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Xi Tan, PhD, PharmD, Vincent D. Marshall, MS, Roger T. Anderson, PhD, Joseph Donohoe, PhD, Fabian Camacho, MS, MA, and Rajesh Balkrishnan, PhD

Abstract: There is a paucity of literature systemically examining the effects of access to cancer care resources on adjuvant endocrine therapy (AET) use behaviors, especially in underserved regions such as the Appalachian region in the United States, where gaps in healthcare access are well documented. The objectives of this study were to explore AET adherence and persistence in Appalachia, delineate the effects of access to care cancer on adherence/persistence, and evaluate the influences of adherence and persistence on overall survival.

A retrospective cohort study from 2006 to 2008 was conducted among female breast cancer survivors living in the Appalachian counties of 4 states (PA, OH, KY, and NC). We linked cancer registries to Medicare claims data and included patients with invasive, nonmetastatic, hormone-receptor-positive breast cancer who received guideline-recommended AET. Medication adherence was defined as corresponding to a Medication Possession Ratio (MPR) $\geq$0.8 and logistic regression was utilized to assess predictors of adherence. Medication nonpersistence was defined as the discontinuation of drugs after exceeding a 60-day medication gap, and multivariate adjusted estimates of nonpersistence were obtained using the Cox proportional hazards (PH) model.

About 31% of the total 428 patients were not adherent to AET, and 30% were not persistent over an average follow-up period of 421 days. Tamoxifen, relative to aromatase inhibitors, was associated with higher odds of adherence (odds ratio = 2.82, $P < 0.001$) and a lower risk of nonpersistence (hazard ratio = 0.40, $P < 0.001$). Drug-related side effects like pain may be an important factor leading to nonadherence and early discontinuation. In addition, aromatase inhibitor (AI) adherence and persistence were significantly influenced by out-of-pocket drug costs, dual eligibility status, and coverage gaps. Nonadherence to and nonpersistence with AET were associated with higher risks of all-cause mortality.

Our findings of suboptimal AET adherence/persistence in Appalachia as well as positive associations between AET adherence/persistence and overall survival outcomes further underscore the importance of ensuring appropriate AET use in this population to reduce breast cancer mortality disparities. Our findings also suggest that intervention strategies focusing on individualized treatment and medication-related factors may improve adjuvant treatment use.

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Abbreviations: AET = adjuvant endocrine therapy, AI = aromatase inhibitor, ARC = Appalachian Regional Commission, ARF = Area Resource File, CCI = Charlson Comorbidity Index, CDC = Centers for Disease Control and Prevention, CMS = Centers for Medicare and Medicaid services, CoC = Commission on Cancer, Cox PH = Cox proportional hazards, HMO = Health Maintenance Organization, HPSA = Health Professional Shortage Area, HR = hormone-receptor, IRB = Institution Review Board, LIS = low-income subsidies, MPR = Medication Possession Ratio, NCHS = National Center for Health Statistics, NCI = National Cancer Institute, NPI = National Provider Identifiers, OR = odds ratio, SD = standard deviation, UPIN = Unique Physician Identification Numbers.

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INTRODUCTION

Adjuvant endocrine therapy (AET) is a secondary prevention therapy recommended for use among hormone-receptor (HR) positive breast cancer survivors for a period of 5 to 10 years after surgery to reduce recurrence and improve survival.[1–4] Additionally, patient adherence to and persistence with AET are critical in maximizing treatment benefits; this has been identified as a significant issue in clinical practice, with nonadherence and nonpersistence rates as high as 59% and 73%, respectively.[5,6] The current literature showed a broad range of adherence and early discontinuation rates ranging from 41% to 95.7% and 12% to 73%, respectively.[5,6] Variations in adherence and persistence in these studies may be attributable to heterogeneity in methodology and study population. There is no gold standard method for measuring adherence and persistence of AET in clinical practice, nor is there a good biomarker available to measure the use of tamoxifen or aromatase inhibitors (AIs).[7] In the studies using medical and pharmacy claims data, AET adherence was usually defined as Medication Possession Ratio (MPR) $\geq$80%, while nonpersistence/discontinuation was operationalized as the discontinuation of drugs after exceeding a permissible gap,[8] which ranged from 45 to 180 days depending on the study.[5] The discrepancies in persistence definitions may result in variations in discontinuation rates. In addition, factors that were consistently shown to be negatively associated with AET adherence or persistence included extreme age, increasing out-of-pocket costs of AET, seeing a general practitioner versus an oncologist during

follow-up care, switching between drugs, and treatment-associated side effects.[5,6,9]

With the growing number of breast cancer survivors, breast cancer care should not only provide active treatment but also survivorship care such as posttreatment monitoring and risk-reducing maintenance behaviors. However, there are very few studies that systemically examine the effects of access to cancer care resources on AET use behaviors, especially in underserved regions where patients suffer from the deficiencies of access to care, such as the Appalachian region. Additionally, in clinical practice, the literature regarding direct therapeutic outcomes associated with AET adherence and persistence remains underdeveloped. Therefore, the objectives of this study were to describe the prevalence of adherence to and persistence with AET among Appalachian breast cancer survivors; assess the effects of access to cancer care resources on AET adherence and persistence; evaluate the influences of AET adherence and persistence on survival after controlling for access factors.

METHODS

Study Design and Data Source

A retrospective cohort study from January 1, 2006 to December 31, 2008 was conducted among female breast cancer survivors living in the Appalachian counties of 4 states (PA, OH, KY, and NC). The overall study design comprises 3 main periods: the baseline period (1 year before the breast cancer diagnosis), the diagnosis-to-AET period (the interval between the diagnosis and the initiation of AET), and the follow-up period (from the date of the first AET prescription filled until death or the end of the observation period, December 31, 2008).

Multiple data sources were integrated for final analyses: individual characteristics from cancer registries and Medicare claims data; system-level characteristics from the Appalachian Regional Commission (ARC) data reports, the 2010 U.S. census, the Area Resource File (ARF), the National Center for Health Statistics (NCHS), Centers for Disease Control and Prevention (CDC), and the National Cancer Institute (NCI); and provider/facility characteristics mainly from Medicare provider files. First, we linked female breast cancer cases in the cancer registries to Medicare claims data using patient identifiers including name, social security number, gender, and birthdate. Then, the cross-link was established between patient data and system-level characteristics using county codes. The Unique Physician Identification Numbers (UPIN) and National Provider Identifiers (NPI) were utilized to link patient claims to provider factors. The final dataset for statistical analyses had completely deidentified information. Data use was approved by the Centers for Medicare and Medicaid services (CMS) and cancer registries, and the study was approved by the University of Michigan's Institution Review Board (IRB).

Study Population

We included adult women who were diagnosed with confirmed stage I to III, HR positive, primary breast cancer in 2007. Other inclusion criteria were continuous enrollment in Medicare Parts A, B, and D, recorded history of primary breast cancer treatment, eligibility for AET, and no AET use before the primary breast cancer treatment. Patients who were enrolled in a Health Maintenance Organization (HMO) or Medicare Advantage Program or had conflicting information across data sources were excluded from the study. Then we extracted a subset group of subjects who received guideline-recommended AET, which referred to the receipt of AET within 1 year following diagnosis.[10] To facilitate the measurement of medication adherence and persistence, we ensured that we followed patients for a period of at least 6 months.

Outcome Measures

Adherence

We calculated AET adherence for each individual using the MPR. It is defined as the ratio of the amount of days for which the drug was dispensed divided by the number of days for which drug was needed,[11,12] which was determined in this study using the following equation:[13,14]

$$\text{Medication Possession Ratio (MPR)} = \text{number of days' supply} / (\text{number of follow-up days} - \text{number of inpatient days})$$

Additionally, the MPR was truncated between 0 and 1.2, as well as dichotomized into adherence and nonadherence using the conventional cutoff point of 0.8 ($0 \leq \text{MPR} < 0.8$: nonadherence; $0.8 \leq \text{MPR} \leq 1.2$: adherence). For those who switched between tamoxifen and AI, we precluded any double-counting of the days when the patient took both tamoxifen and AI.

Persistence

Medication persistence is defined as the act of complying with a provider's recommendations to use medications for a prescribed length of time[8] and is commonly operationalized in retrospective claims data studies as the discontinuation of drugs after exceeding a permissible gap.[8,15] We defined AET nonpersistence as a minimum 60-day medication fill gap. Patients who switched drugs within 60 days were still considered persistent.

Survival

Overall survival was defined as the period from AET initiation until death or the end of our observation.

Covariate Measures

We included the following access factors: county economic status, county-level educational attainment, urban or rural geographic residence, county-level infant and cancer mortality rates, Health Professional Shortage Area (HPSA) designation, age, marital status, state of residence, annual median household income (at the census block group level), dual Medicare and Medicaid eligibility indicator, average travel time from the patient to the 3 closes mammography centers, breast cancer stage, tumor size, lymph node status, patients' comorbidities as measured by Charlson Comorbidity Index (CCI),[16] treatment facility's Commission on Cancer (CoC) accreditation status, number of beds, the provider's specialty and graduation year, the number of breast-cancer-related follow-up visits (codes used are listed in Supplement Digit Content 1), and timeliness of primary treatment initiation.

We also assessed the type of breast cancer treatments and the type of AET (procedure and drug codes are listed in Supplement Digit Content 2), as well as the following medication-related factors: the average monthly out-of-pocket drug costs; whether patients reached the out-of-pocket threshold and began to receive catastrophic coverage; the number of unique prescription drugs coadministered during follow-up; the season

at the initiation of AET: it was included in analyses because the seasonal weather condition may have influences on travel and transportation especially in a largely rural and mountainous environment such as Appalachia, which in turn may affect patient behaviors of picking up their drugs; AET-associated side effects: we utilized proxy measures for AET-associated side effects (eg, osteoporosis, hot flashes/night sweats, arthralgia) using the indicators of the use of evidence-based prescription drugs for them. As per clinical recommendations for managing AET-associated side effects,[17–19] we created dummy variables indicating whether or not patients used antidepressants (fluoxetine, paroxetine, venlafaxine, citalopram, gabapentin), bisphosphonates (zoledronic acid, alendronate, risedronate), and pain medications (opioids, gabapentin, pregabalin) during follow-up.

Statistical Analyses

We conducted descriptive analyses by using means for continuous variables and frequencies and percentages for binary and categorical variables. Preliminary bivariate association analyses were conducted to find potential predictors of adherence, persistence, and survival. We conducted 2-tailed *t*-tests for continuous predictors of adherence and Chi-square tests for binary and categorical predictors of adherence. We used Kaplan–Meier survival curves and log-rank tests to assess the associations between each binary/categorical variable and persistence or survival time, as well as univariate Cox regression analyses to evaluate the relationships between each continuous variable and persistence or survival time.

Multivariate logistic regression was used to assess the relationship between access to cancer care and AET adherence. For the sake of parsimony, we incorporated potentially significant predictors with a *P*-value <0.25 in the bivariate association analyses into the final multivariate logistic model with a robust standard error.

We obtained multivariate adjusted estimates of nonpersistence (discontinuation) using the Cox proportional hazards (PH) model. We included in the final model only those predictors for which $P < 0.25$ in the bivariate association analyses. We utilized the Efron method to handle ties. We checked the proportional hazard assumption of the variables by using the Schoenfeld and scaled Schoenfeld residuals. If a variable did not meet the assumption, we estimated a stratified Cox model based on the variable.[20] We also utilized Cox PH models to assess whether AET adherence and persistence influence all-cause mortality.

Sensitivity analyses were also conducted by redefining AET adherence and persistence as MPR cutoff points ranging from 0.6 to 0.9 and a 90-day medication fill gap, respectively. The statistical significance level was set to $P < 0.05$. We used R 3.0.2 (R Foundation for Statistical Computing, Vienna, Austria) for general data management, ArcGIS 10.1 (ESRI, Redlands, CA) for geo-related data management, and Stata 13 (StataCorp LP, College Station, TX) for analyses.

RESULTS

Our final study sample consisted of 428 Medicare-enrolled women with breast cancer living in the 125 Appalachian counties of 4 states (KY, NC, OH, and PA) who initiated AET within 1 year after the diagnosis. Eligible patients were followed for a period of 181 to 706 days, with an average of 421 days. The mean MPR was 0.83 (standard deviation [SD] = 0.24, range = [0.06, 1.2]), and approximately 69.4% were adherent to AET. The average AET persistence time was 347.6 days, and the early discontinuation rate was about 30.1%. Table 1 describes county-level characteristics. The results confirmed the deficiencies in access to care in Appalachia including economically distressed or at risk populations (43.2%), largely rural environments (67.2%), and healthcare professional shortages (88%), as well as low community educational levels and high infant and cancer mortality rates. The percentages of less than high school graduate (18.8%) and at least a bachelor's degree among persons aged 25 and over (15.9%) and living in these Appalachian counties were worse than national averages (15% and 27.9%, respectively). The mean infant mortality rate (7.2 per 1000 births) and cancer mortality rate (197.7 per 100,000 population) of these Appalachian counties were also higher than the national average estimates (6.75 per 1000 births and 173.8 per 100,000 population, respectively). Bivariate association analyses showed that adherent and persistent patients were more likely to live in counties with a lower infant mortality rate ($P = 0.05$ and $P = 0.24$, respectively). But, overall, we did not find bivariate associations with strong significance between county-level factors and adherence/persistence. Table 2 presents the descriptive analysis results of individual, facility/provider, and medication-related characteristics. During the follow-up period, eligible patients had 2.25 breast-cancer-related follow-up visits, on average. An average of approximately 11.6 prescription drugs was coadministered to patients. Approximately 26.4% of the population reached the catastrophic coverage threshold. Moreover, the use rates of antidepressants, bisphosphonates, and pain medications that can treat AET-associated side effects were about 9.1%, 21.5%, and

TABLE 1. Descriptive Statistics of System-Level Characteristics (by County) (N = 125)

Variables	Mean (SD)
Percentage of less than high school graduate among persons aged 25 and over (%)	18.8 (7.7)
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	15.9 (6.4)
Infant death rate per 1000 births	7.2 (0.85)
Annual age-adjusted, cancer-related death rate per 100,000 population	197.7 (28.8)
	Frequency (%)
ARC's county economic status	
Distressed	30 (24.0%)
At risk	24 (19.2%)
Others	71 (56.8%)
Annual median household income (US dollar), quartile*	
Low ($9768–$31,408.5)	107 (25%)
Second ($31,408.5–$41,552)	107 (25%)
Third ($41,552–$51,577.5)	107 (25%)
High ($51,577.5–$15,0625)	107 (25%)
Urban–rural classification	
Metropolitan	41 (32.8%)
Nonmetropolitan	84 (67.2%)
Health Professional Shortage Area (HPSA) designation	
Whole county in HPSA	40 (32.0%)
Part county in HPSA	70 (56.0%)
Not in HPSA	15 (12.0%)

ARC = Appalachian Region Commission, SD = standard deviation.
* At the census block group level.

TABLE 2. Descriptive Statistics of Individual, Facility/Provider, and Medication-Related Characteristics (N = 428)

Variables	Mean (SD)
Average travel time to the 3 closest mammography centers (minute)	15.9 (10.2)
Baseline Charlson Comorbidity Index (CCI)	0.63 (0.95)
Baseline number of hospitalizations	0.38 (0.97)
No. of breast-cancer-related follow-up visits	2.25 (2.44)
Average monthly out-of-pocket costs (US dollar)	50.0 (64.2)
No. of unique prescription drugs coadministered	11.6 (6.24)
Follow-up time (day)	421.2 (116.3)
	Frequency (%)
Age at diagnosis	
<65	35 (8.2%)
65–74	155 (36.2%)
75–84	187 (43.7%)
≥85	51 (11.9%)
Marital status	
Married	140 (32.7%)
Not married	288 (67.3%)
State	
KY	61 (14.3%)
NC	77 (18.0%)
OH	75 (17.5%)
PA	215 (50.2%)
Dual Medicare and Medicaid eligibility status	
Dual eligible	121 (28.3%)
Medicare only	307 (71.7%)
Catastrophic coverage indicator	
Yes	113 (26.4%)
No	315 (73.6%)
Stage	
Stage I	239 (55.8%)
Stage II	149 (34.8%)
Stage III	40 (9.4%)
Tumor size	
<1 cm	84 (19.6%)
1–2 cm	215 (50.2%)
>2 cm	129 (30.1%)
Lymph node status	
Negative	312 (72.9%)
Positive	116 (27.1%)
Commission on Cancer (CoC) accreditation	
Yes	272 (63.6%)
No	156 (36.4%)
Facility beds	
<100	70 (16.4%)
100–199	91 (21.3%)
≥200	267 (62.4%)
	Frequency (%)
Facility ownership	
Nonprofit	364 (85.0%)
Others	64 (15.0%)
Provider's specialty	
Oncology	116 (27.1%)
General practitioner	259 (60.5%)
Other	53 (12.4%)
Provider's graduation year	
Before 1980	163 (38.1%)
1980s	186 (43.5%)
After 1989	79 (18.5%)
Breast cancer surgery type	
Mastectomy	166 (38.8%)
Breast conserving surgery (BCS) + radiation	139 (32.5%)
BCS, no radiation	123 (28.7%)
Chemotherapy	
Yes	215 (50.2%)
No	213 (49.8%)
Timeliness of primary treatment initiation	
Timely treatment (surgery within 60 days)	398 (93.0%)
Delayed treatment (surgery beyond 60 days)	30 (7.0%)
Use of antidepressants	
Yes	39 (9.1%)
No	389 (90.9%)
Use of bisphosphonates	
Yes	92 (21.5%)
No	336 (78.5%)
Use of pain medications	
Yes	43 (10.0%)
No	385 (90.0%)
Season at the initiation of AET	
Spring	97 (22.7%)
Summer	103 (24.1%)
Fall	103 (24.1%)
Winter	125 (29.2%)

Note: The percentages of some variables may not add up to 100% due to rounding errors.
AET = adjuvant endocrine therapy, SD = standard deviation.

10%, respectively. Dual eligibility status, catastrophic coverage, lymph node status, and use of pain medications had significant bivariate associations with AET adherence and persistence ($P < 0.05$).

Tables 3 and 4 show factors significantly associated with AET adherence and discontinuation: AET drug class, catastrophic coverage, and use of pain medications. Please note that because dual eligibility status and provider specialty did not meet the proportional hazard assumption, our final Cox PH model of AET discontinuation was stratified by these 2 variables. Patients receiving catastrophic coverage benefits had about 3-fold odds of adhering to AET (odds ratio [OR] = 3.25, $P = 0.001$) and a 44% lower risk of discontinuing AET (hazard ratio = 0.56, $P = 0.03$). Coadministration of pain medications was associated with 68% reduced odds of adherence to AET (OR = 0.32, $P = 0.003$) and an estimated 2.5 times increased risk of AET nonpersistence (hazard ratio = 2.47, $P = 0.002$). Tamoxifen was associated with greater likelihood of adherence (OR = 2.82, $P = 0.003$) and persistence (hazard ratio = 0.40, $P = 0.002$) than AIs.

We next stratified our population into those who took tamoxifen and those who took AIs and reestimated the models. We found that increased out-of-pocket prescription drug costs were associated with reduced likelihood of adherence in the AI group (OR = 0.99, $P = 0.008$), but the results were not significant in the tamoxifen group. In terms of side effects, we found that using pain medications was significantly associated with poor adherence (OR = 0.41, $P = 0.03$) and persistence (hazard ratio = 1.94, $P = 0.05$) to AI but not to tamoxifen. We then

TABLE 3. Predictors of Adherence to Adjuvant Endocrine Therapy (AET) Among Appalachian Women With Breast Cancer: Multivariate Logistic Regression (N = 428)

Variable	Adherence to AET, Odds Ratio (95% CI)	*P*-Value
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	0.997 (0.957, 1.039)	0.89
Infant death rate per 1000 births	1.16 (0.66, 2.04)	0.60
Annual age-adjusted, cancer-related death rate per 100,000 population	1.01 (0.99, 1.02)	0.30
Baseline Charlson Comorbidity Index (CCI)	1.08 (0.83, 1.40)	0.56
Average monthly out-of-pocket costs (US dollar)	0.997 (0.993, 1.001)	0.09
Health Professional Shortage Area (HPSA) designation		
Whole county in HPSA	Reference	Reference
Part county in HPSA	1.19 (0.49, 2.91)	0.70
Not in HPSA	1.26 (0.45, 3.55)	0.66
State		
KY	0.39 (0.14, 1.13)	0.08
NC	0.43 (0.07, 2.60)	0.36
OH	0.66 (0.30, 1.42)	0.29
PA	Reference	Reference
Dual Medicare and Medicaid eligibility status		
Dual-eligible	1.26 (0.59, 2.68)	0.56
Medicare-only	Reference	Reference
Catastrophic coverage indicator		
Yes	**3.25 (1.67, 6.33)**	**0.001**
No	Reference	Reference
Lymph node status		
Negative	Reference	Reference
Positive	1.51 (0.86, 2.66)	0.16
Commission on Cancer (CoC) accreditation		
Yes	0.89 (0.53, 1.50)	0.66
No	Reference	Reference
Provider specialty		
Oncology	1.25 (0.73, 2.16)	0.42
General practitioner	Reference	Reference
Other	0.54 (0.26, 1.10)	0.09
Breast cancer surgery type		
Mastectomy	Reference	Reference
Breast conserving surgery (BCS) + radiation	0.74 (0.40, 1.35)	0.32
BCS, no radiation	0.66 (0.36, 1.21)	0.18
Use of bisphosphonates		
Yes	1.39 (0.78, 2.46)	0.26
No	Reference	Reference
Use of pain medications		
Yes	**0.32 (0.15, 0.67)**	**0.003**
No	Reference	Reference
AET drug class		
Tamoxifen	**2.82 (1.42, 5.64)**	**0.003**
Aromatase inhibitor (AI)	Reference	Reference
Switching between 2 drug classes	2.20 (0.85, 5.66)	0.10

$P < 0.05$ is considered to be statistical significant.
AET = adjuvant endocrine therapy, 95% CI = 95% confidence interval.

stratified the population by dual-eligible enrollees versus Medicare only enrollees. Those dual-eligible enrollees who qualified for low-income subsidies (LIS) did not experience the drug coverage gap experienced by Medicare-only enrollees; we did not find that receiving catastrophic coverage benefits significantly affected AET adherence or persistence among these dual-eligible enrollees. For Medicare-only enrollees, however, receiving catastrophic coverage significantly improved AI adherence (OR = 6.20, $P = 0.001$) and persistence (hazard ratio = 0.31, $P = 0.01$) but did not have significant impacts on tamoxifen use. The results of using differing definitions of adherence and persistence in our sensitivity analyses showed that AET drug class and catastrophic coverage were robust predictors of AET adherence while AET drug class and the use of pain medication were stable predictors of AET persistence.

During the study period, all-cause death occurred in 15 patients (3.5% of our sample). The Kaplan–Meier survival curves by AET medication adherence and persistence (shown in Figures 1 and 2) showed that patients who were not adherent to or persistent with AET had a higher risk of death, both with

TABLE 4. Factors Associated With Discontinuation of Adjuvant Endocrine Therapy (AET) Among Appalachian Women With Breast Cancer: Cox Proportional Hazards (PH) Model, Stratified by the Provider's Specialty and the Patient's Dual Eligibility Status (N = 428)

Variable	AET Discontinuation, Hazard Ratio (95% CI)	*P*-Value
Percentage of at least a bachelor's degree among persons aged 25 and over (%)	0.99 (0.96, 1.02)	0.64
Infant death rate per 1000 births	1.08 (0.90, 1.31)	0.40
Annual age-adjusted, cancer-related death rate per 100,000 population	1.00 (0.99, 1.01)	0.81
Baseline Charlson Comorbidity Index (CCI)	0.96 (0.77, 1.19)	0.71
Age at diagnosis		
<65	0.47 (0.16, 1.36)	0.16
65–74	Reference	Reference
75–84	1.10 (0.73, 1.66)	0.65
≥85	1.17 (0.63, 2.19)	0.62
Marital status		
Married	1.13 (0.76, 1.69)	0.54
Not married	Reference	Reference
Annual median household income (US dollar), quartile		
Low ($9768–$31,408.5)	Reference	Reference
Second ($31,408.5–$41,552)	1.26 (0.73, 2.17)	0.40
Third ($41,552–$51,577.5)	1.06 (0.61, 1.85)	0.84
High ($51,577.5–$15,0625)	1.25 (0.71, 2.20)	0.44
Catastrophic coverage indicator		
Yes	**0.56 (0.33, 0.95)**	**0.03**
No	Reference	Reference
Lymph node status		
Negative	Reference	Reference
Positive	0.69 (0.43, 1.10)	0.12
Commission on Cancer (CoC) accreditation		
Yes	1.22 (0.76, 1.94)	0.41
No	Reference	Reference
Facility beds		
<100 beds	1.20 (0.65, 2.21)	0.57
100–199 beds	0.75 (0.44, 1.28)	0.29
≥200 beds	Reference	Reference
Breast cancer surgery type		
Mastectomy	Reference	Reference
Breast conserving surgery (BCS) + radiation	1.14 (0.70, 1.86)	0.60
BCS, no radiation	1.50 (0.94, 2.40)	0.09
Use of bisphosphonates		
Yes	0.75 (0.46, 1.20)	0.23
No	Reference	Reference
Use of pain medications		
Yes	**2.47 (1.41, 4.33)**	**0.002**
No	Reference	Reference
AET drug class		
Tamoxifen	**0.40 (0.22, 0.71)**	**0.002**
Aromatase inhibitor (AI)	Reference	Reference
Switching between 2 drug classes	0.86 (0.41, 1.80)	0.70

$P < 0.05$ is considered to be statistical significant.
AET = adjuvant endocrine therapy, 95% CI = 95% confidence interval.

significant log-rank test results ($P = 0.04$ and 0.01, respectively). Multivariate adjusted Cox PH models also supported these findings (shown in Tables 5 and 6). Eligible breast cancer survivors who were not adherent to or persistent with AET had greatly higher risks of death than those who were adherent or persistent (both $P = 0.003$), after controlling for other factors. Additionally, other significant factors associated with increased risk of all-cause death were increased age and being treated in non-CoC accredited facilities. The conclusions did not differ if we changed the definitions of adherence and persistence.

DISCUSSION

Our study is among the first to delineate the manner in which multidimensional determinants of access to cancer care affect patient medication use behaviors, specifically, adherence

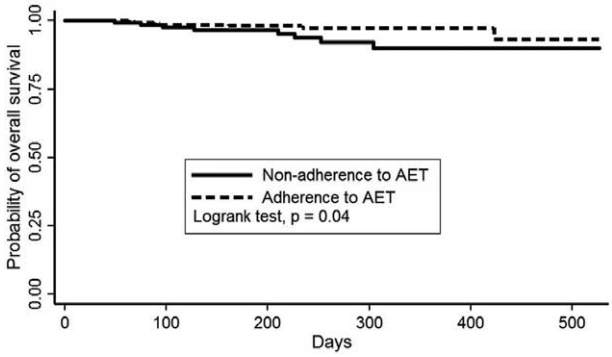

FIGURE 1. Kaplan–Meier curves of overall survival by adjuvant endocrine therapy (AET) adherence. Patients who were not adherent to AET (solid line) had a higher risk of death than those who were adherent (dash line), and the log-rank test showed significant result ($P = 0.04$). Note: The start time of survival analysis was 180 days after the initiation of AET because our study design only included patients who were alive for at least 180 days after the initiation of AET.

to and persistence with adjuvant treatments, in Appalachia. The AET adherence rate and early discontinuation rate in the first 2 years among Appalachian women with invasive, nonmetastatic, HR-positive breast cancer were 69% and 30%, respectively. We found that adherence rates in previous studies using US pharmacy claims data were in the range of 70% to 80%,[21–24] and the discontinuation rates were fairly consistent at around 20%.[22,25–27] Overall, AET adherence and persistence seems to be lower in Appalachia compared to the rest of the United States.

Our findings suggested that adherence to and persistence with AET were primarily related to the medication-related factors. Tamoxifen was associated with better medication use outcomes than AIs, which may be attributable to different adverse effect profiles and drug costs. The use of pain medications, presumably to treat AI-related musculoskeletal pain, was significantly associated with poor adherence and persistence, which may partially explain the worse medication use outcomes associated with AIs. Other research showed that

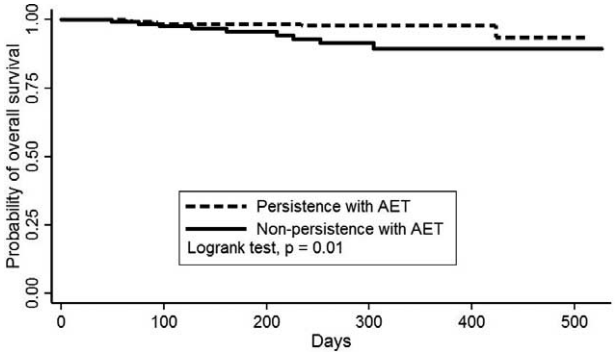

FIGURE 2. Kaplan–Meier curves of overall survival by adjuvant endocrine therapy (AET) persistence. Patients who were not persistent with AET (solid line) had a higher risk of death than those who were persistent (dash line), and the log-rank test showed significant result ($P = 0.01$). Note: The start time of survival analysis was 180 days after the initiation of AET because our study design only included patients who were alive for at least 180 days after the initiation of AET.

AET-induced side effects like musculoskeletal pain may increase physical burden on patients, cause misbeliefs about AET use, and adversely affect patients' intentions to adhere to the medication.[28,29] Our study supports this conclusion and highlights the need to develop interventions that focus on individualized side-effect management and better patient education about AET use.

In addition, tamoxifen generally involves lower costs to both patients and third-party payers than AIs, so it may be associated with reduced financial burden in the long run. We found a negative relationship between out-of-pocket drug costs and adherence among patients who used AIs only (OR = 0.99, $P = 0.008$) but did not find a significant relationship among those who used tamoxifen only. The relationship may be influenced by several factors: type of Medicare healthcare plan, dual eligibility status that can determine the qualification for LIS, whether patients enter the coverage gap, and whether patients receive catastrophic coverage benefits beyond the out-of-pocket threshold. Riley et al[21] found that adherence rates did not differ much between patients with and without LIS in the tamoxifen group but adherence to AIs was significantly improved if patients received LIS. In the present study, however, we did not establish a significant interaction between AET drug class and dual eligibility status to predict adherence or persistence. Previous research found that AET adherence declined when Medicare-only patients without LIS entered in the coverage gap compared to precoverage gap[21]; our study further found that AI adherence and persistence improved significantly after these patients got out of the coverage gap and received catastrophic coverage benefits, but we found no significant changes in tamoxifen adherence and persistence in the same circumstances.

Even with the constraints of small sample size and short follow-up time, we found significant positive relationships between nonadherence/nonpersistence to AET and all-cause mortality. Hershman et al[30] found that nonpersistence and nonadherence to AET were significantly associated with increased hazard of all-cause death by 26% and 49%, respectively. Similarly, McCowan et al[31] identified a 10% increase in the hazard of all-cause mortality among those who were not adherent to tamoxifen, compared to those who were adherent, as well as a significantly lower risk of death associated with use of tamoxifen over a long duration. In addition, we found in the Kaplan–Meier curves that 480 to 580 days showed the largest survival difference (300–400 days in the figures since the start time of the figures was 180 days following the initiation of AET). As per the Kaplan–Meier curve in the Hershman et al[30] that assessed 10-year survival difference, the effect of adherence to AET on survival became prominent since 1.5 to 2 years after initiation. The smaller difference in the tails of our figures may be attributable to the very limited number of subjects left in both arms because 90% of our study population had less than 581-day follow-up time. The effects of adherence/persistent with AET would be even clearer if we had larger sample size and longer follow-up that can cover the whole clinical course of AET. Nevertheless, our findings plus previous evidence may imply the importance of ensuring appropriate AET use in the pursuit of additional gains in survival. It is also noteworthy that AET adherence and persistence may have different influences on survival. By definition, AET persistence emphasizes more on the recommended length of time, which was determined by clinical evidence of benefits in breast cancer outcomes.[32,33] AET adherence focuses on whether patients can use AET everyday as recommended to keep a steady drug level that is

TABLE 5. The Association Between Adjuvant Endocrine Therapy (AET) Nonadherence and All-Cause Mortality Among Appalachian Women With Invasive, Nonmetastatic, and Hormone Receptor Positive Breast Cancer, Using Cox Proportional Hazards (PH) Model (N = 428)

Variable	All-Cause Mortality, Hazard Ratio (95% CI)	*P*-Value
Adherence to AET		
Yes	Reference	Reference
No	**9.15 (2.11, 39.62)**	**0.003**
Age at diagnosis (year)	**1.14 (1.04, 1.25)**	**0.004**
Marital status		
Married	1.75 (0.26, 11.57)	0.56
Not married	Reference	Reference
Dual Medicare and Medicaid eligibility status		
Dual eligible	3.07 (0.76, 12.41)	0.12
Medicare only	Reference	Reference
Stage		
Stage I	Reference	Reference
Stage II	1.46 (0.20, 10.40)	0.71
Stage III	1.25 (0.10, 16.05)	0.86
Tumor size		
<1 cm	Reference	Reference
1–2 cm	0.20 (0.02, 1.57)	0.12
>2 cm	0.46 (0.04, 4.60)	0.51
Commission on Cancer (CoC) accreditation		
Yes	**0.12 (0.02, 0.72)**	**0.02**
No	Reference	Reference
Facility beds		
<100 beds	1.54 (0.29, 8.08)	0.61
100–199 beds	3.07 (0.56, 16.64)	0.19
≥200 beds	Reference	Reference
Breast cancer surgery type		
Mastectomy	Reference	Reference
Breast conserving surgery (BCS)	0.47 (0.12, 1.92)	0.30
Baseline number of hospitalizations	0.99 (0.65, 1.49)	0.95
No. of breast-cancer-related follow-up visits	0.56 (0.30, 1.07)	0.08
No. of unique prescription drugs coadministered	0.97 (0.88, 1.07)	0.60

$P < 0.05$ is considered to be statistical significant.
AET = adjuvant endocrine therapy, 95% CI = 95% confidence interval.

warranted to maximize the drug effectiveness and improve clinical outcomes. However, again, long follow-up time that can cover the whole recommended clinical course of AET may be needed to differentiate the effects of AET adherence and persistence on breast cancer outcomes.

This study had several limitations. First, the relatively short length of the follow-up period and small sample size limited our ability to conduct further analyses such as breast-cancer-related survival or the changes in adherence and persistence over the whole recommended clinical course of AET (5–10 years). Second, we did not include some detailed information and potential predictors, such as accurate drug indications, prescribers' characteristics, pharmacy type, and patient attitudes and beliefs about long-term AET use. Third, when using administrative claims data to assess medication adherence/persistence, we assumed that the claims were billed in an accurate and timely manner, AET was obtained only through Medicare Part D, and the medication was actually taken by the patients. These assumptions may not always be true under all circumstances, which may cause measurement errors. For example, patients might obtain AET from other sources than through Medicare Part D, which may not be captured in our dataset especially when in the coverage gap. Dually eligible patients may receive additional benefits from their Medicaid programs to help with their out-of-pocket money, which were not considered in our calculation of out-of-pocket drug costs. Finally, the generalization of results may be limited to our target population that was Medicare enrollees with breast cancer who lived in Appalachia and were first-time users of tamoxifen and AIs. We did not study ovarian suppression/ablation, or the use of tamoxifen or AIs as primary treatments or neoadjuvant therapy for breast cancer, or AET use in a general breast cancer patient population, which is typically younger than our study population.

CONCLUSION

AET adherence and persistence are suboptimal in Appalachia. They differ between drug classes possibly as a result of distinct adverse effect profiles and differences in patient affordability stemming from drug costs and health plan benefits. Additionally, we confirm the substantial benefits of adherence to and persistence with AET in achieving the advancement of overall survival. Therefore, this study suggests the value of

TABLE 6. The Relationship Between Adjuvant Endocrine Therapy (AET) Nonpersistence and All-Cause Mortality Among Appalachian Women With Invasive, Nonmetastatic, and Hormone Receptor Positive Breast Cancer, Using Cox Proportional Hazards (PH) Model (N = 428)

Variable	All-Cause Mortality, Hazard Ratio (95% CI)	*P*-Value
Persistence with AET		
Yes	Reference	Reference
No	**9.48 (2.14, 41.95)**	**0.003**
Age at diagnosis (year)	**1.12 (1.02, 1.22)**	**0.01**
Marital status		
Married	1.35 (0.22, 8.43)	0.75
Not married	Reference	Reference
Dual Medicare and Medicaid eligibility status		
Dual eligible	2.79 (0.67, 11.57)	0.16
Medicare only	Reference	Reference
Stage		
Stage I	Reference	Reference
Stage II	1.22 (0.17, 8.92)	0.84
Stage III	1.17 (0.09, 14.59)	0.90
Tumor size		
<1 cm	Reference	Reference
1–2 cm	0.23 (0.03, 1.71)	0.15
>2 cm	0.42 (0.04, 4.39)	0.47
Commission on Cancer (CoC) accreditation		
Yes	**0.11 (0.02, 0.72)**	**0.02**
No	Reference	Reference
Facility beds		
<100 beds	1.47 (0.29, 7.54)	0.64
100–199 beds	2.17 (0.45, 10.37)	0.33
≥200 beds	Reference	Reference
Breast cancer surgery type		
Mastectomy	Reference	Reference
Breast conserving surgery (BCS)	0.31 (0.07, 1.45)	0.14
Baseline number of hospitalizations	0.95 (0.62, 1.46)	0.81
No. of breast-cancer-related follow-up visits	0.55 (0.30, 1.01)	0.05
No. of unique prescription drugs coadministered	0.97 (0.88, 1.07)	0.51

$P < 0.05$ is considered to be statistical significant.
AET = adjuvant endocrine therapy, 95% CI = 95% confidence interval.

adding a component focusing on medication management related to AET use to current cancer care models in Appalachia with the ultimate goal of reducing breast cancer mortality disparities.

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