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Racial and Geographic Disparities in Endocrine Therapy Adherence Among Younger Breast Cancer Survivors

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Abstract

Objectives: African American (AA) women with breast cancer (BrCA) have higher mortality than any other race. Differential mortality has been attributed to non-adherence to endocrine therapy (ET). ET can lower the risk of dying by one-third; yet 50 to 75% of all women are nonadherent to ET. Despite the wealth of research examining adherence to ET, understanding which groups of women at risk for poor adherence is not well-established. The aim of this investigation was to describe endocrine therapy (ET) adherence by race and geographic location among a cohort of younger BrCA survivors.

Methods: Cancer registry records were linked to administrative data from Medicaid and a private insurance plan in South Carolina. Inclusion criteria included: European-American (EA) or AA race, three years of continuous enrollment in the insurance plan after diagnosis, and breast cancer diagnosis between 2002 and 2010. Adherence was measured by computing a medication possession ratio (MPR) based upon refill service dates and the number of pills dispensed. Adjusted least squared means were calculated by racial and geographic group using ANACOVA methods.

RESULTS: The average MPR for EA women was significantly higher at 96% compared to 92% for AA women ($p<0.01$). After adjustment for years on hormone therapy, age, and number of pharmacies utilized, rural AA women had an average MPR of 90% compared to 95% for EA women ($p<0.01$).

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CONCLUSION: AA women residing in rural areas demonstrate significantly lower adherence compared to their EA counterparts. Interventions are needed to improve adherence which may ameliorate AA mortality disparities.

Keywords

Breast Cancer; Endocrine Therapy; Adherence; African American; Rural

Introduction

In 2020, 276,480 women will be diagnosed in the US with breast cancer, the most common cancer diagnosed in women and 42,170 women will die from the disease.{American Cancer Society, 2020 #5464} Incidence of breast cancer (BrCA) in European American (EA) and African American (AA) women has recently converged to equal rates. Based on SEER data from 1989 to 2015, mortality due to breast cancer in EA and AA women has significantly declined[2] which has been attributed to earlier detection and better treatment of BrCA. However, researchers using non-SEER data (MI and entire US) have not found similar declining mortality rates.[3,4] In fact, AA women have greater BrCA mortality than any other race.[5] This difference may be due to the fact that only 13 states or territories in the US report to SEER. Differential mortality has been attributed to biological factors, health disparities, and non-adherence to endocrine therapy (ET), the most common oral anti-cancer therapy for women with BrCA.[6]

Women with hormone positive breast cancer are initially prescribed ET to reduce the likelihood of recurrence but later may receive it for metastatic disease.[7,8] About two-thirds of all BrCA's are hormone receptor positive.[9] ET, the recommended adjunct treatment for hormone-receptor positive BrCA can reduce recurrence by 40% and lower the risk of dying by one-third.[9] Alarmingly, 50 to 75% of all women are nonadherent to their ET prescription.[10–14] Adherence is defined as maintenance of recommended therapy throughout a specified time period.[15] Despite the wealth of research examining adherence to ET, understanding which groups of women at risk for poor adherence is still not well-establshed.[6,7,13,16,17] For example, Reeder-Hayes et al. found 17% worse adherence in AA women than EA women.[17] More recently, Kesmodel et al. reported higher adherence to aromatase inhibitors was more likely in EA women compared with AA women (estimated odds ratio=2.8).[18] Since ET continues for up to ten years, understanding adherence differences between AA and EA women is vital.[12,19] A weakness in previous research on ET adherence is both a lack of heterogeneous (geographically, economically, and racially) cohorts and reliable reporting on cancer treatment.[20] Few, if any studies, have been conducted combining the strengths of a claims-based data system reflective of high-risk subgroups and a central cancer registry in a cohort of patients under the age of 65 years.

Our cohort of women with BrCA originates from South Carolina. Nationally and in South Carolina (SC), mortality remains higher among AA women with BrCA than other racial/ethnic groups despite lower incidence.[21] AA women in SC have a 55% higher mortality-to-incidence ratio than EA women.[22] Several additional factors make the examination of a SC cohort that includes younger EA and AA women important. Almost half (42%) of AA

women in SC live in rural areas with limited access to cancer care.[23,24] Approximately, 16% of working EA and AA women ages 18 to 64 have incomes below the federal poverty line.[25] These barriers[2] are known to be associated with poor adherence making SC an ideal setting to examine ET adherence and compare ethnic and geographical differences. Thus, our purpose was to describe and compare the association of race and rurality with ET adherence among younger breast cancer survivors.

Materials and Methods

Design and Population

This retrospective cohort investigation utilized data from a larger study, A Geospatial Investigation of Breast Cancer (1R15CA179355–01A1). We combined administrative claims data from South Carolina's Medicaid Program and a state-based, private payor health plan to data on matching BrCA cases from the South Carolina Central Cancer Registry (SCCCR). Probabilistic matching procedures were utilized to match three personal identifiers including name, date of birth, and social security number. By combining these claims-based datasets with tumor-specific information from the SCCCR, we were able to capitalize upon the richness of data contained within each individual database. This linkage created a cohort of AA and EA women (< 65 years of age since Medicare was not included) with complete screening, treatment, and mortality information including all medical procedures, co-morbid conditions, prescriptions, and corresponding dates of service across the cancer continuum. Our uniquely formed cohort provided a comprehensive overview of the medical history of each participant so that we could fully describe ET adherence and compare EA and AA adherence. The total number of prescription records in the cohort was 1,594,767.

Inclusion criteria for the study included 'AA' or 'EA' race (derived from SCCCR which utilizes North American Association of Central Cancer Registries (NAACCR) coding standards); Medicaid or the state-based private payor designated as primary payor source; and diagnosed with a first primary, histopathologically-confirmed female breast cancer between 2002 to 2010 identified from the SCCCR with a corresponding record in the Medicaid or private payor database. Additionally, the final cohort only included those cases with 36 months (N=2155) of continuous insurance program eligibility post BrCA diagnosis. This allowed us to eliminate bias from misclassification due to lack of treatment information (e.g. services were received while covered by other insurance programs). Cases were excluded if there was a history of a previous cancer other than basal cell or squamous cell of the skin.

Measures

For measures of race and geographic location utilized in the analyses, we used data derived from the SCCCR patient record. Race was based on patient self-report, recorded by the healthcare provider, and abstracted by the SCCCR. For geographic location, we used urban and rural designations derived from Rural-Urban Commuting Area Codes (RUCA) codes at the census tract level, which was based upon the geocoded residential address at the time of diagnosis contained within the SCCCR.

All hormonal treatment data were derived from administrative claims data contained within the private payor or Medicaid files. There are two classifications of oral agents for ET: selective estrogen receptor modulators (SERMS) and aromatase inhibitors (AIs). The SERMs we included were tamoxifen, toremifene and raloxifene; the AI's included anastrozole, letrozole, and exemestane. Megestrol acetate is an endocrine metabolic agent used for some hormone suppression. Other intravenous or intramuscular agents are also available but given their alternative indication for non-ET purposes, megestrol and other non-oral agents were not included in this analysis. Cases were excluded if they did not have at least two drug records for endocrine therapy (final N=1532). Based upon standardized drug codes found within the private payor and Medicaid files, we created a variable for hormonal treatment (yes/no). In addition, we utilized dates of service to compute days between diagnosis and first recorded treatment for days until first hormonal treatment). Finally, we created variables to assess the number of recorded hormonal therapy treatments.

Institutional Review Board

This research project was reviewed and ultimately exempt from the Institutional Review Board (IRB) by the primary research site, the University of South Carolina in Columbia, South Carolina since all data utilized for this investigation were de-identified for security and privacy purposes. Further, the data were blinded to specific insurance type due to data use agreements. The key to the dataset was retained by the data providers in the event that further data clarification was needed from the primary record. For data use agreements, additional IRB oversight was required from the Department of Health and Environmental Control, which serves as the IRB for datasets described below.

Analysis—SAS version 9.4 (Cary, NC) was used for all data management and statistical analyses. After the de-identified data were received, the study data manager performed routine outlier and logic checks. Any improbable values were verified with the data providers and rectified where possible. If no resolution was possible, the observation was set to missing. We did not detect any pattern in this occurrence, therefore, we considered this random. According to the ISPOR definition of adherence, we operationalized adherence as the interval between refills. The medication possession ratio (MPR) calculation was adapted from formulas reported by Hess and et al.[26]

$$\frac{\text{Total days supply in ET refill period}}{\text{Number of days in between service dates of ET refills}}$$

Previous methods for the MPR have defined the denominator as the difference between the last claim date and the first claim date. Our adapted version allowed us to take into consideration multiple medications and variations in the total amount of pills dispensed for each individual medication. Each individual MPR was calculated using the number of pills in an individual medication divided by the difference between the time of previous and current dispensation of that individual medication. Multiple MPRs were then generated for each medication refill dispensed for the individual. These MPRs were averaged over the duration of their observation period to derive a summary average for each BrCA case.

Descriptive statistics including frequencies and means were computed as appropriate for the cohort using SAS version 9.4. T-tests and chi-square test were used to compare these statistics by race. An analysis of variance (ANACOVA) was used to compare adjusted least square means by race and geographic location (rurality). The PROC GLM procedure was used to compute crude and adjusted MPRs. Confounding and effect modification were explored for age, grade, stage, geographic location, marital status, diagnosis year, number of pharmacies utilized, and insurance type. Only those variables which demonstrated a p-value less than 0.05 were kept in the final adjusted model. An alpha level of 0.05 was used to determine statistical significance. Due to a priori hypothesized effect modification of race by demographic variables, we used a less conservative alpha level of 0.20 for exploring statistical interaction[27] in initial exploratory models. Adequate adherence was defined as an MPR of 80 %.[28–32]

Results

The demographic characteristics of the cohort by race are shown in Table 1. Approximately 25% of the cohort was AA. Compared to AA women, EA women were significantly older at diagnosis, had lower grade disease, and were on ET for slightly longer time periods. Also, EA women were more likely to live in urban areas, be married and used fewer pharmacies, in comparison to their AA counterparts. EA women had a significantly higher MPR compared to AA women (96% vs 92%, $p<0.01$). Further, AA women had significantly different estrogen receptor negative status and progesterone receptor negative status than EA women. PR Table 2 compares cohort demographics by adherence (≥ 80%). Adherent women were more likely to be older, married, use fewer pharmacies, and have shorter number of years on ET.

Average MPRs by race are displayed in Table 3. Both geographic location and insurance type were significantly associated with racial differences in MPR. Among both urban and rural dwelling women, AA women had significantly lower MPRs compared to EA women with rural AA women having a lower average of 91%. AA women had significantly lower MPR than EA women among one insurance type, but not the other and the insurance group with significant differences (Type 1) had higher MPRs for both racial groups compared to the other insurance type.

Crude and adjusted MPRs are shown in Table 4. Even after adjusting for years of endocrine therapy, age, and number of pharmacies utilized, AA women had a lower average MPR compared to EA women (92% vs 94%, $p<0.01$). Since rurality of the patient's residence proved to significantly interact with race ($p=0.07$), we stratified our models by urban vs. rural residence. After adjusting for years of endocrine therapy, age, and number of pharmacies, AA women residing in rural census tracts had a significantly lower average MPR compared to EA women, 91% vs 95%, $p<0.01$.

Because our adherence rates were much higher than usually reported in the literature,[10–14] we completed further analysis of the dataset. In imputed analysis,[33] we assigned an MPR of 0 if the women in the cohort only had one prescription in the database because our computations for MPR required two prescriptions. In this case, the overall MPR dropped to

91%. EA women had significantly lower MPR, 86% vs. 91%, p<0.01. Further, we identified those women who were not prescribed ET but were ET-positive which is not concordant with current treatment guidelines. For those women, we assigned an MPR of 0; the population average MPR decreased further with AA women having the worse adherence. See Table 5 for details.

Discussion

Our unique study used the entire population of women in SC who were diagnosed with breast cancer and insured by Medicaid or a private payor combined with Cancer Registry data focused exclusively on women younger than 65. Our study is unlike the vast majority of studies on adherence which used single data sources such as Medicaid or Medicare data sources.[34] We demonstrated statistically significant differences in adherence to ET between EA and AA women, with AA women having poorer adherence than their EA counterparts. Further, we identified rural-urban differences in adherence, with lower adherence rates among women living in rural versus urban areas. This finding was particularly true for AA women. These findings are particularly important in that treatment adherence is poorly studied in disparities health services research.[35]

Given the robustness of our analysis, our findings strongly substantiate adherence differences between AA and EA women and adds depth to the state of the science.[166] While these differences were statistically significant, the differences themselves may appear small. We note that AA women had significantly higher grade disease than EA women which may be an important prognostic factor,[36] and small differences in adherence are clinically significant. Our findings indicate a strong need for interventions to improve adherence in AA women with BrCA. Furthermore, our results indicate certain sub-populations (rural, AAs) who should be targeted for intervention. However, the majority of AA women in our study were ER positive which points to the critical importance of emphasizing adherence to these AA women. Further, more research into the clinical significance of these differences is greatly needed to improve survival in AA women with BrCA.

Rural-urban differences may be due to pharmacy deserts, which are usually associated with inner cities or may be related to financial contraints.[37–39] However, all counties in SC have some medically underserved areas and 65 % are completely medically underserved.[40] Women in urban areas may have better access to multiple pharmacies where comparison price shopping is possible whereas rural women may be limited by lack of transportation and choice of pharmacy. Further analyses of our data indicate that rural residing women were more likely to go to a single pharmacy compared to women residing in urban areas. Therefore, more work should be done to determine if the relationship with pharmacists in a single pharmacy enhance adherence or if rural women have limited financial choices which impact adherence.

The statistically significant disparities noted for adherence for one insurance type, but not noted for the other type, is particularly interesting. One could hypothesize that socioeconomic status may be driving some of this association even when plan coverage is standardized and recipients are paying identical co-payments. Combined with the fact that

no significant differences were noted in the other plan, these findings provide indirect evidence that differences in biological processing and side effect experiences may not be driving these adherence patterns.

Our findings are particularly significant as our data were derived from women across an entire state, with diverse socio-economic situations (Medicaid and private insurance). Even those women on private insurance were socio-economically diverse. Furthermore, the private our data encompassed their entire cancer medical history. To our knowledge, this is the first study that utilized combined data into such a comprehensive dataset of women under the age of 65. Given that the only publicly available registry-administrative data source only includes women 65 or older and that racial disparities for AA women are more burdensome for younger women, the importance of our findings are further underscored.

Our findings may be particularly informative for providers that serve rural residents and demonstrate the need for additional support of their AA patients. Based upon our results, health insurance coverage alone does not guarantee adherence. Having a conversation with their patients about concerns about their medications or barriers to taking their medication may help to improve adherence. There may also be a role for patient navigation as health care navigators can direct patients to additional financial resources or special programs able to offer assistance, which may be needed. Regardless, additional research is needed to fully understand what may be driving or inhibiting adherence from both the patients' and providers' perspectives.

A limitation of the study is that we did not have women enrolled in Medicare that may have eliminated some cases when women transitioned to Medicare coverage. Additionally, we may have not fully captured women who were dually eligible for Medicare and Medicaid after Medicare regulations changed to Part D for prescriptions rather than Medicaid.[41] Further, our sample does not provide any information on women who were prescribed hormonal therapy but never initiated it. In our sample, the mean MPR was quite high suggesting overall good adherence within the period studied. However, since three years of continuous enrollment may not give the full picture of adherence to endocrine therapy since guideline-concordant care recommends five to ten years of treatment.[42] Another study limitation is that the use of MPR as an adherence measure does not account for over-adherence, e.g. prescriptions may be refilled up to a week before all medication has been taken.[43] Further, the study did not account for switching from one hormonal therapy to another drug. Another limitation is the lack of clinical data such as side effects since we were using cancer registry data linked with administrative claims data.

At first glance, the time period captured in the data (2002–2013; including 3 years of treatment data) may be considered limiting; however, it should be pointed out that mandated state reporting of cancer cases is lagged by 3 years. Additionally, it is an intensive administrative and data management effort to link data sources owned by different state or federal agencies. For example, as of January 2020, only cancer cases through 2015 were included with an additional year of medical claims data are available for the SEER-Medicare linked cohort. Consequently, the 11 years of complete record data comprises a strength of our study.

In conclusion, our findings provide strong evidence for persistent racial disparities in breast cancer treatment for younger AA women. Those living in rural areas appear to be particularly at risk for non-adherence. As there is a strong relationship between treatment adherence and survival.[7,44,45] these results may partially explain the mortality disparities also experience by AA women.

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Table 1.

Descriptive statistics for breast cancer cohort by race, 2002–2010.

Variable	European American (n = 1142) Mean±SD/n(%)	African American (n = 390) Mean±SD/n(%)	P-value
Age (years)	52 ± 7	51 ± 7	**<.01**
Grade			
Grade I	252 (24.3)	78 (21.5)	**<.01**
Grade II	497 (47.9)	140 (38.6)	
Grade III/IV	289 (27.8)	145 (39.9)	
Stage			
In-situ	181 (16.0)	82 (21.1)	0.07
Local	550 (48.5)	176 (45.4)	
Regional/Distant	404 (35.5)	130 (33.5)	
ER Status			
Positive	689 (78.8)	210 (66.5)	**<0.01**
Negative	185 (21.2)	106 (33.5)	
PR Status			
Positive	594 (68.2)	174 (55.4)	**<0.01**
Negative	277 (31.8)	140 (44.6)	
Geographic location			
Rural	237 (20.8)	134 (34.4)	**<.01**
Urban	905 (79.2)	256 (65.6)	
Marital Status			
Married	755 (66.1)	151 (38.7)	**<.01**
Single	387 (33.9)	239 (61.3)	
Diagnosis Year			
2002 – 2004	339 (29.7)	104 (26.7)	**0.02**
2005 – 2007	377 (33.0)	110 (28.2)	
2008 – 2010	426 (37.3)	176 (45.1)	
Number of Pharmacies			
1	938 (82.1)	289 (74.1)	**0.01**
2	64 (5.6)	30 (7.7)	
3	58 (5.1)	31 (7.9)	
4+	82 (7.2)	40 (10.3)	
Insurance Type			
Type I	922 (80.7)	226 (58.0)	**<.01**
Type II	220 (19.3)	164 (42.0)	
Years on HT	2.2 ± 0.7	2.1 ± 0.7	**<.01**
Average MPR	0.958 ± 0.117	0.925 ± 0.155	**<.01**
Median MPR	0.929 ± 0.133	0.874 ± 0.191	**<.01**

Table 2.

Descriptive Statistics by Adherence Classification (<80% vs. ≥ 80%), 2002–2010.

Variable	Adherent N = 1392	Non-adherent N = 140	P-value
Age (years)	52 ± 7	48 ± 8	<.010
Grade			
Grade I	304 (23.8)	26 (21.3)	0.17
Grade II	588 (45.9)	49 (40.2)	
Grade III/IV	387 (30.3)	47 (38.5)	
Stage			
In-situ	230 (16.6)	33 (23.7)	0.10
Local	663 (47.9)	63 (45.4)	
Regional/Distant	491 (35.5)	43 (30.9)	
Geographic location			
Rural	335 (24.1)	36 (25.7)	0.66
Urban	1057 (75.9)	104 (74.3)	
Marital Status			
Married	839 (60.3)	67 (47.9)	0.01
Single	553 (39.7)	73 (52.1)	
Diagnosis Year			
2002 – 2004	408 (29.3)	35 (25.0)	0.55
2005 – 2007	441 (31.7)	46 (32.9)	
2008 – 2010	543 (39.0)	59 (42.1)	
Number of Pharmacies			
1	1127 (81.0)	100 (71.4)	<0.01
2	88 (6.3)	6 (4.3)	
3	80 (5.7)	9 (6.4)	
4+	97 (7.0)	25 (17.9)	
Years on HT	1.082 ± 0.976	2.315 ± 0.604	<0.01

Table 3.

Average medication possession ratio (MPR) by demographic characteristics, 2002–2010.

Variable	N	Mean ± SD	p-value
Stratum-specific results			
Urban			
European American	867	0.957 ± 0.119	0.02
African American	239	0.934 ± 0.149	
Rural			
European American	233	0.962 ± 0.105	<0.01
African American	124	0.908 ± 0.165	
Insurance Type 1			
European American	892	0.965 ± 0.113	<0.01
African American	213	0.935 ± 0.145	
Insurance Type 2			
European American	208	0.929 ± 0.125	0.28
African American	150	0.911 ± 0.167	

Table 4.

Crude and adjusted MPR's by race and rural/urban status, 2002–2008.

Race	Unadjusted MPR	p-value	Adjusted* MPR	p-value
European American	0.958	<0.01	0.943	<0.01
African American	0.925		0.918	
Stratum-specific results				
Urban				
European American	0.957	0.01	0.941	0.09
African American	0.934		0.926	
Rural				
European American	0.962	<0.01	0.947	<0.01
African American	0.908		0.905	

*Adjusted for years of hormone therapy, age, and number of pharmacies utilized.

Table 5.

Imputed MPR comparisons for single prescription or no prescription in estrogen positive women

	Original MPR Mean± SD (N=1463)	**p-value**	**Imputed MPR (including those with 1 Rx) Mean± SD (N=1525)**	**p-value**	**Imputed MPR (including those who should have received) Mean± SD (N=1645)**	**p-value**
Overall	0.95 ± 0.13	NA	0.91 ± 0.25	NA	0.84 ± 0.32	NA
Race						
EA	0.96 ± 0.12	<0.01	0.93 ± 0.20	<0.01	0.86 ± 0.31	<0.01
AA	0.92 ± 0.15		0.86 ± 0.28		0.80 ± 0.35	
Geography						
Rural	0.94 ± 0.13	0.34	0.91 ± 0.21	0.94	0.88 ± 0.26	0.03
Urban	0.95 ± 0.13		0.91 ± 0.23		0.84 ± 0.33	
Rural						
EA	0.96 ± 0.11	<0.01	0.95 ± 0.13	<0.01	0.93 ± 0.20	<0.01
AA	0.91 ± 0.16		0.83 ± 0.30		0.79 ± 0.34	
Urban						
EA	0.96 ± 0.12	<0.01	0.92 ± 0.21	<0.01	0.85 ± 0.32	0.02
AA	0.93 ± 0.15		0.87 ± 0.27		0.80 ± 0.35	