC compared to 1470 age-matched women with incident HF without BC; and 338 women with prevalent HF and BC compared to 1690 age-matched women with prevalent HF without BC

Characteristics	Incident HF			Prevalent HF		
	Without BC (N = 1470)	With BC (N = 294)	P-value	Without BC (N = 1690)	With BC (N = 338)	P-value
Age (years), median (IQR)	77 (68–85)	77 (68–85)		79 (73–86)	79 (73–86)	
HF diagnosis, n (%)			<0.01			<0.01
Outpatient clinic	467 (31.8)	117 (39.8)		781 (46.2)	162 (47.9)	
Inpatient department	1003 (68.2)	177 (60.2)		909 (53.8)	176 (52.1)	
Time between HF diagnosis and SwedeHF enrolment (years), median (IQR)	0.0 (0.0–0.0)	0.0 (0.0–0.0)	0.36	2.1 (0.4–5.5)	1.8 (0.4–5.0)?	0.12
Year of SwedeHF enrolment, n (%)			0.20			0.20
2008	297 (20.2)	65 (22.1)		396 (23.4)	89 (26.3)	
2009	224 (15.2)	52 (17.7)		298 (17.6)	52 (15.4)	
2010	251 (17.1)	39 (13.3)		248 (14.7)	44 (13.0)	
2011	273 (18.6)	50 (17.0)		294 (17.4)	63 (18.6)	
2012	243 (16.5)	41 (13.9)		198 (11.7)	43 (12.7)	
2013	182 (12.4)	47 (16.0)		256 (15.1)	47 (14.0)	
Specialty enrolling, n (%)			0.62			0.63
Cardiology	674 (50.8)	145 (53.1)		812 (53.7)	156 (51.8)	
Internal medicine	641 (48.3)	127 (46.5)		684 (53.7)	142 (47.2)	
Geriatrics	12 (0.9)	1 (0.4)		15 (1.0)	3 (1.0)	
Follow-up time (years), median (IQR)	2.2 (0.9–2.8)	2.0 (0.8–4.0)		1.8 (0.7–3.4)	2.1 (0.7–3.5)	
Mean	2.0	2.0		2.0	2.0	
Maximum	6.0	6.0		6.0	6.0	
Time between BC and HF (years), median (IQR)	NA	6.2 (3.3–8.4)	NA	NA	6.2 (2.8–8.4)	NA
<1 year, n (%)	NA	25 (8.5)		NA	24 (7.1)	
1–5 years, n (%)	NA	95 (32.3)		NA	114 (33.7)	
>5 years, n (%)	NA	174 (59.2)		NA	200 (59.2)	
New BC or metastatic disease after HF, n (%)			<0.01			<0.01
BC	12 (0.8)	55 (19)	<0.01	10 (0.6)	72 (21.3)	<0.01
Metastases	24 (1.6)	13 (4.4)	<0.01	17 (1.0)	15 (4.4)	<0.01

BC, breast cancer; HF, heart failure; IQR, interquartile range; NA, not applicable.

Discussion

In this registry-based study, the risk of death from any-cause, CVD, and HF did not differ between patients with and without BC in the iHF and pHF groups. Among pHF patients, those with BC had less often myocardial infarction and were less often treated with aspirin and coronary revascularization than those without BC. Also, patients with pHF and BC received less cardiovascular device therapies such as implantable cardioverter-defibrillators and/or cardiac resynchronization therapy than patients with pHF without BC.

Breast cancer patients diagnosed with HF during or after cancer treatment are usually treated according to general HF guidelines.^{11,20} However, these guidelines are based on patients without known BC, and it remains unknown if they are appropriate for HF patients diagnosed with BC. Cardiotoxic BC treatment or metabolic effects of

some BC treatments may increase the risk of HF, and the risk of death from CVD.^{12,21–24}

Several studies have shown that patients with cancer and HF have a worse prognosis and higher rate of all-cause mortality than patients diagnosed with cancer alone or HF alone.^{24,25} The results of this study do not support these findings. However, a median follow-up time of 2 years is probably too short to find a difference in mortality between HF patients with and without BC. Age is among the most important risk factors of all-cause mortality and CVD, including HF.^{26,27} In this study, the numbers of comorbidities, except for myocardial infarction, and cardiovascular risk factors appeared to be similar between patients with and without BC. This has been shown in other studies, probably as HF and BC share similar risk factors like hypertension and menopausal status.^{28,29}

The lower rate of aspirin prescription among BC patients in the pHF group may reflect the higher percentage of patients with

Table 2 Cardiovascular risk factors, comorbidities, clinical presentation, medical and device therapy at enrolment in SwedeHF of 294 women with incident HF and BC compared to 1470 age-matched women with incident HF without BC; and 338 women with prevalent HF and BC compared to 1690 age-matched women with prevalent HF without BC

	Incident HF			Prevalent HF		
	Without BC (N = 1470)	With BC (N = 294)	P-value	Without BC (N = 1690)	With BC (N = 338)	P-value
Cardiovascular risk factors						
Body mass index (kg/m ²), mean (SD)	27.6 (6.4)	26.8 (5.5)	0.12	27.2 (6.1)	27.1 (5.6)	0.89
Smoking, n (%)			0.25			0.22
Never	541 (36.8)	120 (40.8)		645 (38.2)	140 (41.4)	
Former (>6 months cessation)	335 (22.8)	52 (17.7)		436 (25.8)	83 (24.6)	
Current (<6 months cessation)	175 (11.9)	34 (11.6)		114 (6.7)	21 (6.2)	
Unknown	419 (28.5)	88 (29.9)		495 (29.3)	94 (27.8)	
Hypertension, n (%)	829 (56.4)	153 (52.0)	0.26	922 (54.6)	184 (54.4)	0.24
Unknown	25 (1.7)	3 (1.0)		47 (2.8)	9 (2.7)	
Diabetes, n (%)			0.90			0.89
Type 1	15 (1.0)	3 (1.0)		26 (1.5)	5 (1.5)	
Type 2	247 (16.8)	43 (14.6)		382 (22.6)	67 (19.8)	
Unknown	15 (1.0)	10 (3.4)		26 (1.5)	9 (2.7)	
Pre-existing comorbidities, n (%)						
Myocardial infarction	268 (18.2)	43 (14.6)	0.15	484 (28.6)	73 (21.6)	<0.01
Unstable angina	83 (5.6)	9 (3.1)	0.08	141 (8.3)	28 (8.3)	1.00
Stable angina	188 (12.8)	31 (10.5)	0.33	446 (26.4)	88 (26.0)	0.95
Atrial fibrillation/flutter	492 (33.5)	93 (31.6)	0.59	964 (57.0)	186 (55.0)	0.51
Stroke	199 (13.5)	37 (12.6)	0.71	281 (16.6)	52 (15.4)	0.63
Clinical presentation						
Heart rate (b.p.m.), mean (SD)	77 (17)	78 (16)	0.16	75 (16)	75 (17)	0.97
Blood pressure, systolic/diastolic (mmHg), mean (SD)	132/74 (23/13)	130/74 (21/12)	0.28/0.43	129/72 (21/12)	128/71 (22/12)	0.71/0.28
NYHA functional classification, n (%)			0.39			0.41
I	114 (7.8)	19 (6.5)		88 (5.2)	19 (5.6)	
II	437 (29.7)	103 (35.0)		496 (29.3)	119 (35.2)	
III	275 (18.7)	57 (19.4)		483 (28.6)	89 (26.3)	
IV	34 (2.3)	5 (1.7)		61 (3.6)	9 (2.7)	
Missing/unknown	610 (41.5)	110 (37.4)		562 (33.3)	102 (30.2)	
Electrocardiography rhythm, n (%)			0.50			0.50
Sinus rhythm	855 (58)	185 (63)		824 (49)	171 (51)	
Atrial fibrillation	524 (35.6)	94 (32.0)		661 (39.1)	129 (38.2)	
Other	67 (4.6)	12 (4.1)		172 (10.2)	30 (8.9)	
Missing/unknown	24 (1.6)	3 (1.0)		33 (2.0)	8 (2.4)	
Ejection fraction			0.88			0.88
<30%	255 (17.3)	48 (16.3)		326 (19.3)	57 (16.9)	
30–39%	280 (19.0)	63 (21.4)		359 (21.2)	65 (19.2)	
40–49%	283 (19.3)	56 (19.0)		303 (17.9)	57 (16.9)	
≥50%	367 (25.0)	75 (25.5)		405 (24.0)	92 (27.2)	
Unknown	285 (19.4)	52 (17.7)		297 (17.6)	67 (19.8)	
Primary aetiology of HF, n (%)			0.23			0.24
Hypertension	229 (15.6)	37 (12.6)		234 (13.8)	43 (12.7)	
Ischaemic heart disease	183 (12.4)	35 (11.9)		229 (13.6)	41 (12.1)	
Dilating cardiomyopathy	27 (1.8)	2 (0.7)		35 (2.1)	9 (2.7)	
Alcohol cardiomyopathy	2 (0.1)	1 (0.3)		0 (0.0)	0 (0.0)	
Valvular heart disease	59 (4.0)	8 (2.7)		72 (4.3)	18 (5.3)	
Unknown	970 (66.0)	211 (71.8)		1120 (66.3)	227 (67.2)	

Continued

Table 2 Continued

	Incident HF			Prevalent HF		
	Without BC (N = 1470)	With BC (N = 294)	P-value	Without BC (N = 1690)	With BC (N = 338)	P-value
Treatment						
Beta-blocker, n (%)	921 (62.7)	184 (62.6)	1.00	1462 (86.5)	298 (88.2)	0.48
Agents acting on the renin–angiotensin system, n (%)	871 (59.3)	184 (62.6)	0.30	1393 (82.4)	290 (85.8)	0.15
Angiotensin-converting enzyme inhibitor	615 (41.8)	126 (42.9)	0.75	987 (58.4)	199 (58.9)	0.90
Angiotensin receptor blocker	328 (22.3)	70 (23.8)	0.59	561 (33.2)	122 (36.1)	0.31
Mineral corticoid receptor antagonist, n (%)	166 (11.3)	36 (12.2)	0.62	623 (36.9)	118 (34.9)	0.54
Calcium channel blockers, n (%)	374 (25.4)	77 (26.2)	0.83	438 (25.9)	81 (24.0)	0.50
Diuretics, n (%)	877 (59.7)	176 (59.9)	>0.99	1506 (89.1)	301 (89.1)	>0.99
Statins, n (%)	539 (36.7)	96 (32.7)	0.21	765 (45.3)	149 (44.1)	0.72
Aspirin, n (%)	636 (43.3)	120 (40.8)	0.48	932 (55.1)	161 (47.6)	0.01
Coronary revascularization, n (%)	166 (11.3)	24 (8.2)	0.12	274 (16.2)	40 (11.8)	<0.01
Device therapy, n (%)			>0.99			0.03
Implantable cardioverter-defibrillators	5 (0.3)	2 (0.7)		27 (1.6)	2 (0.6)	
Cardiac resynchronization therapy/ +implantable cardioverter-defibrillators	4 (0.3)	1 (0.3)		50 (3.0)	3 (0.9)	

BC, breast cancer; HF, heart failure.

ischaemic heart disease. The number of patients who received cardiac devices was very low in all groups. Devices were placed in only 3.0% ($n=50$) pHF patients without BC and in 0.9% ($n=3$) pHF patients with BC. These rates are lower than the implantation rates of 5–12% in the general Swedish HF population during the study period.³⁰ The SwedeHF may have missed patients treated with device therapy. Also treating physicians may be more careful with device treatment among HF patients with BC. Guidelines recommend initiation and titration of medication such as angiotensin-converting enzyme inhibitor and if indicated device therapy such as implantable cardioverter-defibrillators and/or cardiac resynchronization therapy.^{11,20} In these patients, biventricular pacing using a resynchronization device can lead to an improvement in longevity and reduces HF hospitalizations. Also, implantable cardioverter-defibrillator can prevent sudden death.³¹ However, SwedeHF does not collect electrocardiogram data on QRS duration, making it difficult to detect the true implantation rate. The angiotensin II receptor blocker, neprilysin inhibitor, which today is included in basic HF treatment and decrease mortality and morbidity, was not available in clinical practice during the current observation period.³²

Strengths and limitations of the study

We acknowledge this study has limitations. NPR has high validity for cardiovascular diagnoses, however, misclassification may have

occurred. By combining different registries, misclassification bias was minimized. Another limitation is that neither BC stage nor treatment was available from these registers. Therefore, we were unable to study these determinants. The number of HF deaths may be underestimated in this study as treating physicians may report HF death as death from CVD. In the iHF and pHF patient groups, patients without BC before SwedeHF enrolment have developed BC and metastases after enrolment in SwedeHF during follow-up of this study. This may be partly explaining the lack of difference in the risk of death from any-cause, CVD, and HF comparing patients with and without BC. As we hypothesized that potentially cardiotoxic cancer treatment increases the risk of these causes of death. Another limitation is that this study lacks information on left ventricular assist device (LVAD) and heart transplantation as these are reserved for selected patients with more advanced HF.³³ SwedeHF does not register advanced HF treatment such as vasoactive drugs, LVAD, or heart transplantation, thus any difference between the groups regarding these aspects are not studied.

Conclusions

To conclude, this study showed that HF patients with BC are not at increased risk of death from any-cause, CVD, and HF compared to HF patients without BC. Prevalent HF patients with BC had less often myocardial infarction and were less often treated with aspirin and

Table 3 Cumulative incidence all-cause, cardiovascular, and HF related mortality of 294 female patients with incident HF with BC compared to 1470 age-matched female patients with incident HF without BC; and 338 female patients with prevalent HF with BC compared to 1690 age-matched female patients with prevalent HF without BC enrolled in the Swedish HF Register between 2008 and 2013

	Incident HF		Prevalent HF	
	Without BC (N = 1470)	With BC (N = 294)	Without BC (N = 1690)	With BC (N = 338)
Total person years	3571	704	3652	785
All-cause mortality				
Cumulative incidence, % (95% CI)				
1 year	16.1 (14.1–18.0)	15.3 (11.0–19.5)	22.8 (20.7–24.8)	20.5 (15.9–24.7)
2 years	23.2 (20.9–25.5)	28.4 (22.5–33.8)	35.1 (32.6–37.5)	32.5 (27.0–37.7)
5 years	43.2 (39.5–46.6)	43.2 (34.8–50.5)	60.5 (57.1–63.6)	57.6 (50.0–64.0)
Number of events	462	95	754	151
HR, age adjusted (95% CI)	1.00 (Ref)	1.04 (0.83–1.29)	1.00 (Ref)	0.94 (0.79–1.12)
P-value		0.76		0.49
Cardiovascular mortality				
Cumulative incidence, % (95% CI)				
1 year	12.0 (10.3–13.8)	10.1 (6.5–13.6)	17.3 (15.4–19.2)	14.3 (10.3–18.1)
2 years	16.8 (14.8–18.9)	18.9 (13.7–23.8)	25.4 (23.0–27.7)	21.6 (16.7–26.3)
5 years	29.9 (26.4–33.2)	28.9 (20.9–36.1)	45.1 (41.3–48.6)	40.0 (32.2–46.9)
Number of events	307	57	503	95
HR, age adjusted (95% CI)	1.00 (Ref)	0.94 (0.71–1.24)	1.00 (Ref)	0.89 (0.71–1.10)
P-value		0.66		0.28
HF-related mortality				
Cumulative incidence, % (95% CI)				
1 year	1.6 (1.0–2.3)	1.5 (0.0–2.9)	3.0 (2.1–3.9)	2.9 (1.0–4.8)
2 years	2.2 (1.4–3.0)	2.0 (0.2–3.8)	5.1 (3.8–6.3)	3.4 (1.3–5.5)
5 years	4.0 (2.6–5.5)	2.9 (0.4–5.4)	11.4 (8.6–14.2)	6.9 (3.2–10.6)
Number of events	38	6	94	15
HR, age adjusted (95% CI)	1.00 (Ref)	0.80 (0.34–1.90)	1.00 (Ref)	0.75 (0.43–1.29)
P-value		0.62		0.30

BC, breast cancer; CI, confidence interval; HF, heart failure; HR, hazard ratio.

coronary revascularization than those without BC. Also, the patients with pHF and BC received less cardiovascular device therapies such as implantable cardioverter-defibrillators and/or cardiac resynchronization therapy than patients with pHF without BC. Future studies may investigate whether there are differences in pathogenesis comparing HF patients with BC and HF patients without BC. Adapting recommendations for HF patients with BC is important to improve treatment for specialized cardiology outpatient clinics.

Supplementary material

Supplementary material is available at *European Heart Journal – Quality of Care and Clinical Outcomes* online.

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Figure 2 Kaplan–Meier estimates of cumulative incidence of deaths due to any cause (A), cardiovascular disease (B), and heart failure (C) in 3972 women enrolled in the Heart Failure Register. Incident heart failure and prevalent heart failure group included women enrolled within 1 month and after 1 month after heart failure diagnosis, respectively.

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