Circulation: Heart Failure

ORIGINAL ARTICLE

Characteristics and Outcomes of Women Developing Heart Failure After Early Stage Breast Cancer Chemotherapy

A Population-Based Matched Cohort Study

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BACKGROUND: The prognosis of heart failure (HF) after early stage breast cancer (EBC) treatment with anthracyclines or trastuzumab is not well-characterized.

METHODS: Using administrative databases, women diagnosed with HF after receiving anthracyclines or trastuzumab for EBC in Ontario during 2007 to 2017 (the EBC-HF cohort) were categorized by cardiotoxic exposure (anthracycline alone, trastuzumab alone, sequential therapy with both agents) and matched on age with ≤3 cancer-free HF controls to compare baseline characteristics. To study prognosis after HF onset, we conducted a second match on age plus important HF prognostic factors. The cumulative incidence function was used to describe risk of hospitalization or emergency department visits (hospital presentations) for HF and cardiovascular death.

RESULTS: A total of 804 women with EBC developed HF after anthracyclines (n=312), trastuzumab (n=112), or sequential therapy (n=380); they had significantly fewer comorbidities than 2411 age-matched HF controls. After the second match, the anthracycline-HF cohort had a similar 5-year incidence of HF hospital presentations (16.5% [95% CI, 12.0%–21.7%]) as controls (17.1% [95% CI, 14.4%–20.1%]); the 5-year incidence was lower than matched controls for the trastuzumab-HF (9.7% [95% CI, 4.7%–16.9%]; controls 16.4% [95% CI, 12.1%–21.3%]; P=0.03) and sequential-HF cohorts (2.7% [95% CI, 1.4%–4.8%]; controls 10.8% [95% CI, 8.9%–13.0%]; P<0.001). At 5 years, the incidence of cardiovascular death was 2.9% (95% CI, 1.2%–5.9%) in the anthracycline-HF cohort vs. 9.5% (95% CI, 6.9%–12.6%) in controls, and 1.7% (0.6%–3.7%) for women developing HF after trastuzumab vs. 4.3% (95% CI, 3.1–5.8%) for controls.

CONCLUSIONS: Women developing HF after cardiotoxic EBC chemotherapy have fewer comorbidities than cancer-free women with HF; trastuzumab-treated women who develop HF have better prognosis than matched HF controls.

Key Words: anthracyclines ■ cardiotoxicity ■ heart failure ■ hospitalization ■ trastuzumab

As survival improves after early stage breast cancer (EBC) diagnosis,[1] treatment-related complications have become important considerations.[2] Anthracycline- and trastuzumab-based chemotherapy are cardiotoxic, contributing to an increased risk of heart failure (HF) in EBC survivors.[3,4] While several studies report a high incidence of HF following EBC chemotherapy,[3–5] it remains unclear if this has similar outcomes as HF from other causes. There are less data specifically pertaining to EBC survivors, who constitute

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WHAT IS NEW?

- This study shows that women diagnosed with heart failure (HF) after cardiotoxic early stage breast cancer chemotherapy have fewer comorbidities than similarly aged controls developing HF from other causes.
- After matching on key prognostic factors, women developing HF after trastuzumab had a lower risk of hospitalization or emergency department visits for HF compared with HF controls.
- Women developing HF after cardiotoxic chemotherapy may have a lower risk of cardiovascular death than other women with HF from other causes.

WHAT ARE THE CLINICAL IMPLICATIONS?

- Early stage breast cancer patients developing HF after cardiotoxic chemotherapy may be less likely to have contraindications to guideline-directed HF treatment than similarly aged women developing HF from other causes.
- Women developing HF after trastuzumab have a better prognosis than HF from other causes. This should lower the threshold for using trastuzumab in the treatment of women with early stage breast cancer at higher risk for cardiotoxicity.
- The low risk of adverse outcomes in women who develop HF after trastuzumab is relevant to decision-making about continuing or stopping trastuzumab after development of mild cardiotoxicity.

Nonstandard Abbreviations and Acronyms

CVD	cardiovascular disease
EBC	early stage breast cancer
ED	emergency department
HF	heart failure
IHD	ischemic heart disease
IQR	interquartile ranges
OHIP	Ontario Health Insurance Plan

a large survivorship group with better prognosis than most cancers,[1] thus making CVD more relevant as a competing risk.[2–4,6,7] Today, patient counseling about the risks of anthracycline and trastuzumab is driven by data on the incidence of cardiotoxicity without a good understanding of its consequences. This is an important distinction which needs to be considered when making chemotherapy decisions that balance the risk of cancer recurrence against those of HF.

We compared the characteristics and outcomes of women with EBC who developed HF after anthracyclines or trastuzumab with cancer-free women who developed HF from other causes. Previously, we observed that EBC patients receiving cardiotoxic chemotherapy had fewer comorbidities than women with alternate treatments.[4] Moreover, HF outside the cancer setting is usually driven by long-term, patient-specific factors (eg, ischemic heart disease [IHD], hypertension, diabetes, alcohol, and genetics), while chemotherapy is usually a short-term exposure administered by health care providers. Accordingly, we hypothesized that women developing HF after EBC chemotherapy would have a lower prevalence of preexisting CVD, its risk factors, and noncardiovascular comorbidities. We also hypothesized that women with HF following EBC chemotherapy have a better prognosis than women with HF from other causes.

METHODS

Data Sources

We conducted a retrospective population-based matched cohort study in Ontario, Canada, where medically necessary services are universally available to all residents under the Ontario Health Insurance Plan. This study was conducted with linkage of administrative databases using unique encoded identifiers at ICES (formerly the Institute for Clinical Evaluative Sciences) as previously described.[3,4,6] The use of data in this project was authorized under section 45 of Ontario's Personal Health Information Protection Act, which does not require review by a Research Ethics Board. While data sharing agreements prohibit ICES from making the data set publicly available, access may be granted to those who meet prespecified criteria for confidential access, available at https://www.ices.on.ca/DAS.

Cohort Creation

We identified all women with a first breast cancer diagnosis between January 1, 2007, and December 31, 2017. We also used a validated algorithm[8] to identify all women who had their first-ever diagnosis of HF in Ontario between 2007 and 2017. Women were included if they had at least one diagnostic code indicating an in-hospital diagnosis of HF, or ≥2 diagnostic codes for HF within 365 days of each other based on emergency department (ED) records or physician billing claims. Patients were categorized by setting of HF diagnosis: hospital, ED without hospitalization, or outpatient. For patients diagnosed in hospital, the index date was that of discharge. For women diagnosed without hospitalization, the index date was the date of the first documentation of HF.

We applied the following exclusion criteria to all women: missing or invalid key data (Ontario Health Insurance Plan number, age, sex), age <18 years or >105 years, prior cancer (excluding the index breast cancer), long-term care residence, <1 year of Ontario Health Insurance Plan eligibility, and death on/before the HF diagnosis date. For cancer-free women with HF, we excluded those without physician contact in the year preceding HF diagnosis. We also applied the following exclusions to women with breast cancer: stage 0 disease, stage 4/distant metastases, death within 2 weeks of cancer diagnosis (since they may have had unrecognized advanced cancer), chemotherapy/radiation before cancer diagnosis, no exposure to anthracyclines or trastuzumab within 1 year of cancer

diagnosis, exposure to atypical or undetermined chemotherapy for EBC within 1 year of EBC diagnosis (including women in clinical trials), and HF diagnosis before chemotherapy initiation.

The women with EBC who met study criteria and developed new-onset HF following cardiotoxic chemotherapy for EBC are henceforth referred to as the EBC-HF cohort. This cohort was subcategorized into those treated with anthracyclines only, trastuzumab only, or sequential therapy with both agents (henceforth referred to as the anthracycline-HF, trastuzumab-HF, and sequential-HF cohorts, respectively). We identified cancer-free controls from the remaining pool of cancer-free women with newly diagnosed HF. The index date was that of HF diagnosis.

We created 2 matched samples, which were each used to fulfill one study objective. In each matched sample, women in the EBC-HF cohort were matched with up to 3 cancer-free HF controls. Since the pool of potential controls was substantially larger than the EBC-HF cohort, this allowed us to increase study power while being unlikely to introduce meaningful bias. To study differences in baseline characteristics between the 2 groups, we matched women in the EBC-HF cohort with cancer-free controls on dates of birth and HF diagnosis (±180 days). This is henceforth referred to as the first match. To study outcomes after HF diagnosis, we conducted a second match that additionally accounted for important HF prognostic factors on the index date since we hypothesized that the EBC-HF cohort would be healthier than cancer-free HF controls. Accordingly, we matched women in the 2 groups on age and date of HF diagnosis (as in the first match) plus setting of HF diagnosis (hospital, ED, or outpatient), IHD,[9] acute myocardial infarction,[10] valvular disease, hypertension,[11] diabetes,[12] and chronic kidney disease,[13] thereby forcing controls to be identical to EBC patients on these important prognostic factors. This analysis excluded women who died during the index hospitalization or ED visit (to enable follow-up), or had multiple HF events on the index date (eg, admitted to hospital the same day after discharge from ED) since it was important to avoid ambiguity when matching on this important prognostic factor. This is henceforth referred to as the second match.

The primary outcome was a composite of hospitalizations or ED visits for HF (henceforth referred to as hospital presentations). Death before HF hospital presentation was treated as a competing risk. The date of last follow-up was March 31, 2019. The secondary outcome was cardiovascular death, with noncardiovascular death treated as a competing risk. Cause of death data was unavailable beyond December 31, 2018, making that the date of last follow-up for cardiovascular death. Accordingly, the cardiovascular death analysis was limited to women developing HF between 2007 and 2016.

Statistical Analysis

Baseline characteristics were summarized using medians (with interquartile ranges [IQR]) for continuous variables and counts (with percentages) for categorical variables. Statistical significance of differences between the EBC-HF and control groups was determined using univariable regression estimated using generalized estimating equations to account for matching.

Outcomes were assessed separately for the anthracycline-HF, trastuzumab-HF, and sequential-HF cohorts, with comparison to their respective controls. To estimate the uptake of guideline-directed medical therapy for HF, we determined the proportion of women aged >66 years who filled at least one prescription for an angiotensin antagonist, β-blocker, or mineralocorticoid receptor antagonist in the 6 months following HF diagnosis. Statistical significance was determined using logistic regression models estimated using generalized estimating equations. The cumulative incidence function was used to describe the risk of outcomes over time; statistical significance was determined by a univariable Fine-Gray regression model accounting for matched sets.[14] All analyses were conducted using SAS Version 9.4 (SAS Institute Inc, Cary, NC). Statistical significance was defined as a 2-tailed $P<0.05$. Since we used administrative databases encompassing the whole provincial population, missing data were assumed to be negligible unless stated otherwise. Cells with <6 individuals are hidden as per ICES institutional privacy policies.

Sensitivity Analyses

We considered the possibility that the EBC-HF cohort may have better outcomes due to inclusion of women with asymptomatic cardiac dysfunction detected by routine screening during chemotherapy. Thus, we studied the consistency of the association in 2 EBC subgroups that are less likely to have asymptomatic cardiac dysfunction (and their matched controls): (1) women diagnosed with HF >12 months after starting chemotherapy and (2) women whose first-ever HF diagnosis was made in-hospital. We also conducted a subgroup analysis after excluding women with prior IHD. The fourth sensitivity analysis used an outcome definition that was restricted to hospitalizations where HF was the most responsible diagnosis (ie, excluding ED visits). We studied the consistency of association by comparing the HR associated with EBC status from Fine-Gray regression models incorporating the full cohort with the HR from models limited to these subgroups.

RESULTS

Baseline Characteristics

Between 2007 and 2017, 25216 women received anthracyclines or trastuzumab (16546 anthracyclines only, 2532 trastuzumab only, 6138 sequential therapy). The inclusion criteria were fulfilled by 804 women who constituted the EBC-HF cohort. We identified 130541 cancer-free women who developed HF and were eligible for selection as controls (Figure I in the Data Supplement). To compare baseline characteristics at time of HF diagnosis, we matched 804 women from the EBC-HF cohort to 2411 cancer-free controls on date of birth and date of HF diagnosis (Table). The median age at HF diagnosis for both cohorts was 61 years (IQR, 52–69 years). Women in the EBC-HF cohort were more likely to be diagnosed with HF as outpatients (rather than hospital or ED) compared with cancer-free controls and less likely to have preexisting IHD, atrial fibrillation, hypertension, diabetes, or noncardiovascular comorbidities. They were also less likely to reside in neighborhoods with lower incomes than cancer-free HF controls.

Table I in the Data Supplement details baseline characteristics of the anthracycline-HF, trastuzumab-HF, and

Table. Baseline Characteristics of Women Who Developed HF After Exposure to Anthracyclines or Trastuzumab (EBC-HF Cohort) and Cancer-Free Controls Who Developed HF and Were Matched on Dates of Birth and HF Diagnosis (±180 Days)

	EBC-HF cohort	Cancer-free controls	*P* value
n	804	2411	
Age, y, median (interquartile range)	61 (52–69)	61 (52–69)	*
Year of HF diagnosis			0.16
2007, n (%)	6 (0.8)	20 (0.8)	
2008, n (%)	33 (4.1)	101 (4.2)	
2009, n (%)	33 (4.1)	97 (4.0)	
2010, n (%)	52 (6.5)	153 (6.3)	
2011, n (%)	62 (7.7)	194 (8.0)	
2012, n (%)	74 (9.2)	212 (8.8)	
2013, n (%)	70 (8.7)	212 (8.8)	
2014, n (%)	86 (10.7)	258 (10.7)	
2015, n (%)	113 (14.1)	342 (14.2)	
2016, n (%)	125 (15.6)	369 (15.3)	
2017, n (%)	150 (18.7)	453 (18.8)	
Source of HF diagnosis			<0.001
Hospitalization, n (%)	186 (23.1)	1017 (42.2)	
Emergency department, n (%)	14 (1.7)	50 (2.1)	
Outpatient (physician billing), n (%)	604 (75.1)	1344 (55.7)	
Income quintile			<0.001
Missing, n (%)	<6†	6 (0.2)	
1, n (%)	160–164†	671 (27.8)	
2, n (%)	159 (19.8)	529 (21.9)	
3, n (%)	171 (21.3)	468 (19.4)	
4, n (%)	169 (21.0)	383 (15.9)	
5, n (%)	140 (17.4)	354 (14.7)	
Rural residence, n (%)	89 (11.1)	307 (12.7)	0.20
Ischemic heart disease, n (%)	112 (13.9)	738 (30.6)	<0.001
Acute myocardial infarction, n (%)	23 (2.9)	209 (8.7)	<0.001
Percutaneous coronary intervention, n (%)	19 (2.4)	210 (8.7)	<0.001
Coronary artery bypass graft surgery, n (%)	6 (0.8)	60 (2.5)	0.005
Atrial fibrillation, n (%)	103 (12.8)	408 (16.9)	0.003
Diabetes, n (%)	187 (23.3)	926 (39.4)	<0.001
Hypertension, n (%)	428 (53.3)	1644 (68.2)	<0.001
Stroke, n (%)	<6†	72 (3.0)	<0.001
Peripheral vascular disease, n (%)	45 (5.6)	293 (12.2)	<0.001
Valvular disease, n (%)	11 (1.4)	100 (4.2)	<0.001
Chronic kidney disease, n (%)	41 (5.1)	280 (11.6)	<0.001
Asthma, n (%)	49 (6.1)	195 (8.1)	0.06
Chronic obstructive pulmonary disease, n (%)	82 (10.2)	412 (17.1)	<0.001
Excessive alcohol use, n (%)	11 (1.4)	90 (3.7)	0.002
Dementia, n (%)	15 (1.9)	66 (2.7)	0.14
Data below pertain to patients aged ≥66 y (n=1188)			
n	297	891	
Angiotensin-converting enzyme inhibitor, n (%)	112 (37.7)	353 (39.6)	0.57
Angiotensin receptor blocker, n (%)	100 (33.7)	276 (31.0)	0.38
β-blocker, n (%)	145 (48.8)	436 (48.9)	0.97
Mineralocorticoid receptor antagonist, n (%)	20 (6.7)	46 (5.2)	0.31
Calcium channel blocker, n (%)	100 (33.7)	394 (44.2)	0.001
Thiazide diuretic, n (%)	99 (33.3)	328 (36.8)	0.29
Loop diuretic, n (%)	114 (38.4)	340 (38.2)	0.94
Statins, n (%)	145 (48.8)	535 (60.0)	<0.001

EBC indicates early stage breast cancer; and HF, heart failure.

*Women in the 2 groups were matched on these variables.

†Cells with <6 individuals are suppressed as per ICES institutional privacy policies. To prevent the back calculation of suppressed cells, an additional cell may be suppressed.

sequential-HF cohorts and their matched controls. Women in the trastuzumab-HF cohort (median age 66 years, IQR, 54–76) were older than those in the anthracycline-HF cohort (median age 65, IQR, 57–72 years), who were in turn older than the sequential-HF cohort (median age 57, IQR, 50–65 years). Women in the anthracycline-HF cohort were more likely to be diagnosed with HF in-hospital (38.8%) relative to the trastuzumab-HF (18.8%) and sequential-HF (11.6%) patients ($P<0.001$). Anthracycline-treated women were first diagnosed with HF in similar settings as their cancer-free controls. Conversely, women in the trastuzumab-HF and sequential-HF cohorts were more likely diagnosed in the outpatient setting than their matched controls. As illustrated in Figure II in the Data Supplement, HF was diagnosed earlier in trastuzumab-exposed women compared with women in the anthracycline-HF cohort. Anthracycline-treated women were diagnosed at a median of 987 (303–1919) days after starting chemotherapy, compared with 318 (206–656) days for the trastuzumab-HF and 339 (231–565) days for the sequential-HF cohorts.

Hospital Presentations for HF

After the second match, which additionally incorporated important HF prognostic factors (setting of HF diagnosis, IHD, acute myocardial infarction, valvular disease, hypertension, diabetes, and chronic kidney disease), we retained 750 women in the EBC-HF cohort and 2199 cancer-free controls. These matching criteria yielded a healthier subset of patients with HF (Table II in the Data Supplement) than those produced by the first match. We excluded 19 EBC-HF patients from the first match who died during the hospitalization/ED visit when HF was first diagnosed or had multiple HF events on the index date and were unable to match 35 women with controls given the more stringent matching criteria for the second match. Women in the EBC-HF cohort were more likely to be prescribed some elements of guideline-directed medical therapy than cancer-free controls in the 6 months following HF diagnosis (Table III in the Data Supplement).

Over a median follow-up of 3.6 years (IQR, 1.9–6.3 years), 62 women (8.3%) in the EBC-HF cohort were hospitalized or visited an ED for HF, compared with 299 women (13.8%) in the control group. The risk of HF hospital presentations in the EBC-HF cohort relative to cancer-free controls differed based on the cardiotoxic exposure. Figure 1 illustrates that there was no difference ($P=0.69$) between the anthracycline-HF cohort (5-year incidence 16.5% [95% CI, 12.0%–21.7%]) and matched controls (17.1% [95% CI, 14.4%–20.1%]). Conversely, women in the trastuzumab-HF cohort had a lower risk ($P=0.03$) of HF hospital presentations (5-year incidence 9.7% [95% CI, 4.7%–16.9%]) than matched controls (16.4% [95% CI, 12.1%–21.3%]), as illustrated in Figure 2. Figure 3 illustrates even larger differences in the risk of HF hospital presentations ($P<0.001$) between the sequential-HF cohort (5-year incidence 2.7% [95% CI, 1.4%–4.8%]) and their cancer-free controls (10.8% [95% CI, 8.9%–13.0%]). Sensitivity analyses within the anthracycline-HF group showed that the incidence of hospital presentations did not significantly differ between the EBC and control groups (Figure 4). The direction of the association between EBC status and incidence of outcomes was consistent across sensitivity analyses conducted in trastuzumab-exposed women (Figure 4).

Cardiovascular Death

This analysis included 603 women from the EBC-HF cohort and 1763 cancer-free controls, whose baseline

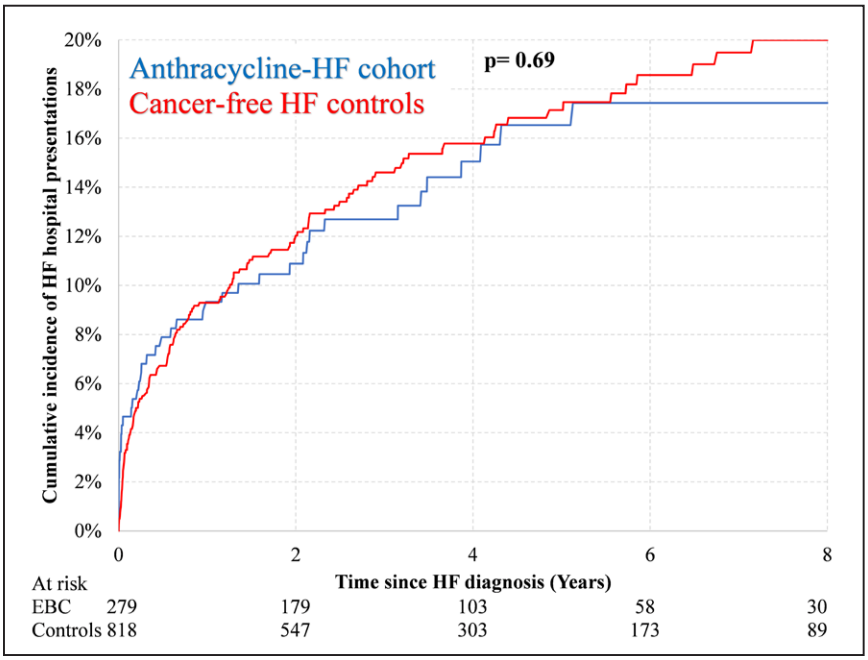

Figure 1. Cumulative incidence of hospital presentations for heart failure (HF), depicted in blue for women treated with anthracyclines without trastuzumab and red for cancer-free controls who were matched on age, year of HF diagnosis, setting of HF diagnosis, ischemic heart disease, acute myocardial infarction, valvular disease, hypertension, diabetes, and chronic kidney disease.
EBC indicates early stage breast cancer.

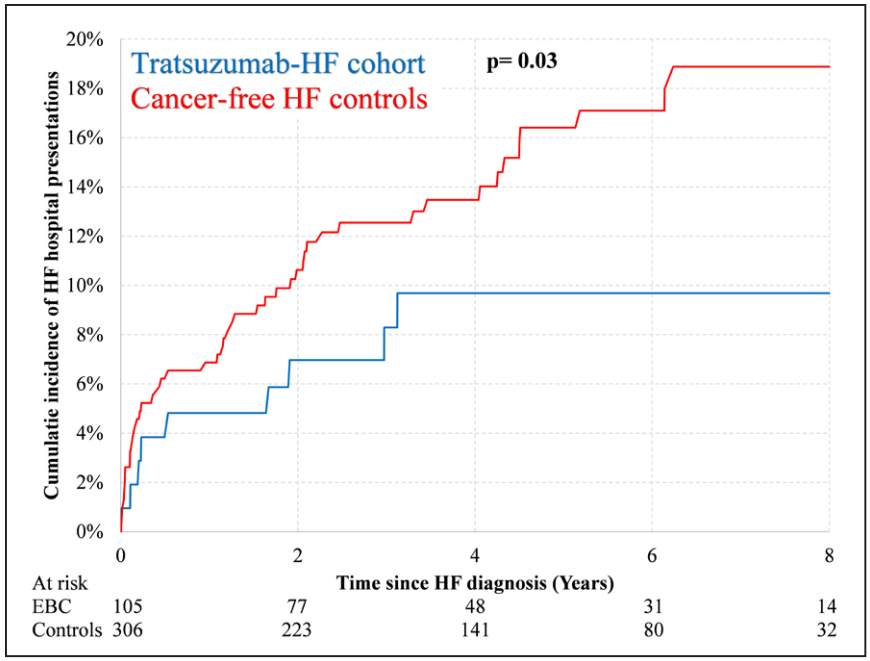

Figure 2. Cumulative incidence of hospital presentations for heart failure (HF), depicted in blue for women treated with trastuzumab (but not anthracyclines) and red for cancer-free controls who were matched on age, year of HF diagnosis, setting of HF diagnosis, ischemic heart disease, acute myocardial infarction, valvular disease, hypertension, diabetes, and chronic kidney disease.
EBC indicates early stage breast cancer.

characteristics are detailed in Table IV in the Data Supplement. Over a median follow-up of 3.5 (IQR, 2.0–6.0) years, 13 (2.2%) women from the EBC-HF cohort died from CVD, while 34 (5.6%) died from cancer and 37 (6.1%) died of other causes. Within the control cohort, 89 (5.1%) women died from CVD, 42 (2.4%) died from cancer, and 126 (7.2%) died of other causes. Given low event counts, results were pooled for women developing HF after trastuzumab (trastuzumab-HF and sequential-HF cohorts). Figure 5 illustrates a lower risk of cardiovascular death in the anthracycline-HF cohort compared with their cancer-free controls (P=0.05). The 5-year incidence of cardiovascular death was 2.9% (95% CI, 1.2%–5.9%) in the anthracycline-HF cohort and 9.5% (95% CI, 6.9%–12.6%) in cancer-free controls. There was a significantly lower risk of cardiovascular death (P=0.03) for women developing HF after trastuzumab, as illustrated in Figure 6. The 5-year incidence of cardiovascular death was 1.7% (0.6%–3.7%) for women developing HF after trastuzumab and 4.3% (95% CI, 3.1%–5.8%) for matched controls.

DISCUSSION

This population-based matched cohort study compared the characteristics and outcomes of women diagnosed

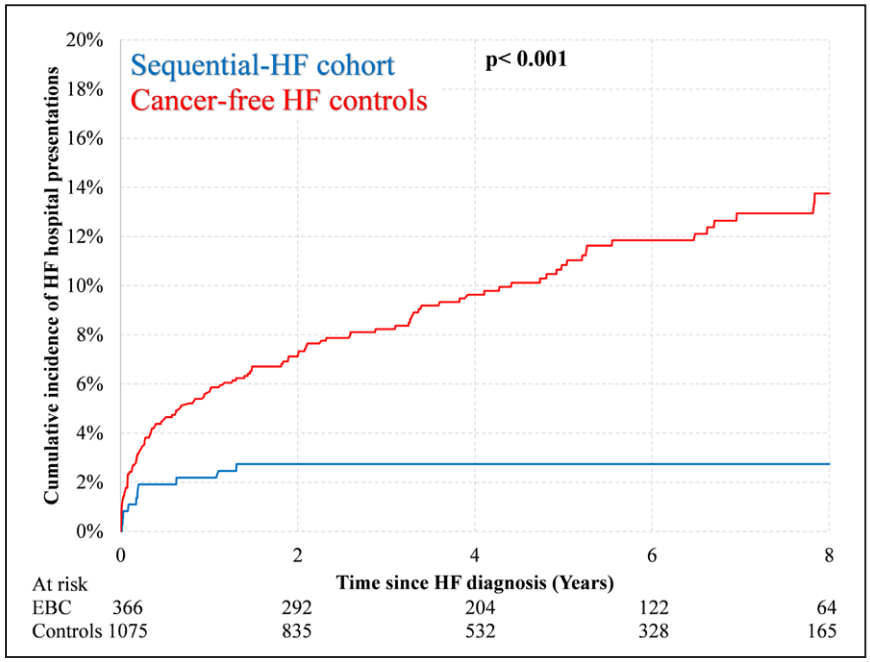

Figure 3. Cumulative incidence of hospital presentations for heart failure (HF), depicted in blue for women who received sequential therapy and red for cancer-free controls who were matched on age, year of HF diagnosis, setting of HF diagnosis, ischemic heart disease, acute myocardial infarction, valvular disease, hypertension, diabetes, and chronic kidney disease.
EBC indicates early stage breast cancer.

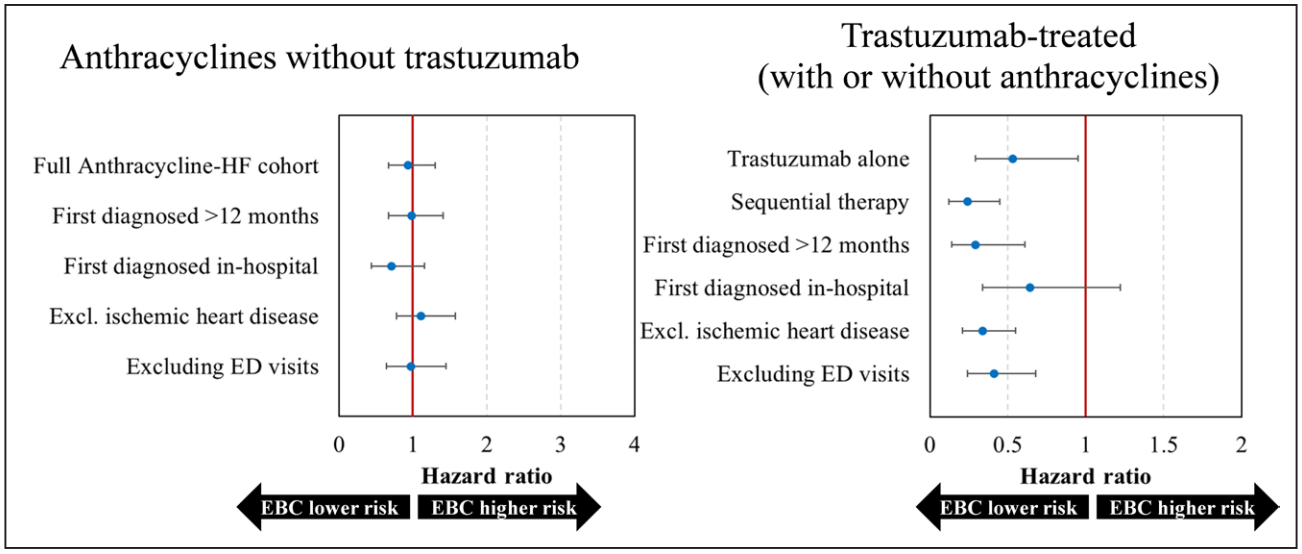

Figure 4. Summary of the results of sensitivity analyses for women who developed heart failure (HF) after exposure to anthracyclines without trastuzumab and their matched controls (left) and women who developed HF after exposure to trastuzumab (with and without anthracyclines) and their matched controls (right).
We present the hazard ratio associated with early stage breast cancer (EBC) status from Fine-Gray regression models limited to EBC-HF patients in each subgroup and their matched controls. EBC indicates early stage breast cancer; and ED, emergency department.

with HF after EBC chemotherapy with similarly aged cancer-free controls who developed HF from other causes. Our main findings (summarized in Figure 7) are (1) women in the EBC-HF cohort had fewer comorbidities than cancer-free HF controls; (2) women developing HF after trastuzumab-based chemotherapy had a lower risk of HF hospital presentations than cancer-free HF controls who were matched on setting of HF diagnosis, IHD, acute myocardial infarction, valvular disease, hypertension, diabetes, and chronic kidney disease, while the anthracycline-HF cohort had similar risk to matched controls; and (3) women developing HF after anthracyclines or trastuzumab may have a lower risk of cardiovascular death than cancer-free HF controls.

Trastuzumab-associated cardiomyopathy may have better outcomes because it is often reversible, in contrast to the less-reversible cardiotoxicity that is classically associated with anthracyclines.[15] In our study, women diagnosed with HF after trastuzumab (with or without anthracyclines) were more likely to be diagnosed in the outpatient setting within a year of chemotherapy initiation (ie, during treatment) than those treated with anthracyclines alone. This likely reflects earlier detection of mild cardiac dysfunction through cardiac surveillance, which

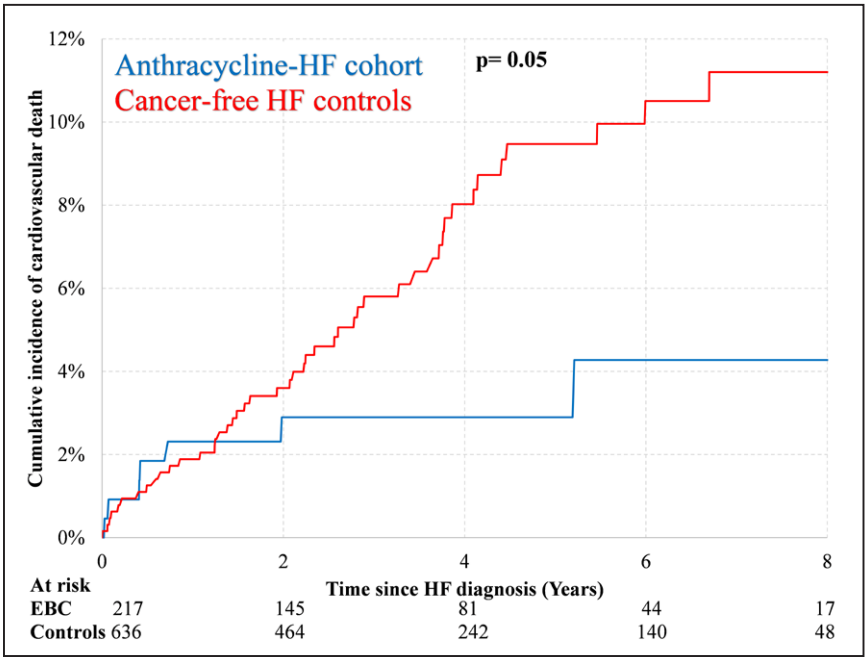

Figure 5. Cumulative incidence of cardiovascular death, depicted in blue for the anthracycline-heart failure (HF) cohort and red for cancer-free controls who were matched on age, year of HF diagnosis, setting of HF diagnosis, ischemic heart disease, acute myocardial infarction, valvular disease, hypertension, diabetes, and chronic kidney disease.
EBC indicates early stage breast cancer.

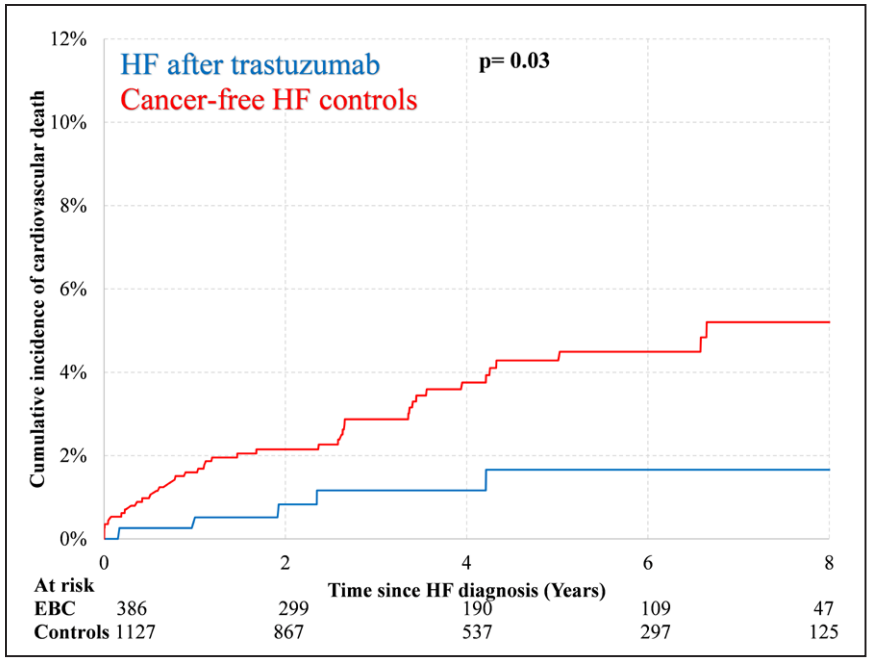

Figure 6. Cumulative incidence of cardiovascular death, depicted in blue for a combination of the trastuzumab-heart failure (HF) and sequential-HF groups, and red for cancer-free controls who were matched on age, year of HF diagnosis, setting of HF diagnosis, ischemic heart disease, acute myocardial infarction, valvular disease, hypertension, diabetes, and chronic kidney disease.
EBC indicates early stage breast cancer.

is mandated for trastuzumab reimbursement in Ontario. Interestingly, women developing HF after anthracyclines without trastuzumab had a worse prognosis than those diagnosed after sequential therapy or trastuzumab alone. This may be explained by differences in the setting of HF presentation and delays between chemotherapy initiation and recognition of HF. Compared with trastuzumab-treated women, those developing HF after anthracyclines alone were diagnosed after longer delays following chemotherapy and were less likely to be diagnosed in the outpatient setting. Long-term follow-up studies support the divergent temporal patterns that we observed between chemotherapy initiation and recognition of HF in trastuzumab-treated women and those treated with anthracyclines alone.[16–21]

Although unselected women with EBC have more cardiovascular risk factors than cancer-free women,[4] EBC patients receiving cardiotoxic chemotherapy have fewer comorbidities than untreated patients.[4,6] Here, we observe that this channeling bias propagates into the baseline characteristics of the EBC-HF cohort, which appeared healthier than cancer-free HF controls. This may also reflect the fact that HF after EBC is driven by chemotherapy, which is usually a self-limited insult, rather than long-term patient-specific factors that underlie most causes of HF (eg, IHD). The recognition of a lower comorbidity burden in the EBC-HF cohort is an important, clinically relevant observation since it is an important predictor of prognosis and can limit treatment options after HF diagnosis.[22,23] Since the EBC-HF cohort had less comorbidities than cancer-free HF controls, we studied outcomes after conducting a second match to achieve balance on important prognostic factors, but this also meant that the control group that we studied was healthier than typical HF cohorts.

Most prior research on HF prognosis following chemotherapy pertains to anthracycline-associated HF. A seminal paper reported 3.5-fold higher mortality in 15 patients with anthracycline-induced cardiomyopathy compared with 616 patients with idiopathic cardiomyopathy but did not distinguish cancer-related from cardiovascular deaths.[24] Other studies were mostly limited to patients with advanced HF and cannot be generalized to most patients developing HF after chemotherapy.[21,25–27] Importantly, these studies did not distinguish between different cancers. Women with breast cancer have better cancer-specific prognoses than individuals with other malignancies.[1] Thus, these studies may be inappropriate to guide decisions pertaining to the risk-benefit balance of potentially cardiotoxic chemotherapy for EBC.

There are minimal data on outcomes for HF following trastuzumab. Our group and others have shown that women treated with sequential therapy have the highest likelihood of being diagnosed with HF.[3,5] This study provides important context to such data. Although trastuzumab-treated women are most likely to be diagnosed with HF, the subsequent cardiovascular prognosis after its recognition is relatively good. Thus, we highlight an important distinction between the incidence of cardiotoxicity and its associated consequences, a concept that may be underappreciated in cardio-oncology. This has important implications considering the current motivation for continuing trastuzumab after development of stage-B HF.[28] Recent studies[29,30] have demonstrated that ≈10% of such women will progress to Stage-C HF despite cardioprotective therapies and close follow-up. Our study provides further perspective by demonstrating that the prognosis of these HF cases may be better than HF from other causes.

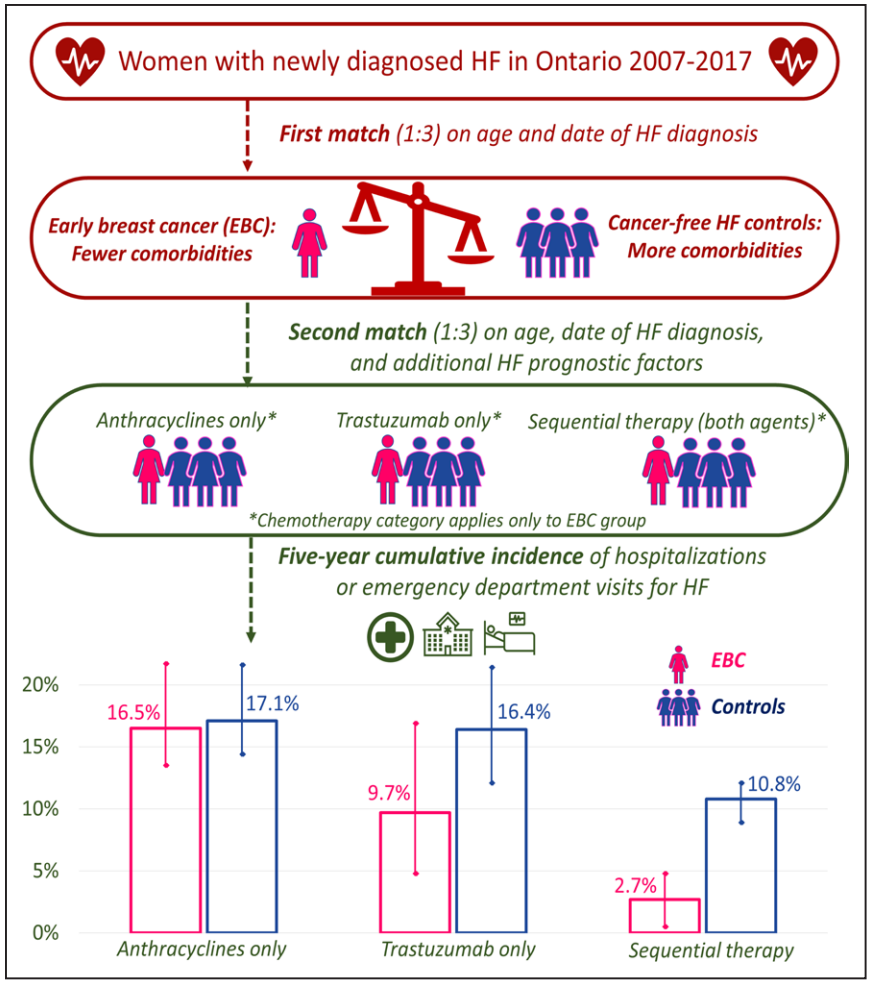

Figure 7. Graphical abstract summarizing overall study findings. EBC indicates early stage breast cancer; and HF, heart failure.

This study has several limitations. Our reliance on administrative data meant that we were unable to study functional status and quality of life. Our outcome definitions were limited to hospital-based and fatal events to prioritize specificity. The median follow-up was also relatively short. Moreover, we could not account for medication use in women aged <66 years or for other relevant data such as ejection fraction, HF subtype (reduced versus preserved ejection fraction), smoking, and obesity. There is also potential for residual confounding, since trastuzumab-treated women were likely diagnosed with milder or subclinical HF due to screening practices. Nonetheless, these are representative of HF cases included in most studies reporting estimates of cardiotoxicity incidence that are communicated to patients.

CONCLUSIONS

Women developing HF after anthracycline and trastuzumab treatment for EBC had less comorbidities than women who developed HF from other causes. When HF occurred after trastuzumab, it was associated with a lower risk of future HF hospital presentations than matched controls. Conversely, women developing HF after anthracyclines had a comparable risk of HF hospital presentations as matched controls. The risk of cardiovascular death was lower in women developing HF after EBC chemotherapy than those developing HF from other causes. These data provide important context to the reported incidence of cardiotoxicity after EBC chemotherapy.

ARTICLE INFORMATION

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Supplemental Material

Tables I–IV
Figures I–II

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