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ORIGINAL REPORT

Congestive Heart Failure in Older Women Treated With Adjuvant Anthracycline Chemotherapy for Breast Cancer

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ABSTRACT

Purpose
Limited data are available on long-term cardiac safety of adjuvant anthracycline chemotherapy in breast cancer patients over age 65 years. We evaluated rates and predictors of congestive heart failure (CHF) in this population.

Patients and Methods
We used the Surveillance, Epidemiology, and End Results Medicare database and included women with no history of CHF who were age 66 to 80 years and diagnosed with stage I to III breast cancer from 1992 to 2002. Cumulative rates of CHF were estimated, and multivariable Cox regression analysis was used to determine factors associated with the development of CHF.

Results
A total of 43,338 women were included. Anthracycline-treated women were younger, with fewer comorbidities and more advanced disease than women who received nonanthracycline or no chemotherapy ($P < .001$ for each). The adjusted hazard ratio (HR) for CHF was 1.26 (95% CI, 1.12 to 1.42) for women aged 66 to 70 treated with anthracycline compared with other chemotherapy. For women aged 71 to 80, adjuvant chemotherapy type was not associated with CHF. The following baseline characteristics were significant predictors of CHF: age (HR, 1.79 per 10 years; 95% CI, 1.66 to 1.93), black race (HR, 1.40; 95% CI, 1.30 to 1.50), trastuzumab treatment (HR, 1.46; 95% CI, 1.21 to 1.77), hypertension (HR, 1.45; 95% CI, 1.39 to 1.52), diabetes (HR, 1.74; 95% CI, 1.66 to 1.83), and coronary artery disease (HR, 1.58; 95% CI, 1.39 to 1.79). Left-sided radiotherapy did not confer an elevated risk of CHF (HR, 1.04; 95% CI, 0.98 to 1.11).

Conclusion
Women aged 66 to 70 years who received adjuvant anthracyclines had significantly higher rates of CHF. The difference in rates of CHF continued to increase through more than 10 years of follow-up.

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INTRODUCTION

Anthracyclines are among the most effective drugs for the treatment of patients with breast cancer. Data from the Oxford Overview indicate that 6 months of adjuvant anthracycline-based polychemotherapy reduces the annual breast cancer death rate by 38% for women younger than 50 years and 20% for women aged 50 to 69 years. Anthracyclines are significantly more effective than cyclophosphamide, methotrexate, and fluorouracil chemotherapy, with an absolute survival benefit of 3% at 5 years and 4% at 10 years.[1] Women aged 70 years and older appear to have a risk reduction similar to women aged 50 to 69.[2-4] However, the small number of older women on clinical trials[5,6] precludes a definite conclusion regarding the benefit of chemotherapy in women 70 years and older.

Anthracycline-associated cardiotoxicity has been recognized for almost as long as anthracyclines have been used,[7-11] and clinical benefits must be weighed against the risk of serious cardiotoxicity. Short-term cardiotoxicity has been well-established in clinical trials.[12,13] Among patients treated with four cycles of doxorubicin and cyclophosphamide on National Surgical Adjuvant Breast and Bowel Project B-31, 17% of patients developed asymptomatic cardiac disease, defined as a decline in left ventricular ejection fraction of more than 10% to an ejection fraction less than 55%.[13] Symptomatic congestive heart failure (CHF) is the most serious and feared complication of anthracycline-based chemotherapy, with an incidence of 5% to 48%, depending on the cumulative dose received.[14] Although doses below 500 mg/m^2 are considered safer, cardiomyopathy occurs at lower cumulative doses.[14]

Of particular relevance to breast cancer patients, this effect is more pronounced in older patients and females.[7,14,15]

Limited data are available on the long-term consequences of exposure to anthracyclines. Among pediatric patients, cardiac abnormalities are known to increase with longer follow-up, suggesting that reports of cardiac function immediately post-treatment or at 3 years may substantially underestimate long-term consequences of therapy.[16-18] Among anthracycline-treated adult patients, the long-term incidence of CHF remains unclear. Several studies have assessed cardiac function in patients previously treated on adjuvant clinical trials, but only a select population of survivors consented for further study.[19,20] These patients may not be representative of women in the community, because women participating in clinical trials tend to be younger than the average woman with breast cancer. Data are particularly sparse on the cardiotoxicity of anthracyclines in elderly patients with breast cancer. Patients older than 65, whose age-associated comorbidities may confer a higher risk of anthracycline cardiotoxicity, are often excluded from clinical trials.[5,6] Consequently, little is known about the true incidence or predictors of CHF in this group.

Doyle et al[21] recently reported increased risk of cardiac complications among anthracycline-treated breast cancer survivors older than 65. Our study builds on this work by including significantly longer follow-up and more recent data, addressing the predictive value of specific comorbidities and other treatments received (eg, trastuzumab), and analyzing patterns of surveillance for cardiac complications in elderly breast cancer patients. We have previously employed the Surveillance, Epidemiology, and End Results (SEER)-Medicare database to describe the efficacy of chemotherapy in women older than 65.[4] The present analysis was designed to better characterize cardiac complications that may offset the benefits of anthracycline chemotherapy in this population.

PATIENTS AND METHODS

We used the SEER-Medicare–linked database for this study. At present, cancer patients diagnosed through 2002 have been linked to their Medicare records, and their claims are available through 2004.

In the SEER-Medicare database, 210,899 women were diagnosed with breast cancer from January 1992 to December 2002. The following women were excluded from our study population: 24,152 with a previous or second cancer diagnosis; 3,589 without histologic confirmation of breast cancer, 546 with unknown month of diagnosis, 76,419 outside the ages 66 to 80 years at diagnosis, 21,324 with noninvasive breast cancer, 1,876 with metastatic breast cancer, 11,183 not covered by both Medicare A and B for 1 year before and after the diagnosis; 25,003 health maintenance organization (HMO) members; and 5,729 with CHF before breast cancer diagnosis. The remaining 43,338 women were included.

Adjuvant chemotherapy use within a year of diagnosis was identified through the Common Procedural Terminology J codes in SEER-Medicare files. The included codes were J8510, J8520, J8521, J8530 to J8999, and J9000 to J9999.[22-25] We excluded the codes of J9202 (goserelin), J9209 (mesna), 9212 to 9214 (interferon), and 9217 to 9218 (leuprolide acetate) because these drugs are not cytotoxic chemotherapeutic agents. Chemotherapy was classified as an anthracycline-based regimen if J codes for doxorubicin, mitoxantrone, daunorubicin, or epirubicin were present. Using International Classification of Diseases, ninth revision (ICD-09) diagnosis and procedure codes, comorbid conditions during the year before a breast cancer diagnosis were searched from Medicare inpatient, outpatient, and physician claims data. Number of physician visits in the year before breast cancer diagnosis was assessed. Echocardiogram and multiple gated acquisition scan (MUGA) claims were evaluated starting 1 year after breast cancer diagnosis and before CHF diagnosis. A comorbidity score was calculated using Klabunde's adaptation of the Charlson comorbidity index from the macro provided by National Cancer Institute.[26-28]

CHF diagnoses were identified through claims in Medicare inpatient, outpatient, and physician/supplier files. The ICD-09 code of CHF is 428. For Outpatient and Physician/Supplier claims, we required that CHF diagnoses appear on at least two different claims more than 30 days apart.

Statistical Analyses

Patient characteristics were compared using the χ^2 test for categoric variables and t test for continuous variables. Time to CHF was calculated in months from the date of breast cancer diagnosis to the date of first CHF claim. Patients were lost to follow-up when they lost full coverage of both Medicare Part A and Part B or enrolled in HMOs. The cutoff date for follow-up was December 31, 2003. Patients were excluded at the last follow-up if they had not had CHF.

The primary end point of this study was a diagnosis of CHF. Time-to-event curves for CHF were calculated using the conditional Kaplan-Meier method by type of adjuvant chemotherapy. Multivariate Cox proportional hazards models were used to calculate the hazard of CHF after adjusting for confounding variables. The proportional hazard assumption was assessed with a smoothed plot of weighted Schoenfeld residuals.[29] The interaction between age and adjuvant chemotherapy was tested using the product term of these two variables in the model. Analyses were adjusted for number of physician visits in the year before diagnosis, age, race, year of diagnosis, tumor American Joint Committee on Cancer Modified third edition stage, grade, radiotherapy, late anthracycline use, trastuzumab use, and comorbidity (either Charlson scores or individual conditions). All computer programming and analyses were performed with the SAS system (SAS Inc, Cary, NC).[30]

Propensity Scoring

Propensity scoring is a technique used to estimate the likelihood that an individual patient will be treated, based on the patient's predictive baseline characteristics.[31,32] The probability of receiving chemotherapy was calculated using a logistic regression model that incorporated age, diagnosis year, SEER region, race, surgery, radiotherapy, stage, grade, estrogen receptor (ER) status and Charlson comorbidity index. We then assigned a propensity score to each patient according to the probability of receiving chemotherapy. This composite propensity score was substituted for the actual covariates in a multivariate model. The results observed using the propensity score did not differ appreciably from the multivariate model using the individual covariates. Therefore, the complete multivariate Cox model is presented.

RESULTS

Our final study population comprised 43,338 women aged 66 to 80 years with stage I to III breast cancer. Of these women, 34,705 (80%) received no adjuvant chemotherapy, 4,712 received an adjuvant anthracycline (11%), and 3,921 (9%) received nonanthracycline adjuvant chemotherapy. The median age at diagnosis was 73.2 years (range, 66 to 80 years). Median follow-up was 56 months (range, 13 to 156 months). A total of 10,096 patients (23.3%) had subsequent claims for CHF.

The three cohorts exhibited important differences in baseline characteristics (Table 1). In general, patients who received chemotherapy were younger and healthier at baseline, with more advanced breast cancer than those who did not receive chemotherapy. Although the two groups who received chemotherapy were more similar to each other than to the untreated group, anthracycline-treated patients were still slightly younger and healthier than patients who received other adjuvant chemotherapy. Black women were over-represented, and those with chronic medical conditions were under-represented in the

Table 1. Baseline Characteristics of Patients According to Chemotherapy Subgroups

Variable	% of Patients			P
	No Adjuvant Chemotherapy (n = 34,705)	Adjuvant Anthracycline (n = 4,712)	Adjuvant Other Chemotherapy (n = 3,912)	
Year of diagnosis				
1992	8.13	2.76	7.04	< .0001
1993	7.52	2.55	6.17	
1994	7.39	3.01	5.99	
1995	7.54	3.61	5.92	
1996	7.43	3.86	6.17	
1997	7.22	5.14	7.63	
1998	6.85	5.65	9.41	
1999	7.01	8.34	7.37	
2000	13.35	20.5	14.33	
2001	13.64	22.28	15.58	
2002	13.92	22.3	14.38	
Age at diagnosis, years				
66-70	30.12	54.67	42.13	< .0001
71-75	36.47	32.15	35.71	
76-80	33.41	13.18	22.16	
Race/ethnicity				
White	87.36	85.31	85.62	< .0001
Black	5.09	7.09	6.5	
Other	7.56	7.6	7.88	
AJCC stage				
I	68.93	13.33	25.22	< .0001
II	28.21	66.89	65.14	
III	2.86	19.78	9.64	
Grade				
1	22.54	7.43	10.35	< .0001
2	40.04	34.34	32.64	
3	21.73	48.13	43.23	
Unknown	15.69	10.1	13.77	
Estrogen-receptor status				
Negative	8.75	28.44	30.48	< .0001
Positive	73.12	56.32	54.88	
Unknown	18.13	15.24	14.64	
Surgery type				
Breast conserving	54.03	35.1	39.68	< .0001
Mastectomy	44.96	62.14	58.94	
No surgery	1.01	2.76	1.38	
Radiation				
No	53.28	49.49	58.74	< .0001
Left breast	22.54	24.41	19.61	
Right breast	21.93	21.86	17.39	
Unknown	2.24	4.24	4.26	
Anthracycline > 1 year after diagnosis				
No	98.95	97.39	94.64	< .0001
Yes	1.05	2.61	5.36	
Trastuzumab				
No	99.76	97.13	97.65	< .0001
Yes	0.24	2.87	2.35	
Charlson comorbidity score				
0	69.47	74.47	72.12	< .0001
1	19.75	17.87	19.03	
2+	10.79	7.66	8.85	
Comorbidities				
Hypertension	55.49	53.74	56.01	.0515
Diabetes	14.38	13.73	15.61	.042
Coronary artery disease	1.99	0.96	2.12	< .0001
Peripheral vascular disease	5.92	3.86	4.69	< .0001
Chronic bronchitis/emphysema	3.35	2.36	2.68	.0002
Myocardial infarction	0.57	0.25	0.61	.0172

Abbreviation: AJCC, American Joint Committee on Cancer.

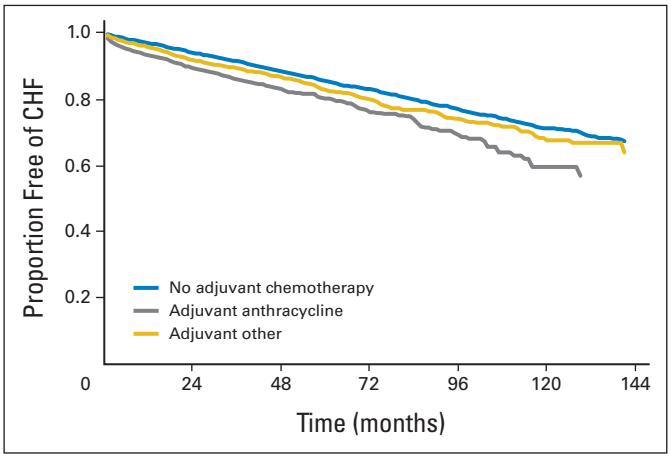

Fig 1. Women aged 66 to 70 years: freedom from congestive heart failure (CHF) by adjuvant chemotherapy type.

anthracycline-treated group. Patients treated with any chemotherapy generally had higher-grade tumors and more ER-negative disease.

Initial analysis indicated a highly significant interaction between age and adjuvant anthracycline treatment ($P = .0007$). The median age of patients who were treated with chemotherapy was 70 years. Therefore, subsequent analyses were conducted with patients divided according to age (66 to 70 *v* 71 to 80 years). Despite being younger and healthier than their counterparts who received other regimens, women aged 66 to 70 who were treated with adjuvant anthracycline-based chemotherapy were more likely to develop CHF (Fig 1). At 5 years of follow-up, 19% of anthracycline-treated patients had a diagnosis of CHF compared with 18% of patients treated with other chemotherapy and 15% of those who did not receive chemotherapy (Table 2). At 10 years, the absolute differences are more pronounced: 38.4% of the anthracycline-treated group had been diagnosed with CHF compared with 32.5% of the nonanthracycline chemotherapy and 29% of the no-chemotherapy group. For every time point studied, anthracycline-treated patients were more likely to have a diagnosis of CHF; however, with longer follow-up, the separation between anthracycline-treated patients and the other two groups becomes more pronounced. For women aged 71 to 80 years, there are no significant differences between the three groups in rates of CHF (Fig 2). Of note, the cumulative rate of CHF is higher for this group than for women aged 66 to 70 (Table 3).

Cox multivariate analysis adjusted for covariates confirmed these results (Table 4). The patients treated with nonanthracycline adjuvant chemotherapy were used as the referent group, because they were most similar to the anthracycline-treated cohort in baseline patient and tumor characteristics. Women aged 66 to 70 treated with anthracyclines had a statistically significant 26% higher risk of developing CHF compared with women treated with nonanthracycline regimens. No significant differences in rates of CHF according to adjuvant treatment type emerged among women aged 71 to 80.

Other independent predictors of heart failure are shown in Table 4. For each 10-year increase in age, patients had a near doubling of the heart failure risk. Black patients had a 49% higher risk of developing CHF. Left-sided compared with right-sided breast irradiation was not associated with a significant increase in heart failure. Women who

Table 2. Cumulative Incidence of CHF by Adjuvant Treatment Type for Patients Aged 66 to 70 Years

Time (months)	No. at Risk	Cumulative No. With Event	Probability of No Event	95% CI
Adjuvant anthracycline				
0	2,576	0	1.000	
12	2,409	177	0.931	0.922 to 0.941
36	1,601	341	0.861	0.847 to 0.875
60	549	401	0.813	0.795 to 0.831
96	166	441	0.711	0.677 to 0.747
120	65	457	0.616	0.564 to 0.672
144	18	461	0.561	0.494 to 0.638
Adjuvant other				
0	1,652	0	1.000	
12	1,587	73	0.956	0.946 to 0.966
36	1,183	170	0.893	0.878 to 0.909
60	679	242	0.823	0.803 to 0.845
96	303	298	0.732	0.702 to 0.762
120	165	316	0.675	0.638 to 0.714
144	67	321	0.640	0.595 to 0.689
No chemotherapy				
0	10,452	0	1.000	
12	10,150	317	0.970	0.966 to 0.973
36	7,931	866	0.914	0.909 to 0.920
60	4,884	1,278	0.856	0.848 to 0.864
96	2,614	1,655	0.771	0.760 to 0.782
120	1,368	1,807	0.713	0.713 to 0.726
144	446	1,876	0.654	0.636 to 0.673

Abbreviation: CHF, congestive heart failure.

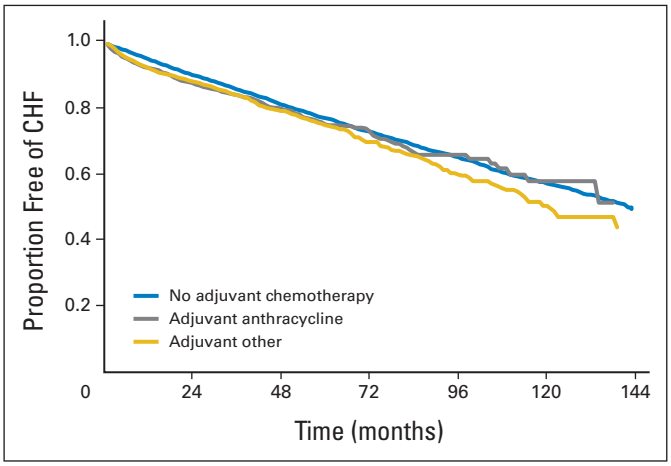

Fig 2. Women aged 71 to 80 years: freedom from congestive heart failure (CHF) by adjuvant chemotherapy type.

received anthracyclines after the first year had a higher risk of being diagnosed with heart failure (hazard ratio [HR], 1.53; 95% CI, 1.34 to 1.53). Trastuzumab was approved for HER-2/*neu*–overexpressing metastatic breast cancer in 1998. Although the number of patients treated was small, trastuzumab therapy was a significant predictor of a subsequent diagnosis of CHF (HR, 1.44; 95% CI, 1.19 to 1.74). Coronary artery disease, emphysema, diabetes, hypertension, and peripheral vascular disease emerged as highly significant predictors of a subsequent diagnosis of CHF (Table 5). Interaction terms for radiation therapy, race, trastuzumab use, and comorbidity with anthracycline use were not significant, indicating that these variables are risk factors for heart failure in general but do not indicate patients at higher risk for anthracycline-induced heart failure.

We evaluated cardiac surveillance to determine whether different treatment groups were subjected to more rigorous monitoring for cardiac complications. Anthracycline-treated patients actually had fewer claims for echocardiograms/MUGAs ($P < .0001$) and fewer visits to cardiologists ($P < .0001$) than did patients who did not receive an anthracycline (Fig 3). No differences were observed in number of echocardiogram/MUGA claims for patients subsequently diagnosed with CHF compared with those without a CHF diagnosis (data not shown).

A total of 7,969 (18.4%) patients died during the follow-up period. Deaths were attributed to breast cancer in 3,016 women (37.8% of deaths), whereas CHF was rarely listed as the primary cause of death, occurring in only 107 patients (1.3% of deaths).

DISCUSSION

In this large, observational data set, we found that women aged 66 to 70 years treated with adjuvant anthracycline chemotherapy had a statistically significant increase in the risk of being diagnosed with CHF. At 5 years of follow-up, we observed absolute differences of 1% and 4.6% respectively in rates of CHF between anthracycline-treated women in this age group and those who received other adjuvant chemotherapy or no chemotherapy. After 10 years, the increased risk of CHF in anthracycline-treated patients was amplified rather than attenuated, with absolute differences of 5.9% and 9.7% when

Table 3. Cumulative Incidence of CHF by Adjuvant Treatment Type for Patients Aged 71-80 Years

Time (months)	No. at Risk	Cumulative No. With Event	Probability of No Event	95% CI
Adjuvant anthracycline				
0	2,136	0	1.000	
12	1,967	178	0.917	0.905 to 0.928
36	1,232	334	0.835	0.819 to 0.852
60	397	423	0.739	0.715 to 0.764
96	87	448	0.656	0.619 to 0.696
120	35	456	0.572	0.511 to 0.641
144	7	462	0.349	0.222 to 0.549
Adjuvant other				
0	2,269	0	1.000	
12	2,095	187	0.918	0.906 to 0.929
36	1,420	357	0.835	0.819 to 0.851
60	676	471	0.744	0.723 to 0.766
96	216	552	0.605	0.572 to 0.640
120	104	578	0.508	0.465 to 0.555
144	24	591	0.392	0.325 to 0.472
No chemotherapy				
0	24,253	0	1.000	1.000 to 1.000
12	23,027	1,335	0.945	0.942 to 0.948
36	16,705	3,420	0.853	0.849 to 0.858
60	9,108	4,796	0.764	0.758 to 0.771
96	4,067	5,828	0.647	0.639 to 0.657
120	1,829	6,204	0.566	0.555 to 0.580
144	500	6,351	0.493	0.478 to 0.500

Abbreviation: CHF, congestive heart failure.

Table 4. Cox Proportional Hazards Model for Association Between Baseline Characteristics and Subsequent CHF, Adjusted for Charlson Comorbidity Index

Variable	Hazard Ratio	95% CI
Age 66-70 years		
Adjuvant therapy received		
Nonanthracycline	1.00	Reference
Anthracycline	1.26	1.12 to 1.42
None	0.90	0.86 to 0.99
Age 71-80 years		
Adjuvant therapy received		
Nonanthracycline	1.00	Reference
Anthracycline	1.01	0.90 to 1.13
None	0.92	0.86 to 0.99
Physician visits, No. in the year prior to breast cancer diagnosis	1.02	1.01 to 1.02
Year of diagnosis		
1992	1.00	Reference
1993	0.90	0.82 to 0.98
1994	0.95	0.87 to 1.03
1995	0.90	0.82 to 0.98
1996	0.92	0.84 to 1.01
1997	0.92	0.84 to 1.01
1998	0.87	0.79 to 0.96
1999	0.85	0.76 to 0.93
2000	0.89	0.82 to 0.97
2001	0.80	0.73 to 0.88
2002	0.85	0.77 to 0.94
Age per 10 years	1.74	1.61 to 1.87
Race/ethnicity		
White	1.00	Reference
Black	1.49	1.39 to 1.61
Other	0.91	0.85 to 0.99
AJCC stage		
I	1.00	Reference
II	1.14	1.09 to 1.19
III	1.43	1.31 to 1.56
Grade		
1	1.00	Reference
2	1.08	1.02 to 1.15
3	1.13	1.06 to 1.21
Unknown	1.11	1.03 to 1.18
Radiation		
Right breast	1.00	Reference
Left breast	1.04	0.97 to 1.10
None	1.17	1.11 to 1.23
Unknown	1.26	1.10 to 1.43
Anthracycline > 1 year after diagnosis		
No	1.00	Reference
Yes	1.53	1.34 to 1.53
Trastuzumab		
No	1.00	Reference
Yes	1.40	1.12 to 1.75
Charlson comorbidity score		
0	1.00	Reference
1	2.05	1.95 to 2.16
2+	3.62	3.42 to 3.83

Abbreviations: CHF, congestive heart failure; AJCC, American Joint Committee on Cancer.

Table 5. Cox Proportional Hazards Model for Congestive Heart Failure by Pre-Existing Conditions

Comorbidity	Hazard Ratio	95% CI
Coronary artery disease	1.58	1.39 to 1.79
Chronic bronchitis/emphysema	1.68	1.54 to 1.84
Diabetes	1.74	1.66 to 1.83
Hypertension	1.45	1.39 to 1.52
Peripheral vascular disease	1.31	1.22 to 1.41
Myocardial infarction	0.94	0.75 to 1.19

NOTE. Adjusted for type of adjuvant chemotherapy, trastuzumab use, anthracycline received > 1 year after diagnosis, number of physician visits in the year prior to breast cancer diagnosis, year of diagnosis, age, race, stage, grade, and radiotherapy type.

comparing anthracycline-treated patients to the other or no adjuvant chemotherapy groups, respectively. This effect emerged even though anthracycline-treated patients appeared to have been selected for a more favorable cardiac risk profile and were not subjected to more rigorous surveillance for cardiac complications, as shown in our analyses. Clinical trials, which typically have shorter follow-up, may underestimate the long-term risks of CHF in anthracycline-treated patients.

Rates of CHF in our study were high. However, epidemiologic data document dramatic increases in the prevalence of heart failure,

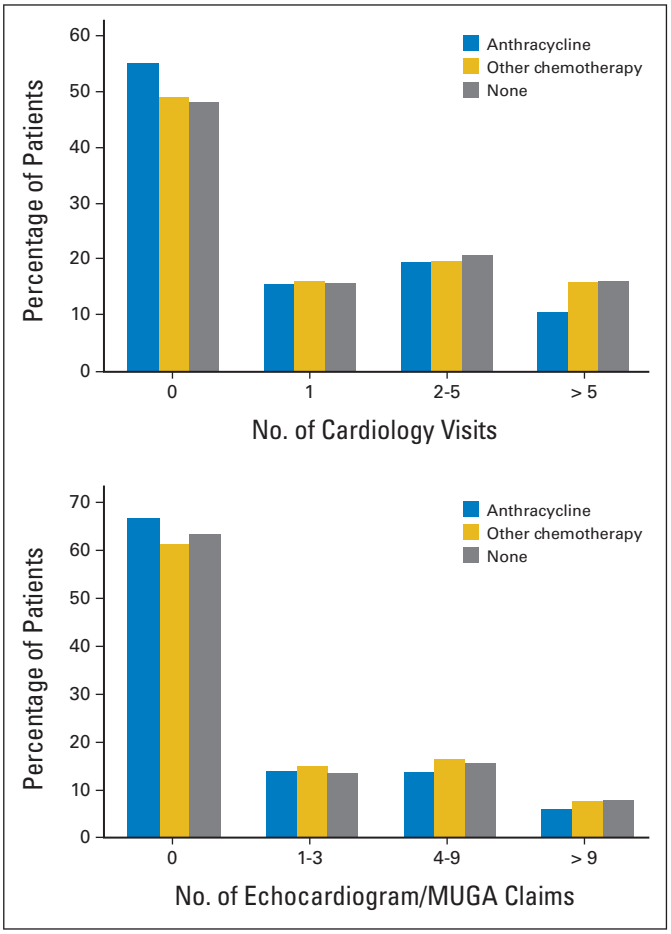

Fig 3. (A) Number of cardiology visits from 12 months after breast cancer diagnosis until a diagnosis of congestive heart failure (CHF) or end of follow-up, by adjuvant treatment type. (B) Number of echocardiogram/multiple gated acquisition scan (MUGA) claims submitted from 12 months after breast cancer diagnosis until a diagnosis of CHF or end of follow-up, by adjuvant treatment type. Chemo, chemotherapy.

particularly in the elderly, through the 1990s.[33-36] Heart failure is now the leading reason for hospitalization in elderly populations.[33,35] Although comparison with rates of CHF in an elderly noncancer population and with younger breast cancer patients would have been ideal, these data were not available to us. It is unlikely that ICD-9 code 428 overestimated heart failure in our population, given previous validation studies which showed that this diagnostic code is highly specific for clinical CHF. In fact, these studies have shown that ICD-9 coding consistently underestimates clinically documented CHF, by as much as 30%.[37-39]

We found that black women were more likely to receive adjuvant anthracycline chemotherapy. This likely reflects the increased frequency of advanced stage, hormone-receptor–negative disease in this group. Black race also emerged as an independent risk factor for the development of heart failure. Extremely little data from clinical trials is available for black women older than 65 years.[40] In the US population, heart failure mortality is 40% higher among blacks than whites.[41] In this context, our findings suggest that older black women warrant careful monitoring during and after chemotherapy, particularly if other comorbidities are present.

We could find no evidence of increased risk of heart failure among anthracycline-treated women age 71 to 80. Higher baseline rates of CHF in older women may explain this finding. Alternatively, selection biases were likely stronger in the oldest patients, such that only the healthiest of these patients received anthracyclines. Another possibility is that women older than 70 received lower cumulative doses of anthracyclines, either because their physicians did not administer full doses or because they discontinued therapy prematurely as a result of noncardiac toxicities.

This finding highlights the limitations of an observational study such as ours. The multivariate model cannot capture or control for all possible selection biases. The SEER-Medicare data provide no information on chemotherapy doses, and number of claims submitted is not an accurate reflection of cumulative dose received. We relied solely on ICD-9 coding to determine CHF incidence, and have no information on illness severity or functional consequences. We also were unable to reliably distinguish diastolic and systolic heart failure from the claims. However, this is unlikely to change the clinical implications of our results given that systolic and diastolic heart failure confer similarly poor outcomes.[42] Although it is reassuring that CHF was rarely submitted as a cause of death, this most likely reflects substantial under-reporting of CHF as a cause of death in general.[43] Finally, our model could not account for all relevant comorbidities. For instance, although obesity and tobacco use might be expected to increase subsequent rates of CHF,[44,45] these diagnoses are poorly ascertained by ICD-9 coding.[46,47]

Previous work has established long-term cardiotoxicity among anthracycline-treated pediatric patients. We confirm previous findings demonstrating increased rates of cardiac complications in anthracycline-treated elderly populations at 5 years,[21] and our work shows continued increases in CHF rates with prolonged follow-up. The inclusion of more recent data yielded an important finding: Trastuzumab had a significant impact on the likelihood of CHF even in the small number of patients at risk. This is the first examination of the impact of trastuzumab on CHF using the SEER-Medicare database; this finding warrants follow-up study, particularly in the era of adjuvant trastuzumab. Additionally, ours is the first analysis to our knowledge to better define the effect of common comorbid conditions on the likelihood of CHF in this population. We found that anthracycline-treated patients were not subjected to more intensive cardiac monitoring. In addition to strengthening the validity of our results, this may represent an area for improvement in the follow-up care of these patients. As promising strategies to limit anthracycline-induced cardiomyopathy emerge,[48] it will be important to promptly identify patients who might benefit.

The finding of significantly higher rates of CHF and continued increase with longer follow-up in women aged 66 to 70 years treated with adjuvant anthracycline chemotherapy has important clinical implications. Although treatment of CHF has improved dramatically in the last decade, a diagnosis of heart failure still confers significant morbidity, mortality, and cost, particularly in patients older than 65 years.[35,36] A previous analysis using the SEER-Medicare data set showed no difference in breast cancer outcomes for older women treated with anthracycline versus nonanthracycline chemotherapy.[4] Given the incidence of breast cancer in this age group, the growth of this segment of our population, and the increased life expectancy of women in this age group, informed decisions about adjuvant therapy are essential. Our findings underscore the need for prospective studies in older women, with careful monitoring and longer follow-up to quantify the risk of CHF and to define chemotherapy regimens with the best therapeutic ratio for this group.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

The author(s) indicated no potential conflicts of interest.

AUTHOR CONTRIBUTIONS

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