Original Article

Adjuvant Tamoxifen Adherence in Men With Early-Stage Breast Cancer

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BACKGROUND: Most breast cancers (BCs) in men are hormone receptor–positive. Adjuvant tamoxifen is part of the standard treatment of these patients. Small, single-institution studies have suggested that men have high rates of discontinuing adjuvant endocrine treatment. The authors examined rates of tamoxifen discontinuation and medication adherence in a large population-based cohort of male patients with BC. **METHODS:** In the Surveillance, Epidemiology, and End Results–Medicare database, male patients with invasive nonmetastatic BC, diagnosed between 2007 and 2013, who were ≥65 years old, had Part D coverage, and had tamoxifen prescriptions within 1 year of diagnosis were identified. Adherence was defined as a medication possession ratio of ≥80% among those patients who were filling tamoxifen prescriptions. Logistic regression model was used to assess predictors of tamoxifen adherence. **RESULTS:** A total of 451 patients met eligibility criteria. The median age at diagnosis was 75 years. The median follow-up was 32.5 months. The rates of tamoxifen discontinuation were 15.8%, 24.3%, 31.3%, 36.9%, and 48.3% at 1, 2, 3, 4, and 5 years after diagnosis, respectively. Among the men who were still taking tamoxifen, the corresponding adherence rates were 76.9%, 73.6%, 68.7%, 64.8%, and 60.2%. In the adjusted model, significant predictors of lower adherence included residing in a high poverty area (odds ratio [OR], 0.77; 95% confidence interval [CI], 0.28-2.12) and a Charlson comorbidity score of ≥2 (OR, 0.46; 95% CI, 0.22-0.97). **CONCLUSION:** Older men with breast cancer have high rates of tamoxifen discontinuation, with 48% of all patients discontinuing tamoxifen before the end of year 5. Additionally, even among those patients continuing tamoxifen, a substantial number of patients are nonadherent. Further research should evaluate potentially modifiable reasons for treatment discontinuation and lack of adherence to tamoxifen. ***Cancer* 2022;128:59-64**. © *2021 American Cancer Society*.

KEYWORDS: adherence, hormone receptor positive, male breast cancer (MBC), medication possession ratio (MPR), tamoxifen.

INTRODUCTION

Male breast cancer is rare and accounts for 1% of all breast cancers, however, the incidence of male breast cancer appears to be rising.[1-3] Data from the Surveillance, Epidemiology and End Results (SEER) program showed that the age-adjusted incidence rate increased from 0.85 cases per 100,000 men in the general population in 1975 to 1.43 cases per 100,000 in 2011.[3] Although rates are increasing, men continue to not be included in many of the clinical trials ongoing for breast cancer, and therefore, we are left to extrapolate conclusions and treatment recommendations from studies that enrolled women.[4]

Hormone-positive breast cancer represents the largest subgroup of male breast cancer in both the localized and advanced setting, comprising over 95% of cases in men.[4-7] In women with early-stage breast cancer, adjuvant tamoxifen has been shown to not only reduce risk of systemic recurrence or a contralateral breast cancer by up to 50% but it also has a significant overall survival benefit.[8-10] For this reason, and because of the efficacy in men with metastatic breast cancer, adjuvant tamoxifen has been adopted as part of the standard treatment of early-stage breast cancer in men. Prior small, single-institution studies have suggested that men may have high rates of discontinuing adjuvant endocrine treatment. This may lead to worse outcomes because prior adjuvant studies have suggested that there is more benefit in a longer duration of adjuvant tamoxifen in men.[2,5] We examined rates of tamoxifen discontinuation and medication adherence in a large population-based cohort of older men with breast cancer.

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See editorial on pages 22-24, this issue.

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MATERIALS AND METHODS

Study Participants

We identified male patients 65 years old or older who were diagnosed with stage I to III hormone receptor–positive breast cancer between 2007 and 2013, received tamoxifen within 1 year of diagnosis, and had Part D coverage within 12 months after the first prescription of tamoxifen. Patient, tumor, and treatment characteristics including age, diagnosis years, race/ethnicity, geographic region, census variables, stage, tumor grade, radiation, surgery type, and survival status were defined with the SEER summary file (PEDSF) and census tract files. Patients' comorbidity scores were calculated by the Klabunde modification of the Charlson comorbidity index.[11,12] Patients who did not have full 1-year Medicare A and B coverage before the first prescription of tamoxifen were coded as "unknown" for comorbidity. Patients' tamoxifen usage including date of prescription and days of supply were obtained from Part D claims.

End Points

The cumulative incidence of drug discontinuation was calculated for each year after diagnosis. Medication possession ratio (MPR) was defined as the proportion of days with filled prescriptions for tamoxifen. Adherence was defined as a MPR of greater than or equal to 80% among those patients who were filling tamoxifen prescriptions.[13] For patients who died during the study period, MPR was calculated as the proportion of tamoxifen possession up until the date of death. Drug discontinuation was defined as at least 120 days without any available filled tamoxifen, and the date of last supply of the drug was considered as the discontinuation date.

Statistical Analysis

Cumulative incidences and 95% confidence intervals (95% CIs) of tamoxifen discontinuation subject to competing risk (death) were calculated for each year after the first prescription of tamoxifen. Multivariable Cox regression models were applied to estimate the hazard ratio (HR) and 95% CI for drug discontinuation. Logistic regression models were applied to assess the factors associated with tamoxifen adherence within 1 year of diagnosis. *P* values less than .05 were considered statistically significant; all tests were two-sided. Education and poverty variables were reported as quartiles with quartile 1 representing the lowest educational level and lowest rates of poverty, quartile 4 representing the highest, and quartiles 2 and 3 representing the interquartile range. This study was exempted by the institutional review board at The University of Texas MD Anderson Cancer Center. All the statistical analyses were performed using SAS Enterprise Guide 7.1 (SAS Institute, Inc, Cary, North Carolina).

TABLE 1. Patient Characteristics Among a Cohort of 451 Male Breast Cancer Patients Treated With Tamoxifen in the SEER-Medicare Database

	No.	%
All subjects	451	100.0
Age group, y		
Range	65-92	
Mean (median)	75 ± 7 (75)	
65-70	136	30.2
71-75	106	23.5
76-80	101	22.4
>80	108	24.0
Race		
Non-Hispanic White	370	82.0
Hispanic	25	5.5
Non-Hispanic Black	36	8.0
Other	20	4.4
Stage		
I	151	33.5
II	218	48.3
III	82	18.2
Surgery		
Breast conserving	29	6.4
Mastectomy	404	89.6
No surgery/unknown	18	4.0
Radiation therapy		
No/unknown	353	78.3
Yes	98	21.7
Charlson comorbidity score		
0	153	33.9
1	75	16.6
2+	68	15.1
Unknown	155	34.4

Abbreviation: SEER, Surveillance, Epidemiology, and End Results.

RESULTS

We identified 451 patients who met eligibility criteria. Patient baseline characteristics are summarized in Table 1. The median age at diagnosis was 75 years (range, 65-92 years). Median follow-up was 32.5 months (range, 1-93 months). Among patients with known hormone receptor status who were prescribed tamoxifen, 99% had hormone receptor–positive cancers. The rates of tamoxifen discontinuation were 15.8% (95% CI, 12.6%-19.3%), 24.3% (95% CI, 20.3%-28.5%), 31.3% (95% CI, 26.8%-36.0%), 36.9% (95% CI, 31.8%-42.0%), and 48.3% (95% CI, 41.8%-54.5%) at 1, 2, 3, 4, and 5 years after first tamoxifen prescription, respectively (Table 2) subject to competing risk of death. Among men who were prescribed tamoxifen, the mean medication possession ratios were 85.3% (n = 451), 81.9% (n = 371), 79.1% (n = 303), 77.4% (n = 244), and 75.1% (n = 196), at

TABLE 2. Cumulative Incidence of Tamoxifen Discontinuation

	1 y	2 y	3 y	4 y	5 y
Cumulative incidence, %	15.8	24.3	31.3	36.9	48.3
95% CI	12.6-19.3	20.3-28.5	26.8-36.0	31.8-42.0	41.8-54.5

Abbreviation: CI, confidence interval.

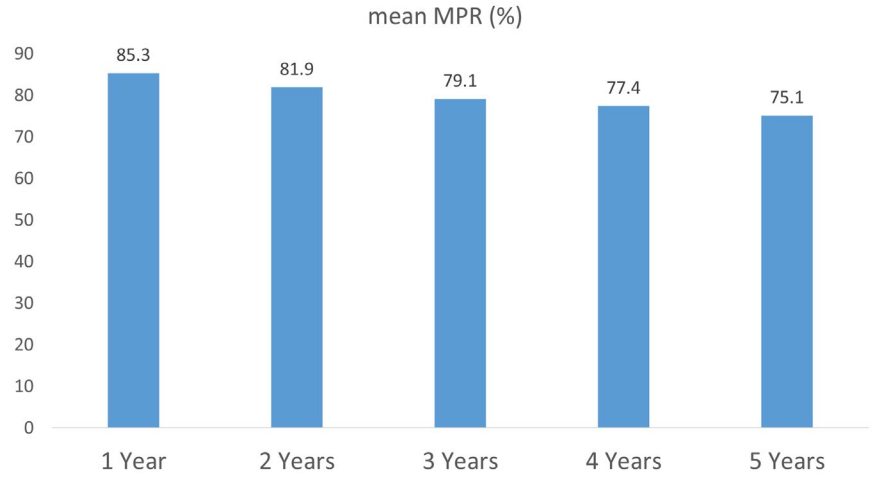

Figure 1. A total of 1 to 5 years of mean medication possession ratio among male patients. The number of patients for 1 to 5 years are 451, 371, 303, 244, and 196, respectively.

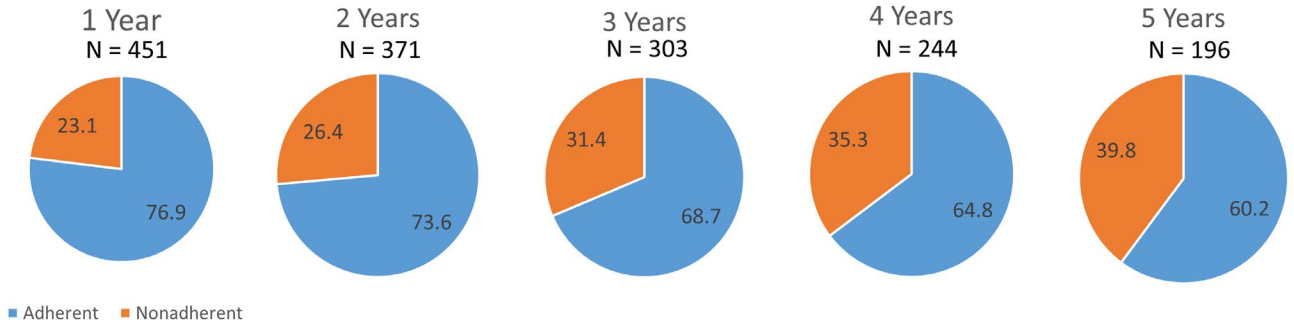

Figure 2. Cumulative proportion of adherent and nonadherent male patients with breast cancer.

years 1, 2, 3, 4, and 5, respectively, as shown in Figure 1. Using an 80% or greater medication possession ratio to define adherence, the yearly adherence rates were 76.9%, 73.6%, 68.7%, 64.8%, and 60.2%, at years 1 through 5, respectively (Fig. 2).

Table 3 shows the predictors of adherence within 12 months of first tamoxifen prescription. In the adjusted model, diagnosis age of 76 to 80 years (OR, 2.75; 95% CI, 1.26-6.02) and residing in metro (OR, 2.40; 95% CI, 1.20-4.82) or less urban areas (OR, 8.54; 95% CI, 1.81-40.3) had higher odds of adherence. A Charlson comorbidity score of ≥2 (OR, 0.46; 95% CI, 0.22-0.97) was a significant predictor of lower adherence. Table 4 shows the factors associated with risk of drug discontinuation. Men diagnosed at over 80 years of age (HR, 1.73; 95% CI, 1.09-2.75) had a higher risk of tamoxifen discontinuation.

DISCUSSION

Adherence to oral therapy has been an increasing problem in medical care, especially with chronic medical therapy.

TABLE 3. Predictors of Tamoxifen Adherence Among a Cohort of 451 Male Breast Cancer Patients Treated With Tamoxifen in the SEER-Medicare Database Within 12 Months From First Prescription

	Univariable		Multivariable	
	OR	95% CI	OR	95% CI
Age group, y				
65-70	Ref		Ref	
71-75	0.98	0.54-1.75	0.82	0.42-1.63
76-80	2.47	1.21-5.06	2.75	1.26-6.02
>80	0.83	0.47-1.46	1.00	0.52-1.92
Race				
Non-Hispanic White	Ref		Ref	
Hispanic	2.15	0.63-7.37	2.92	0.72-11.9
Non-Hispanic Black	0.59	0.28-1.22	0.48	0.17-1.38
Non-Hispanic other	0.88	0.31-2.50	0.82	0.25-2.65
Year of diagnosis				
2007	Ref		Ref	
2008	0.96	0.40-2.30	0.93	0.35-2.45
2009	0.80	0.34-1.90	0.83	0.32-2.17
2010	1.19	0.48-2.93	1.23	0.46-3.27
2011	0.86	0.37-1.97	0.77	0.30-1.99
2012	1.07	0.45-2.52	1.17	0.44-3.11
2013	0.89	0.38-2.07	0.98	0.38-2.50
Urban/rural				
Big metro	Ref		Ref	
Metro	1.84	1.06-3.18	2.40	1.20-4.82
Urban	0.72	0.24-2.18	1.33	0.36-4.86
Less urban	3.48	1.03-11.8	8.54	1.81-40.3
Rural	0.54	0.15-1.97	1.13	0.21-5.99
Marriage status				
Married	Ref		Ref	
Not married	0.67	0.41-1.09	0.75	0.43-1.33
Unknown	1.08	0.39-2.98	1.13	0.36-3.52
Education				
Q1: 0 to ≤7.32	Ref		Ref	
Q2: >7.32 to ≤14.76	0.76	0.41-1.40	0.76	0.38-1.52
Q3: >14.76 to ≤25.42	1.24	0.65-2.38	1.45	0.65-3.22
Q4: >25.42	0.88	0.48-1.63	0.91	0.36-2.34
Poverty				
Q1: 0 to ≤3.86	Ref		Ref	
Q2: >3.86 to ≤7.21	0.87	0.46-1.65	1.07	0.52-2.20
Q3: >7.21 to ≤13.74	0.77	0.41-1.43	0.66	0.29-1.47
Q4: >13.74	0.84	0.45-1.58	0.77	0.28-2.12
Stage				
I	Ref		Ref	
II	0.81	0.50-1.32	0.75	0.42-1.33
III	1.25	0.63-2.47	1.10	0.47-2.56
Surgery				
Mastectomy	Ref		Ref	
Breast conserving	0.93	0.38-2.24	1.05	0.37-3.04
No surgery	0.77	0.27-2.21	1.14	0.30-4.31
Radiation therapy				
Yes	Ref		Ref	
No	0.77	0.44-1.34	0.81	0.41-1.59
Unknown	0.56	0.13-2.37	0.43	0.08-2.42
Grade				
Well differentiated	Ref		Ref	
Moderately differentiated	2.10	1.07-4.11	1.54	0.71-3.32
Poorly differentiated	2.23	1.08-4.58	2.18	0.94-5.04
Unknown	2.05	0.58-7.25	1.30	0.28-6.10
Charlson comorbidity score				
0	Ref		Ref	
1	0.67	0.35-1.28	0.71	0.34-1.47
2+	0.55	0.28-1.05	0.46	0.22-0.97
Unknown	0.90	0.52-1.57	1.01	0.53-1.91

Abbreviations: CI, confidence interval; OR, odds ratio; Q, quartile; Ref, Reference; SEER, Surveillance, Epidemiology, and End Results.

There have been relatively few studies focusing on adherence to oral antineoplastic agents outside of participation in a clinical trial. There is variability in reported adherence rates of antineoplastic agents ranging from 20% to 100%.[14] Studies evaluating adherence to adjuvant tamoxifen in women with early-stage breast cancer revealed adherence estimates ranging from 25% to 96%.[8,14-16] However, few studies have looked at adherence rates to adjuvant tamoxifen in men.

One of the first retrospective analyses on discontinuation rates of tamoxifen in men was published in 1994 by Anneli et al.[17] This study examined tamoxifen-related side effects among male patients with breast cancer treated with tamoxifen in the adjuvant setting and revealed a 20.8% discontinuation rate in 24 patients within the first year of starting tamoxifen.[17] Another study of 59 male patients with breast cancer treated with antihormonal therapy (either tamoxifen or aromatase inhibitors), in either the adjuvant or metastatic settings, revealed a 23.7% discontinuation rate over the span of 5 years.[18] Our study evaluated discontinuation rates of 451 male patients with breast cancer and demonstrated that within 5 years of diagnosis, the discontinuation rate was 48.3%. Even among men who continued tamoxifen, the rate of adherence was 60.2% over 5 years. Partridge et al[8] used similar claims-based methodology evaluating 492 women with early-stage breast cancer who filled tamoxifen prescriptions in 1991 and had long-term follow-up. They described long-term adherence rates of 83%, 68%, 61%, and 50% during years 1, 2, 3, and 4.[8] Hershman et al[19] performed a comparable study in women using data from automated pharmacy records from Kaiser Permanente of Northern California Health Systems and showed that the proportion of women who continued hormonal therapy (including both tamoxifen and aromatase inhibitor) decreased from 86% in year 1 to 60% in year 4.5. Of the patients who continued,

TABLE 4. Predictors for Tamoxifen Discontinuation Risk Among a Cohort of 451 Male Breast Cancer Patients Treated With Tamoxifen in the SEER-Medicare Database

	Univariable		Multivariable	
	HR	95% CI	HR	95% CI
Age group, y				
65-70	Ref		Ref	
71-75	1.11	0.73-1.69	1.36	0.84-2.19
76-80	0.68	0.42-1.10	0.71	0.43-1.17
>80	1.72	1.15-2.58	1.73	1.09-2.75
Race				
Non-Hispanic White	Ref		Ref	
Hispanic	0.75	0.38-1.48	0.79	0.37-1.69
Non-Hispanic Black	0.94	0.51-1.75	1.06	0.48-2.31
Non-Hispanic other	0.46	0.17-1.25	0.36	0.12-1.02
Year of diagnosis				
2007	Ref		Ref	
2008	0.86	0.53-1.42	0.95	0.55-1.63
2009	0.65	0.38-1.11	0.72	0.40-1.29
2010	0.77	0.45-1.32	0.82	0.46-1.45
2011	0.68	0.39-1.20	0.76	0.41-1.41
2012	0.73	0.40-1.33	0.82	0.43-1.58
2013	0.72	0.36-1.44	0.74	0.36-1.54
Urban/rural				
Big metro	Ref		Ref	
Metro	0.97	0.68-1.38	0.93	0.59-1.46
Urban	1.06	0.43-2.60	0.71	0.25-2.01
Less urban	0.67	0.34-1.33	0.45	0.19-1.06
Rural	0.86	0.27-2.72	0.57	0.15-2.11
Marriage status				
Married	Ref		Ref	
Not married	1.36	0.97-1.91	1.20	0.82-1.76
Unknown	1.14	0.59-2.17	1.19	0.60-2.36
Education				
Q1: 0 to ≤7.32	Ref		Ref	
Q2: >7.32 to ≤14.76	0.76	0.41-1.40	0.76	0.38-1.52
Q3: >14.76 to ≤25.42	1.24	0.65-2.38	1.45	0.65-3.22
Q4: >25.42	0.88	0.48-1.63	0.91	0.36-2.34
Poverty				
Q1: 0 to ≤3.86	Ref		Ref	
Q2: >3.86 to ≤7.21	0.87	0.46-1.65	1.07	0.52-2.20
Q3: >7.21 to ≤13.74	0.77	0.41-1.43	0.66	0.29-1.47
Q4: >13.74	0.84	0.45-1.58	0.77	0.28-2.12
Stage				
I	Ref		Ref	
II	0.89	0.64-1.26	1.00	0.68-1.46
III	0.89	0.57-1.39	1.05	0.61-1.81
Surgery				
Mastectomy	Ref		Ref	
Breast conserving	1.07	0.59-1.92	0.96	0.49-1.90
No surgery	2.08	1.02-4.26	1.70	0.73-3.97
Radiation therapy				
Yes	Ref		Ref	
No	1.48	0.99-2.22	1.54	0.96-2.47
Unknown	1.34	0.41-4.39	1.46	0.41-5.25
Grade				
Well differentiated	Ref		Ref	
Moderately differentiated	0.67	0.41-1.10	0.79	0.46-1.36
Poorly differentiated	0.59	0.34-1.00	0.72	0.40-1.29
Unknown	0.67	0.27-1.69	0.76	0.27-2.16
Charlson comorbidity score				
0	Ref		Ref	
1	0.97	0.63-1.50	1.04	0.65-1.68
2+	0.79	0.48-1.30	0.76	0.44-1.30
Unknown	0.65	0.44-0.95	0.65	0.42-1.00

Abbreviations: CI, confidence interval; HR, hazard ratio; Q, quartile; Ref, Reference; SEER, Surveillance, Epidemiology, and End Results.

adherence decreased from 78% in year 1 to 70% at year 4.5, however, only 49% of the overall population evaluated was fully adherent for the entire 4.5 years.[19] These studies suggest slightly lower adherence rates (50%) in women compared to what was seen in the male patients (60%) in this study. Discontinuation of adjuvant hormonal therapy in women is associated with a statistically significant decrease in survival, with estimated survival at 10 years of 80.7% for women who continued hormonal therapy versus 73.6% for those who discontinued it. Those women who both continued adjuvant endocrine therapy and were adherent had a 10-year estimated survival of 81.7% versus 77.8% in those who were nonadherent.[19]

Reasons for nonadherence to tamoxifen in both men and women can be difficult to determine. A prior study by Pemmaraju et al[2] revealed that the most common toxicities resulting in discontinuation of tamoxifen in MBC patients included weight gain and sexual dysfunction each seen in up to 22% of men evaluated. In our study, we found that patients with higher number of comorbidities, and who were older, were more at risk for discontinuing tamoxifen earlier.

There are important limitations to this study. Although use of claims-based methodology did help gather information on a large cohort of MBC patients, this study population is limited to older men. In this study, we could only measure prescriptions filled and did not assess whether the patients took the medicine. These data also lack clinical data to evaluate whether discontinuation was associated with the toxicities caused by tamoxifen or progression of disease. However, using claims to detect recurrences has been shown to miss a larger percentage of patients with recurrence and has a low sensitivity.[20] There is no gold standard approach to measure adherence, which also limits this

study. Nonetheless, this is the largest study investigating adherence to adjuvant tamoxifen in male breast cancer.

Conclusions

In conclusion, we demonstrate that up to 15.8% of older men with early breast cancer stop taking their tamoxifen within 1 year of initiation of adjuvant therapy. Adherence declines as time progresses, and by 5 years, almost half of the men prescribed adjuvant tamoxifen have stopped taking it, which could increase risk of recurrence and death from breast cancer. It is important that oncologists are aware of these rates of discontinuation to be mindful to encourage MBC patients to adhere to their tamoxifen. Further studies looking at the root causes for discontinuation and the patient population at risk for nonadherence are essential.

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CONFLICT OF INTEREST DISCLOSURES

Mariana Chavez-MacGregor received consulting fees from Exact Sciences, Novartis, Pfizer, and AstraZeneca; participated on a data safety monitoring board or advisory board for Roche and AstraZeneca; and had a paid or unpaid leadership or fiduciary role in the Legacy Community Health Board of Directors and the Hope Foundation Board of Directors. The other authors made no disclosures.

AUTHOR CONTRIBUTIONS

Oluchi Oke: Conceptualization, data curation, investigation, methodology, project administration, resources, validation, visualization, writing–original draft, and writing–review and editing. **Jiangong Niu**: Data curation, investigation, formal analysis, software, and writing–review and editing. **Mariana Chavez-MacGregor:** Methodology, visualization, and writing–review and editing. **Hui Zhao:** Conceptualization, software, and writing–review and editing. **Sharon H. Giordano:** Conceptualization, data curation, funding acquisition, investigation, methodology, project administration, supervision, resources, software, validation, visualization, writing–original draft, and writing–review and editing.

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