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Geographic disparities in adherence to adjuvant endocrine therapy in Appalachian women with breast cancer

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Abstract

Background: Appalachia is a largely rural, mountainous, poor and underserved region of the United States. Adherence to adjuvant endocrine therapy among Appalachian women with breast cancer is suboptimal.
Objectives: To explore small-area geographic variations and clustering patterns of breast cancer patient adherence to adjuvant endocrine therapy and associated factors in Appalachia.
Methods: In this retrospective study, we analyzed Medicare claims data linked with cancer registries from four Appalachian states (PA, OH, KY, and NC) in 2006–2008. We included adult women who were diagnosed with stage I–III, hormone-receptor positive, primary breast cancer and who newly started adjuvant endocrine therapy after the primary treatment for breast cancer. Hot spot analysis was conducted to explore geographic variations in adjuvant endocrine therapy adherence. Geographically weighted logistic regression (GWLR) was used to examine whether the impacts of factors associated with adherence varied across the region.
Results: Breast cancer patients living in PA and OH showed higher adherence to adjuvant endocrine therapy than those living in KY and NC. We identified clusters of high adherence in most of PA but poor adherence in Erie County, PA and in Buncombe, Transylvania, Henderson, and Polk Counties, NC. Adherence to adjuvant endocrine therapy was significantly associated with the Health Professional Shortage Area designation, catastrophic coverage, dual-eligibility status of Medicaid and Medicare, adjuvant endocrine therapy drug class, and side effects. And among these factors, the impacts of dual-eligibility status and the use of pain medications to treat side effects on adherence were more pronounced in KY and NC than in PA.
Conclusions: There were significant geographic disparities in adherence to adjuvant endocrine therapy in the Appalachian counties in PA, OH, KY, and NC. This study explored these geographic areas with poor

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adherence as well as geographically varying effects of predictors on adherence; our results may provide more localized information that may be used to improve adjuvant therapy use and breast cancer care in these high-risk and underserved areas.

Keywords: Appalachia; Breast cancer; Adjuvant endocrine therapy; Adherence; Geographically weighted regression

Introduction

Adjuvant endocrine therapy (AET) is an important treatment modality for hormone-receptor (HR) positive breast cancer due to its significant benefits in reducing recurrence and mortality.[1–4] To achieve the optimal clinical benefits, adherence to AET is crucial.[5–7] The current literature has identified many individual characteristics that may be inversely related to AET adherence such as extreme age (younger [under 40–45 years old] or older [over 75–85 years old]), higher out-of-pocket drug costs, switching drugs, drug class (aromatase inhibitors vs. tamoxifen), suboptimal patient-centered communication, lack of perceived self-efficacy in patient–physician interaction, and adverse drug reactions,[5,8–11] but the literature has paid limited attention to geography or associated factors. In fact, geography can serve as a proxy or composite measure for various observed and unobserved variables that may be related to medication adherence, such as access to care, available health resources, socioeconomic status, disease burden, race/ethnicity, and culture.[12] Examining geography and associated factors may help advance AET adherence research by further explaining individual variations in AET adherence that cannot be fully explained by individual characteristics. Small-area geographic variations in medication adherence may be attributable to the neighborhood effect, which describes the social interactions impacting an individual's behavior or outcomes.[13] Theoretically, people residing in the same neighborhood are more likely to share common social norms, cultural background, socioeconomic status, and systemic and lifestyle characteristics compared to people living in different neighborhoods, which may further shape health behaviors, including medication-taking behaviors, above the individual-level.[14] There may also be provider neighborhood effects, such as possible ineffective or inadequate patient-provider communication in the Health Professional Shortage Area (HPSA) that leads to the failure to underscore the importance of AET adherence, or similar prescribing or practice behaviors under the influence of similar policies, regulations or interventions in one area.

The Appalachian region of the United States (US) covers 204,452 square miles in 420 counties along the spine of the Appalachian Mountains.[15] This region contains all of West Virginia, and portions of 12 other states: New York, Pennsylvania, Ohio, Maryland, Kentucky, Virginia, Tennessee, North Carolina, South Carolina, Georgia, Alabama, and Mississippi. The Appalachian population in the US is a special population of interest in cancer research because it consistently suffers from a significant cancer burden, with higher cancer incidence and mortality than the non-Appalachian population.[16,17] In terms of breast cancer, compared to other regions, Appalachia experienced a slower decline in breast cancer mortality,[18] and its patients receive guideline-recommended breast cancer screening and primary treatment at lower rates than those in other regions.[19–21] The factors leading to poor access to and utilization of care in this region may include rural residence, geographic isolation, lack of public transportation, underdeveloped telecommunication infrastructure, high poverty and unemployment rates, inadequate medical resources, a shortage of healthcare professionals, lower levels of educational attainment, and attitudinal and cultural factors.[20,22,23] Given the largely rural, mountainous environment and unsatisfactory patient adherence to AET in Appalachia as a whole,[5] we need to measure geographic variations in AET adherence beyond the general urban and rural classification. The identification of "hot spots" that require monitoring and intervention can help local communities to develop strategies to improve cancer treatment use and outcomes. However, there have been very few studies examining geographic disparities in adjuvant cancer treatment use in this region, primarily due to the lack of data and of a representative study sample. Therefore, we pursued the following study aims:

1) to explore small-area geographic variations and clustering patterns of AET adherence; and 2) to examine spatial non-stationarity of the relationships between potential predictors and AET adherence.

Material and methods

Study design and study population

In this retrospective study, we analyzed Medicare claims data linked with cancer registries from four Appalachian states (PA, OH, KY, and NC) between January 1, 2006 and December 31, 2008. We only assessed the Appalachian counties in these four states, not including the non-Appalachian counties. The study design included a baseline period that began one year before the diagnosis date, and patients were followed from the date of the first AET prescription until death or until the end of the study. AET assessed in this study were tamoxifen and aromatase inhibitors (AIs) including anastrozole, letrozole, and exemestanes. We utilized the sample identified in our previous study,[5] and Fig. 1 shows the flowchart for obtaining the study sample. We included adult women who lived in Appalachian counties in PA, OH, KY, and NC and who were diagnosed with stage I–III, HR-positive, primary breast cancer in 2007. Due to data availability, the study sample was limited to women who were continuously enrolled in Medicare Parts A, B, and D but not enrolled in a Health Maintenance Organization (HMO) or the Medicare Advantage Program during the study period. Then new users of AET were selected based on their eligibility for AET and guideline recommendations.[24] To better assess adherence, a minimum follow-up period of six months was required for all eligible patients.

Data sources

We utilized a unique dataset that linked Medicare claims data and four Appalachian states' cancer registries; three of the four states were not included in the Surveillance, Epidemiology, and End Results (SEER) program. The linkage was established using patient identifiers including name, social security number, gender, and birthdate, a method validated in previous studies.[5,25,26] County-level characteristics were acquired using county names or codes from the Appalachian Regional Commission (ARC) data reports and Area Health Resources Files (AHRF). Completely de-identified data were used for final analyses. The study was approved by the Institutional Review Board (IRB) of the University of Michigan, and data use was approved by the Centers for Medicare and Medicaid Services (CMS) and each state's cancer registry.

Outcome measures

AET adherence was measured using the Medication Possession Ratio (MPR). The MPR is a commonly used medication adherence measure using administrative claims data that has been adopted widely in AET adherence research.[8,9] The numerator was number of days' supply of medication and the denominator was number of follow-up days minus the number of inpatient days. A higher MPR means better adherence. The MPR was also truncated between 0 and 1.2 and used 0.8 as the cut-off point for adherence or non-adherence ($0 \leq MPR \leq 0.8$ as non-adherence; $0.8 \leq MPR \leq 1.2$ as adherence). The cut-off point of 0.8 seems to have clinical relevance, which has shown to be significantly associated with all-cause mortality.[5] The MPR was treated as a continuous variable in hot spot analyses and a dummy variable in geographic weighted logistic regression and regular logistic regression.

Covariate measures

We adapted the constructs from Andersen's expanded behavioral model for health service use[27,28] as the theoretical background and integrated the findings of empirical work regarding AET adherence to guide this study.[5,8–11] Area-level characteristics, individual patient level characteristics including predisposing factors, enabling factors, need-related factors, as well as medication-related factors together may predict AET adherence, which may, in turn, impact health outcomes. The area-level factors included in this study were: the percentage of residents aged 25 and over with less than a high school diploma at the county-level; urban-rural classification (metropolitan or not); the Health Professional Shortage Area (HPSA) designation (entirely within an HPSA, partially within an HPSA, or not within an HPSA); annual median household income at the census-block-group level (in quartiles). We also assessed individual-level potential factors that may impact AET adherence: age at diagnosis; marital status (yes/no); breast cancer stage (I, II, III); tumor size (<1 cm, 1–2 cm, >2 cm, unknown); lymph node status (negative or positive), comorbidities calculated by the Charlson Comorbidity Index (CCI)[29] from which the primary diagnosis of female

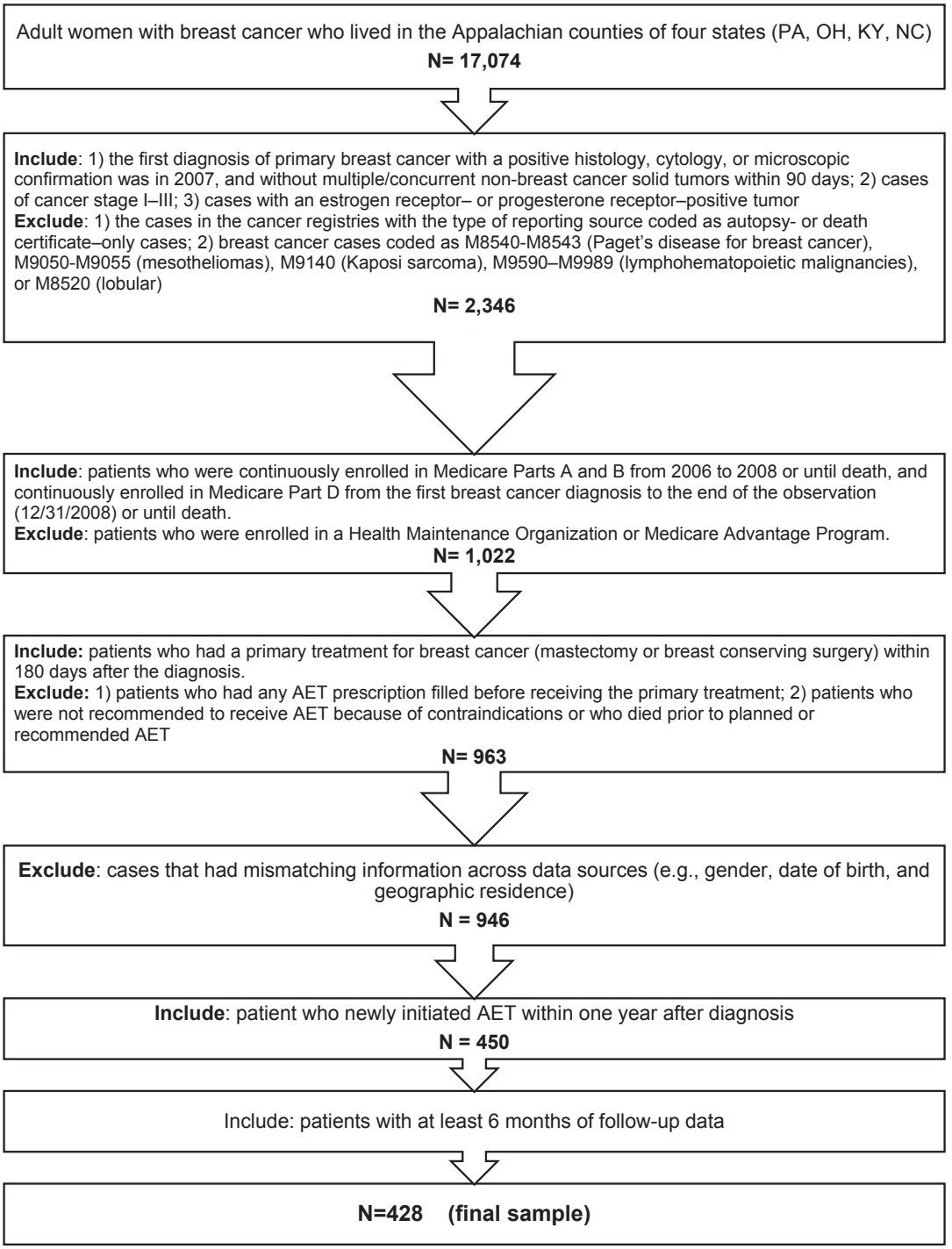

Fig. 1. Flowchart for obtaining the study sample.

breast cancer was excluded; patient's average travel time to the three closest mammography centers (in minutes); patient dual-eligibility for Medicaid and Medicare; and catastrophic coverage indicator (for which patients who had ever reached the out-of-pocket threshold during follow-up were categorized as "yes"). For medication-related factors, we included AET drug classes (tamoxifen, AI, or switching between the two classes), and also utilized the indicators of whether a patient had evidence-based pharmacological treatments (prescription drugs) for AET-associated side effects as a proxy measure for relevant side effects (e.g., osteoporosis and arthralgia).[30-32] Therefore we also included the dummy variables of whether patients used bisphosphonates (zoledronic acid, alendronate, risedronate) or pain medications (opioids, gabapentin, pregabalin).

Statistical analyses

Descriptive analyses were conducted using means for continuous variables as well as for the frequencies and percentages of binary and categorical variables. Geocodes were provided by state registries, and if missing, were calculated from registry-provided patient addresses. The analyses were based on point data, not aggregated data.

In order to identify geographic clustering patterns of AET adherence in aim 1, a hot spot analysis was conducted by evaluating Getis-Ord Gi* statistics,[33] including z-scores and *P* values, for each individual geocoded MPR value. To display a heat map of z-scores, Gi scores (similar to Gi* but omitting the reference point) were additionally estimated on a grid of points which covered the region. Since grid points do not have an MPR value, the calculation of Gi score at each grid point was based on the surrounding sample points with available MPR. At each grid and sample point, the Gi* formula[33,34] required as input the MPR of 428 sample points as well as spatial weights to each point. Weights were chosen to vary according to the inverse to straight line distance, bounded at 1 for close neighbors to avoid unstable values. The choice of appropriate weights may affect the smoothness of the heat map. If weights only incorporate information from surrounding points, hot spots may be unreliable due to small sample sizes, failure of distribution assumptions, and edge effects, among other reasons.[33] On the other hand, if weights incorporate information from distant points without decay, the sensitivity to regional hot spots of the method will be low. To address these conflicting trade-offs, a compromise was made by varying the scale of the inverse decay function (10,25,50,100 miles) and choosing the intermediate map which smoothed local effects but preserved regional variation. After calculating the GI* scores in the grid, the discrete surface was interpolated using Kriging interpolation. Regions with large z-scores indicated clustering of high MPR values (better adherence) compared to the regional mean and appeared as red "hot spots" in the map; regions with blue "cold spots" indicated clustering of low MPR values (poorer adherence). Areas in which MPR values were not significantly different from neighborhood areas were considered as neither hot spots nor cold spots. In addition, spatial autocorrelation was evaluated using Moran's I test for the presence of spatial autocorrelation.

The analysis for aim 2 sought to examine spatial non-stationarity of the relationships between potential predictors and AET adherence, which is equivalent to uncovering whether there were interactions between the predictors and geographical location. We utilized geographically weighted logistic regression (GWLR)[35] in which regression weights can vary as a function of geographical location. A logistic regression was used to study AET adherence (yes/no):

$$logit(p_i) = \sum \beta_j(u_i, v_i)x_{ij},$$

where u_i, v_i are spatial coordinates, p_i is probability of adherence measured as MPR $\geq$ 0.8, x_{ij} is the jth predictor of observation i (including the intercept), and β_j is the corresponding regression weight. A SAS macro developed for GWLR with spatial point data was used to estimate the parameters.[36] The GWLR algorithm proceeds by fitting local regressions at each location: each observation is weighted by a decay function assigning lower weights as a function of increasing distance, based on the hypothesis that observations nearer to each other have a greater influence on each other's parameter estimates compared to observations that are further apart. We examined two decay functions: bi-square and Gaussian.[37] The bandwidth of the decay functions was allowed to vary at each location based on the distance to the n-th nearest neighbor. Since the data was geographically sparse, an adaptive bandwidth was chosen instead of a fixed bandwidth that does not vary by location.[38] An optimal value for n was selected by searching for the minimum value of the corrected Akaike Information

Criteria for finite sample sizes (AICc) to maximize model fit. Furthermore, multicollinearity was examined by assessing local correlations of the non-stationary parameter estimates with other parameter estimates as well as variance inflation factors (VIF) that were calculated at each location and weighted using GWLR weights. The AICc was used to compare model fitting between GWLR and regular logistic regression.

A Monte Carlo simulation[39] was used to further identify those predictors that might impact AET adherence differently across the study region. Firstly, the 428 spatial locations were randomly shuffled at each of 1000 iterations. As in a permutation test, the results from random shuffles would be expected to look similar to those of the real data under the null hypothesis of no spatial variation. Under the null hypothesis of stationarity, the standard deviation of regression weights from the real data should fall within the simulated distribution. A *P*-value can be obtained by comparing the percentile rank of this standard deviation relative to the distribution, and the null hypothesis is rejected if the standard deviation is sufficiently large compared to the distribution. The hypothesis of stationarity was also examined separately by comparing the dispersion of beta weights in the local regressions to the standard error of the regular regression model.

To display variables whose effects were found to be non-stationary, we evaluated local estimates in the form of odds ratios in a detailed grid of points (including the sample points), which covered the region. A raster plot was then created from the grid which produced a heat map of odds ratios displayed along a color ramp. Significant results for the local odds ratios from local tests of significance were displayed as contour, or isolines. We utilized SAS 9.4 for data management and ArcGIS 10.2 (ESRI, Redlands, CA) for geographic data management and analysis. Significance was considered as a *P*-value lower than 0.05 in the regular logistic regression or a non-zero % *P*-value in the geographically weighted logistic regression.

Results

A total of 428 eligible women with an average age of 74.8 years old were included in the study. Table 1shows the basic characteristics of the study sample. The MPR values ranged from 0.06 to 1.20, with a mean of 0.83 and a standard deviation (SD) of 0.24. Only about 69.4% of the population were adherent to AET. Significant bivariate predictors of MPR >0.80 at $\alpha = 0.05$ included having dual status (65.8% yes vs. 78.5% no), having catastrophic coverage (82.3% yes vs. 64.8 no), positive lymph nodes (76.7% yes vs. 66.7% no), and use of pain medications (51.2% yes, vs. 71.4 no).

The heat map for smoothed MPR values shows that most areas in PA and OH have high AET adherence (Fig. 2). MPR values calculated over a circular neighborhoods centered on hot spots identified by Gi* Z-scores (Fig. 3) show an average MPR of 0.68 in the cold spots and 0.92 in the only hot spot, compared to the regional average of 0.83. We found high adherence in most of PA except for low adherence clusters in Erie County, PA. There is also substantial variation in AET adherence in NC, with low adherence clustered in Asheville and surrounding area (including Buncombe, Transylvania, Henderson, and Polk Counties). Moran's *I* test of spatial autocorrelation was statistically significant, suggesting the presence of positive spatial autocorrelation (clustering patterns) of MPR values (Moran's $I = 0.034$, $P < 0.001$) (Table 2).

Table 3 shows the results of GWLR and regular logistic regression of AET adherence. To display the distribution of local GWLR estimates for each variable, the minimum, maximum, and median the spatial distribution of odds ratios are shown in the table. The "% *P*-value" column shows the percent of local regressions among the sample points in which the odds ratios and corresponding regression weights were statistically significant. Variables with a % *P*-value of 0 failed to be statistically predictive in any of the local regressions, whereas variables with a non-zero % *P*-value showed the fraction of sample points where the local regression estimates were statistically significant. In both GWLR and regular models, AET adherence was significantly associated with HPSA designation, catastrophic coverage, AET drug class, and AET-related side effects. Those who lived in a county that was only partially in an HPSA versus completely within an HPSA, had ever reached the out-of-pocket threshold during follow-up, took tamoxifen versus aromatase inhibitors, or did not use pain medications for treating AET-related side effects were more likely to be adherent to AET. Besides these significant factors, results from geographically weighted logistic regression also suggested that those who had dual-eligibility of Medicare and Medicaid had a higher likelihood of adherence compared to those with Medicare only (median odds ratio [OR] = 1.61, % *P*-value = 34%).

Table 1
Characteristics of the study sample ($N = 428$)

Variables	Mean (SD)	MPR ≤ .80	MPR > .80	*P*-value
		$N = 131$	$N = 297$	
Percentage with less than high school diploma among persons aged 25 and over (%)	15.8 (6.6)	15.4 (6.3)	15.9 (6.7)	0.509
Average travel time to the three closest mammography centers (minutes)	15.9 (10.2)	16.5 (10.6)	15.7 (10.1)	0.466
Age at diagnosis	74.8 (8.8)	74.2 (8.4)	75.0 (9.1)	0.383
Baseline Charlson Comorbidity Index (CCI)	0.63 (0.95)	0.54 (0.75)	0.67 (1.02)	0.138
Annual median household income (US dollars)	43.4K (18.2K)	42.9 (17.4)	43.6 (18.6)	0.692
Frequency (%)				
Annual median household income (US dollars), quartile				0.717
Low ($9768–$31,408.5)	107 (25%)	28 (26.2)	79 (73.8)	
Second ($31,408.5–$41,552)	107 (25%)	35 (32.7)	72 (67.3)	
Third ($41,552–$51,577.5)	107 (25%)	34 (31.8)	73 (68.2)	
High ($51,577.5–$15,0625)	107 (25%)	34 (31.8)	73 (68.2)	
Urban-rural classification				0.654
Metropolitan	225 (52.6%)	71 (31.6)	154 (68.4)	
Non-metropolitan	203 (47.4%)	60 (29.6)	143 (70.4)	
Health professional shortage area (HPSA) designation				0.094
Whole county in HPSA	90 (21.0%)	36 (40.0)	54 (60.0)	
Part of county in HPSA	302 (70.6%)	85 (28.2)	217 (71.9)	
Not in HPSA	36 (8.4%)	10 (27.8)	26 (72.2)	
Marital status				0.354
Married	140 (32.7%)	47 (33.6)	93 (66.4)	
Not married	288 (67.3%)	84 (29.2)	204 (70.8)	
Dual Medicare and Medicaid eligibility status				0.010
Yes	121 (28.3%)	26 (21.5)	95 (78.5)	
No	307 (71.7%)	105 (34.2)	202 (65.8)	
Catastrophic coverage indicator				<0.001
Yes	113 (26.4%)	20 (17.7)	93 (82.3)	
No	315 (73.6%)	111 (35.2)	204 (64.8)	
Stage				0.432
Stage I	239 (55.8%)	79 (33.1)	160 (67.0)	
Stage II	149 (34.8%)	42 (28.2)	107 (71.8)	
Stage III	40 (9.4%)	10 (25.0)	30 (75.0)	
Tumor size				0.541
<1 cm	84 (19.6%)	23 (27.4)	61 (72.6)	
1–2 cm	215 (50.2%)	71 (33.0)	144 (67.0)	
>2 cm	129 (30.1%)	37 (28.7)	92 (71.3)	
Positive lymph nodes				0.044
Yes	116 (27.1%)	27 (23.3)	89 (76.7)	
No	312 (72.9%)	104 (33.3)	208 (66.7)	
AET drug class				0.075
Tamoxifen	80 (18.7%)	17 (21.3)	63 (78.8)	
Aromatase inhibitors (AIs)	319 (74.5%)	107 (33.5)	212 (66.5)	
Switching between the two classes	29 (6.8%)	7 (24.1)	22 (75.9)	
Use of bisphosphonates				0.116
Yes	92 (21.5%)	22 (23.9)	70 (76.1)	
No	336 (78.5%)	109 (32.4)	227 (67.6)	
Use of pain medications				<0.006
Yes	43 (10.0%)	21 (48.8)	22 (51.2)	
No	385 (90.0%)	110 (28.6)	275 (71.4)	

Note: The percentages of some variables may not add up to 100% due to rounding errors.

SD = standard deviation, AET = adjuvant endocrine therapy. *P*-values are for chi-square and *t*-test comparison tests between MPR ≤ 0.80, >0.80.

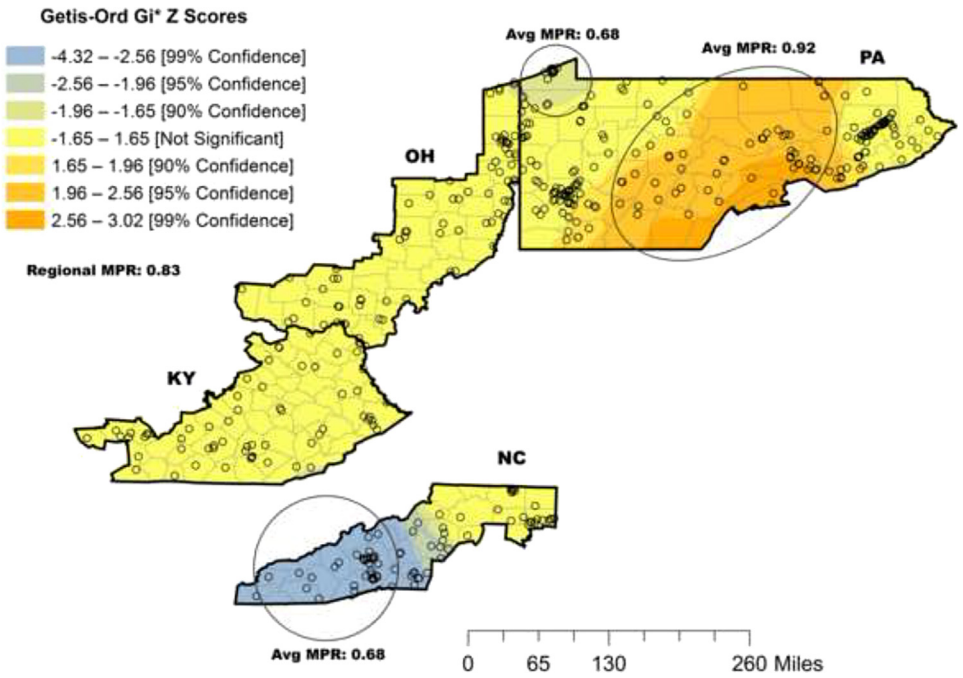

Fig. 2. Hot spot heat map of adherence to adjuvant endocrine therapy (AET) using Gi* scores. Note: Points show geolocation of 428 observations in the sample. Average MPR values are calculated over the points inside the ellipses surrounding the hot and cold spots. Gi* Z-score categories correspond to regions of high statistical confidence (99%, 95%, and 90%).

Geographically weighted logistic regression had a better model fit than the regular logistic regression model (AICc = 517.5 vs. 520.0, respectively), suggesting potential spatial non-stationarity of these associations across the study region. And we found no evidence of multicollinearity in geographically weighted regression.

Table 3 shows standard deviation of the local regression parameter estimates (SD), the results from the Monte Carlo permutation test *P*-value for the GWLR, and the standard errors for the parameter estimates of the global model (SE). Small MC *P*-values (<0.05) resulted in rejecting the hypothesis of stationarity. Significant geographic variations for dual-eligibility status and pain-medication use on AET adherence across the region were observed (Monte Carlo $P = 0.005$ and 0.012, respectively). In all variables except the latter two, the dispersion of local estimates was considerably lower than the SE. Despite dual-eligibility and pain medication being selected as non-stationary, we note that dispersion scores, however, are not larger than the SE. Under gross violations of stationary, it would be expected for the dispersion scores to significantly exceed the SE.

The geographic distribution of odds ratios for non-stationary variables is shown in Figs. 3 and 4. There were larger effects of dual-eligibility status and pain-mediation use on AET adherence in KY and NC compared to PA. Contour lines were added separate regions were local tests of significance had $P < 0.05$ and $P < 0.01$. In the case of pain medication, $P < 0.05$ for all except the easternmost PA section, and $P < 0.01$ for KY, NC, and most of OH. For dual-eligibility, $P < 0.05$ for KY, NC, and parts of OH.

Moran's I test for spatial autocorrelation detected a significant clustering of those with dual-eligibility of Medicare and Medicaid in KY (Moran's $I = 0.073$, $P < 0.001$). The test also identified notable clusters of the whole county in HPSA in NC, and part of the county in HPSA in most of PA. But no significant clustering for catastrophic coverage or the use of pain medication as a proxy measure of AET-related side effects was found.

Interestingly, it was found that the intercept in the GWLR, which is also allowed to vary spatially, was not found to be non-stationary (MC *P*-value = 0.335). This suggests that, after adjusting for the covariates in this model, no significant

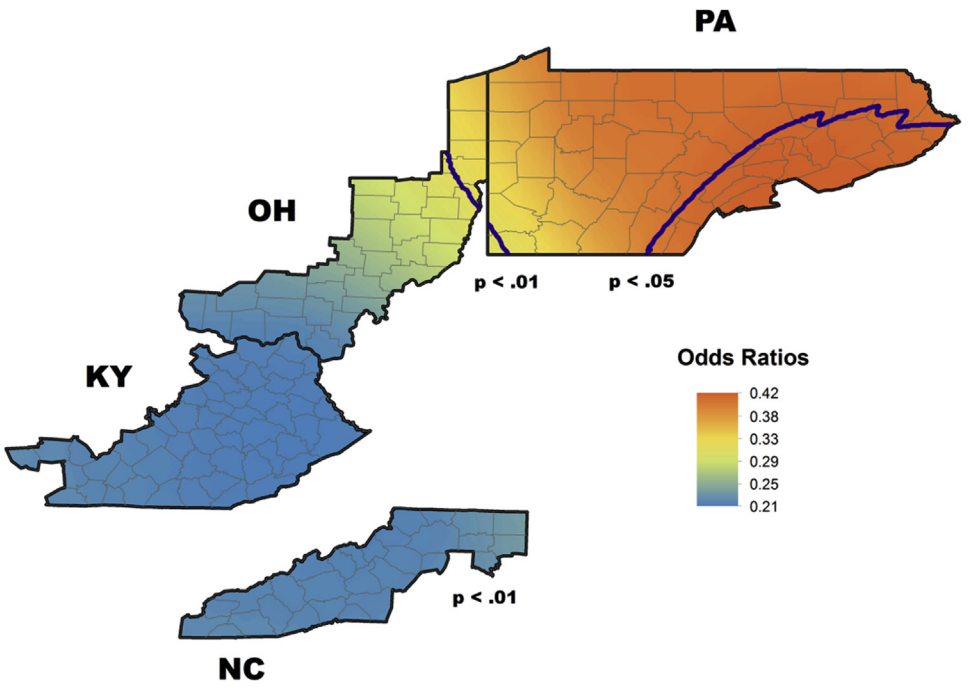

Fig. 3. Geographic distribution of odds ratios of the use of pain medication for treating AET-related side effects in the GWLR of AET adherence. Note: Heat map evaluates local odds ratios for pain medication on AET (comparing local prediction for pain medications vs. no pain medication utilization). Contour lines separate regions were significance test for local odds ratios had a $P < 0.05$ (All except parts of PA) and $P < 0.01$ (KY,NC, and most of OH). Significant regions have smaller odds ratios indicating pain medication user are increasingly less likely to be adherent compared to non-users. All regions had OR <1 (with mininum at 0.21 and maximum at 0.42).

residual variation due to unmeasured spatially varying factors is detectable. On the other hand, an unadjusted GWLR null model with only spatially varying intercept yields an MC P-value <0.001, suggesting the presence of regional variation and compatible with the findings from the heat map (Fig. 2).

Discussion

Patient adherence to AET is essential to maximize its significant benefits in cancer outcomes for HR-positive breast cancer survivors; therefore disparities in AET adherence may partly contribute to the disparities in breast cancer outcomes including mortality. Appalachia has experienced substantial cancer disparities over the years. In this study, we used innovative geographic analytic tools and a unique dataset linking Medicare claims with cancer registries from four Appalachian states (PA, OH, KY, and NC) to identify disparities within disparities — geographic disparities in AET adherence in Appalachia. Our findings can help provide more precisely targeted local information that may be used to improve adjuvant therapy use and cancer care in Appalachia.

From the heat map and hot spot analysis of AET adherence, we can see significant geographic variations in AET adherence in our study region. Overall, breast cancer patients living in PA and OH show higher adherence to AET than those living in KY and NC. The geographic distribution of adherence to antidiabetics, antihypertensives, and antilipidemics in the US Medicare population also seem to follow similar trends in these areas.[12] Kimmick et al (2014) also found that Pennsylvanians with breast cancer were more likely to receive guideline-recommended endocrine therapy, chemotherapy, and radiation therapy than those patients residing in North Carolina.[26]

In addition, our study identified significant disparities in AET adherence within PA and NC: most of PA had good adherence except the Erie area, while most of NC had poor adherence. There may be

Table 2
Results from GWLR and regular logistic regression predicting adherence to adjuvant endocrine therapy (AET)

Variable	Distribution of GWLR local estimates AICc = 517.5				Regular logistic regression AICc = 520.0
	Minimum OR	Median OR	Maximum OR	% *P*-value[§§]	OR[§]
Percentage with less than high school diploma among persons aged 25 and over	1.02	1.03	1.03	0%	1.02
Metropolitan (yes/no)	0.81	0.90	1.00	0%	0.87
Health professional shortage area (HPSA) designation					
Entirely within an HPSA	0.49	0.54	0.61	22%	0.52*
Partly within an HPSA	Reference				
Not within an HPSA	0.84	0.88	0.93	0%	0.90
Annual median household income					
Low ($9768–$31,408.5)	0.81	0.94	1.20	0%	1.08
Second ($31,408.5–$41,552)	0.74	0.85	0.95	0%	0.89
Third ($41,552–$51,577.5)	0.76	0.89	0.96	0%	0.96
High ($51,577.5–$15,0625)	Reference				
Average travel time to the three closest mammography centers (minutes)	0.97	0.98	0.98	0%	0.98
Age	1.01	1.01	1.02	0%	1.01
Marital status (yes/no)	0.97	1.03	1.17	0%	1.06
Baseline Charlson Comorbidity Index (CCI)	1.03	1.03	1.08	0%	1.04
Dual-eligibility (yes/no)	1.27	1.61	2.67	34%	1.71
Breast cancer stage					
Stage I	0.83	1.05	1.32	0%	1.21
Stage II	0.91	1.02	1.27	0%	1.11
Stage III	Reference				
Positive lymph nodes (yes/no)	1.29	1.59	1.95	0%	1.72
Catastrophic coverage (yes/no)	2.68	2.85	3.03	100%	2.76**
Adjuvant endocrine therapy (AET) class					
Aromatase inhibitors	Reference				
Tamoxifen	2.07	2.29	3.15	93%	2.68**
Switching between the two classes	1.26	1.59	1.91	0%	1.62
AET-related side effects					
Use of bisphosphonates (yes/no)	1.30	1.41	1.88	0%	1.52
Use of pain medication (yes/no)	0.21	0.34	0.42	81%	0.30**

Note: [§] OR = odds ratios = exp (regression weight). [§§] "% *P*-value" shows the percent of local regression estimates in which the OR and regression weights was significant. The bandwidth selection procedure using AIC criterion for the GWLR was set as 279 nearest neighbors with Gaussian decay function.

*$P < 0.05$, **$P < 0.01$.

some explanations for the geographic variations in AET adherence in our study region, such as community socioeconomic status (not merely measuring income); transportation (e.g., whether the patient has a private car); and geographic access to medications (e.g., travel distance to the nearest pharmacy, pharmacy density in the area, type of pharmacy, and medication stock).[40,41]

In this study, by using geographically weighted logistic regression, we found that AET adherence was primarily related to medication-related factors (e.g., AET drug class, adverse drug effects), cost-related issues (e.g., catastrophic coverage indicator, dual-eligibility of Medicare and Medicaid), and access to care (e.g., health provider resources). Besides the first two individual aspects, which were

Table 3
Variation of GWLR estimates and standard errors

Variable	GWLR		Regular logistic regression
	Standard deviation of local regression weights (SD)	Monte Carlo *P*-value	Global standard error (SE)
Percentage with less than high school diploma among persons aged 25 and over	0.00	0.709	0.02
Metropolitan (yes/no)	0.07	0.482	0.30
Health professional shortage area (HPSA) designation			
Entirely within an HPSA	0.06	0.526	0.30
Partly within an HPSA	Reference		
Not within an HPSA	0.02	0.982	0.43
Annual median household income			
Low ($9768–$31,408.5)	0.14	0.188	0.35
Second ($31,408.5–$41,552)	0.08	0.412	0.33
Third ($41,552–$51,577.5)	0.09	0.380	0.32
High ($51,577.5–$15,0625)	Reference		
Average travel time to the three closest mammography centers (minutes)	0.00	0.780	0.01
Age	0.00	0.994	0.01
Marital status (yes/no)	0.06	0.392	0.26
Baseline Charlson Comorbidity Index (CCI)	0.02	0.727	0.13
Dual-eligibility (yes/no)	0.26	0.005	0.32
Breast cancer stage			
Stage I	0.14	0.498	0.57
Stage II	0.12	0.465	0.48
Stage III	Reference		
Positive lymph nodes (yes/no)	0.11	0.388	0.39
Catastrophic coverage (yes/no)	0.04	0.825	0.32
Adjuvant endocrine therapy (AET) class			
Aromatase inhibitors	Reference		
Tamoxifen	0.15	0.101	0.32
Switching between the two classes	0.13	0.383	0.47
AET-related side effects			
Use of bisphosphonates (yes/no)	0.14	0.071	0.29
Use of pain medication (yes/no)	0.27	0.012	0.38

Note: SD = standard deviation of logistic regression beta weights; SE = standard error of global model assuming equality of parameters; MC *P*-value = stationarity test *P*-value from Monte Carlo Simulation.

consistent with existing literature,[5,8–10] this study also contributes evidence on the influences of community-level characteristics or geographic aspects on AET adherence, particularly in poor and underserved regions like Appalachia. We found that persons living in a county that belonged, to a larger degree, in a health professional shortage area were less likely to adhere to AET. As discussed above, this relationship may, to a large extent, explain why persons with better AET adherence cluster in most of PA while those with poorer adherence cluster in NC: in NC, there are notable clusters of areas in which the whole county is in an HPSA, while in most of PA, only part of each county is in an HPSA. Not only patient access to care but also the quality of care in these HPSAs may impact patient use of these potentially life-saving drugs.

In addition, the extent to which Medicaid/Medicare dual-eligibility and the use of pain medications for AET-associated musculoskeletal pain influence AET adherence may vary across the Appalachian states in our study. We speculate that these variations may be partly due to differences in health policy and clinical practice.

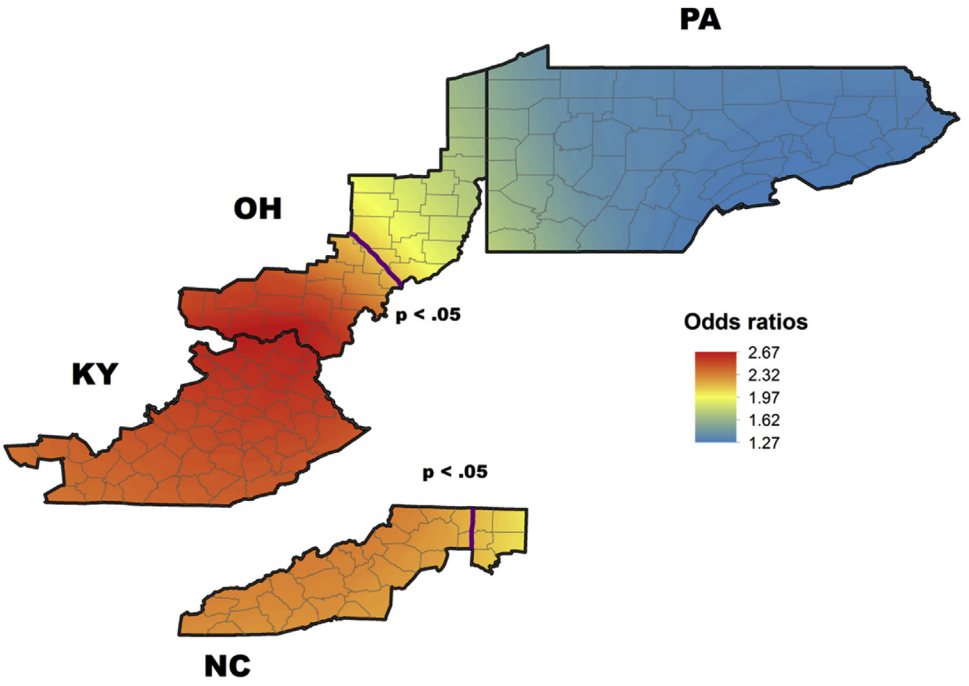

Fig. 4. Geographic distribution of odds ratios of dual-eligibility of Medicaid and Medicare in the GWLR of AET adherence. Note: Heat map evaluates local odds ratios for dual-eligibility on AET (comparing local prediction for dual eligbility vs. no dual-eligibility). Contour line separates region were significance test for local odds ratios had a $P < 0.05$ (KY, NC, and parts of OH). Significant regions indicating larger effect of dual-eligibility on adherence. All regions had OR >1 (with mininum at 1.27 and maximum at 2.67).

Although dual-eligible beneficiaries are generally more vulnerable in health, with more chronic and severe health conditions, and more economically distressed,[42] they are entitled to several additional health benefits such as automatic enrollment in Part D drug plans and no monthly premium or deductibles. Many states' Medicaid programs also help with copayments or out-of-pocket costs for drugs that are not included in the Medicare Part D formulary. These differences in health benefits may mitigate patients' financial burdens and difficulties with access to medications and drug utilization. Therefore, the impact of dual-eligibility status on AET adherence may be more pronounced in economically distressed areas. But the variations of the impact may be diminished with the progress of current healthcare reform including policies to gradually close Medicare Part D donut hole and expand Medicaid coverage. In addition, the lack of continuous medication management services for cancer survivors or lack of seamless care transition from specialty care to primary care in these underserved areas may also influence patient adherence to AET in a long run.

Our findings should be considered in the context of several limitations. First, pharmacy claims data may not always accurately represent patients' actual medication-taking behavior; it may also miss those patients who paid cash to get their prescriptions. These factors may bias our estimations of the receipt of AET and AET adherence. Second, given the limited data availability and accessibility, our study lacked some detailed information such as prescribers' information, treatment facility location, accurate drug indications, and pharmacy type, factors that we leave to future research. Third, we only used proxy measures of AET-related adverse effects such as musculoskeletal pain, which may lead to measurement bias. Fourth, GWLR is still a relative new methodology in the medical fields and is evolving, especially when applied to spatial variability in medication adherence and associated factors. It involves some challenges and issues that are still being debated, such as multicollinearity, kernel bandwidth

selection, multiple hypothesis testing, and model misspecification,[43-46] which may increase the likelihood of false-positive conclusions of non-stationarity in the parameter estimates. Fifth, the data we used from 2006 to 2008 may not reflect the most current situation in this population. Also given the impact of currently ongoing reform in the US on Medicare Part D policy, cost-associated non-adherence may be alleviated to some extent as a whole in recent years, which may warrant future temporal and geographic analysis to evaluate these influences on AET adherence across different areas. Lastly, the generalization of our results may be limited to initial oral AET use among elderly Appalachian women with invasive, non-metastatic, HR-positive breast cancer. We did not include those who used endocrine therapy as a primary treatment (rather than surgery) or those who used ovarian suppression. Our population was also generally older than the typical breast cancer patient population; therefore, caution should be used when generalizing the results to other populations.

Conclusions

This study is among the first to demonstrate the utility and feasibility of using geographic techniques as a tool to account for geographic variations and neighborhood effects on medication adherence and its predictors in a specified region. It explored specific geographic areas in Appalachia with poor AET adherence as well as geographically varying effects of predictors on AET adherence, which may help direct future research, policy, and interventions to focus on these high-risk areas and communities.

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