Research Article

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Racial Differences in Adjuvant Endocrine Therapy Use and Discontinuation in Association with Mortality among Medicare Breast Cancer Patients by Receptor Status

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Abstract

Background: There are racial disparities in breast cancer mortality. Our purpose was to determine whether racial/ethnic differences in use and discontinuation of adjuvant endocrine therapy (AET) differed by hormone receptor status and whether discontinuation was associated with mortality.

Methods: We conducted a retrospective cohort study with SEER/Medicare dataset of women age ≥65 years diagnosed with stage I–III breast cancer in Medicare Part-D from 2007 to 2009, stratified by hormone receptor status. We performed multivariable logistic regressions to assess racial differences for the odds of AET initiation and Cox proportional hazards models to determine the risk of discontinuation and mortality.

Results: Of 14,902 women, 64.5% initiated AET <12 months of diagnosis. Among those with hormone receptor–positive cancer, 74.8% initiated AET compared with 5.6% of women with negative and 54.0% with unknown-receptor status. Blacks were less likely to initiate [OR, 0.76; 95% confidence interval (CI), 0.66–0.88] compared with whites. However, those with hormone receptor–positive disease were less likely to discontinue (HR, 0.89; 95% CI, 0.80–0.98). Women who initiated with aromatase inhibitors had increased risk of discontinuation compared with women who initiated tamoxifen (HR, 1.12; 95% CI, 1.05–1.20). Discontinuation within 12 months was associated with higher risk of all-cause (HR, 1.75; 95% CI, 1.74–2.00) and cancer-specific mortality (HR, 2.76; 95% CI, 1.74–4.38) after controlling for race/ethnicity.

Conclusions: There are racial/ethnic differences in AET use and discontinuation. Discontinuing treatment was associated with higher risk of all-cause and cancer-specific mortality regardless of hormone receptor status.

Impact: This study underscores the need to study factors that influence discontinuation and the survival benefits of receiving AET for hormone receptor–negative breast cancer. *Cancer Epidemiol Biomarkers Prev; 26(8); 1266–75. ©2017 AACR.*

Introduction

Blacks and Hispanics have an increased risk of breast cancer death compared with non-Hispanic whites (1–4). These racial/ethnic mortality disparities have been attributed to differences in cancer prognostic (2, 3, 5, 6), sociodemographic factors (4), and the initiation and timing of treatment (2, 4). One way to significantly reduce breast cancer mortality is to improve adherence to effective, recommended treatment (7). Adhering to guidelines for adjuvant endocrine therapy (AET) is associated with improved disease-free survival for women with early-stage breast cancer (8–12); however, adherence rates for recommended treatment remain low. It is estimated that between 55% and 75% of breast cancer patients received recommended AET medication in a 1-year period (13). Discontinuation of AET is associated with the number of other medications prescribed for comorbidities (14), demographic characteristics such as age (15, 16) and the side effects (13, 17–21). Previous studies have examined higher discontinuation for minorities as compared with white women (15, 22).

The National Comprehensive Cancer Network (NCCN) recommends that postmenopausal women with early-stage hormone receptor–positive breast cancer receive an aromatase inhibitor (AI) for 5 years, or tamoxifen for 2 to 3 years, followed by an AI to complete 5 years, or tamoxifen alone for 5 years, if AIs are contraindicated (23). The guidelines suggest that postmenopausal women can begin with tamoxifen or AIs, and understanding whether discontinuation is associated with each drug during the first 12 months of treatment postdiagnosis may provide additional evidence to physicians and patients when deciding one drug over another.

Nearly two-thirds of breast cancer cases in the United States are hormone receptor positive (estrogen or progesterone receptor) and are eligible for AET (23–25). Although recommendations from both the NCCN and the American Society of Clinical Oncology (ASCO) recommend AET for women with stage I–III cancer, none of the organizations recommended AET for women with hormone receptor–negative disease (23, 26). However, women with hormone receptor–negative breast cancer may still receive AET for the following reasons. First, determining hormone receptor–positive status using IHC was initially defined as having ≥10% positive tumor cells (27). However, subsequent studies have identified improved disease-free survival for patients with

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≥1% positive tumor cells (28) and even >0% (29). Second, classification of hormone receptor status differed among institutions. Although SEER defined hormone receptor–positive status as having ≥1% positive tumor cells (30), other institutions or providers may consider those patients with any percentage of positive tumor cells (>0%) to be eligible for AET (27, 28). Third, studies have recently shown that even those with hormone receptor–negative breast cancer may experience lower risk of disease-free survival from receiving tamoxifen (31, 32). Therefore, we aimed to examine the patterns of initiation, discontinuation, and mortality associated with AET in these populations. To the best of our knowledge, this would be the first study to examine these research questions in a large, nationwide cohort of elderly women with breast cancer since Medicare Part-D was implemented in 2006 and oral AET was covered under that plan.

Furthermore, what remains unclear is whether there are racial/ethnic differences in initiation and discontinuation by hormone receptor status and whether discontinuing AET is associated with all-cause mortality. We hypothesized that AET discontinuation would be associated with a higher risk of death, regardless of hormone receptor status, and after controlling for AET discontinuation, there would be no significant differences in the risk of mortality among Hispanics, blacks, and non-Hispanic whites.

Materials and Methods

Data source

This study utilized the NCI's SEER (Surveillance, Epidemiology, and End Results) and Medicare-linked database for cases in 2007 to 2009 with Medicare Part-D claims up to December 2010 (33, 34). Briefly, available SEER information includes patient demographics, primary tumor site, tumor morphology, stage at diagnosis, first course of treatment, and vital statistics. Medicare data contain detailed diagnoses, procedures, and billing information for inpatient, outpatient, and pharmacy claims.

Study design and population

This was a retrospective cohort study of women ≥65 years with stage I–III breast cancer who were enrolled in Medicare for ≥12 months before and after the date they filled their first AET prescription (either tamoxifen or AI). Women were excluded if they were not enrolled in Medicare Part-D, did not have both Parts A and B, or were enrolled with an HMO from the year of diagnosis to the last follow-up. We stratified the analysis into three cohorts to reflect NCCN recommendations. NCCN strongly recommends AET for women with stage I–III, hormone receptor–positive breast cancer (Group 1) but does not recommend for hormone receptor–negative (Group 2) or unknown status for stage I–III (Group 3; ref. 23).

Independent variables

We identified women who belonged to four racial/ethnic groups: non-Hispanic white, non-Hispanic black/African American, Hispanic, and Asian, which were described elsewhere (30).

Women with breast cancer were categorized in the SEER registry as hormone receptor positive, negative, or unknown based on tumor specimen values (30). If, at a minimum, one tumor specimen assay was noted to be positive for estrogen or progesterone receptors, then the patient was considered to have hormone receptor–positive disease (30). The SEER, as of 2010, considered hormone receptor–positive breast cancer if ≥1% cells stained positive (30).

Demographic information included age (median 75) and marital status. Socioeconomic status information obtained from the 2000 U.S. Census included tertiles of the percentage of residents living below the federal poverty level (FPL) at the census tract level (<5.4%, 5.4%–11.8%, and ≥11.8%) and whether they lived in a metropolitan region (4, 34). Tumor characteristics included AJCC tumor stage, size, grade, and lymph node status. Radiotherapy and surgery were identified from SEER data or through procedure codes in Medicare claims made <6 months of diagnosis, and chemotherapy use was identified only from Medicare claims <6 months of diagnosis using the methods described elsewhere (4). Comorbidity scores were then generated and described in detail elsewhere (35–37). We calculated average 30-day out-of-pocket payments for AET medication (38, 39).

Dependent variables

Initiation of AET (tamoxifen or AI) was considered a single prescription based on the drug name up to 1 year after the date of diagnosis (40). AIs were defined as anastrozole, exemestane, or letrozole. We created a binary variable (yes or no) for initiation if a woman filled a prescription for any AET medication and an indicator for the type of AET (AI or tamoxifen) at initiation. A woman could only initiate AET therapy with AI or tamoxifen based on the first prescription following cancer diagnosis. We categorized patients as having discontinued therapy (yes or no) if they initiated therapy, and the calculated drug supply based on the last prescription date plus any surplus from a prior prescription indicated a minimum of 120-day supply gap with no AET medication on hand. All patients for the discontinuation measure were followed from their initial prescription date until the end of the study period (December 31, 2010). We censored other patients at the end of the study period or until they went >2 consecutive months without Medicare Part-D coverage or died. The median and mean length of follow-up from initiation to discontinuation was 523 days and 580 days, respectively (range, 5–1,460 days). All-cause mortality and breast cancer–specific mortality were defined separately as dead (of any causes or breast cancer specific) or alive at the last follow-up of vital statistics (December 31, 2011) to be censored. The median and mean length of follow-up from diagnosis to death was 1,205 and 1,214 days, respectively (range, 320–1,845 days).

Statistical analysis

Differences in the distribution of sociodemographic and tumor characteristics were first examined across racial/ethnic groups and then by AET initiation. Multivariable logistic regression models were performed to assess the association of race/ethnicity and AET initiation, controlling for tumor prognostic, sociodemographic, and clinical treatment factors. We performed Cox proportional hazards regressions to estimate the association between race/ethnicity and AET discontinuation and to determine the risk of all-cause and cancer-specific mortality in association with AET discontinuation. For this model, we included AET discontinuation within 12 months as every patient in the cohort was alive and had at least 12 consecutive months of continuous enrollment in Part-D after their first AET prescription. All analyses were stratified by hormone receptor status and controlled for prognostic and treatment factors.

Results

We identified 14,902 Medicare patients with stage I–III breast cancer enrolled in Part-D (Table 1). Greater than four fifths (81.8%) had hormone receptor–positive breast cancer, and the remaining were hormone receptor negative (13.3%) or unknown status (6.0%). The cohort consisted predominately of non-Hispanic whites (81.1%), followed by non-Hispanic blacks (7.2%), Hispanics (6.1%), and Asian (4.8%). A larger proportion of blacks (71.2%) and Hispanics (60.8%) compared with non-Hispanic whites (29.6%) lived in areas where >11.8% lived below the FPL. A greater proportion of non-Hispanic whites (83.0%) than blacks (71.9%) and Hispanics (77.6%) was diagnosed with hormone

Table 1. Characteristics of women with diagnosed breast cancer by race/ethnicity, 2007–2009

	Non-Hispanic white *n* (%)	Non-Hispanic black *n* (%)	Hispanic *n* (%)	Asian *n* (%)
Total	12,178 (81.1)	1,085 (7.2)	923 (6.1)	716 (4.8)
Age (years)				
65–69	3,206 (26.3)	292 (26.9)	295 (32.1)	199 (27.8)
70–74	2,805 (23.0)	273 (25.2)	228 (24.7)	172 (24.0)
75–79	2,520 (20.7)	224 (20.7)	183 (19.8)	172 (24.0)
≥80	3,647 (30.0)	296 (27.3)	217 (23.5)	173 (24.2)
Marital status				
Married	5,023 (41.3)	185 (17.1)	314 (24.0)	254 (49.4)
Unmarried	6,722 (55.2)	848 (78.2)	575 (62.3)	348 (48.6)
Unknown	433 (3.6)	52 (4.8)	34 (3.7)	14 (2.0)
SES (% living below FPL)				
1st tertile (<5.4)	4,322 (35.5)	109 (10.1)	146 (15.8)	215 (30.0)
2nd tertile (5.4–11.8)	4,251 (34.9)	203 (18.7)	216 (23.4)	253 (35.3)
3rd tertile (>11.8)	3,605 (29.6)	773 (71.2)	561 (60.8)	248 (34.6)
SEER registry region				
Northeast	2,554 (21.0)	229 (21.1)	151 (16.4)	50 (7.0)
South	3,168 (26.0)	528 (48.7)	<4%*	<3%*
Midwest	1,580 (13.0)	109 (10.1)	<2%*	<2%*
West	4,876 (40.0)	219 (20.2)	726 (78.7)	635 (88.7)
Metropolitan area (yes)	9,625 (79.0)	917 (84.5)	845 (91.6)	685 (95.7)
Comorbidity scores				
0	6,992 (57.4)	411 (37.9)	448 (48.5)	360 (50.3)
1	3,082 (25.3)	299 (27.6)	266 (28.8)	235 (32.8)
2	1,204 (9.9)	168 (15.5)	110 (11.9)	75 (10.5)
3+	900 (7.4)	207 (19.1)	99 (10.7)	46 (6.4)
Year of diagnosis				
2007	3,956 (32.5)	363 (33.5)	295 (32.0)	230 (32.1)
2008	4,043 (33.2)	354 (32.6)	310 (33.6)	237 (33.1)
2009	4,176 (34.3)	368 (33.9)	318 (34.5)	249 (34.8)
Tumor size (cm)				
<2.0	7,519 (61.7)	483 (44.5)	466 (50.5)	410 (57.3)
≥2.0	4,623 (38.0)	<56%*	<49%*	<43%*
Unknown	36 (0.3)	<2%*	<2%*	<2%*
Number of positive nodes				
0	7,906 (64.9)	565 (52.1)	547 (59.3)	460 (64.3)
≥1	2,768 (22.7)	331 (30.5)	270 (29.3)	183 (25.6)
Unknown	1,504 (12.4)	189 (17.4)	106 (11.5)	73 (10.2)
Tumor grade				
Well differentiated	3,178 (26.1)	168 (15.5)	186 (20.2)	173 (24.2)
Moderately differentiated	5,445 (44.7)	428 (39.5)	402 (43.6)	305 (42.6)
Poorly differentiated	2,956 (24.3)	413 (38.1)	282 (30.6)	206 (28.8)
Unknown	599 (4.9)	76 (7.0)	53 (5.7)	32 (4.5)
Surgery treatment				
None	294 (2.4)	73 (6.7)	32 (3.5)	16 (2.2)
BCS	7,216 (59.3)	512 (47.2)	505 (54.7)	368 (51.4)
Mastectomy	4,668 (38.3)	500 (46.1)	386 (41.8)	332 (46.4)
Chemotherapy (yes)	2,849 (23.4)	332 (30.6)	310 (33.6)	204 (28.5)
Radiotherapy (yes)	6,864 (56.4)	515 (47.5)	537 (58.2)	380 (53.1)
Hormone receptor status				
ER^+ or PR+	10,111 (83.0)	780 (71.9)	716 (77.6)	577 (80.6)
ER− and PR^-	1,507 (12.4)	234 (21.6)	144 (15.6)	101 (14.1)
Unknown	560 (4.6)	71 (6.5)	63 (6.83)	38 (5.3)
AJCC stage				
I	7,038 (57.8)	454 (41.8)	445 (48.2)	386 (53.9)
II	4,010 (32.9)	463 (42.7)	337 (36.5)	248 (34.6)
III	1,130 (9.3)	168 (15.5)	141 (15.3)	82 (11.5)

Abbreviations: AJCC, American Joint Committee on Cancer; BCS, breast conservation therapy; PR, progesterone receptor; SES, socioeconomic status.
*Actual percentages were not reported to avoid $n < 11$ reporting, as required by the data user agreement.

receptor–positive breast cancer. A larger proportion of blacks and Hispanics compared with non-Hispanic whites had stage III breast cancer (15.5% and 15.3% vs. 9.3%).

A total of 64.5% initiated AET regardless of hormone receptor status (Table 2). Among hormone receptor–positive breast cancer patients, 74.8% initiated therapy. Notably, more women with hormone receptor–positive breast cancer initiated therapy with AIs (61.8%) than with tamoxifen (12.9%). Among hormone receptor–negative and unknown status breast cancer patients, 5.6% and 54.0% initiated AET, respectively. Among hormone receptor–positive and hormone receptor–unknown patients, a greater proportion of Hispanics initiated AET than any other racial/ethnic group (79.2% and 63.5%, respectively). A smaller proportion of women over the age of 80 and those with 3 or more comorbidities initiated AET compared with younger women or those with fewer comorbidities regardless of hormone receptor status. Women in areas where $\geq$11.8% of the population lived below the FPL initiated AET regardless of hormone receptor status.

Blacks had lower odds of AET initiation within 12 months of diagnosis compared with non-Hispanic whites [OR, 0.76; 95% confidence interval (CI), 0.66–0.88] after controlling for all demographic, treatment, and prognostic factors (Table 3). Older women (over 80 years) compared with younger women (65–69) had lower odds of AET initiation among hormone receptor–positive patients (OR, 0.69; 95% CI, 0.61–0.79). Also, women with more comorbidities, compared with none, had lower odds of AET initiation. Women who lived in areas where $\geq$11.8% of the population lived below the FPL had higher odds of initiating AET than those who lived in areas where <5.4% were below the FPL (OR, 1.16; 95% CI, 1.05–1.28). Initiation of tamoxifen was less likely among non-Hispanic blacks compared with whites (OR, 0.70; 95% CI, 0.55–0.89) and less likely among women with three or more comorbidities compared with 0 (OR, 0.79; 95% CI, 0.64–0.97), whereas Hispanics had higher odds of AI initiation compared with whites with hormone receptor–positive breast cancer (OR, 1.30, 95% CI, 1.09–1.55). Older women (age $\geq$80) were also less likely to initiate AET with AIs compared with younger women (age 70–74; OR, 0.51; 95% CI, 0.45–0.56).

A total of 80.6% of women discontinued therapy during the study period. Among women with hormone receptor–positive breast cancer who initiated AET, non-Hispanic blacks had a lower risk of AET discontinuation than did non-Hispanic whites (HR, 0.89; 95% CI, 0.80–0.98) during the study period after controlling for all other factors (Table 4). The risk of discontinuing AET was greater for women with hormone receptor–positive cancer who initiated therapy with AIs than with tamoxifen (HR, 1.12; 95% CI, 1.05–1.20).

AET discontinuation within 12 months of initiation was associated with a significantly higher risk of all-cause mortality among women with hormone receptor–positive (HR, 1.70; 95% CI, 1.48–1.95) and negative (HR, 11.65; 95% CI, 2.33–58.39) breast cancer, but not among those with unknown hormone receptor status (Table 5). Discontinuation of AET within 12 months of diagnosis was also associated with a 2.7-fold increased risk of breast cancer–specific mortality compared with those who did not discontinue therapy (HR, 2.76; 95% CI, 1.74–4.38) after controlling for all other factors. Women from areas where $\geq$11.8% live below the FPL had an increased risk of all-cause death than women in areas with <5.4% living below the FPL (HR, 1.25; 95% CI, 1.05–1.47). In the age-adjusted analysis, blacks had a 92% increased risk of death compared with non-Hispanic whites (HR, 1.92; 95% CI, 1.59–2.30). No significant differences in the risk of death were observed between blacks and Hispanics compared with non-Hispanic whites after controlling for discontinuation, poverty status, and all other treatment and prognostic factors.

Discussion

In this retrospective cohort study of Medicare patients, a substantial proportion of women with hormone receptor–unknown breast cancer initiated AET, even though these patients were not expected to receive AET based on ASCO and NCCN clinical guidelines. Also, the odds of AET initiation and the risk of AET discontinuation differed by race/ethnicity and AET drug type, regardless of hormone receptor status. Those who discontinued AET, regardless of hormone receptor status positive or negative, had a significantly higher risk of all-cause mortality.

We previously reported AET initiation among older women with hormone receptor–positive, stage I–III breast cancer and found that 74.8% initiated therapy within 12 months (40). Other studies have found initiation between 68% and 70%, but those women were younger and commercially insured (41, 42) and may have better initiation rates than our study population. We also found that blacks, compared with non-Hispanic whites, had lower odds of initiating AET, but after stratifying by hormone receptor status, there was no association. Previous studies showed that Hispanics (41, 43) and blacks (43, 44) have lower odds of AET initiation compared with whites. These previous studies were conducted among different study populations and used AET initiation self-report, a younger cohort, or both.

We observed racial/ethnic differences in discontinuation of AET. We have reported AET adherence for stage I–III, hormone receptor–positive breast cancer patients but did not find a significant difference among Hispanic and black patients over non-Hispanic whites, after controlling for sociodemographic, prognostic, and treatment factors (45). What is even more interesting is that we found that the risk of AET discontinuation was greater for women who initiated therapy with the AIs than with tamoxifen among those with hormone receptor–positive breast cancer. This may be influenced by other factors, such as AI side effects, which we did not control for in this study (10, 11, 46, 47). Similar to other studies, we did find that discontinuing AET was associated with medication cost (12, 48), comorbidities (49), and age (49). Previous studies have examined lower adherence rates for non-whites, a finding that may contribute to the disparities in breast cancer mortality observed between minorities and whites (15, 22, 50). However, after controlling for AET discontinuation, we did not observe racial/ethnic differences in the risk of all-cause mortality. We found that discontinuation of AET was independently associated with a higher risk of all-cause mortality, which is corroborated by Hershman and colleagues (12), who studied a younger population but did not examine discontinuation among hormone receptor–negative or unknown cancer. However, they found that Hispanics had a lower risk of death than non-Hispanic whites (12). We did not observe this association in older Medicare women with breast cancer.

No studies have examined AET initiation and discontinuation in women with hormone receptor–negative or unknown breast cancer. In our study, 5.6% of hormone receptor–negative and 54% of unknown status breast cancer patients initiated AET. Although the sample size was limited among the hormone receptor–negative patients who initiated AET, still, women with

Table 2. Patients initiating AET among all women diagnosed with breast cancer by therapy type, 2007–2009

	Patients (%) receiving AET by type (any, tamoxifen, or AIs)			
		AJCC tumor stage I–III		
	Total cohort ***n*** **= 14,902**	**ER$^+$ or PR$^+$** ***n*** **= 12,184**	**ER$^-$ and PR$^-$** ***n*** **= 1,986**	**ER/PR unknown** ***n*** **= 732**
Initiation of any AET				
Total cohort	64.5	74.8	5.6	54.0
Race/ethnicity				
Non-Hispanic white	65.0	74.4	5.3	54.5
Non-Hispanic black	57.2	73.1	6.4	50.7
Hispanic	67.0	79.2	7.6	63.5
Asian	65.4	77.5	5.9	39.5
Age (years)				
65–69	69.5	81.1	6.0	61.2
70–74	69.7	81.1	6.2	57.6
75–79	65.1	74.5	5.9	58.7
≥80	55.4	64.0	4.6	45.2
SES (% living below FPL)				
1st tertile (<5.4)	64.9	75.1	3.8	49.7
2nd tertile (5.4–11.8)	64.5	73.7	6.0	55.9
3rd tertile (>11.8)	64.1	75.6	6.9	54.8
Comorbidity scores				
0	66.5	76.4	5.8	59.6
1	63.6	74.5	4.5	48.5
2	61.3	70.6	6.1	53.1
3+	58.6	69.7	7.3	45.4
Initiation of tamoxifen				
Total cohort	17.6	12.9	2.1	10.7
Race/ethnicity				
Non-Hispanic white	12.0	13.6	2.1	10.9
Non-Hispanic black	8.0	9.5	<5%	<16%
Hispanic	8.6	9.8	<8%	<17%
Asian	9.5	10.8	<11%	<29%
Age (years)				
65–69	10.4	11.8	2.8	8.8
70–74	11.2	12.8	<3%	<13%
75–79	11.3	12.9	<3%	<9%
≥80	12.5	14.2	2.0	11.9
SES (% living below FPL)				
1st tertile (<5.4)	9.6	11.0	<2%	<9%
2nd tertile (5.4–11.8)	11.8	13.5	<3%	<8%
3rd tertile (>11.8)	12.6	14.4	2.7	13.0
Comorbidity scores				
0	12.1	13.6	2.4	13.2
1	11.0	12.7	<3%	<10%
2	10.2	11.5	<6%	<12%
3+	9.7	11.5	<6%	<13%
Initiation of AIs				
Total cohort	53.2	61.8	3.5	43.4
Race/ethnicity				
Non-Hispanic white	53.0	60.9	3.3	43.6
Non-Hispanic black	49.2	63.6	<5%	<40%
Hispanic	58.4	69.4	<8%	<56%
Asian	55.9	66.7	<11%	<29%
Age (years)				
65–69	59.1	69.3	3.2	52.4
70–74	58.5	68.3	4.6	45.0
75–79	53.8	61.6	4.1	50.4
≥80	42.9	49.8	2.6	33.2
SES (% living below FPL)				
1st tertile (<5.4)	55.3	64.1	2.7	41.3
2nd tertile (5.4–11.8)	52.6	60.2	3.6	47.9
3rd tertile (>11.8)	51.7	61.2	4.2	41.8
Comorbidity scores				
0	54.4	62.9	3.4	46.4
1	52.7	61.8	3.2	39.2
2	51.1	59.1	<6%	<44%
3+	48.9	58.3	<6%	<41%

Abbreviations: AJCC, American Joint Committee on Cancer; PR, progesterone receptor; SES, socioeconomic status.

Table 3. Multivariable logistic regression for the adjusted odds of AET initiation among women diagnosed with breast cancer, 2007–2009 ($n = 14{,}902$)

		AOR[a] (95% CI) of AET initiation AJCC tumor stage I–III		
	Total cohort	**ER^+ or PR^+**	**ER^-/PR^-**	**ER/PR unknown**
Initiation of any AET				
Race/ethnicity				
Non-Hispanic white	1 (reference)	1 (reference)	1 (reference)	1 (reference)
Non-Hispanic black	0.76 (0.66–0.88)	0.84 (0.70–1.00)	1.08 (0.57–2.04)	0.96 (0.53–1.73)
Hispanic	1.16 (1.00–1.36)	1.20 (0.99–1.46)	1.32 (0.64–2.71)	1.47 (0.78–2.77)
Asian	1.13 (0.95–1.34)	1.25 (1.01–1.54)	1.15 (0.46–2.84)	0.69 (0.33–1.47)
Age (years)				
65–69	1	1	1	1
70–74	0.95 (0.86–1.06)	1.00 (0.88–1.14)	0.96 (0.57–1.63)	0.81 (0.49–1.32)
75–79	0.73 (0.66–0.81)	0.69 (0.61–0.79)	0.86 (0.48–1.53)	0.90 (0.54–1.49)
≥80	0.50 (0.45–0.56)	0.47 (0.41–0.53)	0.57 (0.31–1.06)	0.65 (0.40–1.04)
SES (% living below FPL)				
1st tertile (<5.4)	1	1	1	1
2nd tertile (5.4–11.8)	1.06 (0.96–1.16)	1.02 (0.92–1.13)	1.67 (0.96–2.89)	1.13 (0.69–1.84)
3rd tertile (>11.8)	1.16 (1.05–1.28)	1.17 (1.04–1.32)	1.78 (1.00–3.15)	1.16 (0.70–1.92)
Comorbidity scores				
0	1	1	1	1
1	0.95 (0.87–1.03)	0.95 (0.86–1.05)	0.75 (0.45–1.23)	0.67 (0.46–0.99)
2	0.86 (0.76–0.97)	0.81 (0.71–0.94)	1.00 (0.52–1.94)	0.74 (0.44–1.23)
3+	0.83 (0.73–0.95)	0.82 (0.70–0.96)	1.10 (0.57–2.13)	0.79 (0.46–1.37)
Initiation of tamoxifen				
Race/ethnicity				
Non-Hispanic white	1	1	1	1
Non-Hispanic black	0.70 (0.55–0.89)	0.70 (0.54–0.90)	1.05 (0.36–3.01)	1.05 (0.43–2.57)
Hispanic	0.80 (0.62–1.02)	0.78 (0.60–1.01)	1.32 (0.41–4.22)	0.68 (0.24–1.95)
Asian	0.87 (0.67–1.13)	0.84 (0.63–1.10)	1.31 (0.29–6.01)	0.90 (0.28–2.94)
Age (years)				
65–69	1	1	1	1
70–74	1.05 (0.91–1.22)	1.07 (0.63–1.10)	0.64 (0.26–1.56)	1.81 (0.84–3.90)
75–79	1.03 (0.88–1.20)	1.07 (0.91–1.25)	0.64 (0.25–1.67)	0.92 (0.40–2.15)
≥80	1.09 (0.94–1.27)	1.13 (0.96–1.32)	0.64 (0.25–1.65)	1.37 (0.64–2.92)
SES (% living below FPL)				
1st tertile (<5.4)	1	1	1	1
2nd tertile (5.4–11.8)	1.12 (0.98–1.28)	1.10 (0.96–1.27)	2.19 (0.85–5.64)	0.69 (0.92–1.61)
3rd tertile (>11.8)	1.30 (1.12–1.50)	1.27 (1.09–1.48)	2.00 (0.75–5.37)	1.20 (0.53–2.75)
Comorbidity scores				
0	1	1	1	1
1	0.90 (0.80–1.02)	0.93 (0.82–1.05)	0.56 (0.24–1.32)	0.65 (0.35–1.21)
2	0.81 (0.68–0.98)	0.81 (0.67–0.98)	0.91 (0.31–2.71)	0.55 (0.25–1.24)
3+	0.79 (0.64–0.97)	0.81 (0.65–1.01)	1.14 (0.40–3.22)	0.28 (0.09–0.86)
Initiate AIs				
Race/ethnicity				
Non-Hispanic white	1	1	1	1
Non-Hispanic black	0.89 (0.78–1.02)	1.02 (0.87–1.21)	1.15 (0.52–2.51)	0.93 (0.52–1.68)
Hispanic	1.25 (1.08–1.45)	1.30 (1.09–1.55)	1.22 (0.49–3.05)	1.63 (0.88–3.03)
Asian	1.18 (1.00–1.39)	1.30 (1.08–1.57)	1.03 (0.34–3.17)	0.69 (0.31–1.52)
Age (years)				
65–69	1	1	1	1
70–74	0.94 (0.85–1.03)	0.97 (0.86–1.08)	1.18 (0.61–2.30)	0.64 (0.40–1.04)
75–79	0.75 (0.68–0.83)	0.73 (0.65–0.82)	1.03 (0.49–2.14)	0.93 (0.57–1.52)
≥80	0.51 (0.46–0.56)	0.50 (0.45–0.56)	0.56 (0.25–1.26)	0.56 (0.35–0.90)
SES (% living below FPL)				
1st tertile (<5.4)	1	1	1	1
2nd tertile (5.4–11.8)	1.00 (0.92–1.09)	0.96 (0.88–1.06)	1.46 (0.74–2.88)	1.28 (0.78–2.09)
3rd tertile (>11.8)	1.02 (0.93–1.13)	1.01 (0.92–1.13)	1.68 (0.83–3.93)	1.07 (0.64–1.76)
Comorbidity scores				
0	1	1	1	1
1	0.99 (0.92–1.08)	1.00 (0.91–1.09)	0.88 (0.48–1.63)	0.82 (0.55–1.21)
2	0.95 (0.85–1.07)	0.93 (0.82–1.06)	1.11 (0.49–2.51)	0.97 (0.58–1.61)
3+	0.93 (0.82–1.06)	0.99 (0.90–1.08)	1.06 (0.47–2.42)	1.25 (0.72–2.18)

Abbreviations: AJCC, American Joint Committee on Cancer; AOR, adjusted OR; PR, progesterone receptor; SES, socioeconomic status.
[a]AOR controlled for marital status, metropolitan area, tumor size, node status, tumor grade, tumor stage, surgical treatment, and chemotherapy and radiation treatment.

Table 4. Multivariable HR of time to discontinuation during study period among breast cancer patients who initiated AET, 2007–2009

			HR[a] (95% CI) of discontinuation of AET AJCC tumor stage I–III		
	Discontinued AET (%)	**Total cohort (n = 9,618)**	**ER^+ or PR^+ (n = 9,110)**	**ER^-/PR^- (n = 112)**	**ER/PR unknown (n = 396)**
Total cohort	80.6				
Type of AET at initiation					
Tamoxifen	80.8	1 (reference)	1 (reference)	1 (reference)	1 (reference)
AI	80.6	1.12 (1.05–1.20)	1.12 (1.05–1.20)	1.66 (0.91–3.04)	1.23 (0.87–1.73)
AET OOP cost for 30-day supply					
$0–2.35	78.7	1	1	1	1
$2.36–6.99	81.8	1.45 (1.34–1.56)	1.06 (0.98–1.15)	1.19 (0.55–2.58)	0.99 (0.69–1.42)
$7.00–34.99	85.6	1.53 (1.41–1.65)	1.43 (1.32–1.54)	3.69 (1.69–8.00)	1.40 (0.93–2.11)
$35.00–93.50	81.5	0.95 (0.87–1.03)	1.53 (1.41–1.66)	0.86 (0.33–2.21)	1.38 (0.86–2.07)
>$93.50	75.9	1.12 (1.05–1.20)	0.94 (0.87–1.02)	0.91 (0.37–2.25)	0.88 (0.56–1.40)
Race/ethnicity					
Non-Hispanic white	80.8	1	1	1	1
Non-Hispanic black	76.7	0.91 (0.83–1.01)	0.89 (0.80–0.98)	0.72 (0.30–1.72)	1.43 (0.91–2.23)
Hispanic	82.7	1.01 (0.92–1.12)	1.02 (0.92–1.13)	1.10 (0.45–2.72)	0.93 (0.59–1.46)
Asian	80.6	0.83 (0.74–0.92)	0.83 (0.72–0.93)	0.29 (0.08–1.02)	0.97 (0.52–1.81)
Age (years)					
65–69	81.6	1	1	1	1
70–74	82.5	1.03 (0.97–1.10)	1.04 (0.97–1.10)	0.94 (0.45–1.96)	1.08 (0.76–1.55)
75–79	81.4	1.02 (0.96–1.09)	1.03 (0.96–1.10)	1.86 (0.83–4.15)	0.85 (0.59–1.22)
≥80	76.9	1.04 (0.97–1.12)	1.04 (0.97–1.12)	1.70 (0.70–4.13)	1.18 (0.81–1.71)
SES (% living below FPL)					
1st tertile (<5.4)	79.9	1	1	1	1
2nd tertile (5.4–11.8)	81.9	1.01 (0.96–1.07)	1.02 (0.96–1.08)	0.91 (0.45–1.82)	0.74 (0.50–1.09)
3rd tertile (>11.8)	80.1	1.02 (0.96–1.09)	1.02 (0.96–1.10)	1.83 (0.82–4.08)	0.79 (0.53–1.18)
Comorbidity scores	81.3				
0	81.3	1	1	1	1
1	81.5	1.04 (0.99–1.10)	1.05 (1.00–1.11)	0.66 (0.35–1.27)	0.86 (0.63–1.17)
2	78.9	1.07 (0.99–1.61)	1.08 (1.00–1.18)	0.93 (0.41–2.12)	0.99 (0.68–1.45)
3+	74.9	1.07 (0.97–1.17)	1.05 (0.95–1.15)	1.22 (0.51–2.93)	1.29 (0.78–2.13)

Abbreviations: AJCC, American Joint Committee on Cancer; PR, progesterone receptor; OOP, out-of-pocket cost; SES, socioeconomic status.
[a]HR controlled for marital status, metropolitan area, tumor size, node status, tumor grade, tumor stage, surgical treatment, and chemotherapy and radiation treatment.

hormone receptor–negative breast cancer who discontinued AET had significantly increased risk of death. There are a few important points to consider when discussing the results of this finding. Previous studies based on medical claims data only for AET adherence or discontinuation included any women who filled a prescription for AET and might have included women with hormone receptor–negative cancer because those data do not allow for differentiation of hormone receptor status (12, 22, 39). Women may be on AET despite having hormone receptor–negative breast cancer because they may have IHC assay >0% with positive tumor cells but were classified as negative based on a changing cut-off point of >1%, which may vary based on institutional guidelines (27, 28). Next, women with hormone receptor–negative breast cancer may be on AET for primary prevention of metachronous disease as it may reduce the risk of contralateral primary breast cancer (51, 52). Tamoxifen use can significantly improve 5-year disease-free survival in hormone receptor–positive breast cancer using IHC assay >0% cutoff (29). Recently, a study found that the benefit of tamoxifen response in hormone receptor–negative breast cancer (using <1% tumor positive as cutoff) was mediated by androgen receptor expression (31). Another study found that estrogen receptor (ER) β1 status is a significant predictor of disease-free survival in ERα-negative breast cancers treated with tamoxifen (32). Both of these receptor expressions (androgen receptor and ERβ1) are not currently assessed in the SEER dataset but could explain our study results that AET discontinuation in hormone receptor–negative breast cancer is, at least partially, associated with increased mortality risk.

Although previous studies of AET patterns and outcomes used only medical claims or pharmacy data without details on tumor characteristics (39, 48, 53), we were able to examine initiation, discontinuation, and all-cause mortality by hormone receptor status, stage at diagnosis, and other prognostic factors because Medicare claims data were linked to the SEER registry database. Our measure of discontinuation was defined as patients with 120 consecutive days without AET coverage. Therefore, we observed a slightly lower rate of discontinuation than previous studies that used 45 or 90 days without coverage as a measure (12, 22). Even with a conservative discontinuation measure, women who discontinued treatment within 12 months of initiation had a greater risk of death than those who did not, even after controlling for all other factors. Furthermore, because we had complete medical claims, pharmacy, and SEER registry data, this is one of the most comprehensive studies examining racial/ethnic differences in AET patterns and outcomes.

Our study was limited, however, by the population, which only included women ≥65 years and enrolled in Medicare Part-D. Therefore, results may not be generalizable to younger patients or those without comprehensive prescription drug coverage. Second, unmeasured confounding factors, such as psychosocial factors, related to the quality of care women receive (e.g., physician–patient communication) may influence their AET continuation but could not be captured in this study (54). Third, calculating

Table 5. Multivariable HR of all-cause and breast cancer–specific mortality among patients diagnosed with breast cancer who initiated AET, 2007–2009

		HR[a] (95% CI) of mortality AJCC tumor stage I–III		
	Total cohort (n = 9,618)	**ER$^+$ or PR$^+$ (n = 9,110)**	**ER$^-$/PR$^-$ (n = 112)**	**ER/PR unknown (n = 396)**
All-cause mortality				
Number of deaths	1,142	1,044	22	76
AET type at initiation				
Tamoxifen	1 (reference)	1 (reference)	1 (reference)	1 (reference)
AI	0.97 (0.83–1.14)	1.03 (0.87–1.21)	0.38 (0.09–1.62)	0.48 (0.27–0.86)
Discontinuation within 12 months				
No	1	1	1	1
Yes	1.76 (1.54–2.00)	1.70 (1.48–1.95)	11.65 (2.33–58.39)	1.69 (0.94–3.04)
Race/ethnicity				
Non-Hispanic white	1	1	1	1
Non-Hispanic black	1.05 (0.86–1.29)	1.07 (0.86–1.32)	3.65 (0.65–20.56)	0.88 (0.39–1.96)
Hispanic	0.84 (0.64–1.09)	0.82 (0.62–1.09)	8.24 (0.56–120.16)	1.12 (0.47–2.71)
Asian	0.51 (0.34–0.75)	0.53 (0.35–0.79)	0.72 (0.01–82.80)	–
Age (years)				
65–69	1	1	1	1
70–74	1.19 (0.96–1.48)	1.18 (0.94–1.48)	2.04 (0.19–21.86)	0.68 (0.25–1.87)
75–79	1.51 (1.22–1.86)	1.53 (1.23–1.89)	0.79 (0.06–9.88)	1.32 (0.52–3.38)
≥80	2.55 (2.09–3.10)	2.49 (2.03–3.05)	8.19 (0.81–82.7)	3.15 (1.33–7.45)
SES (% living below poverty)				
1st tertile (<5.4)	1	1	1	1
2nd tertile (5.4–11.8)	1.09 (0.92–1.27)	1.11 (0.94–1.31)	2.14 (0.21–21.57)	0.85 (0.35–2.07)
3rd tertile (>11.8)	1.25 (1.05–1.47)	1.24 (1.04–1.48)	1.63 (0.12–22.26)	1.19 (0.52–2.72)
Comorbidity scores				
0	1	1	1	1
1	1.45 (1.23–1.67)	1.44 (1.23–1.68)	1.59 (0.23–11.16)	1.25 (0.60–2.64)
2	2.39 (2.01–2.83)	2.33 (1.94–2.79)	0.49 (0.01–46.43)	4.43 (2.19–8.63)
3+	3.21 (2.72–3.79)	3.06 (2.56–3.65)	2.34 (0.37–14.80)	6.49 (3.28–12.83)
Breast cancer–specific mortality				
Number of breast cancer deaths	83	75	—[b]	—[b]
AET type at initiation				
Tamoxifen	1	1		
AI	1.02 (0.56–1.88)	1.36 (0.66–2.78)		
Discontinuation within 12 months				
No	1	1		
Yes	2.76 (1.74–4.38)	2.95 (1.82–4.76)		
Race/ethnicity				
Non-Hispanic white	1	1		
Non-Hispanic black	0.66 (0.29–1.53)	0.67 (0.27–1.68)		
Hispanic	0.97 (0.40–2.36)	1.03 (0.42–2.51)		
Asian	0.55 (0.13–2.34)	0.60 (0.14–2.58)		
Age (years)				
65–69	1	1		
70–74	0.97 (0.44–2.16)	0.90 (0.40–2.03)		
75–79	0.88 (0.38–2.04)	0.85 (0.36–2.00)		
≥80	2.85 (1.39–5.81)	2.70 (1.30–5.63)		
SES (% living below poverty)				
1st tertile (<5.4)	1	1		
2nd tertile (5.4–11.8)	1.76 (0.96–3.21)	1.94 (1.05–3.58)		
3rd tertile (>11.8)	1.63 (0.85–3.12)	1.59 (0.80–3.16)		
Comorbidity scores				
0	1	1		
1	1.51 (0.87–2.61)	1.53 (0.87–2.67)		
2	2.59 (1.38–4.85)	2.32 (1.19–4.52)		
3+	1.76 (0.89–3.48)	1.25 (0.57–2.74)		

Abbreviations: AJCC, American Joint Committee on Cancer; PR, progesterone receptor; SES, socioeconomic status.

[a]HR controlled for marital status, metropolitan area, tumor size, node status, tumor grade, tumor stage, surgical treatment, and chemotherapy and radiation treatment.

[b]We did not show any number of cases <11 for confidentiality reasons because it is required by the data use agreement of SEER-Medicare data.

discontinuation using prescription claims assumes that patients take their medications as often as they refill prescriptions. However, pharmacy records are considered the most accurate and valid estimation of actual medication use in large populations over time (55, 56). Fourth, 4.9% of the cohort had unknown and 13.4% had hormone receptor–negative status. Although we combined these groups in stratified analyses, those with unknown receptor status could be hormone receptor positive and hence misclassified, leading to biased estimates. Also, as previously discussed, women were categorized as having hormone

receptor–negative status (<1% positive IHC) but may have actually had hormone receptor–positive disease according to the less stringent definition used in other studies (>0% positive IHC).

Conclusions

About three fourths of patients with hormone receptor–positive breast cancer initiated AET, and over 50% of women with hormone receptor–unknown and more than 5% of those with hormone receptor–negative status received AET. AET discontinuation was associated with a significantly higher risk of all-cause mortality, regardless of hormone receptor status and tumor stage. Overall, our study underscores the importance of continuing AET for all breast cancer patients who initiate treatment. Future studies are needed to explore the survival benefits of receiving AET for hormone receptor–negative breast cancer in other populations and to study the factors that influence AET discontinuation.

Disclosure of Potential Conflicts of Interest

No potential conflicts of interest were disclosed.

Disclaimer

The interpretation and reporting of these data are the sole responsibilities of the authors.

Authors' Contributions

Conception and design: A.J. Farias, X.L. Du
Development of methodology: A.J. Farias, X.L. Du
Acquisition of data (provided animals, acquired and managed patients, provided facilities, etc.): X.L. Du
Analysis and interpretation of data (e.g., statistical analysis, biostatistics, computational analysis): A.J. Farias, X.L. Du
Writing, review, and/or revision of the manuscript: A.J. Farias, X.L. Du
Administrative, technical, or material support (i.e., reporting or organizing data, constructing databases): A.J. Farias, X.L. Du
Study supervision: X.L. Du

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References

1. Ooi SL, Martinez ME, Li CI. Disparities in breast cancer characteristics and outcomes by race/ethnicity. Breast Cancer Res Treat 2011;127:729–38.
2. Silber JH, Rosenbaum PR, Clark AS, Giantonio BJ, Ross RN, Teng Y, et al. Characteristics associated with differences in survival among black and white women with breast cancer. JAMA 2013;310:389–97.
3. Banegas MP, Li CI. Breast cancer characteristics and outcomes among Hispanic Black and Hispanic White women. Breast Cancer Res Treat 2012;134:1297–304.
4. Du XL, Fang S, Meyer TE. Impact of treatment and socioeconomic status on racial disparities in survival among older women with breast cancer. Am J Clin Oncol 2008;31:125–32.
5. O'Brien KM, Cole SR, Tse CK, Perou CM, Carey LA, Foulkes WD, et al. Intrinsic breast tumor subtypes, race, and long-term survival in the Carolina Breast Cancer Study. Clin Cancer Res 2010;16:6100–10.
6. Carey LA, Perou CM, Livasy CA, Dressler LG, Cowan D, Conway K, et al. Race, breast cancer subtypes, and survival in the Carolina Breast Cancer Study. JAMA 2006;295:2492–502.
7. De Geest S, Sabaté E. Adherence to long-term therapies: evidence for action. Eur J Cardiovasc Nurs 2003;2:323.
8. Davies C, Godwin J, Gray R, Clarke M, Cutter D, Darby S, et al. Relevance of breast cancer hormone receptors and other factors to the efficacy of adjuvant tamoxifen: patient-level meta-analysis of randomised trials. Lancet 2011;378:771–84.
9. Haque R, Ahmed SA, Fisher A, Avila CC, Shi J, Guo A, et al. Effectiveness of aromatase inhibitors and tamoxifen in reducing subsequent breast cancer. Cancer Med 2012;1:318–27.
10. Howell A, Cuzick J, Baum M, Buzdar A, Dowsett M, Forbes JF, et al. Results of the ATAC (Arimidex, Tamoxifen, Alone or in Combination) trial after completion of 5 years' adjuvant treatment for breast cancer. Lancet 2005;365:60–2.
11. Coombes RC, Hall E, Gibson LJ, Paridaens R, Jassem J, Delozier T, et al. A randomized trial of exemestane after two to three years of tamoxifen therapy in postmenopausal women with primary breast cancer. N Engl J Med 2004;350:1081–92.
12. Hershman DL, Shao T, Kushi LH, Buono D, Tsai WY, Fehrenbacher L, et al. Early discontinuation and non-adherence to adjuvant hormonal therapy are associated with increased mortality in women with breast cancer. Breast Cancer Res Treat 2011;126:529–37.
13. Banning M. Adherence to adjuvant therapy in post-menopausal breast cancer patients: a review. Eur J Cancer Care 2012;21:10–9.
14. Kimmick G, Anderson R, Camacho F, Bhosle M, Hwang W, Balkrishnan R. Adjuvant hormonal therapy use among insured, low-income women with breast cancer. J Clin Oncol 2009;27:3445–51.
15. Partridge AH, Wang PS, Winer EP, Avorn J. Nonadherence to adjuvant tamoxifen therapy in women with primary breast cancer. J Clin Oncol 2003;21:602–6.
16. Fink AK, Gurwitz J, Rakowski W, Guadagnoli E, Silliman RA. Patient beliefs and tamoxifen discontinuance in older women with estrogen receptor–positive breast cancer. J Clin Oncol 2004;22:3309–15.
17. Adisa AO, Lawal OO, Adesunkanmi AR. Paradox of wellness and non-adherence among Nigerian women on breast cancer chemotherapy. J Cancer Res Ther 2008;4:107–10.
18. Winterhalder R, Hoesli P, Delmore G, Pederiva S, Bressoud A, Hermann F, et al. Self-reported compliance with capecitabine: findings from a prospective cohort analysis. Oncology 2011;80:29–33.
19. Cella D, Fallowfield LJ. Recognition and management of treatment-related side effects for breast cancer patients receiving adjuvant endocrine therapy. Breast Cancer Res Treat 2008;107:167–80.
20. Browall M, Ahlberg K, Karlsson P, Danielson E, Persson LO, Gaston-Johansson F. Health-related quality of life during adjuvant treatment for breast cancer among postmenopausal women. Eur J Oncol Nurs 2008;12:180–9.
21. Lorizio W, Wu AH, Beattie MS, Rugo H, Tchu S, Kerlikowske K, et al. Clinical and biomarker predictors of side effects from tamoxifen. Breast Cancer Res Treat 2012;132:1107–18.
22. Hershman DL, Tsui J, Wright JD, Coromilas EJ, Tsai WY, Neugut AI. Household net worth, racial disparities, and hormonal therapy adherence among women with early-stage breast cancer. J Clin Oncol 2015;33:1053–9.

23. National Comprehensive Cancer Network. NCCN Clinical Practice Guidelines in Oncology (NCCN Guidelines®), Breast Cancer 2014; Version 2.2015. Fort Washington, PA: National Comprehensive Cancer Network; 2015 [cited 2015 May]. Available from: www.nccn.org.
24. American Cancer Society. Breast Cancer Facts & Figures 2013–2014. Atlanta, GA: American Cancer Society; 2013.
25. DeSantis C, Ma J, Bryan L, Jemal A. Breast cancer statistics, 2013. CA Cancer J Clin 2014;64:52–62.
26. Rugo HS, Rumble RB, Macrae E, Barton DL, Connolly HK, Dickler MN, et al. Endocrine therapy for hormone receptor-positive metastatic breast cancer: American Society of Clinical Oncology Guideline. J Clin Oncol 2016;34:3069–103.
27. Regan MM, Viale G, Mastropasqua MG, Maiorano E, Golouh R, Carbone A, et al. Re-evaluating adjuvant breast cancer trials: assessing hormone receptor status by immunohistochemical versus extraction assays. J Natl Cancer Inst 2006;98:1571–81.
28. Hammond ME, Hayes DF, Wolff AC, Mangu PB, Temin S. American society of clinical oncology/college of american pathologists guideline recommendations for immunohistochemical testing of estrogen and progesterone receptors in breast cancer. J Oncol Pract 2010;6:195–7.
29. Honma N, Horii R, Iwase T, Saji S, Younes M, Ito Y, et al. Proportion of estrogen or progesterone receptor expressing cells in breast cancers and response to endocrine therapy. Breast 2014;23:754–62.
30. Surveillance Epidemiology and End Results Program. Site Specific Collaborate Stage Data Collection System. Version 02.02 (2010). Available from: http://web2.facs.org/cstage202/breast/Breastschema.html.
31. Hilborn E, Gacic J, Fornander T, Nordenskjöld B, Stål O, Jansson A. Androgen receptor expression predicts beneficial tamoxifen response in oestrogen receptor-α-negative breast cancer. Br J Cancer 2016;114:248–55.
32. Honma N, Horii R, Iwase T, Saji S, Younes M, Takubo K, et al. Clinical importance of estrogen receptor-beta evaluation in breast cancer patients treated with adjuvant tamoxifen therapy. J Clin Oncol 2008; 26:3727–34.
33. Nattinger AB, McAuliffe TL, Schapira MM. Generalizability of the surveillance, epidemiology, and end results registry population: factors relevant to epidemiologic and health care research. J Clin Epidemiol 1997;50:939–45.
34. Du XL, Fang S, Vernon SW, El-Serag H, Shih YT, Davila J, et al. Racial disparities and socioeconomic status in association with survival in a large population-based cohort of elderly patients with colon cancer. Cancer 2007;110:660–9.
35. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373–83.
36. Romano PS, Roos LL, Jollis JG. Adapting a clinical comorbidity index for use with ICD-9-CM administrative data: differing perspectives. J Clin Epidemiol 1993;46:1075–9.
37. Hu CY, Delclos GL, Chan W, Du XL. Assessing the initiation and completion of adjuvant chemotherapy in a large nationwide and population-based cohort of elderly patients with stage-III colon cancer. Med Oncol 2011;28:1062–74.
38. Farias AJ, Du XL. Association between out-of-pocket costs, race/ethnicity, and adjuvant endocrine therapy adherence among medicare patients with breast cancer. J Clin Oncol 2017;35:86–95.
39. Farias AJ, Hansen RN, Zeliadt SB, Ornelas IJ, Li CI, Thompson B. The association between out-of-pocket costs and adherence to adjuvant endocrine therapy among newly diagnosed breast cancer patients. Am J Clin Oncol 2016 Nov 23. [Epub ahead of print].
40. Farias AJ, Du XL. Ethnic differences in initiation and timing of adjuvant endocrine therapy among older women with hormone receptor-positive breast cancer enrolled in Medicare Part D. Med Oncol 2016;33:19.
41. Livaudais JC, Hershman DL, Habel L, Kushi L, Gomez SL, Li CI, et al. Racial/ethnic differences in initiation of adjuvant hormonal therapy among women with hormone receptor-positive breast cancer. Breast Cancer Res Treat 2012;131:607–17.
42. Yung RL, Hassett MJ, Chen K, Gesten FC, Roohan PJ, Boscoe FP, et al. Initiation of adjuvant hormone therapy by Medicaid insured women with nonmetastatic breast cancer. J Natl Cancer Inst 2012;104:1102–5.
43. Freedman RA, Virgo KS, He Y, Pavluck AL, Winer EP, Ward EM, et al. The association of race/ethnicity, insurance status, and socioeconomic factors with breast cancer care. Cancer 2011;117:180–9.
44. Wang X, Du XL. Socio-demographic and geographic variations in the utilization of hormone therapy in older women with breast cancer after Medicare Part-D coverage. Med Oncol 2015;32:599.
45. Farias AJ, Du XL. The association between race/ethnicity, out-of-pocket costs for medication, and adherence to tamoxifen and aromatase inhibitors among women with breast cancer enrolled in Medicare Part D. J Clin Oncol 2017;35:86–95.
46. Chlebowski RT, Geller ML. Adherence to endocrine therapy for breast cancer. Oncology 2006;71:1–9.
47. Chlebowski RT, Kim J, Haque R. Adherence to endocrine therapy in breast cancer adjuvant and prevention settings. Cancer Prev Res 2014;7:378–87.
48. Neugut AI, Subar M, Wilde ET, Stratton S, Brouse CH, Hillyer GC, et al. Association between prescription co-payment amount and compliance with adjuvant hormonal therapy in women with early-stage breast cancer. J Clin Oncol 2011;29:2534–42.
49. He W, Fang F, Varnum C, Eriksson M, Hall P, Czene K. Predictors of discontinuation of adjuvant hormone therapy in patients with breast cancer. J Clin Oncol 2015;33:2262–9.
50. Ursem CJ, Bosworth HB, Shelby RA, Hwang W, Anderson RT, Kimmick GG. Adherence to adjuvant endocrine therapy for breast cancer: importance in women with low income. J Womens Health 2015;24:403–8.
51. Gierach GL, Curtis RE, Pfeiffer RM, Mullooly M, Ntowe EA, Hoover RN, et al. Association of adjuvant tamoxifen and aromatase inhibitor therapy with contralateral breast cancer risk among US women with breast cancer in a general community setting. JAMA Oncol 2016 Oct 6. [Epub ahead of print].
52. Rutqvist LE, Johansson H, Signomklao T, Johansson U, Fornander T, Wilking N. Adjuvant tamoxifen therapy for early stage breast cancer and second primary malignancies. Stockholm Breast Cancer Study Group. J Natl Cancer Inst 1995;87:645–51.
53. Hershman DL, Kushi LH, Shao T, Buono D, Kershenbaum A, Tsai WY, et al. Early discontinuation and nonadherence to adjuvant hormonal therapy in a cohort of 8,769 early-stage breast cancer patients. J Clin Oncol 2010;28:4120–8.
54. Farias AJ, Ornelas IJ, Hohl SD, Zeliadt SB, Hansen RN, Li CI, et al. Exploring the role of physician communication about adjuvant endocrine therapy among breast cancer patients on active treatment: a qualitative analysis. Support Care Cancer 2017;25:75–83.
55. Choo PW, Rand CS, Inui TS, Lee ML, Cain E, Cordeiro-Breault M, et al. Validation of patient reports, automated pharmacy records, and pill counts with electronic monitoring of adherence to antihypertensive therapy. Med Care 1999;37:846–57.
56. Steiner JF, Koepsell TD, Fihn SD, Inui TS. A general method of compliance assessment using centralized pharmacy records. Description and validation. Med Care 1988;26:814–23.