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CME

Incidence of Heart Failure or Cardiomyopathy After Adjuvant Trastuzumab Therapy for Breast Cancer

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CME Objective for This Article: At the conclusion of this activity, the learner should be able to estimate heart failure and cardiomyopathy rates following adjuvant trastuzumab therapy and chemotherapy in a population of older women with early stage breast cancer.

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Incidence of Heart Failure or Cardiomyopathy After Adjuvant Trastuzumab Therapy for Breast Cancer

Objectives The purpose of this study was to estimate heart failure (HF) and cardiomyopathy (CM) rates after adjuvant trastuzumab therapy and chemotherapy in a population of older women with early-stage breast cancer.

Background Newer biologic therapies for breast cancer such as trastuzumab have been reported to increase HF and CM in clinical trials, especially in combination with anthracycline chemotherapy. Elderly patients, however, typically have a higher prevalence of cardiovascular risk factors and have been underrepresented in trastuzumab clinical trials.

Methods Using Surveillance, Epidemiology, and End Results-Medicare data from 2000 through 2007, we identified women 67 to 94 years of age with early-stage breast cancer. We calculated 3-year incidence rates of HF or CM for the following mutually exclusive treatment groups: trastuzumab (with or without nonanthracycline chemotherapy), anthracycline plus trastuzumab, anthracycline (without trastuzumab and with or without nonanthracycline chemotherapy), other nonanthracycline chemotherapy, or no adjuvant chemotherapy or trastuzumab therapy. HF or CM events were ascertained from administrative Medicare claims. Poisson regression was used to quantify risk of HF or CM, adjusting for sociodemographic factors, cancer characteristics, and cardiovascular conditions.

Results We identified 45,537 older women (mean age: 76.2 years, standard deviation: 6.2 years) with early-stage breast cancer. Adjusted 3-year HF or CM incidence rates were higher for patients receiving trastuzumab (32.1 per 100 patients) and anthracycline plus trastuzumab (41.9 per 100 patients) compared with no adjuvant therapy (18.1 per 100 patients, $p < 0.001$). Adding trastuzumab to anthracycline therapy added 12.1, 17.9, and 21.7 HF or CM events per 100 patients over 1, 2, and 3 years of follow-up, respectively.

Conclusions HF or CM are common complications after trastuzumab therapy for older women, with higher rates than those reported from clinical trials. (J Am Coll Cardiol 2012;60:2504–12) © 2012 by the American College of Cardiology Foundation

Many cancer therapies confer an increased risk of adverse cardiac outcomes such as heart failure (HF) and cardiomyopathy (CM) (1). Such cardiotoxicity is of particular concern for patients undergoing adjuvant therapy for breast cancer, because several widely used drugs can cause abnormalities in left ventricular function, leading to HF or CM. Anthracycline is a common breast cancer therapy that increases the risk of HF or CM (2,3), which then can persist many years after the conclusion of chemotherapy (4).

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Newer biologic therapies, such as the monoclonal antibody trastuzumab, also may cause cardiotoxicity. Trastuzumab is used to treat breast tumors that overexpress human epidermal growth factor receptor-2 and improves disease-free and overall survival, but at increased risk of cardiotoxicity (5–7). Pooled data from randomized clinical trials estimate that trastuzumab is associated with an absolute increase in HF incidence by 1.6% and abnormalities in left ventricular systolic function by 7.2% (8). However, clinical trials of trastuzumab typically have enrolled younger women without cardiac comorbidities (5–7); in fact, 1 trastuzumab trial excluded patients older than 70 years because of concerns over its safety profile (7). Single-center studies suggest that the risk of HF or CM is substantially higher for older patients: a study of women 70 years of age or older that reported 26.7% of patients (12 of 45) had HF or an asymptomatic decline in left ventricular ejection fraction (LVEF) after trastuzumab therapy over a median duration of 49 weeks (9).

Because 40.8% of women diagnosed with breast cancer in the United States are at least 65 years of age (10) and because risk for cardiovascular events increases with age, it is crucial to understand better the risk of cardiotoxicity associated with trastuzumab and chemotherapy in older adults outside of clinical trials. Given the increasing number of long-term breast cancer survivors exposed to newer breast cancer therapies with the potential for myocardial injury, preventing and managing cancer therapy-induced cardiotoxicity represent an important point of collaboration between oncologists and cardiologists to reduce the burden of HF and CM (11,12). Our study sought to focus on outcomes of HF and CM, the most serious cardiotoxic complications associated with breast cancer therapy. Accordingly, we analyzed data from the Surveillance, Epidemiology, and End Results (SEER)-Medicare linked database to evaluate the use of adjuvant trastuzumab and anthracycline therapy in older women with early-stage breast cancer and the relationship between these cancer therapies with development of HF or CM.

Methods

Data Sources

SEER-Medicare is a database consisting of patient demographics and cancer characteristics from 16 tumor

Abbreviations and Acronyms

A+T = anthracycline plus trastuzumab
CI = confidence interval
CM = cardiomyopathy
HF = heart failure
ICD-9-CM = International Classification of Disease-9th Revision-Clinical Modification
IRR = incidence rate ratio
LVEF = left ventricular ejection fraction
SEER = Surveillance, Epidemiology, and End Results

registries linked to Medicare claims that include date of service, diagnoses, and procedures (including biologic therapy and chemotherapy) from care billed by hospitals, outpatient facilities, and physicians. This database is a collaboration between the National Cancer Institute, SEER, and the Centers for Medicare and Medicaid Services (13).

Study Cohort

Breast cancer cohort. We selected women with an initial primary diagnosis of invasive breast cancer from 2000 through 2007 in SEER with Medicare claims available from 1998 through 2009. We included only patients who were at least 67 years old at the time of their breast cancer diagnosis to ensure a minimum of 2 years of Medicare claims from which to ascertain comorbidities. To identify patients eligible for adjuvant therapy, the cohort consisted of women with early breast cancer (stages I through III) who underwent breast cancer surgery as per Medicare claims (Online Appendix). Patients were excluded if: 1) breast cancer was not the initial primary tumor diagnosis reported to SEER, or Medicare claims indicated any cancer diagnosis in Medicare claims within 2 years before the index diagnosis of breast cancer; 2) the source of diagnosis was autopsy or death certificate; 3) tumor histological examination was not of epithelial origin (Online Appendix) or stage was unknown; 4) month of diagnosis was missing or the patient died during the month of diagnosis; 5) patients did not have continuous fee-for-service Medicare Part A or Part B coverage or at least 1 nondenied Medicare claim during the 2 years before diagnosis through the end of the study period; or 6) chemotherapy or trastuzumab therapy was initiated more than 9 months after breast cancer surgery. Because the intent of our study was to identify incident cardiac events that potentially were attributable to cancer therapy, we excluded patients with a prior inpatient HF or CM Medicare claim or with 2 or more HF or CM outpatient or physician claims more than 30 days apart within 2 years before the diagnosis of breast cancer.

Cancer-free Medicare cohort. To compare HF or CM rates in our study's reference group (SEER-Medicare patients with breast cancer who did not receive adjuvant chemotherapy or trastuzumab) with those of the general Medicare population, we assembled a cohort of female Medicare beneficiaries with no known history of cancer. From the standard 5% Medicare sample, we performed a 1:1 match of female patients without a history of cancer to SEER-Medicare patients who did not receive any adjuvant chemotherapy or trastuzumab therapy, matching on the following characteristics: 1) SEER region of residence; 2) age quartile; 3) number of Elixhauser comorbidities (14) (any vs. none); and 4) quartile of total Medicare costs during the year preceding cancer diagnosis (or the year preceding index date for cancer-free individuals). For cancer-free patients, we selected a random index date within the same calendar year as the diagnosis of cancer of the matched SEER patient.

Chemotherapy and trastuzumab therapy. Receipt of adjuvant chemotherapy and trastuzumab were identified on the basis of the Healthcare Common Procedure Coding System codes (15) (Online Appendix) from Medicare claims billed in the first 12 months after breast cancer surgery. Patients were assigned to the following mutually exclusive treatment groups: 1) trastuzumab (with or without nonanthracycline chemotherapy); 2) anthracycline plus trastuzumab (A+T); 3) anthracycline (without trastuzumab and with or without nonanthracycline chemotherapy); 4) other (nonanthracycline) chemotherapy; or 5) no adjuvant chemotherapy or trastuzumab therapy.

HF or CM outcomes. Cardiotoxicity outcomes of interest included claims with HF or CM diagnoses according to the following International Classification of Disease, 9th Revision, Clinical Modification (ICD-9-CM) codes: HF (402.01, 402.11, 402.91, 404.01, 404.11, 404.91, 404.93, 428.x) or CM (425.x). As recommended by current algorithms, only ICD-9-CM diagnosis codes that appeared in at least 1 inpatient claim or 2 outpatient or physician claims at least 30 days apart were included to increase specificity (16). Because most patients treated with trastuzumab were treated from 2005 onward, we reported cumulative incidence of HF or CM up to 3 years after breast cancer diagnosis.

Cancer characteristics, comorbidities, and socioeconomic status. SEER data includes the following breast cancer characteristics: stage, grade, tumor size, and number of positive lymph nodes. Use of radiation therapy was ascertained from Medicare claims (17). Breast surgery was classified into mastectomy or breast conserving according to ICD-9-CM codes (Online Appendix). Comorbidities were categorized using the Elixhauser method (14), which provides slightly better discrimination compared with other comorbidity classifications (18,19). Comorbidities were identified from inpatient, outpatient, and physician Medicare claims for specific ICD-9-CM codes at any time during the 2 years before the breast cancer diagnosis. We also identified several cardiovascular risk factors, including: coronary artery disease, ischemic stroke or transient ischemic attack, hypertension, diabetes mellitus, renal failure, atrial fibrillation or atrial flutter, and hyperlipidemia, as ascertained by ICD-9-CM codes and the Elixhauser method. We used median household income from the 2000 United States Census according to patient zip code of residence as a proxy for socioeconomic status because patient-level data are not available in SEER.

Statistical Analysis. Baseline patient characteristics were compared across the adjuvant therapy groups using the chi-squared test. Temporal trends in use of adjuvant-

specific treatment were assessed using the Cochrane-Armitage test for binary outcomes and the Jonckheere-Terpstra test for outcomes with more than 2 groups. Cumulative HF or CM incidence rates were compared across adjuvant cancer therapy groups using unadjusted Poisson regression models, with no adjuvant therapy as the reference group. Adjusted Poisson models then were constructed adjusting for potential confounders, including patient demographics (age, race, marital status), breast cancer characteristics, cardiovascular conditions, number of Elixhauser comorbidities (excluding cardiovascular conditions), year of breast cancer diagnosis, SEER registry location, and median household income.

To evaluate generalizability to the overall Medicare population, we compared HF or CM incidence rates between SEER-Medicare cancer patients without adjuvant treatment against the matched cohort of cancer-free female Medicare beneficiaries. Secondary analyses also examined HF and CM outcomes separately. Time-to-event analyses using Cox proportional hazards regression models were explored, but the assumption of proportional hazards between adjuvant treatment groups did not hold; these results were not presented.

Statistical analyses were performed using SAS software version 9.2 (SAS, Inc., Cary, North Carolina). The Yale Human Investigation Committee determined that this analysis did not directly involve human subjects.

Results

The SEER-Medicare cohort consisted of 45,537 women with early-stage breast cancer. Patients were elderly, with a median age of 76 years (mean: 76.2 years, standard deviation: 6.2 years). Overall, 431 (1.0%) received trastuzumab, 431 (0.9%) received A+T, 5,257 (11.5%) received anthracycline-based chemotherapy, 2,712 (5.9%) received other (nonanthracycline) chemotherapy, and 36,700 (80.6%) received no adjuvant chemotherapy or trastuzumab (Table 1). The proportion of patients who received any adjuvant chemotherapy, trastuzumab, or both remained nearly constant across the study period, ranging from 19.8% in 2000 to 21.6% in 2007. Of the 8,837 patients who received any form of adjuvant therapy, the proportion of those who received trastuzumab or A+T increased from 2.6% in 2000 to 22.6% in 2007 ($p < 0.001$) (Fig. 1).

On average, women treated with trastuzumab, A+T, or anthracycline were younger, had more Elixhauser comorbidities, and had fewer cardiovascular conditions compared with patients who received no adjuvant therapy (Table 1). Patients with breast cancer of higher stage, higher grade, larger tumor size, greater number of positive lymph nodes, or who underwent mastectomy were more likely to be treated with trastuzumab, A+T, or anthracycline ($p < 0.001$).

Three years after diagnosis from breast cancer, the observed cumulative incidence of HF or CM was significantly higher ($p < 0.001$) for patients receiving trastuzumab (26.7 per 100 patients) and A+T (28.2 per 100 patients) compared with patients who received with no adjuvant therapy (16.9 per 100 patients) (Table 2). In unadjusted analysis, patients who received anthracyclines were less likely to have HF or CM compared with patients who received no adjuvant therapy (15.3 vs. 16.9 per 100 patients, $p < 0.001$). The 3-year HF or CM incidence for patients who received other types of chemotherapy was not significantly different from patients who received no adjuvant therapy (17.0 vs. 16.9 per 100 patients, $p = 0.89$).

Observed HF or CM incidence rates for women receiving no adjuvant therapy were slightly lower compared with the matched control group of female Medicare beneficiaries without breast cancer after 3 years of follow-up (16.9 vs. 18.7 per 100 patients, $p < 0.001$) (Table 3). However, adjusted 3-year HF or CM incidence rates were not significantly different between women with breast cancer who did not receive adjuvant therapy compared with matched cancer-free controls (17.2 vs. 17.2 per 100 patients, $p > 0.99$).

In the unadjusted Poisson models, patients who received trastuzumab had higher rates of HF or CM after 3 years of follow-up (incidence rate ratio [IRR]: 1.61, 95% confidence interval [CI]: 1.30 to 1.99) as well as those who received A+T (IRR: 1.66, 95% CI: 1.36 to 2.04) compared with patients who received no adjuvant therapy (Table 4). Patients treated with anthracyclines had a paradoxically lower risk of HF or CM (IRR: 0.90, 95% CI: 0.83 to 0.98), and patients treated with other chemotherapy were not significantly different in their risk of HF or CM (IRR: 1.01, 95% CI: 0.91 to 1.12) compared with patients who received no adjuvant therapy.

In the adjusted Poisson models of 3-year HF or CM outcomes, both trastuzumab and A+T were associated with higher risk for HF or CM compared with no adjuvant therapy (IRR: 1.78, 95% CI: 1.43 to 2.21, and IRR: 2.32, 95% CI: 1.87 to 2.87, respectively). Anthracyclines also were associated with a higher risk of HF or CM (IRR: 1.12, 95% CI: 1.02 to 1.23), whereas other chemotherapy treatments were not associated with different risks compared with no adjuvant therapy (IRR: 1.06, 95% CI: 0.95 to 1.18). Risk of HF or CM increased across each age category. Other factors associated with a higher risk of HF or CM included black race, higher comorbidity score, history of coronary artery disease, stroke or transient ischemic attack, diabetes mellitus, hypertension, renal failure, and atrial fibrillation or atrial flutter.

The adjusted cumulative incidence rates of HF or CM increased throughout the 3 years after cancer diagnosis (Table 2). Women receiving adjuvant therapy of trastuzumab, A+T, or anthracycline therapy had significantly higher cumulative incidence rates of HF or CM compared with those receiving no adjuvant therapy at 1, 2, and 3 years after diagnosis ($p < 0.001$). The addition of trastuzumab to anthracycline was estimated to increase the number of HF

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Table 1 Patient Characteristics by Adjuvant Therapy Group

	All Breast Cancer Patients	Trastuzumab	Anthracycline + Trastuzumab	Anthracycline	Other Chemotherapy	None	p Value	Cancer-free Patients	p Value vs. None
Total sample	45,537 (0)	437 (0)	431 (0)	5,257 (0)	2,712 (0)	36,700 (0)		36,700 (0)	
Age group (yrs)									
67–69	7,550 (16.6)	74 (16.9)	153 (35.5)	1,902 (36.2)	608 (22.4)	4,813 (13.1)	<0.001	5,003 (13.6)	0.081
70–74	12,534 (27.5)	153 (35.0)	184 (42.7)	2,082 (39.6)	978 (36.1)	9,137 (24.9)		9,154 (24.9)	
75–79	12,109 (26.6)	100 (22.9)	77 (17.9)	1,047 (19.9)	740 (27.3)	10,145 (27.6)		9,900 (27.0)	
80–94	13,344 (29.3)	110 (25.2)	17 (3.9)	226 (4.3)	386 (14.2)	12,605 (34.3)		12,643 (34.4)	
Race									
White	41,560 (91.3)	387 (88.6)	376 (87.2)	4,668 (88.8)	2,403 (88.6)	33,726 (91.9)	<0.001	31,332 (85.4)	<0.001
Black	2,266 (5.0)	28 (6.4)	29 (6.7)	368 (7.0)	202 (7.4)	1,639 (4.5)		2,240 (6.1)	
Other	1,711 (3.8)	22 (5.0)	26 (6.0)	221 (4.2)	107 (3.9)	1,335 (3.6)		3,128 (8.5)	
Elixhauser score									
0	29,810 (56.7)	296 (24.3)	296 (16.2)	3,813 (13.8)	1,841 (24.0)	23,564 (66.2)	<0.001	23,564 (64.2)	<0.001
1–2	13,951 (35.1)	123 (47.4)	124 (49.7)	1,322 (61.3)	785 (61.9)	11,597 (29.1)		11,597 (31.6)	
3+	1,776 (8.1)	18 (28.4)	11 (34.1)	122 (25.0)	86 (14.0)	1,539 (4.7)		1,539 (4.2)	
Pre-existing cardiovascular conditions									
CAD	1,873 (4.1)	16 (3.7)	16 (3.7)	202 (3.8)	118 (4.4)	1,521 (4.1)	0.76	1,704 (4.6)	0.001
Stroke/TIA	2,298 (5.0)	17 (3.9)	16 (3.7)	183 (3.5)	96 (3.5)	1,986 (5.4)	<0.001	2,100 (5.7)	0.067
Diabetes	7,635 (16.8)	79 (18.1)	69 (16.0)	890 (16.9)	524 (19.3)	6,073 (16.5)	0.005	6,366 (17.3)	0.004
Hypertension	26,399 (58.0)	260 (59.5)	233 (54.1)	2,770 (52.7)	1,536 (56.6)	21,600 (58.9)	<0.001	21,586 (58.8)	0.92
Renal failure	551 (1.2)	11 (2.5)	<11 (<2.6)	45 (0.9)	30 (1.1)	>454 (>1.2)	0.005	>454 (>1.2)	<0.001
Atrial fibrillation/flutter	3,255 (7.1)	26 (5.9)	15 (3.5)	190 (3.6)	187 (6.9)	2,837 (7.7)	<0.001	2,409 (6.6)	<0.001
Hyperlipidemia	22,988 (50.5)	257 (58.8)	239 (55.5)	2,646 (50.3)	1,406 (51.8)	18,440 (50.2)	0.001	16,427 (44.8)	<0.001
Stage									
I	25,832 (56.7)	106 (24.3)	70 (16.2)	724 (13.8)	652 (24.0)	24,280 (66.2)	<0.001		
II	16,002 (35.1)	207 (47.4)	214 (49.7)	3,221 (61.3)	1,679 (61.9)	10,681 (29.1)			
III	3,703 (8.1)	124 (28.4)	147 (34.1)	1,312 (25.0)	381 (14.0)	1,739 (4.7)			
Grade									
1: Well differentiated	10,812 (23.7)	21 (4.8)	<11 (<2.6)	514 (9.8)	309 (11.4)	>9,957 (>27.1)	<0.001		
2: Moderately differentiated	19,370 (42.5)	111 (25.4)	98 (22.7)	1,953 (37.2)	1,008 (37.2)	16,200 (44.1)			
3: Poorly differentiated	11,577 (25.4)	274 (62.7)	291 (67.5)	2,371 (45.1)	1,174 (43.3)	7,467 (20.3)			
4: Undifferentiated; anaplastic	485 (1.1)	13 (3.0)	11 (2.6)	100 (1.9)	37 (1.4)	324 (0.9)			
Unknown	3,293 (7.2)	18 (4.1)	>20 (>4.6)	319 (6.1)	184 (6.8)	<2,752 (<7.5)			
Tumor size (cm)									
<2.0	28,030 (61.6)	140 (32.0)	136 (31.6)	1,710 (32.5)	1,074 (39.6)	24,970 (68.0)	<0.001		
2.0–≤5.0	14,852 (32.6)	236 (54.0)	220 (51.0)	2,761 (52.5)	1,398 (51.5)	10,237 (27.9)			
>5.0	2,279 (5.0)	47 (10.8)	54 (12.5)	685 (13.0)	219 (8.1)	1,274 (3.5)			
Missing	376 (0.8)	14 (3.2)	21 (4.9)	101 (1.9)	21 (0.8)	219 (0.6)			
No. positive lymph nodes									
None	28,709 (63.0)	203 (46.5)	132 (30.6)	1,553 (29.5)	1,161 (42.8)	25,660 (69.9)	<0.001		
1–3	7,767 (17.1)	103 (23.6)	144 (33.4)	1,954 (37.2)	982 (36.2)	4,584 (12.5)			
4+	3,642 (8.0)	103 (23.6)	125 (29.0)	1,537 (29.2)	461 (17.0)	1,416 (3.9)			
None examined	5,211 (11.4)	>17 (>3.9)	17 (3.9)	155 (2.9)	88 (3.2)	<4,934 (<13.4)			
Unknown	208 (0.5)	<11 (<2.5)	13 (3.0)	58 (1.1)	20 (0.7)	>106 (>0.3)			
Surgery									
Breast conserving	26,067 (57.2)	188 (43.0)	163 (37.8)	2,083 (39.6)	1,223 (45.1)	22,410 (61.1)	<0.001		
Mastectomy	19,470 (42.8)	249 (57.0)	268 (62.2)	3,174 (60.4)	1,489 (54.9)	14,290 (38.9)			
Radiation therapy									
Right side	12,199 (26.8)	116 (26.5)	119 (27.6)	1,580 (30.1)	737 (27.2)	9,647 (26.3)	<0.001		
Left side	12,598 (27.7)	117 (26.8)	135 (31.3)	1,740 (33.1)	767 (28.3)	9,839 (26.8)			
None	20,740 (45.5)	204 (46.7)	177 (41.1)	1,937 (36.8)	1,208 (44.5)	17,214 (46.9)			

Values are n (%). Cell sizes smaller than 11 are suppressed per Surveillance, Epidemiology, and End Results-Medicare policy.
CAD = coronary artery disease; TIA = transient ischemic attack.

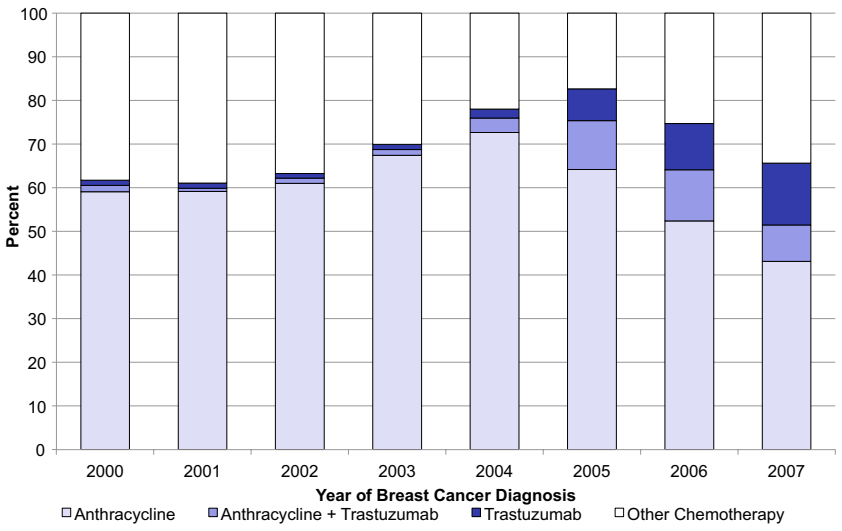

Figure 1 Use of Adjuvant Chemotherapy or Biological Therapy, 2000–2008

Graph showing the distribution anthracycline chemotherapy, nonanthracycline chemotherapy, or trastuzumab among patients who received any adjuvant therapy for breast cancer from 2000 through 2008.

or CM cases by 12.2, 17.9, and 21.7 per 100 patients after 1, 2, and 3 years of follow-up, respectively ($p < 0.001$). Compared with no adjuvant therapy, trastuzumab without anthracycline chemotherapy was estimated to increase the number of HF or CM cases by 9.7, 10.4, and 14.1 per 100 patients after 1, 2, and 3 years of follow-up, respectively ($p < 0.001$).

In secondary analyses examining 3-year HF and CM incidence separately, A+T was associated significantly with HF alone (IRR: 1.65, 95% CI: 1.27 to 2.13) and CM alone (IRR: 8.18, 95% CI: 5.56 to 12.06) compared with no adjuvant therapy in the adjusted models. Trastuzumab without anthracycline chemotherapy was borderline significantly associated with HF alone (IRR: 1.28, 95% CI: 0.98 to 1.66) and was associated significantly with CM alone (IRR: 6.43, 95% CI: 4.29 to 9.64) compared with no adjuvant therapy.

Discussion

The use of trastuzumab in the adjuvant setting for breast cancer increased substantially in the Medicare population from 2000 through 2007. Compared with patients who received no adjuvant chemotherapy or trastuzumab, use of trastuzumab was associated with an absolute 14.0% higher adjusted incidence rate for HF or CM over 3 years. Patients who received both trastuzumab and anthracycline had an absolute 23.8% higher rate, and those treated with anthracycline chemotherapy alone has an absolute 2.1% higher rate of HF or CM events over 3 years.

Intrinsic differences in the mechanisms of cardiotoxicity may be one explanation for why the risk of developing HF or CM was higher with trastuzumab than with anthracycline therapy. Cardiac damage resulting from anthracycline therapy is thought to be the result of free radical injury and oxidative stress, resulting in permanent myocyte loss (20),

Table 2 Cumulative Incidence of Heart Failure or Cardiomyopathy During First 3 Years After Diagnosis by Cancer Therapy

	All Cancer Patients	Anthracycline + Trastuzumab (n = 431)	Anthracycline (n = 5,257)	Trastuzumab (n = 437)	Other Chemotherapy (n = 2,712)	None (n = 36,700)
Observed cumulative incidence						
1 year	7.2	16.4*†	7.7‡	15.7*	7.8	6.8
2 years	12.3	23.8*†	11.9	20.7*	12.4	12.1
3 years	16.9	28.2*†	15.3‡	26.7*	17.0	16.9
Adjusted cumulative incidence						
1 year	7.5	22.0*†	9.8*	16.7*	8.4*	7.0
2 years	13.3	33.2*†	15.3*	23.2*	13.7*	12.8
3 years	18.7	41.9*†	20.2‡	32.1*	19.2	18.1

Values are %. Per 100 patients if surviving for the full time. Poisson model used to measure significance. *$p < 0.001$ versus no adjuvant therapy group. †$p < 0.001$ versus anthracycline group, only in the model containing anthracycline plus trastuzumab and anthracycline adjuvant therapy. ‡$p < 0.05$ versus no adjuvant therapy group.

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Table 3 Cumulative Incidence of Heart Failure or Cardiomyopathy During the First 3 Years in Breast Cancer Patients Without Adjuvant Therapy Versus Cancer-Free Controls

	Breast Cancer, No Adjuvant Therapy (n = 36,700)	Cancer-Free Medicare Controls (n = 36,700)
Observed		
1 year	6.8	8.0*
2 year	12.1	13.7*
3 year	16.9	18.7*
Adjusted		
1 year	6.7	7.0
2 year	12.2	12.4
3 year	17.2	17.2

Values are %. Per 100 patients if surviving for the full time. Poisson model used to measure significance. Adjusted for age, race, Elixhauser score, and pre-existing cardiovascular conditions. *$p < 0.001$.

whereas trastuzumab is hypothesized to block ErbB2 signaling pathways essential for myocyte function. Alternatively, our findings also may reflect differences in patient selection if clinicians were more careful to select the lowest-risk patients for anthracycline, given that cardiotoxicity results in permanent cell damage. Our finding that anthracycline therapy was associated with a lower risk of HF or CM in unadjusted analyses suggests that some selection did occur, but after adjustment, the relationship between treatment and HF or CM became positive, as expected.

Differences in the frequency of follow-up assessment of left ventricular function also may explain in part why patients treated with trastuzumab had higher rates of HF or CM, because more frequent ascertainment of LVEF allows for greater opportunity to detect declines in systolic function. The National Comprehensive Cancer Network guidelines suggest periodic assessment of LVEF during the course of trastuzumab therapy at baseline, 3, 6, and 9 months (21); in contrast, for chemotherapy, typically a baseline LVEF assessment is performed with follow-up assessments made on the basis of symptoms. As such, HF or CM rates may seem to be higher in patients treated with trastuzumab because of additional detection of asymptomatic patients. However, secondary analyses demonstrated an association between trastuzumab and A+T with HF alone without CM. Because of the symptomatic nature of HF, it would be less likely to be influenced by intensity of follow-up LVEF assessment compared with the combined HF or CM outcome.

Our estimates of the increased relative rate of HF or CM associated with adjuvant therapy are consistent with a prior study by Du et al. (22) that reported an increased risk of HF associated with trastuzumab (hazard ratio: 1.97) and with A+T (hazard ratio: 2.37) relative to no adjuvant therapy for women with breast cancer in the SEER-Medicare database from 1998 through 2005. An important distinction is that our study focused on the use of trastuzumab in the adjuvant setting, similar to the randomized clinical trials, whereas Du et al. included women with metastatic (stage IV) disease for whom HF or CM risk is a less important concern relative to the potential benefit of improved survival. Our findings also were comparable with those from a meta-analysis of 5 trastuzumab trials by Viani et al. (23) that reported an odds ratio of 2.45 associated with trastuzumab versus standard adjuvant therapy (predominately anthracycline chemotherapy).

However, it is important to consider that the absolute risk of HF or CM associated with trastuzumab in our study was substantially higher than those reported from 4 major randomized clinical trials of trastuzumab. The proportion of patients with severe HF (New York Heart Association classes III or IV) in these studies ranged from 2% to 4% in the trastuzumab plus standard adjuvant therapy arms over 3.0 to 5.4 years of follow-up and less than 1% in the control standard adjuvant therapy arms that consisted largely of anthracycline chemotherapy (5–7). In contrast, the observed

Table 4 3-Year Unadjusted and Adjusted Incidence Rate Ratios for Heart Failure or Cardiomyopathy

	IRR	95% CI	p Value
Unadjusted			
Chemotherapy/biologic therapy			
Trastuzumab	1.61	1.30–1.99	<0.001
Anthracycline + trastuzumab	1.66	1.36–2.04	<0.001
Anthracycline	0.90	0.83–0.98	0.014
Other chemotherapy	1.01	0.91–1.12	0.80
None (ref)	1.00	1.00–1.00	NA
Adjusted			
Chemotherapy/biologic therapy			
Trastuzumab	1.78	1.43–2.21	<0.001
Anthracycline + trastuzumab	2.32	1.87–2.87	<0.001
Anthracycline	1.12	1.02–1.23	0.021
Other chemotherapy	1.06	0.95–1.18	0.30
Age group (yrs)			
67–69 (reference)	1.00	1.00–1.00	NA
70–74	1.15	1.05–1.27	0.003
75–79	1.40	1.28–1.54	<0.001
80–94	1.98	1.80–2.17	<0.001
Race			
White (reference)	1.00	1.00–1.00	NA
Black	1.22	1.10–1.35	<0.001
Other	0.74	0.62–0.88	0.001
Elixhauser score			
0 (reference)	1.00	1.00–1.00	NA
1 to 2	1.49	1.41–1.57	<0.001
3+	1.98	1.80–2.18	<0.001
Pre-existing cardiovascular conditions			
CAD	1.54	1.41–1.69	<0.001
Stroke/TIA	1.26	1.16–1.38	<0.001
Diabetes	1.63	1.54–1.73	<0.001
Hypertension	1.33	1.26–1.41	<0.001
Renal failure	1.88	1.62–2.19	<0.001
Atrial fibrillation of flutter	2.35	2.19–2.51	<0.001
Hyperlipidemia	0.93	0.88–0.98	0.010

Adjusted model also includes year of diagnosis; Surveillance, Epidemiology, and End Results registry; median income; and breast cancer characteristics.

CI = confidence interval; IRR = incident rate ratio; NA = not applicable; other abbreviations as in Table 1.

3-year cumulative HF or CM incidence rates in our study were considerably higher, at 26.7 and 28.2 per 100 patients for trastuzumab and A+T, respectively, and 15.3 per 100 patients for anthracycline. Although these 3-year HF or CM incidence rates seem high, they must be considered in the context of the baseline HF or CM rates in the female cancer-free Medicare cohort (observed 3-year HF or CM incidence of 18.7 per 100 patients). However, comparisons of HF or CM rates from clinical trials remain challenging because the definition of cardiotoxicity events vary considerably (24), and it is likely that the sensitivity and specificity of HF or CM events between clinically based and claims-based assessments also differ.

The absolute incremental risk of HF or CM attributable to adding trastuzumab to anthracycline therapy was substantially higher for SEER-Medicare patients compared with those of clinical trial cohorts consisting of younger patients. The absolute incremental difference in HF or CM between A+T and anthracycline alone was 17.9 per 100 patients over 2 years in the SEER-Medicare population. In comparison, a meta-analysis of 4 trastuzumab trials reported an absolute incremental increase of 1.6 per 100 patients for New York Heart Association classes III and IV HF and an absolute incremental increase of 7.2 per 100 patients for CM over an average of 2 years of follow-up (8). It is not surprising that HF or CM rates in the SEER-Medicare population were substantially higher compared with the clinical trials. The incidence of HF or CM is known to increase with age (25), and the SEER-Medicare population was considerably older than subjects in the trastuzumab clinical trials. In addition, the clinical trials excluded patients at high risk for HF or CM developing, such as individuals with prior HF, coronary artery disease, arrhythmias, poorly controlled hypertension, or valve disease (5,26). That the clinical trials consisted primarily of low-risk cardiac patients illustrates the usefulness of a registry-based approach to estimate cancer treatment-associated HF or CM rates in the general population.

Our results indicated that patients with breast cancer who did not receive adjuvant therapy had a slightly lower risk of HF or CM developing compared with matched controls of female Medicare beneficiaries without breast cancer. This should not be interpreted to indicate that breast cancer is protective against HF or CM, but rather, this reflects that women who are diagnosed with breast cancer differ in subtle respects from the general population. Most women who are diagnosed with early-stage breast cancer have received the diagnosis as a result of screening mammography, and such patients also are likely to engage in other preventative behaviors that concurrently reduce risk of HF or CM, such as blood pressure or diabetes screening. After adjusting for age, race, and comorbidities, there was no significant difference in 3-year HF or CM incidence between the no adjuvant therapy group and matched cancer-free controls.

Our findings illustrate that the incidence of HF or CM is high for older women in general, regardless of the presence of breast cancer. This suggests that there is a potentially important role for cardiologists before initiation of cancer therapy to optimize patients who are at high risk for developing HF or CM and to detect early signs and symptoms of HF or CM after treatment. Ongoing research evaluating the role of cardiac biomarkers for predicting risk of HF or CM during cancer therapy may prove useful for identifying patients who may benefit from early cardiology referral (27).

Study limitations. Our study is limited in that HF and CM events and comorbidities were ascertained on the basis of administrative codes and were not confirmed clinically. Estimates of HF incidence estimated from Medicare data (28) typically have been higher than those from prospective surveillance cohorts, such as the Framingham Heart Study (29). This may reflect several factors, such as differences in stringency for criteria defining HF or an administrative coding practice of using rule-out diagnoses as indications. However, administrative codes for HF and cardiovascular comorbidities have high specificity (approximately 95%) and positive predictive value (95%) (30–33). Second, information on dose and method of administration for the adjuvant cancer therapies in our study currently is not considered reliable in Medicare claims. Third, clinical data on left ventricular systolic function were not available; as a result, neither the severity of CM nor differentiation of systolic from diastolic HF could be established; future studies using clinical data to differentiate systolic and diastolic HF are warranted. Fourth, although we controlled for a number of cardiac and noncardiac risk factors, we cannot rule out the potential for residual confounding where healthier women were more likely to undergo adjuvant therapy. Furthermore, data on medication use in the SEER-Medicare database were limited, which may introduce residual confounding if cardiovascular therapies such as β-blockers (34) and angiotensin-converting enzyme inhibitors (27) reduce risk of adjuvant therapy HF or CM and if use of these therapies varied significantly by treatment group.

Conclusions

In a cohort of older female Medicare beneficiaries with breast cancer, use of trastuzumab increased by more than 8-fold from 2000 through 2007 among patients receiving any form of adjuvant therapy. The absolute incremental risk of adding trastuzumab to anthracycline for older SEER-Medicare patients was substantially higher than that reported from clinical trials enrolling younger, healthier women.

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Key Words: anthracycline ■ cardiomyopathy ■ chemotherapy ■ epidemiology ■ heart failure ■ trastuzumab.

APPENDIX

For a supplemental table and additional information, please see the online version of this article.