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ARTICLE

Risk of Heart Failure in Breast Cancer Patients After Anthracycline and Trastuzumab Treatment: A Retrospective Cohort Study

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Background Clinical trials demonstrated that women treated for breast cancer with anthracycline or trastuzumab are at increased risk for heart failure and/or cardiomyopathy (HF/CM), but the generalizability of these findings is unknown. We estimated real-world adjuvant anthracycline and trastuzumab use and their associations with incident HF/CM.

Methods We conducted a population-based, retrospective cohort study of 12 500 women diagnosed with incident, invasive breast cancer from January 1, 1999 through December 31, 2007, at eight integrated Cancer Research Network health systems. Using administrative procedure and pharmacy codes, we identified anthracycline, trastuzumab, and other chemotherapy use. We identified incident HF/CM following chemotherapy initiation and assessed risk of HF/CM with time-varying chemotherapy exposures vs no chemotherapy. Multivariable Cox proportional hazards regression models were used to estimate hazard ratios (HRs) and 95% confidence intervals (CIs) with adjustment for age at diagnosis, stage, Cancer Research Network site, year of diagnosis, radiation therapy, and comorbidities.

Results Among 12 500 women (mean age = 60 years, range = 22–99 years), 29.6% received anthracycline alone, 0.9% received trastuzumab alone, 3.5% received anthracycline plus trastuzumab, 19.5% received other chemotherapy, and 46.5% received no chemotherapy. Anthracycline and trastuzumab recipients were younger, with fewer comorbidities than recipients of other chemotherapy or none. Compared with no chemotherapy, the risk of HF/CM was higher in patients treated with anthracycline alone (adjusted HR = 1.40, 95% CI = 1.11 to 1.76), although the increased risk was similar to other chemotherapy (adjusted HR = 1.49, 95% CI = 1.25 to 1.77); the risk was highly increased in patients treated with trastuzumab alone (adjusted HR = 4.12, 95% CI = 2.30 to 7.42) or anthracycline plus trastuzumab (adjusted HR = 7.19, 95% CI = 5.00 to 10.35).

Conclusions Anthracycline and trastuzumab were primarily used in younger, healthier women and associated with increased HF/CM risk compared with no chemotherapy. This population-based observational study complements findings from clinical trials on cancer treatment safety.

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Breast cancer is one of the most common cancers in the United States with an estimated 232 620 new diagnoses in 2011 (1). Chemotherapeutic regimens for invasive breast cancer in women include neoadjuvant or adjuvant anthracycline in combination with cyclophosphamide (2). A major advance in breast cancer treatment has been the incorporation of trastuzumab, a monoclonal antibody against HER2/neu. Approximately 20%–25% of women with breast cancer overexpress HER2 and are recommended for trastuzumab therapy following the completion of anthracycline therapy (3–5). Randomized clinical trials have demonstrated that these regimens are highly effective in improving disease-free survival (6–9); however, side effects are not minimal.

Data from clinical trials indicate that anthracycline use is associated with an approximate 2% increase (10–14) in heart failure and/or cardiomyopathy (HF/CM) incidence, and anthracycline followed by trastuzumab is associated with an approximate 4% increase (15–19). Clinical trial findings were critical in leading to prescribing warnings and protocols for regular cardiac function monitoring before and during treatment (20–22). However, trials typically exclude older women (eg, aged ≥ 70 years) and women with major comorbidities; therefore, the association between anthracycline and/or trastuzumab use and HF/CM in this population is not well understood. The effectiveness of these treatments and risk of cardiotoxicity may differ in community practice. Three

observational studies using Surveillance, Epidemiology, and End Results (SEER) Medicare data have evaluated HF/CM incidence following treatment with anthracycline, but they were limited to older women (aged ≥ 65 years) and did not evaluate trastuzumab (23–25). Therefore, broader population-based estimates of HF/CM risk associated with anthracycline and trastuzumab are unknown.

Using data from the health maintenance organization (HMO) Cancer Research Network (CRN) (26), we evaluated real-world adjuvant anthracycline and trastuzumab use and subsequent incident HF/CM risk among a population-based cohort of women aged 18 years or older and diagnosed with invasive breast cancer. We took advantage of observational administrative health plan data to conduct this comparative safety study of anthracycline therapy, which was previously examined only in clinical trials or SEER-Medicare populations, and trastuzumab therapy, which, to our knowledge, has not been evaluated outside of randomized clinical trials.

Methods

Study Population

The CRN is a consortium of 14 nonprofit research centers based in integrated healthcare delivery organizations within the HMO Research Network (26). We included 12 902 women aged 18 years or older and diagnosed with incident invasive [SEER summary stages—local, which is confined to the breast, or regional, which has spread to the lymph nodes (27)] breast cancer from January 1, 1999 through December 31, 2007. All women were enrolled at least 12 months before diagnosis in these six CRN sites: Group Health Cooperative, Henry Ford Hospital and Health System, Marshfield Clinic, and Kaiser Permanente regions in Colorado, Georgia, and Northwest. Two additional CRN sites (Kaiser Permanente Northern California and Harvard Pilgrim Health Care) used slightly different inclusion criteria for year of breast cancer diagnosis. Because of the large population at Kaiser Permanente Northern California, we included a 10% random sample of women diagnosed between January 1, 2001 and December 31, 2007 (chemotherapy data from 1999 and 2000 were incomplete and not included). Harvard Pilgrim data included women receiving care at Harvard Vanguard Medical Associates (a multispecialty medical practice) and diagnosed from January 1, 1999 through December 31, 2006.

We excluded women diagnosed with HF/CM before breast cancer diagnosis (n = 253 women) or before chemotherapy initiation (n = 96 women) because these diagnoses could not be attributed to chemotherapy use. We also excluded women who did not receive chemotherapy but were diagnosed with HF/CM within 70 days of breast cancer diagnosis (70 days was the median time to "other chemotherapy" initiation; n = 53 women). These women may have been eligible for chemotherapy but likely did not receive it because of their new HF/CM diagnosis (potentially found during cardiac screening before the anticipated chemotherapy initiation). In general, excluded HF/CM patients were older (55% were >75 years) and had more comorbidities (70.8% had a Charlson comorbidity score ≥ 2 [moderate comorbidity]), compared with our included cohort (18% were >75 years and 15% had a Charlson comorbidity score ≥ 2). Over 50% of excluded HF/CM patients did not receive any chemotherapy, although 10% of these women received anthracycline and/or trastuzumab. Our final analytic sample included 12 500 women. Women were followed-up until incident HF/CM diagnosis, health plan disenrollment, death, or the end of follow-up on December 31, 2009, whichever came first.

This study was approved by the Institutional Review Board (IRB) for Group Health Cooperative and five other sites that ceded review to Group Health Cooperative and separately by the Institutional Review Boards at Marshfield Clinic and Henry Ford. We obtained information on women from all sites via a waiver of consent.

Data Collection

We obtained data from each site's Virtual Data Warehouse (VDW), which has been described in detail elsewhere (28). The VDW includes standardized variables derived from administrative databases at each CRN site. A programmer at Group Health Cooperative wrote standardized code for programmers at other sites to execute; programmers then transferred limited datasets to Group Health Cooperative for analysis.

Chemotherapy Exposure

We collected data on chemotherapy administration using validated VDW procedure codes and pharmacy data, which have been reported previously (29). Chemotherapy procedure data included Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT)-4 codes; pharmacy data included National Drug Codes (NDCs). We extracted HCPCS and NDCs specific to anthracycline and trastuzumab and HCPCS, NDCs, and CPT-4 codes related to other chemotherapy and administration dates. Because CPT-4 codes do not specify chemotherapy agents, we coded CPT-4 codes with no other information as "other" chemotherapy. We extracted treatment data up to 24 months after breast cancer diagnosis. We categorized women into five mutually exclusive treatment categories: anthracycline-based only (without trastuzumab; however, women could have received additional chemotherapy such as cyclophosphamide), trastuzumab-based only (without anthracycline; though all but one woman received additional chemotherapy), anthracycline plus trastuzumab (trastuzumab therapy following anthracycline therapy), other chemotherapy, or no chemotherapy.

To validate chemotherapy data, we compared chemotherapy regimens from VDW data with medical record review of 400 women (50 from each CRN site). Sensitivities and specificities exceeded 90% for all treatment categories, and positive predictive values (PPVs) exceeded 90% for anthracycline alone, trastuzumab alone, and anthracycline plus trastuzumab treatment, as reported previously (29).

Heart Failure Outcome

Our primary outcome was HF/CM following breast cancer diagnosis, defined using a previously validated algorithm, though not in breast cancer patients (30). The algorithm uses International Classification of Diseases, Ninth Revision (ICD-9) codes with five different criteria that indicate HF/CM (see Table 1 for criteria, ICD-9 codes, and proportion of women classified by each criteria) (31). We categorized women as having no HF/CM or incident HF/CM (occurring after breast cancer treatment). Because

Table 1. ICD-9 code-based algorithm used to determine HF/CM from administrative data by treatment group*

	Treatment group				
	No chemotherapy	Anthracycline only	Trastuzumab only	Anthracycline + trastuzumab	Other chemotherapy
	(n=5807 women)	(n=3697 women)	(n=112 women)	(n=442 women)	(n=2442 women)
Algorithm criteria	%	%	%	%	%
≥1 primary discharge diagnosis	4.2	2.1	3.6	4.1	5.3
≥3 secondary discharge diagnoses	0.5	0.2	0	0.5	0.4
≥2 outpatient diagnoses	2.8	1.7	7.1	7.0	2.5
≥3 emergency department diagnoses	0	0	0	0	0
≥2 secondary discharge + ≥1 outpatient diagnosis	0.1	0.1	0	0	0.2
None of the above (no HF/CM)	92.5	95.9	89.3	88.5	91.7

* The study population includes 12 500 women diagnosed with incident invasive breast cancer from January 1, 1999 through December 31, 2007. All women were members of one of eight Cancer Research Network (CRN) integrated health plans for 12 or more months before breast cancer diagnosis. Administrative data included ICD-9 codes for HF/CM as noted by a provider in the medical record and available in the CRN Virtual Data Warehouse (VDW; ICD-9 codes: 398.91, 402.x1, 402.x3, 404.x1, 404.x3, 422.90, 425.4, 425.9, 428.xx). Primary and secondary discharge diagnoses were indicated at the time of the patient's release from a hospital. Other diagnoses occurred after emergency department release or an outpatient appointment. The algorithm for this study was based on previous HF claims-based algorithms (30,41), with the addition of the 425 "cardiomyopathy" codes because of the nature of cardiotoxicity. The algorithm was validated on a subset of 400 women as previously reported (31). ICD-9 = International Classification of Diseases, Ninth Revision; HF/CM = Heart failure and/or cardiomyopathy.

administrative data do not capture results of echocardiograms or other methods for measuring left ventricular ejection fraction (LVEF), we could not use LVEF findings in our HF/CM definition. The PPV of the algorithm for any HF/CM diagnosis during the period from 12 months before to 12 months after breast cancer diagnosis was 68.6% (95% confidence interval [CI] = 44.9% to 85.4%), which we have shown earlier (31). The PPV for incident HF/CM during the 12 months after breast cancer diagnosis was 33.3% (95% CI = 12.8% to 63.1%) (31); this estimate was based on only four true-positive HF/CM patients, but it suggests that the performance may be worse for the period after breast cancer diagnosis. PPV also varied by the definition of the gold standard, and the estimates above included 24 "indeterminate" diagnoses (those that could not be definitively classified as HF/CM) as negatives in the gold standard. When we included patients with "indeterminate" HF/CM diagnoses as positives in the gold standard, the PPV of the algorithm increased to 81.9% (95% CI = 58.0% to 93.7%), as reported previously (31). We did not have gold standard data to evaluate the PPV for incident heart failure after chemotherapy initiation or beyond 12 months after breast cancer diagnosis.

Covariates

Each CRN site maintains its own tumor registry in compliance with North American Association of Central Cancer Registries (NAACCR) standards, or contracts with their local state or SEER tumor registries. From tumor registry data, we collected data on breast cancer diagnosis date, age at diagnosis (<55, 55–64, 65–74, ≥75 years), race (American Indian or Alaskan Native, Asian, black, white), ethnicity (non-Hispanic white vs Hispanic), summary stage (localized vs regional), lymph node status (positive vs negative), and radiation therapy (yes vs no) as defined by NAACCR classifications. Using VDW data, we calculated the Charlson comorbidity index (0, 1, 2, ≥3) that weights up to 19 comorbid conditions depending on their seriousness, using the Deyo index based on the presence of relevant ICD-9 codes in the year before breast cancer diagnosis (32,33).

Statistical Analysis

We described the distribution of chemotherapy use by patient characteristics, including the median and interquartile range (25th–75th percentile) for follow-up time (time for follow-up treatment until incident HF/CM diagnosis, health plan disenrollment, death, or December 31, 2009, whichever came first). We then used Cox proportional hazards regression to calculate hazard ratios (HRs) with 95% (CIs) for HF/CM associated with time-varying chemotherapy exposures. Each participant began accruing person-time on the date of chemotherapy initiation (ie, index date) and stopped accruing person-time at the time of incident HF/CM diagnosis, health plan disenrollment, death, or December 31, 2009, whichever came first. We used day 70 after diagnosis as a proxy for the index date for unexposed women. Using time-varying exposures allowed us to account for changes in chemotherapy use. For example, women were considered anthracycline-based-only users until they started trastuzumab therapy; thereafter, they were considered anthracycline plus trastuzumab users. We adjusted all models for covariates that were either jointly associated with chemotherapy and HF/CM risk (confounders) or associated solely with HF/CM risk in a bivariate manner at P values less than .05. These included CRN site (eight sites mentioned earlier), age at diagnosis (grouped as <55, 55–64, 65–74, ≥75 years), Charlson comorbidity index (0, 1, 2, ≥3), summary stage at diagnosis (localized vs regional), year of diagnosis (categorical for each year), and radiation treatment (yes vs no).

Survivor curves and the corresponding cumulative incidence curves were estimated from the adjusted Cox model using the method described by Breslow (34,35). All covariates were set to their respective mean values as estimated from the overall sample. The annual cumulative incidence up to year 5 for each chemotherapy group, both overall and by age group, was estimated at the most proximal event time observed in the data. Numbers of patients at risk are presented as the number under observation at the beginning of each time interval.

In order to assess any violations to the proportional hazards assumption in our primary analysis (average hazards ratios for

chemotherapy exposure during the entire study period), we performed exploratory analyses to characterize changes of the hazard ratio over time for each chemotherapy exposure. Toward this end, we allowed the hazard ratio for each chemotherapy exposure to vary with time by including an interaction with time in our models. The degree to which the proportional hazards assumption was violated for covariates was assessed through the use of the likelihood ratio test for interactions between covariates and time, as well as inspection of residual plots. Interactions with time were statistically significant at *P* values less than .05 for age, stage, site, Charlson score, and year of diagnosis. Review of residual plots yielded very little in the way of substantial proportional hazards violations, and most were focused in areas of sparse data. We conducted sensitivity analyses with stratified models when there was evidence of a potential deviation from the proportional hazards assumption. Sensitivity analyses yielded minimal changes in primary estimates; thus, we present results based on the primary, unstratified analysis.

We conducted several sensitivity analyses in order to address potential limitations and biases in observational administrative data. We conducted Cox regression analyses after changing the proxy index date to 234 days after breast cancer diagnosis (the 75th percentile of time to "other chemotherapy" initiation) in unexposed women; excluding women with comorbidities (Charlson score >1; n = 1854 women); excluding women who initiated therapy more than 12 months after breast cancer diagnosis (n = 519 women); and excluding women diagnosed before 2004 (when there was limited use of trastuzumab in the adjuvant setting; n = 6779 women). Further, we conducted stratified analyses by CRN site and age group.

The majority of analyses were conducted in Stata 11 (StataCorp, College Station, TX); cumulative incidence estimates were estimated with SAS version 9.2 for Windows (SAS Institute Inc, Cary, NC). All hypothesis tests were two-sided, and we considered *P* values less than .05 statistically significant.

Results

Characteristics of Patients by Chemotherapy Use

Among 12 500 women who were diagnosed with invasive breast cancer from January 1, 1999 through December 31, 2007, chemotherapy use was as follows: 5807 (46.5%) received no chemotherapy, 3697 (29.6%) received anthracycline-based chemotherapy alone, 112 (0.9%) received trastuzumab-based therapy without anthracycline, 442 (3.5%) received anthracycline plus trastuzumab, and 2442 (19.5%) received other chemotherapy (Table 2). The mean age of the population was 60 years (range = 22–99 years), 85.8% were of white race, and the median follow-up time was 4.4 years (interquartile range [IQR] = 2.6–6.9 years). Women who received anthracycline alone or anthracycline plus trastuzumab were younger (age <65 years, 86.4% and 89.6%, respectively), diagnosed at later stages (regional SEER summary stage, 54.2% and 61.0%, respectively), had fewer comorbidities (Charlson score ≥2, 10.0% and 7.7%, respectively), and were slightly more likely to receive radiation therapy (yes, 61.0% and 59.4%, respectively) than women who received other chemotherapy (age <65 years, 54.2%; SEER regional summary stage, 25.4%; Charlson score ≥2, 19.8%; and radiation therapy received, 55.2%) or no chemotherapy (age <65 years, 55.3%; regional summary stage, 11.5%; Charlson score ≥2, 16.2%; and radiation therapy received, 58.6%). Recipients of trastuzumab-based therapy without anthracycline, though small in number, were older (age ≥65 years, 32.2%) and had more comorbidities (Charlson score ≥2, 21.4%) than women in other treatment groups.

Risk of HF/CM by Chemotherapy Exposure

Women were followed-up until incident HF/CM diagnosis, health plan disenrollment, death, or December 31, 2009, whichever came first. The adjusted cumulative HF/CM incidence for the first 5 years of follow-up (the median follow-up time was 4.4 years) is shown in Figure 1. The HF/CM incidence among anthracycline recipients increased with increasing follow-up time (year 1 vs year 5, cumulative incidence = 1.2% [95% CI = 1.0% to 1.5%] vs 4.3% [95% CI = 3.5% to 5.0%]) and was similar to the incidence among recipients of other chemotherapy (year 1 vs year 5, cumulative incidence = 1.3% [95% CI = 1.0% to 1.6%] vs 4.5% [95% CI = 3.7% to 5.3%]). The cumulative HF/CM incidence among recipients of anthracycline plus trastuzumab was 6.2% (95% CI = 4.1% to 8.2%) after 1 year of follow-up and continued to increase to 20.1% (95% CI = 14.0% to 25.6%) by 5 years. The risk of incident HF/CM among all women was statistically significantly increased for anthracycline alone (adjusted HR = 1.40, 95% CI = 1.11 to 1.76), trastuzumab without anthracycline (HR = 4.12, 95% CI = 2.30 to 7.42), anthracycline plus trastuzumab (HR = 7.19, 95% CI = 5.00 to 10.35), and other chemotherapy (HR = 1.49, 95% CI = 1.25 to 1.77), compared with no chemotherapy (Table 3).

Risk of HF/CM by Age at Breast Cancer Diagnosis

The 5-year cumulative incidence for HF/CM associated with anthracycline use increased with increasing age (among age <55 years, cumulative incidence = 1.2% [95% CI = 0.0% to 26.1%]; among age 55–64 years, cumulative incidence =2.9% [95% CI = 1.8% to 4.0%]; among age 65–74 years, cumulative incidence = 6.2% [95% CI = 3.9% to 8.5%]; and among age ≥75 years, cumulative incidence = 10.6% [95% CI = 3.9% to 16.9%]; Figure 2, A–D). The 5-year cumulative incidence for HF/CM associated with anthracycline plus trastuzumab use also increased with increasing age (among age <55 years, cumulative incidence = 7.5% [95% CI = 0.0% to 85.9%]; among age 55–64 years, cumulative incidence = 11.4% [95% CI = 4.2% to 18.1%]; among age 65–74 years, cumulative incidence = 35.6% [95% CI = 12.5% to 52.5%]; and among age ≥75 years, cumulative incidence = 40.7% [95% CI = 0.0% to 71.6%]; Figure 2, A–D). The 5-year cumulative incidences for HF/CM associated with other chemotherapy use were greatest among the two oldest age groups (among age 65–74 years, cumulative incidence = 8.7% [95% CI = 6.3% to 11.0%] and among age ≥75 years, cumulative incidence = 18.7% [95% CI = 14.5% to 22.6%]; Figure 2, C and D).

The hazard ratios for HF/CM associated with chemotherapy use decreased with increasing age (Table 3). For example, the hazard ratio for HF/CM associated with anthracycline use alone was statistically significant among women younger than 55 years (HR = 2.52, 95% CI = 1.20 to 5.29) but not among women 55–64 years (HR = 1.61, 95% CI = 0.94 to 2.78) or older. The hazard ratios for incident HF/CM associated with anthracycline plus trastuzumab

Table 2. Characteristics of invasive breast cancer patients by adjuvant treatment*

	Treatment group					
Characteristic	**No chemotherapy (n=5807 women)**	**Anthracycline only (n=3697 women)**	**Trastuzumab only (n=112 women)**	**Anthracycline + trastuzumab (n=442 women)**	**Other chemotherapy (n=2442 women)**	**All (n=12500 women)**
	No. (%)	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**	**No. (%)**
Age at diagnosis, y						
<55	1112 (19.1)	2131 (57.6)	40 (35.7)	272 (61.5)	706 (28.9)	4261 (34.1)
55–64	1489 (25.6)	1063 (28.8)	36 (32.1)	124 (28.1)	617 (25.3)	3329 (26.6)
65–74	1606 (27.7)	423 (11.4)	19 (17.0)	38 (8.6)	622 (25.5)	2708 (21.7)
≥75	1600 (27.6)	80 (2.2)	17 (15.2)	8 (1.8)	497 (20.4)	2202 (17.6)
Race						
American Indian or Alaskan Native	9 (0.2)	11 (0.3)	0 (0.0 0	4 (0.9)	11 (0.5)	35 (0.3)
Asian	203 (3.6)	149 (4.1)	4 (3.6)	27 (6.2)	94 (3.9)	477 (3.9)
Black	443 (7.8)	527 (14.5)	16 (14.5)	51 (11.8)	193 (8.0)	1230 (10.0)
White	5016 (88.5)	2952 (81.1)	90 (81.8)	352 (81.1)	2103 (87.6)	10 513 (85.8)
Ethnicity						
Non-Hispanic	5165 (97.5)	3310 (95.9)	95 (96.0)	386 (95.1)	2237 (96.8)	11 193 (96.8)
Hispanic	133 (2.5)	141 (4.1)	4 (4.0)	20 (4.9)	75 (3.2)	373 (3.2)
Summary stage†						
Localized	5066 (88.5)	1683 (45.8)	67 (60.9)	171 (39.0)	1797 (74.6)	8784 (71.1)
Regional	660 (11.5)	1991 (54.2)	43 (39.1)	268 (61.0)	612 (25.4)	3574 (28.9)
Lymph nodes						
Negative	5181 (89.2)	1654 (44.7)	72 (64.3)	164 (37.1)	1843 (75.5)	8914 (71.3)
Positive	626 (10.8)	2043 (55.3)	40 (35.7)	278 (62.9)	599 (24.5)	3586 (28.7)
Charlson score‡						
0	3983 (68.6)	2897 (78.4)	67 (59.8)	350 (79.2)	1567 (64.2)	8864 (70.9)
1	881 (15.2)	430 (11.6)	21 (18.8)	58 (13.1)	392 (16.1)	1782 (14.3)
2	635 (10.9)	284 (7.7)	13 (11.6)	26 (5.9)	303 (12.4)	1261 (10.1)
≥3	308 (5.3)	86 (2.3)	11 (9.8)	8 (1.8)	180 (7.4)	593 (4.7)
Radiation therapy						
No	2355 (41.4)	1397 (39.0)	58 (54.2)	174 (40.6)	1067 (44.8)	5051 (41.5)
Yes	3331 (58.6)	2182 (61.0)	49 (45.8)	255 (59.4)	1317 (55.2)	7134 (58.5)
Diagnosis year						
1999–2003	3229 (55.6)	2054 (55.6)	26 (23.2)	94 (21.3)	1376 (56.3)	6779 (54.2)
2004–2007	2578 (44.4)	1643 (44.4)	86 (76.8)	348 (78.7)	1066 (43.7)	5721 (45.8)

* Women were diagnosed with breast cancer between January 1, 1999 and December 31, 2007. Chemotherapy use was extracted from the Cancer Research Network (CRN) Virtual Data Warehouse (VDW) procedure and pharmacy data up to 24 months after breast cancer diagnosis. Chemotherapy procedure data included Healthcare Common Procedure Coding System (HCPCS) and Current Procedural Terminology (CPT)-4 codes; pharmacy data included National Drug Codes (NDCs). "Anthracycline only" indicates treatment without trastuzumab, although women could have received additional chemotherapy such as cyclophosphamide. "Trastuzumab only" indicates treatment without anthracycline, although all but one woman received additional chemotherapy. "Anthracycline + trastuzumab" indicates trastuzumab therapy following anthracycline therapy. "Other chemotherapy" indicates CPT-4 codes without any information about specific chemotherapy agents, or HCPCS and NDCs that specified chemotherapy drugs other than anthracycline or trastuzumab. Diagnosis year was categorized as 1999–2003 and 2004–2007 because there was little trastuzumab use in the adjuvant setting before 2004.

† Surveillance, Epidemiology, and End Results (SEER) summary stages: local, which is confined to the breast, or regional, which has spread to the lymph nodes (27).

‡ Charlson comorbidity index, which weights up to 19 comorbid conditions depending on their seriousness, using the Deyo index based on the presence of relevant International Classification of Diseases, Ninth Revision (ICD-9) codes in the year before breast cancer diagnosis (32,33). We categorized the score as 0, 1, 2, and ≥3, which represent an increasing scale of comorbid conditions but do not equate to a specific number of comorbid conditions.

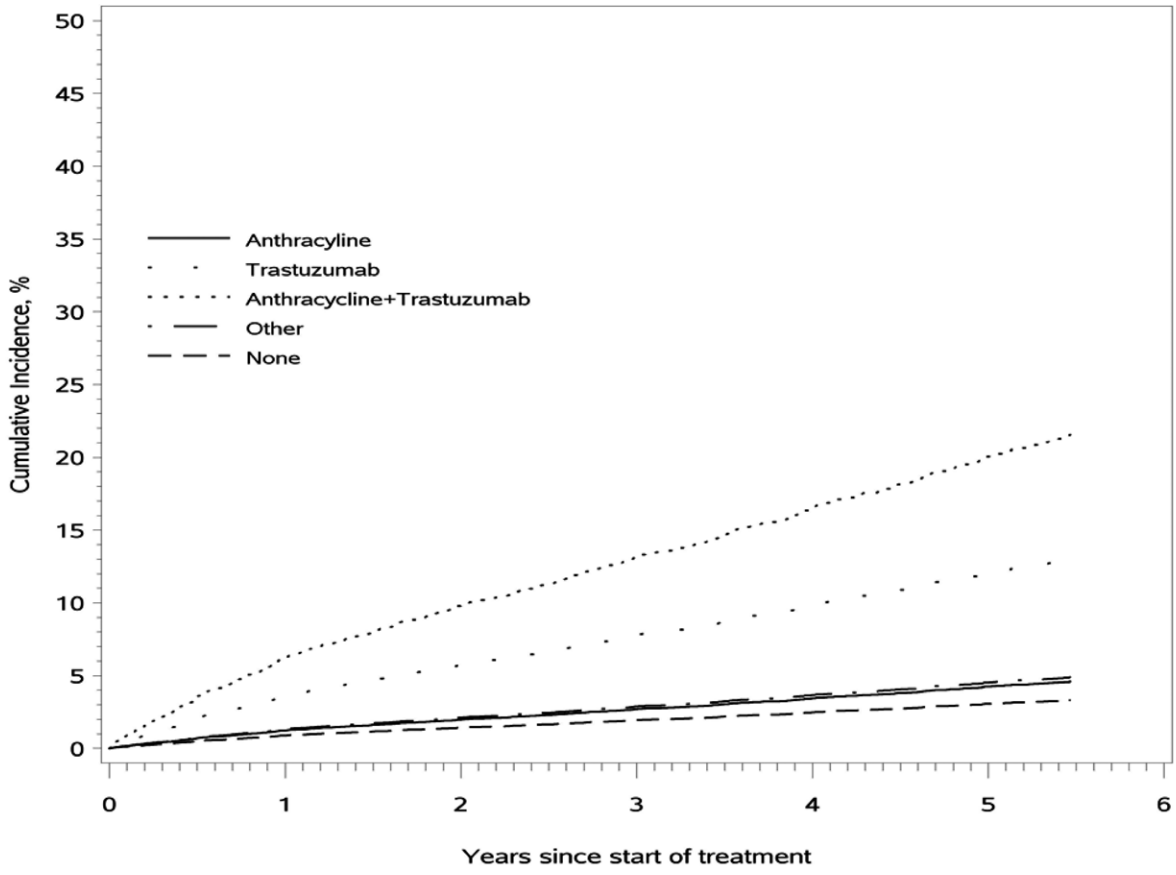
use were statistically significant among the three younger age groups (among age <55 years, HR = 16.36 [95% CI = 6.59 to 40.65]; among age 55–64 years, HR = 6.69 [95% CI = 3.09 to 14.48]; and among age 65–74 years, HR = 8.34 [95% CI = 3.97 to 17.50]). The hazard ratios for HF/CM associated with other chemotherapy use were statistically significant among the three older age groups (among age 55–64 years, HR = 1.82 [95% CI = 1.03 to 3.20]; among age 65–74 years, HR = 1.73 [95% CI = 1.28 to 2.34]; and among age ≥75 years, HR = 1.40 [95% CI = 1.11 to 1.78]).

Sensitivity Analyses

We also conducted several sensitivity analyses to address potential limitations and biases in observational administrative data. No appreciable differences with primary analysis were obtained (Table 3). In general, stronger associations between chemotherapy exposure and incident HF/CM were observed on changing the index date of unexposed women (n = 12 500), and excluding women with higher comorbidity scores (n = 10 646), or women who initiated chemotherapy more than 12 months after diagnosis (n = 11 981). Excluding women diagnosed before 2004 or stratifying by CRN site did not greatly alter results, though confidence intervals were much wider because of the smaller sample size (data not shown).

Discussion

This study had two goals: 1) to describe real-world adjuvant anthracycline and trastuzumab use and 2) to evaluate incident HF/CM



No. of patients at risk	Year 1	Year 2	Year 3	Year 4	Year 5
Anthracycline only	3443	3125	2699	2146	1659
Trastuzumab only	90	78	49	24	13
Anthracycline+ Trastuzumab	347	339	263	179	94
Other chemotherapy	2159	1905	1548	1192	958
None	5235	4798	4076	3288	2590
Cumulative incidence (95% CI), %					
Anthracycline only	1.2 (1.0 to 1.5)	2.0 (1.6 to 2.4)	2.7 (2.2 to 3.2)	3.5 (2.8 to 4.1)	4.3 (3.5 to 5.0)
Trastuzumab only	3.6 (1.5 to 5.6)	5.8 (2.5 to 8.9)	7.8 (3.4 to 12.0)	9.9 (4.3 to 15.1)	12.1 (5.3 to 18.3)
Anthracycline+ Trastuzumab	6.2 (4.1 to 8.2)	9.8 (6.7 to 12.8)	13.2 (9.1 to 17.1)	16.5 (11.5 to 21.3)	20.1 (14.0 to 25.6)
Other chemotherapy	1.3 (1.0 to 1.6)	2.1 (1.7 to 2.5)	2.9 (2.4 to 3.4)	3.7 (3.0 to 4.3)	4.5 (3.7 to 5.3)
None	0.9 (0.7 to 1.0)	1.4 (1.2 to 1.7)	1.9 (1.6 to 2.3)	2.5 (2.1 to 2.9)	3.1 (2.6 to 3.5)

Figure 1. Cumulative incidence of heart failure and/or cardiomyopathy (HF/CM) in women with invasive breast cancer over 5 years by adjuvant chemotherapy group. Adjusted cumulative incidence of HF/CM and number of patients at risk by exposure group (anthracycline only, trastuzumab only, anthracycline + trastuzumab, other chemotherapy, or none) for the first 5 years of follow-up. Cumulative incidence was adjusted for Cancer Research Network (CRN) site (eight sites), age at diagnosis (<55, 55–64, 65–74, ≥75 years), Charlson comorbidity index (0, 1, 2, ≥3), summary stage at diagnosis (local vs regional), year of diagnosis (categorical for each year), and radiation treatment (yes vs no).

risk associated with adjuvant anthracycline and/or trastuzumab use in a population-based cohort of women with breast cancer. In our study, women who received anthracycline alone or anthracycline plus trastuzumab were younger and had fewer comorbidities than women who received other chemotherapy or no chemotherapy. These results suggest substantial individualization of adjuvant chemotherapy administration by age and comorbidity in community practice. The overall risk of incident HF/CM was statistically significantly increased among women who used anthracycline alone compared with no chemotherapy, but the overall risk of incident HF/CM was even greater among women who used trastuzumab. Compared with women who received no chemotherapy, our hazard ratios suggest a fourfold increase in the risk of HF/CM among women who received trastuzumab alone and a sevenfold increase in the risk of HF/CM for those who received anthracycline plus trastuzumab. To our knowledge, this study is the first to examine associations between anthracycline and/or trastuzumab reception and HF/CM in a cohort of breast cancer patients broader than Medicare-eligible women or clinical trial participants.

Consistent with previous studies, the majority of women 65 years or older in our population received no chemotherapy (36). Among older women who did receive chemotherapy, most received agents other than anthracycline or trastuzumab. Women who received anthracycline alone or with trastuzumab tended to have lower comorbidity prevalence, based on Charlson score. On the other hand, the small group of women (0.9%) who received

Table 3. Associations between adjuvant chemotherapy exposure and incident HF/CM among women diagnosed with invasive breast cancer*

	Primary analysis	Sensitivity analyses		
	All women (n=12 500)	Changing index date in unexposed† (n=12 500)	Excluding women with comorbidities‡ (n=10 646)	Excluding late chemotherapy initiators§ (n=11 981)
Chemotherapy use	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)	Adjusted HR (95% CI)
All ages				
No chemotherapy	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Anthracycline only	1.40 (1.11 to 1.76)	1.43 (1.13 to 1.81)	1.52 (1.18 to 1.97)	1.40 (1.11 to 1.77)
Trastuzumab only	4.12 (2.30 to 7.42)	4.33 (2.41 to 7.80)	4.36 (2.21 to 8.58)	5.26 (2.91 to 9.50)
Anthracycline + trastuzumab	7.19 (5.00 to 10.35)	7.35 (5.09 to 10.62)	7.94 (5.36 to 11.76)	7.19 (4.84 to 10.68)
Other chemotherapy	1.49 (1.25 to 1.77)	1.53 (1.29 to 1.83)	1.33 (1.16 to 1.76)	1.44 (1.19 to 1.73)
Age <55 y				
No chemotherapy	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Anthracycline only	2.52 (1.20 to 5.29)	2.65 (1.22 to 5.76)	3.42 (1.42 to 8.24)	2.49 (1.18 to 5.23)
Trastuzumab only	15.46 (4.51 to 52.96)	16.20 (4.62 to 56.77)	15.90 (3.79 to 66.66)	17.60 (5.09 to 60.86)
Anthracycline + trastuzumab	16.36 (6.59 to 40.65)	16.96 (6.62 to 43.46)	18.26 (6.39 to 52.18)	17.31 (6.70 to 44.74)
Other chemotherapy	1.85 (0.77 to 4.45)	1.95 (0.78 to 4.83)	2.69 (0.98 to 7.37)	1.81 (0.74 to 4.44)
Age 55–64 y				
No chemotherapy	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Anthracycline only	1.61 (0.94 to 2.78)	1.56 (0.90 to 2.71)	1.75 (0.94 to 3.28)	1.61 (0.93 to 2.81)
Trastuzumab only	10.76 (3.92 to 29.52)	10.19 (3.69 to 28.10)	14.88 (4.66 to 47.53)	11.81 (4.28 to 32.59)
Anthracycline + trastuzumab	6.69 (3.09 to 14.48)	6.40 (2.94 to 13.94)	10.79 (4.70 to 24.77)	6.05 (2.66 to 13.77)
Other chemotherapy	1.82 (1.03 to 3.20)	1.75 (0.99 to 3.10)	1.77 (0.91 to 3.44)	1.77 (0.98 to 3.19)
Age 65–74 y				
No chemotherapy	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Anthracycline only	1.22 (0.79 to 1.86)	1.30 (0.84 to 2.00)	1.49 (0.94 to 2.35)	1.18 (0.77 to 1.82)
Trastuzumab only	—	—	—	—
Anthracycline + trastuzumab	8.34 (3.97 to 17.50)	9.21 (4.35 to 19.54)	9.37 (4.22 to 20.80)	6.23 (2.74 to 14.18)
Other chemotherapy	1.73 (1.28 to 2.34)	1.81 (1.33 to 2.46)	1.86 (1.31 to 2.64)	1.70 (1.22 to 2.36)
Age ≥75 y				
No chemotherapy	1.00 (referent)	1.00 (referent)	1.00 (referent)	1.00 (referent)
Anthracycline only	0.76 (0.39 to 1.48)	0.78 (0.40 to 1.53)	0.58 (0.25 to 1.36)	0.79 (0.41 to 1.54)
Trastuzumab only	2.57 (0.81 to 8.18)	2.76 (0.86 to 8.79)	2.26 (0.55 to 9.31)	3.64 (1.13 to 11.74)
Anthracycline + trastuzumab	3.54 (0.86 to 14.65)	3.36 (0.81 to 13.94)	3.18 (0.76 to 13.41)	11.30 (2.36 to 54.13)
Other chemotherapy	1.40 (1.11 to 1.78)	1.44 (1.13 to 1.83)	1.16 (0.85 to 1.57)	1.32 (1.02 to 1.72)

* Analyses were conducted using multivariable Cox proportional hazards regression to estimate the risk of HF/CM associated with time-varying chemotherapy exposures to account for changes in chemotherapy use. Each participant began accruing person-time on the date of chemotherapy initiation (ie, index date) and stopped accruing person-time at the time of incident HF/CM diagnosis, health plan disenrollment, death, or December 31, 2009, whichever came first.. All models were adjusted for CRN site (eight sites mentioned earlier), age at diagnosis (<55, 55–64, 65–74, ≥75 years), Charlson comorbidity index (0, 1, 2, ≥3), summary stage at diagnosis (local vs regional), diagnosis year (categorical for each year), and radiation treatment (yes vs no). The primary analysis (first column and first row) included all women; subsequent analyses (following rows) were stratified by age groups (<55, 55–64, 65–74, ≥75 years). Sensitivity analyses were conducted in order to address potential limitations and biases in observational administrative data. HF/CM = heart failure and/or cardiomyopathy; HR = hazard ratio; CI = confidence interval; — = no HF/CM events occurred among these women.

† Increased the index date to 234 days after breast cancer diagnosis in unexposed women to exclude any additional possibility of prevalent HF/CM.

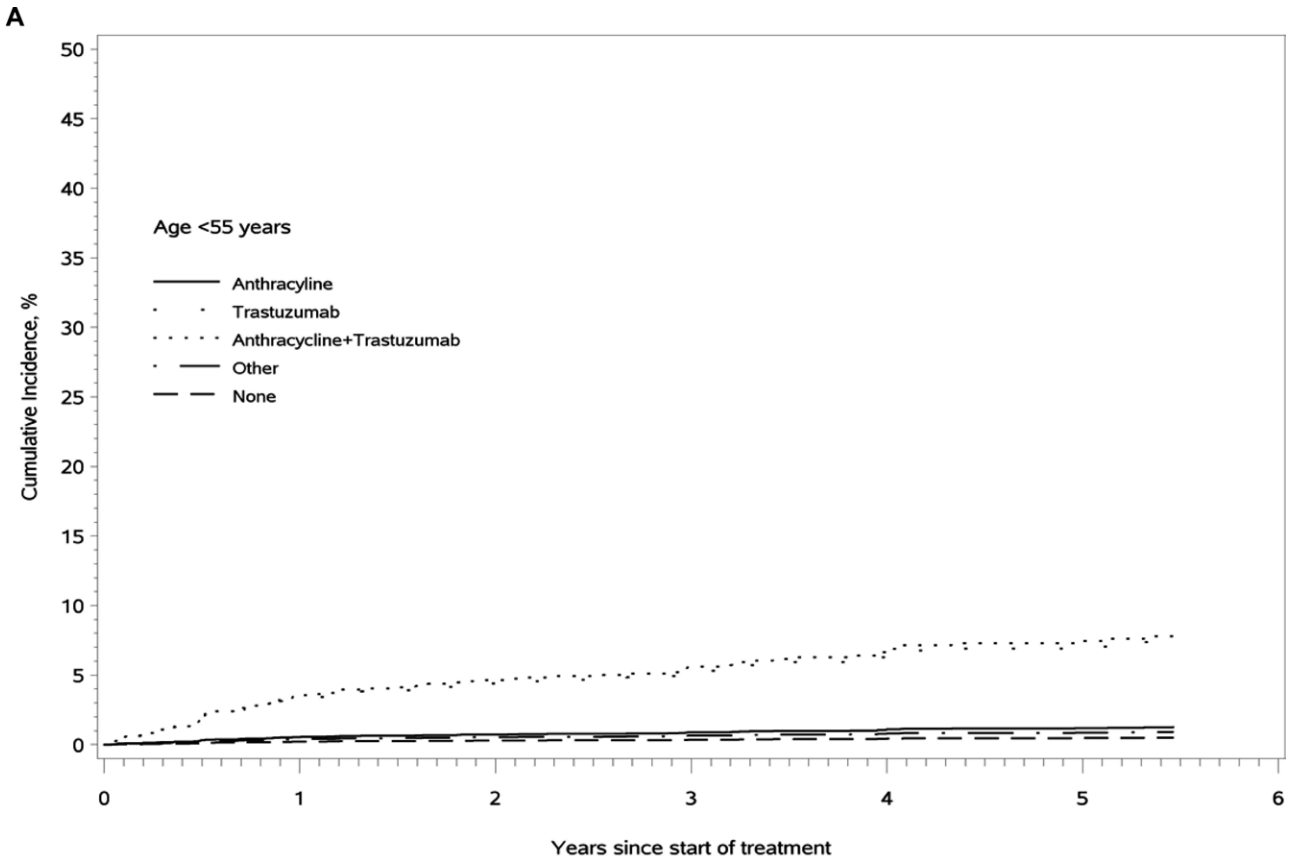
‡ Excluded women with comorbidities (ie, women with a Charlson score >1; n = 1854 women).

§ Excluded late chemotherapy initiators, that is, women who initiated chemotherapy more than 12 months after breast cancer diagnosis (n = 519 women).

trastuzumab alone had the highest prevalence of comorbidities. These findings show that typical clinical trial exclusions based on patients' age and comorbidities do occur in real-world settings but to a lesser extent than in clinical trials (37–39). This treatment selection bias, especially by age, may alter cardiac risk estimates and safety profiles of these drugs in community settings.

Our results for HF/CM risk among women less than 65 years who received anthracycline alone were similar to clinical trial results (10–14). However, the risk of HF/CM among women who received trastuzumab with or without anthracycline in our study—especially among younger women—was unexpectedly higher than clinical trial estimates (15–19). Excluding women with more comorbidities did not substantially change our results. The high hazard ratios associated with anthracycline plus trastuzumab may partially stem from detection bias, as young women receiving these treatments are much more likely to be monitored for cardiac failure than young women receiving no chemotherapy. These results suggest that clinical trials may underestimate the magnitude of HF/CM risk following anthracycline plus trastuzumab use in community practice.

Our results for older women showed little to no increase in HF/CM risk among anthracycline-alone users compared with women who received no chemotherapy. This finding conflicts with SEER-Medicare studies, which have estimated statistically significant hazard ratios ranging from 1.2 to 2.5 (23–25). This discrepancy is likely a result of avoidance of anthracycline-based therapy in older women; only 11.2% of women 65 years or older in our study were prescribed anthracycline. Earlier SEER-Medicare studies included only data from the 1990s; our study of more recent years likely reflects more careful treatment dosing, the



No. of patients at risk	Year 1	Year 2	Year 3	Year 4	Year 5
Anthracycline only	1971	1787	1542	1213	948
Trastuzumab only	33	32	21	13	7
Anthracycline+ Trastuzumab	216	212	159	109	52
Other chemotherapy	633	564	471	373	305
None	980	894	760	612	484
Cumulative incidence (95% CI), %					
Anthracycline only	0.6 (0.0 to 13.1)	0.7 (0.0 to 17.3)	0.9 (0.0 to 20.2)	1.1 (0.0 to 24.3)	1.2 (0.0 to 26.1)
Trastuzumab only	3.4 (0.0 to 57.8)	4.5 (0.0 to 68.7)	5.3 (0.0 to 74.9)	6.5 (0.0 to 81.9)	7.1 (0.0 to 84.3)
Anthracycline+ Trastuzumab	3.5 (0.0 to 59.9)	4.7 (0.0 to 70.7)	5.6 (0.0 to 76.9)	6.9 (0.0 to 83.6)	7.5 (0.0 to 85.9)
Other chemotherapy	0.4 (0.0 to 9.8)	0.5 (0.0 to 13.0)	0.7 (0.0 to 15.2)	0.8 (0.0 to 18.5)	0.9 (0.0 to 19.9)
None	0.2 (0.0 to 5.4)	0.3 (0.0 to 7.2)	0.4 (0.0 to 8.6)	0.4 (0.0 to 10.5)	0.5 (0.0 to 11.3)

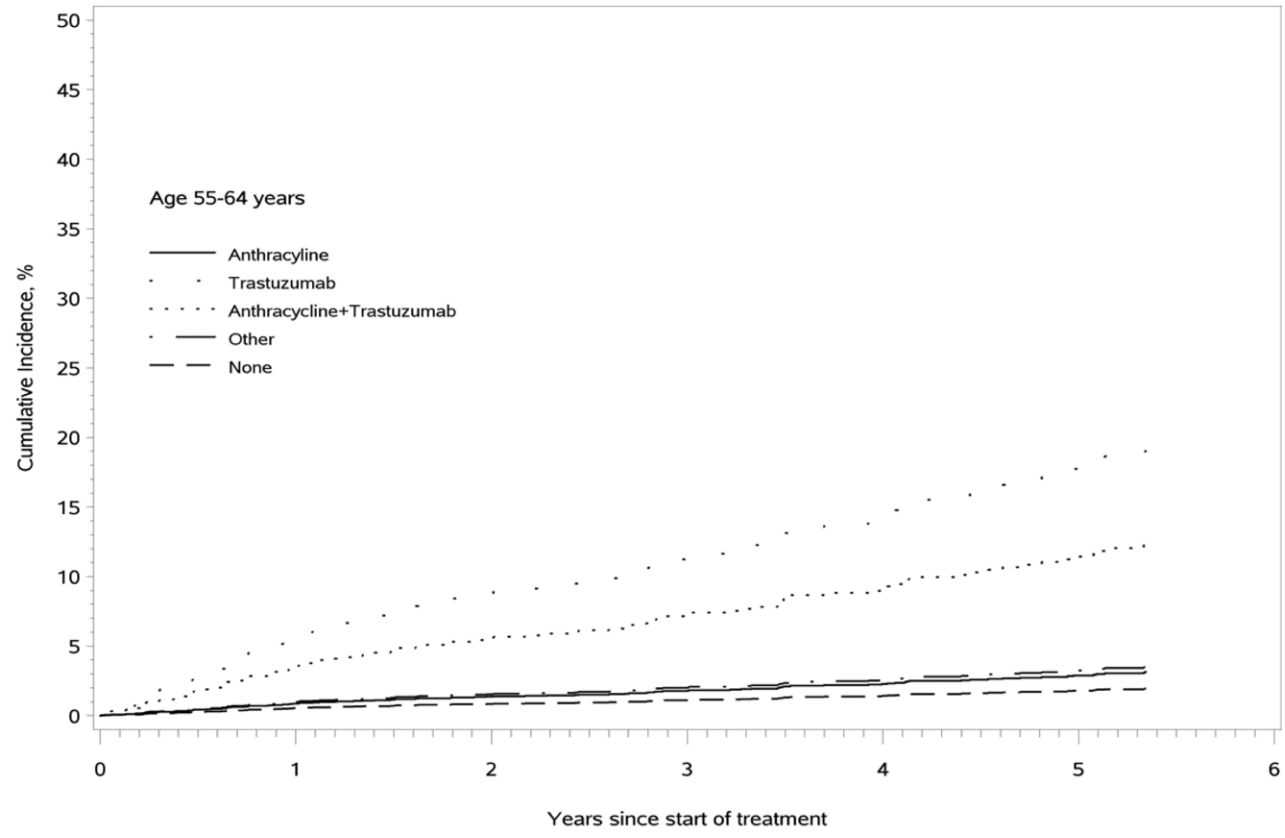
Figure 2. Cumulative incidence of heart failure and/or cardiomyopathy (HF/CM) in women with invasive breast cancer over 5 years by adjuvant chemotherapy and age groups. Adjusted cumulative incidence of HF/CM and number of patients at risk by exposure group (anthracycline only, trastuzumab only, anthracycline + trastuzumab, other chemotherapy, or none) for the first 5 years of follow-up, by age at diagnosis. Cumulative incidence was adjusted for Cancer Research Network (CRN) site (eight sites), age at diagnosis (<55, 55–64, 65–74, ≥75 years), Charlson comorbidity index (0, 1, 2, ≥3), summary stage at diagnosis (local vs regional), year of diagnosis (categorical for each year), and radiation treatment (yes vs no). **A**) Age <55 years. **B**) Age 55–64 years. **C**) Age 65–74 years. **D**) Age ≥75 years.

practice of additional heart monitoring, and availability of non–anthracycline-based treatment alternatives.

Observational comparative safety and effectiveness studies using administrative data are important to conduct for several reasons. First, the ability to collect automated administrative data on a large number of diverse people, as was the case in our study, is often a more cost-effective alternative to extensive medical record review on a small number of patients. But second, and perhaps even more important, observational studies allow for estimation of risks and benefits in community practice, which includes patients who may not be eligible for clinical trials. Clinical trials may provide more relevant estimates for patients who are eligible candidates, but many people are not and still receive these treatments in community practice. Thus, clinical trials may have better internal validity than observational studies because they can reduce bias from confounding factors through randomization; however, their external validity is often worse because of selection bias and eligibility criteria. The opposite is often true for observational studies, with better external validity than clinical trials but at the expense of internal validity.

Therefore, limitations of observational studies, particularly those using administrative data such as ours, cannot be ignored. A primary example in our analyses is that our administrative coding algorithm for incident HF/CM is prone to misclassification. Our PPV for HF/

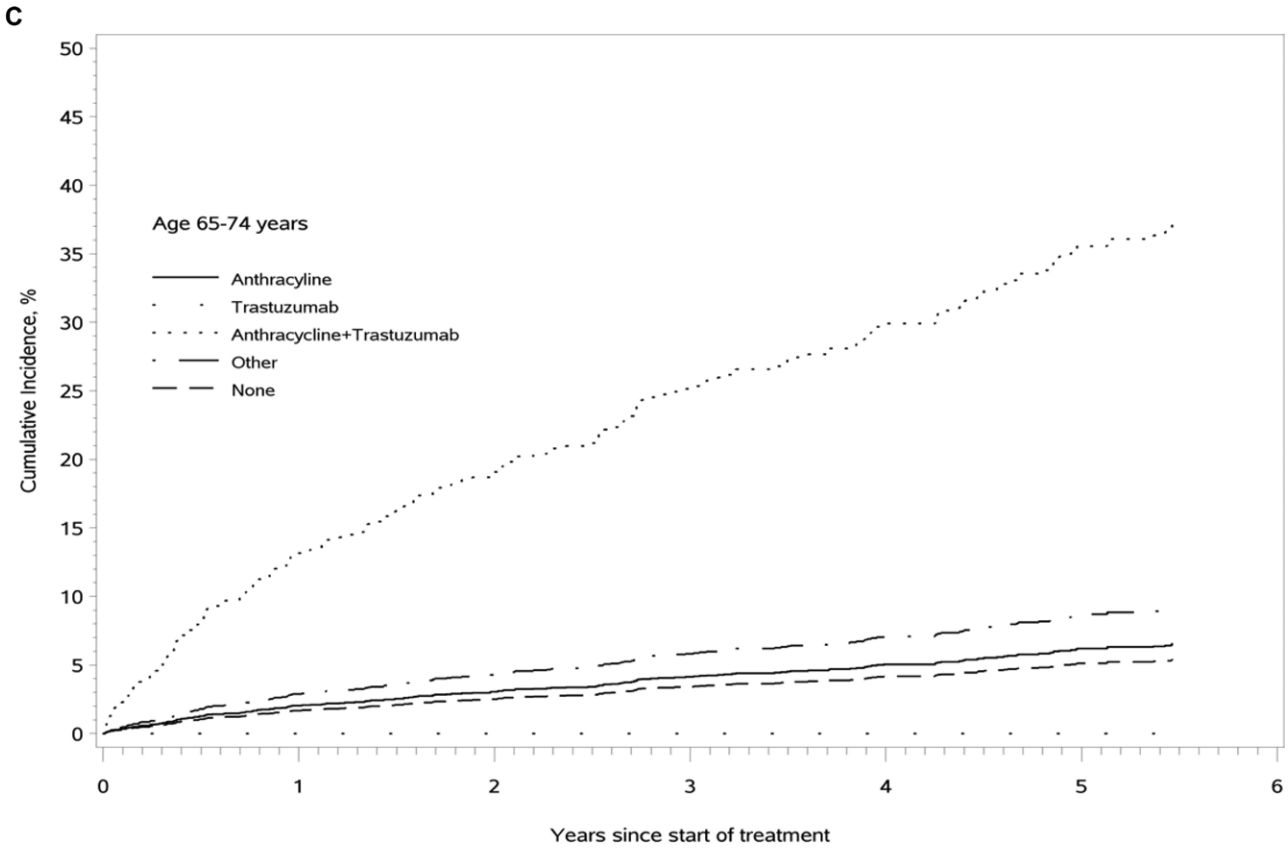
B



No. of patients at risk	Year 1	Year 2	Year 3	Year 4	Year 5
Anthracycline only	1001	912	793	638	480
Trastuzumab only	27	22	15	5	4
Anthracycline+ Trastuzumab	99	97	80	53	34
Other chemotherapy	565	492	398	313	251
None	1355	1252	1081	873	700
Cumulative incidence (95% CI), %					
Anthracycline only	0.9 (0.5 to 1.3)	1.4 (0.8 to 2.0)	1.8 (1.1 to 2.5)	2.3 (1.4 to 3.2)	2.9 (1.8 to 4.0)
Trastuzumab only	5.7 (0.2 to 10.8)	9.0 (0.5 to 16.6)	11.4 (0.8 to 21.0)	14.3 (1.0 to 25.8)	17.7 (12.2 to 31.5)
Anthracycline+ Trastuzumab	3.6 (1.1 to 6.0)	5.7 (1.9 to 9.3)	7.3 (2.6 to 11.8)	9.1 (3.3 to 14.6)	11.4 (4.2 to 18.1)
Other chemotherapy	1.0 (0.5 to 1.5)	1.6 (0.8 to 2.3)	2.0 (1.1 to 3.0)	2.6 (1.4 to 3.7)	3.2 (1.8 to 4.7)
None	0.5 (0.3 to 0.8)	0.9 (0.5 to 1.3)	1.1 (0.6 to 1.6)	1.4 (0.8 to 2.0)	1.8 (1.0 to 2.6)

Figure 2. (Continued)

CM suggests that administrative codes include a substantial percentage of false-positive diagnoses, which would result in overestimated cumulative HF/CM incidence. For example, our 5-year cumulative incidence of HF/CM among women exposed to anthracycline plus trastuzumab may be 13.9%, based on a PPV of 69%, rather than 20.1%; it could range from 6.6% to 16.5% if the PPV was 33% or 82%, respectively. More precise incidence rates would not only require validation of outcomes through chart review but also improved documentation and surveillance for cardiotoxicity in routine practice. If diagnostic coding is more common among patients after treatment with potentially cardiotoxic agents presumably owing to increased surveillance, this may result in overattribution from these observational associations. For example, detection bias or misclassification may explain the increased HF/CM incidence among women receiving trastuzumab alone, although these estimates are based on a small sample size. Increased screening for cardiac disease is also likely to occur immediately after cancer diagnosis and before initiation of chemotherapy, and documentation of cardiac disease in such patients will justify the avoidance of potentially cardiotoxic agents. Because of these potential detection biases, these population-based incidence estimates of cardiotoxicity associated with chemotherapy should be interpreted with caution. Even in the presence of false-positive diagnoses and misclassification, our results suggest a greater risk of HF/CM than that previously estimated from clinical trials. Our study has a few additional limitations. Relying entirely on administrative data limited the details of our data collection and, subsequently, the extent of our analyses. For example, we had no information on drug dose, the types of chemotherapy in the "other chemotherapy" group, LVEF measures, and breast cancer recurrence—elements typically measured and evaluated in clinical trials. For example, LVEF is typically ascertained before anthracycline or trastuzumab administration, and if reduced, the patient would not be considered eligible for clinical



No. of patients at risk	Year 1	Year 2	Year 3	Year 4	Year 5
Anthracycline only	395	360	312	252	200
Trastuzumab only	17	16	9	3	1
Anthracycline+ Trastuzumab	29	27	22	15	6
Other chemotherapy	549	501	409	322	262
None	1492	1408	1218	1025	825
Cumulative incidence (95% CI), %					
Anthracycline only	2.1 (1.2 to 2.9)	3.0 (1.8 to 4.2)	4.1 (2.6 to 5.7)	5.0 (3.2 to 6.9)	6.2 (3.9 to 8.5)
Trastuzumab only	0.0	0.0	0.0	0.0	0.0
Anthracycline+ Trastuzumab	13.4 (3.8 to 21.9)	19.1 (5.9 to 30.4)	25.1 (8.3 to 38.9)	29.9 (10.2 to 45.3)	35.6 (12.5 to 52.5)
Other chemotherapy	2.9 (2.0 to 3.9)	4.3 (3.0 to 5.5)	5.8 (4.2 to 7.4)	7.1 (5.1 to 9.0)	8.7 (6.3 to 11.0)
None	1.7 (1.2 to 2.2)	2.5 (1.8 to 3.2)	3.4 (2.5 to 4.3)	4.2 (3.1 to 5.2)	5.1 (3.9 to 6.4)

Figure 2. (Continued)

trial enrollment. In real-world practice, the frequency of LVEF testing varied widely across CRN sites, and a sizeable proportion never received one of these tests based on a detailed review of the medical record (31). If LVEF testing had been routinely used in clinical practice and available from administrative data, it may have allowed for more appropriate comparisons across exposure groups. Further, we may have been able to evaluate permanent vs transient HF/CM. HF/CM following trastuzumab may be reversible with drug discontinuation, whereas HF/CM following anthracycline may be permanent (18,40). Accurate administrative data on LVEF testing and results would have been necessary to conduct this analysis.

More broadly, selection bias in community-based studies of cancer treatment is likely to be prominent and uncontrollable. We noted profound differences in age, comorbidities, stage of disease, and other factors among women receiving various treatment options. Although our primary analyses attempted to adjust for these differences to account for treatment selection biases and different cardiovascular risk profiles, residual confounding likely still exists, especially among older women. Adjusting for specific cardiovascular-related comorbidities, such as hypertension and diabetes rather than Charlson comorbidity score, may have reduced residual confounding but we did not collect these data at all CRN sites. Therefore, our incidence rates may not represent the "truth" of community practice; however, they show strong signals for associations between anthracycline, trastuzumab, and HF/CM.

In conclusion, we noted increased risks of incident HF/CM associated with anthracycline plus trastuzumab administration. While risk of anthracycline-associated HF/CM among women less than 65 years was similar to results from randomized clinical trials, trastuzumab-associated HF/CM risk (whether administered alone or following anthracycline) was greater than that previously reported. Our results highlight the importance of generalizability in applying clinical trial findings to community settings; although similar to clinical trial results, these population-based results cannot

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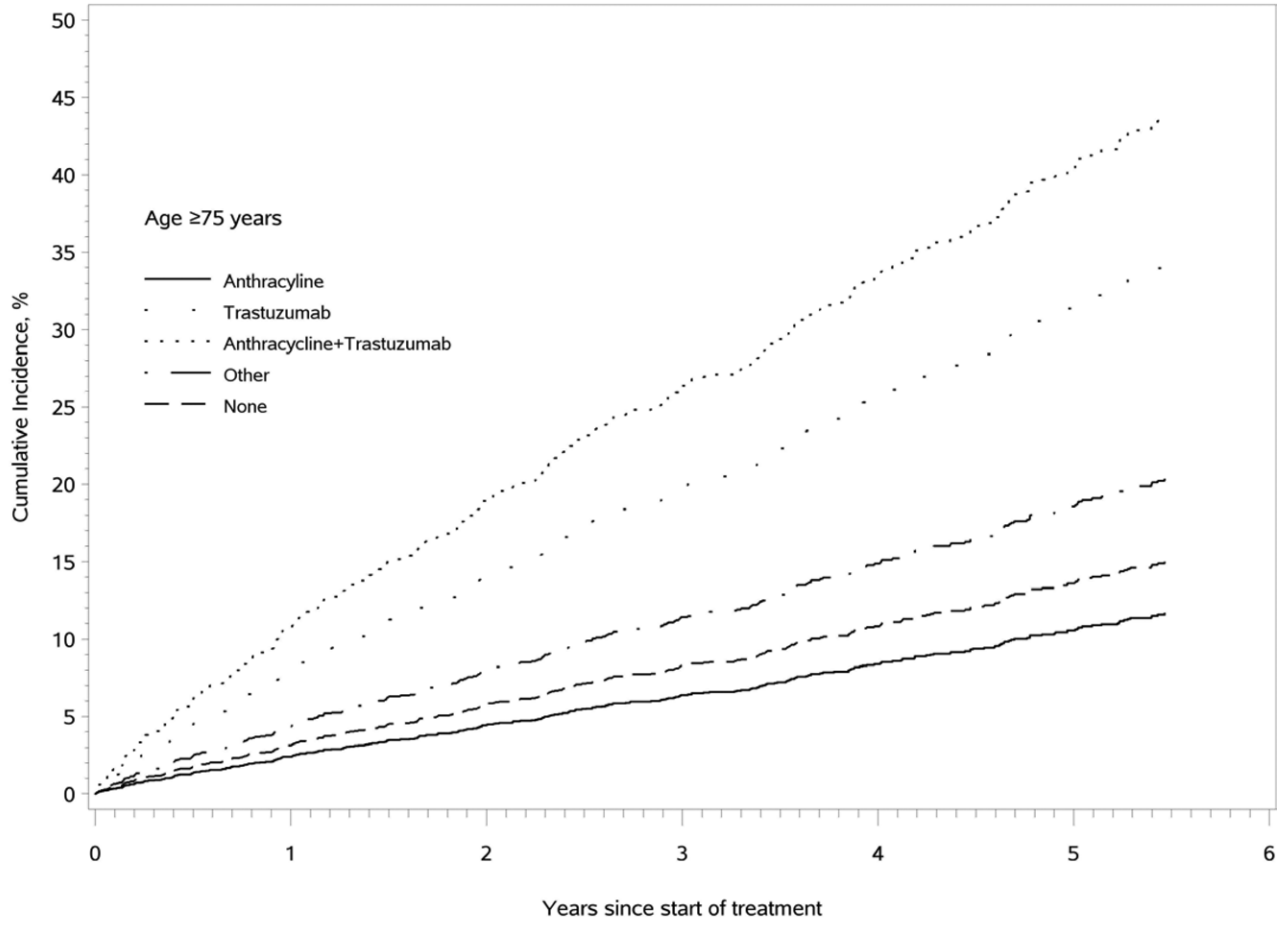

No. of patients at risk	Year 1	Year 2	Year 3	Year 4	Year 5
Anthracycline only	76	66	52	43	31
Trastuzumab only	13	8	4	3	1
Anthracycline+ Trastuzumab	3	3	2	2	2
Other chemotherapy	412	348	270	184	140
None	1408	1244	1017	778	581
Cumulative incidence (95% CI), %					
Anthracycline only	2.4 (0.8 to 4.0)	4.4 (1.5 to 7.3)	6.4 (2.3 to 10.3)	8.4 (3.0 to 13.5)	10.6 (3.9 to 16.9)
Trastuzumab only	7.9 (0.0 to 16.3)	14.2 (0.0 to 28.1)	19.9 (0.0 to 38.0)	25.7 (0.0 to 47.2)	31.5 (0.0 to 55.7)
Anthracycline+ Trastuzumab	10.8 (0.0 to 24.1)	19.0 (0.0 to 40.0)	26.4 (0.0 to .2)	33.6 (0.0 to 62.7)	40.7 (0.0 to 71.6)
Other chemotherapy	4.4 (3.2 to 5.6)	8.0 (6.0 to 10.0)	11.4 (8.8 to 14.0)	14.9 (11.6 to 18.2)	18.7 (14.5 to 22.6)
None	3.2 (2.4 to 3.9)	5.8 (4.6 to 6.9)	8.3 (6.8 to 9.8)	10.9 (9.0 to 12.8)	13.7 (11.4 to 16.0)

Figure 2. (Continued)

be attributed to any single patient in clinical practice. The variability in predictive value of our HF/CM measure is a limitation, and studies with detailed data on LVEF measures will be needed to confirm our findings. Nevertheless, our study demonstrates the added value and potential of observational administrative data to complement clinical trials to achieve a more complete picture of cancer treatment safety.

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