Adherence to Adjuvant Endocrine Therapy in Insured Black and White Breast Cancer Survivors: Exploring Adherence Measures in Patient Data

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ABSTRACT

BACKGROUND: Adjuvant endocrine therapy (AET) is a critical therapy in that it improves survival in women with hormone receptor-positive (HR+) breast cancer (BC), but adherence to AET is suboptimal. The purpose of this study was to fill scientific gaps about predictors of adherence to AET among black and white women diagnosed with BC.

OBJECTIVE: To assess AET adherence in black and white insured women using multiple measures, including one that uses an innovative statistical approach.

METHODS: Black and white women newly diagnosed with HR+ BC were identified from 2 health maintenance organizations. Pharmacy records captured the type of oral AET prescriptions and all fill dates. Multivariable logistic regression was used to identify predictors of adherence defined in terms of proportion of days covered (PDC; ≥80%) and medication gap of ≤10 days. A zero-inflated negative binomial (ZINB) regression model was used to identify variables associated with the total number of days of medication gaps.

RESULTS: 1,925 women met inclusion criteria. 80% were PDC adherent (>80%); 44% had a medication gap of ≤10 days; and 24% had no medication gap days. Race and age were significant in all multivariable models. Black women were less likely to be adherent based on PDC than white women (OR=0.72, 95% CI=0.57-0.90, $P<0.01$), and they were less likely to have a medication gap of ≤10 days (OR=0.65, 95% CI=0.54-0.79, $P<0.001$). Women aged 25-49 years were less likely to be PDC adherent than women aged 65-93 years (OR=0.65, 95% CI=0.48-0.87, $P<0.001$). In the ZINB model, women were without their medication for an average of 37 days (SD=50.5).

CONCLUSIONS: Racial disparities in adherence to AET in the study highlight a need for interventions among insured women. Using various measures of adherence may help better understand this multidimensional concept. There might be benefits from using both more common dichotomous measures (e.g., PDC) and integrating novel statistical approaches to allow tailoring adherence to patterns within a specific sample.

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What is already known about this subject

- Despite the known benefits of adjuvant endocrine therapy, as many as 50% of eligible women either do not initiate their medication or do not complete the recommended 5- to 10-year therapy.
- Racial disparities exist with regard to adherence to adjuvant endocrine therapy, with black women reporting lower adherence rates than their white counterparts.
- There are numerous methods for measuring adherence (e.g., dichotomous stratification of proportion of days covered); however, there are notable advantages and disadvantages to every method (e.g., ability to capture timeliness of refills and inability to capture when medication is taken), prompting the need to explore different methods to calculate and report adherence.

What this study adds

- This study incorporates different statistical methods, including one novel statistical technique (i.e., zero-inflated negative binomial model) to assess medication adherence.
- While all women were insured, black women exhibited lower adherence for all measures than white women, highlighting the need to further examine factors that predict nonadherence among insured women.

It is well known that adjuvant endocrine therapy (AET) effectively reduces recurrence and mortality in women with hormone receptor-positive (HR+) tumors (estrogen receptor-positive [ER+]) or progesterone receptor-positive (PR+).[1-3] Thus, AET is recommended for women with HR+ disease.[1,4] Despite its proven benefit, as many as 50% of eligible women do not initiate AET or do not complete the recommended 5-year course of therapy.[5,6] Failure to complete the full course of AET is linked to the loss of treatment effectiveness and increased risk of morbidity and mortality.[5,7-11] While many women remain on their medication, a substantial proportion of women do not adhere to the appropriate regimen.

Factors that influence AET adherence are complex, but according to the World Health Organization (2001), adherence can be conceptualized within the 5 interacting domains described within the medication adherence framework (i.e., patient-related, therapy-related, socioeconomic, condition-related, health system).[12] In general, variables within these domains (e.g., race and age) have been inconsistent across studies, making tackling AET nonadherence elusive.[13-16]

AET is an important part of treatment for African American (hereafter referred to as "black") and European American (referred to as "white") women, since HR+ breast cancer (BC) is the most common BC in both racial/ethnic groups.[17,18] Unfortunately, reports suggest that black women with HR+ BC experience disparities in mortality compared with their white counterparts.[19,20] Nonadherence to AET may be one contributing factor. Research describing AET adherence patterns in black women versus white women vary but suggest higher nonadherence in black women.[5,21] Possible reasons for observed differences in research reports may relate to the composition of samples across studies (i.e., Medicaid samples, combination of insured and uninsured, and small proportion of black women) and methods used to measure adherence.[1,5,11] Although patterns of adherence to AET are suboptimal even in health maintenance organization (HMO) settings, these types of integrated health systems are an ideal place to examine adherence, given that all women are insured, and they provide an opportunity to examine prescription patterns across diverse patient subgroups within a similar system of care.

One benefit of HMO settings is the capture of pharmacy data to measure adherence. Accepted measures of adherence, such as self-reporting, pill counts, and pharmacy fill rates, each have advantages and disadvantages.[22,23] Pharmacy fill and refill data obtained from prescription records are advantageous because they provide detail on the quantity of medications dispensed over specific periods of time.[5,23] While prescription record data can represent adherence on a continuous scale, most adherence measures are dichotomized because data are often skewed to the left and have large proportions of complete adherence.[24,25]

Dichotomizing data into various cutoffs (e.g, ≤80% or >80%, ≤90% or >90%) leads to loss of statistical power and missed opportunities to examine the full range of data.[5,26-30] Saberi et al. (2011) suggest that tailoring adherence analysis to the actual data within a study population using multiple statistical methods (e.g., zero-inflated negative binomial [ZINB] model and hurdle model) may facilitate understanding adherence across the full range of levels.[30] In this dataset, because 24% of the sample consistently took their medication, not missing a single day, a ZINB model was used to assess the relationship between possible predictors and the number of days without medication.

The overall goal of this study was to examine AET adherence within an insured sample of HR+ women using different methods. Research aims were to identify patient-level and clinical factors that were associated with different patterns of adherence.

Methods

Data Source

Patients' medical records and claims were extracted from 2 integrated health systems: Henry Ford Health System (HFHS) and Kaiser Permanente-Georgia (KPGA). Each site provided electronic data, including patients' pharmacy refill data, from 1998-2010. AET guidelines were consistent during this time frame, recommending AET use up to 5 years.[31] This study was approved by institutional review boards at all institutions.

Study Sites

The HFHS and KPGA sites are located in geographically different regions, with different service delivery models (staff/group model, independent physician association, and preferred provider).

HFHS is one of the nation's leading integrated managed care organizations serving nearly 3.2 million patients annually in the metropolitan Detroit, Michigan, area. HFHS is a nonprofit health care system that consists of 29 medical centers, several group practices, and 6 hospitals providing services in over 40 specialties (e.g., oncology, cardiology, and orthopedics).

Kaiser Permanente is a large, integrated health care system currently providing care to more than 12 million members in 8 regions across the nation. KPGA members receive specialty and primary care services at 26 outpatient facilities across the Atlanta, Georgia, extended metropolitan area. In 2010, KPGA was composed of 3,579 employees (including 555 providers); of the 266,000 members at that time, 33% were black and 30% white.

Sample Selection

The sample was restricted to self-identified black and white women whose tumors were HR+ (ER+ and/or PR+) during the study period of January 1, 1998, to December 31, 2012. We defined HR status by the values set by the National American Association of Central Cancer Registries. Women were selected who filled at least 1 prescription for oral AET (i.e., tamoxifen, anastrozole, exemestane; see Appendix A for complete generic and brand-name list, available in online article) up to 1 year following their BC diagnosis and before the diagnosis of recurrent disease, per the medical record.[32] Informed consent was obtained from all individual participants included in the study.

BC diagnosis had to be between 1998 and 2010 and the first AET fill between 1999 and 2011. Index event was the first AET fill. For each participant, 2 years of data were pulled—1 year before the first AET fill to 1 year after the first AET fill. Each person in the cohort had to be continuously enrolled for a year before the first AET fill through a year after the first AET fill. We bridged any enrollment gaps of 62 days or less. For example, if someone was enrolled for 5 months, then unenrolled for 30 days, then enrolled again and stayed enrolled for the next 18 months, we bridged those 2 enrollment periods together and considered that person to be continuously enrolled for 2 years. AET initiation was confirmed using pharmacy records.

Study Variables

AET Adherence. Three adherence measures were computed using key data per prescription from the pharmacy management database (i.e., the name of the drug, National Drug Code number, date of the first prescription fill, and date of refill).

Adherence measure 1: The proportion of days covered (PDC) calculation was the number of days the member was covered with an AET supply divided by 365. The PDC was based on the actual days of supply in each prescription record and was provided by the pharmacy from each site. To adjust for overlapping prescriptions, we adjusted the start and stop dates to begin the day after the last day's supply of the previous fill.

Adherence measure 2: The total medication gap was the total number of days in the year after the first AET fill that the person was not covered with an AET supply.

Adherence measure 3: Women were classified as adherent by the PDC measure if the number of pills dispensed in prescriptions from the date of the first prescription to the end of follow-up covered at least 80% of the days in that entire period.[33] This conservative measure considers the days within a particular period when a patient was covered for all medications in a regimen; PDC > 80% was regarded as adherent. If someone filled an AET early (before they ran out of AET supply from the previous fill), we adjusted the days of that subsequent pill coverage to start once the previous fill had run out. We assumed that they would not throw out the remaining pills of the previous fill and start the new fill that day. Based on the pattern of gaps in days for the overall sample, we also employed a cutoff point of 10 days (> 10 vs. ≤ 10 days), which corresponded to the 45th percentile in the data.

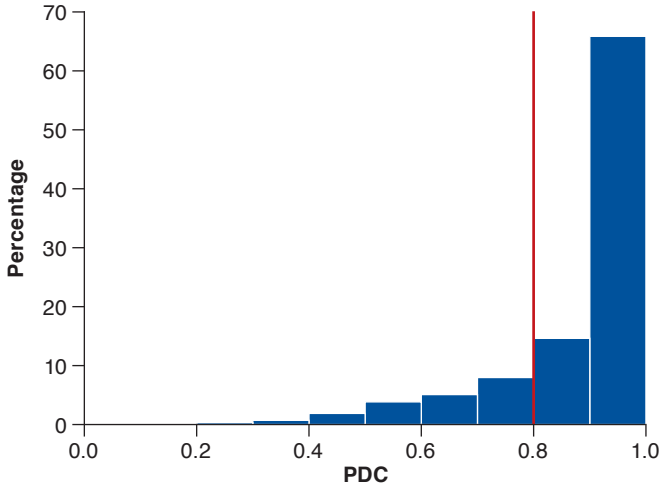
Covariates. Sociodemographic variables included age at AET initiation, race (black or white), and socioeconomic status (SES). SES was determined by geocoding patients' addresses and assigning a census tract code. Clinical variables included stage at diagnosis, tumor size, tumor grade, surgical status, lymph node involvement, total comorbidities, and type of AET. The type of insurance plan (e.g., HMO vs. other, such as point of service) was also taken into account.

Statistical Analysis

Descriptive statistics were employed to summarize all variables with means and standard deviations for continuous variables and frequencies and proportions for categorical variables. Wilcoxon rank sum test was used to test the difference in central tendency for total days of AET medication gap between black and white patients. All tests were assessed at a significance level of 0.05. T-tests were used to detect differences between 2 groups for continuous variables. Chi-square tests were used to assess differences between categorical variables. Multiple logistic regression was used to identify factors (e.g., demographics, tumor size, and cancer stage) associated with PDC adherence (≥ or < 80%) and medication gap (> or ≤ 10 days).

A ZINB model, which estimates the probability of excess zeros through a logit link and estimates the remaining outcomes through a negative binomial distribution, was applied to identify variables associated with medication gap as a count variable.[34] A stepwise procedure was used to choose variables in the above models. Hosmer and Lemeshow goodness-of-fit chi-square test was used to assess the fit of the logistic regression model, and a comparison of the ZINB model and a negative binomial (NB) model was performed using the Vuong test. They showed that the ZINB model provided a significantly better fit to the data. All statistical analyses were conducted using SAS version 9.4 (SAS Institute, Cary, NC), and figures were produced using R version 3.3.3 (R Foundation for Statistical Computing, Vienna, Austria).

FIGURE 1 Distribution of Medication Adherence: PDC



Note: Figure 1 shows the cutoff (red line) of dichotomization for PDC. There were 80% of women who had > 80% of days covered with adjuvant endocrine therapy. PDC = proportion of days covered.

Results

Sample Characteristics

The study consisted of 1,925 patients, of which 63% (n = 1,213) were white and 37% (n = 712) were black. The mean age was 59.5 years (standard deviation = 12.3) with 23.3% in the 25-49 age range. Several differences in individual, clinical, and health care factors were noted by race. Compared with their white counterparts, black women tended to be younger (mean = 57.9 vs. 60.3 years, $P < 0.01$), reside in lower SES areas (40.4% vs. 14%, $P < 0.01$), and possess HMO plans at a lower percentage (78% vs. 85%, $P < 0.001$). Compared with white women, black

TABLE 1 Characteristics of Black and White Women with HR+ Breast Cancer by AET Adherence Status

	All (N = 1,925)			PDC, n (%)					AET Medication Gap, n (%)				
				PDC < 80% 377 (19.6)		PDC ≥ 80% 1,548 (80.4)			Gap ≤ 10 Days 856 (44.5)		Gap > 10 Days 1,069 (55.5)		
	N	n	C%	n	R%	n	R%	*P* Value	n	R%	n	R%	*P* Value
Age													
25-49	1,925	448	23.3	109	24.3	339	75.7	0.008[a]	174	38.8	274	61.2	0.015[b]
50-64		817	42.4	157	19.2	660	80.8		368	45.0	449	55.0	
65-93		660	34.3	111	16.8	549	83.2		314	47.6	346	52.4	
Age (mean ± SD)	1,925	59.5 ± 12.3		57.9 ± 13.0		59.8 ± 12.2		0.006[a]	60.3 ± 12.1		58.8 ± 12.5		< 0.007[a]
Race													
Black	1,925	706	36.7	164	23.2	542	76.8	0.002[a]	266	37.7	440	62.3	< 0.001[c]
White		1,219	63.3	213	17.5	1,006	82.5		590	48.4	629	51.6	
Low SES													
No	1,833	1,398	76.3	259	18.5	1,139	81.5	0.103	636	45.5	762	54.5	0.317
Yes		435	23.7	96	22.1	339	77.9		186	42.8	249	57.2	
Stage													
0	1,539	163	10.6	27	16.6	136	83.4	0.220	77	47.2	86	52.8	0.337
1		724	47.0	117	16.2	607	83.8		350	48.3	374	51.7	
2		539	35.0	104	19.3	435	80.7		240	44.5	299	55.5	
3		113	7.4	26	23.0	87	77.0		46	40.7	67	59.3	
Tumor size													
0-2 cm	1,878	755	40.2	130	17.2	625	82.8	0.033[b]	342	45.3	413	54.7	0.602
≥ 2 cm		1,123	59.8	238	21.2	885	78.8		495	44.1	628	55.9	
Tumor grade													
High	1,823	455	25.0	89	19.6	366	80.4	0.908	193	42.4	262	57.6	0.354
Low		1,368	75.0	271	19.8	1,097	80.2		612	44.7	756	55.3	
Surgery													
No	1,915	58	3.0	9	15.5	49	84.5	0.417	30	51.7	28	48.3	0.257
Yes		1,857	97.0	368	19.8	1,489	80.2		821	44.2	1,036	55.8	
Positive nodes													
Negative/ unknown	1,925	236	12.3	39	16.5	197	83.5	0.206	114	48.3	122	51.7	0.205
Positive		1,689	87.7	338	20.0	1,351	80.0		742	43.9	947	56.1	
Comorbidity score													
0-2	1,925	1,003	52.1	180	17.9	823	82.1	0.164	459	45.8	544	54.2	0.311
3-5		457	23.7	99	21.7	358	78.3		204	44.6	253	55.4	
6+		465	24.2	98	21.1	367	78.9		193	41.5	272	58.5	
HMO													
No	1,925	242	12.6	33	13.6	209	86.4	0.013[b]	115	47.5	127	52.5	0.307
Yes		1,683	87.4	344	20.4	1,339	79.6		741	44.0	942	56.0	
AET type													
Aromatase inhibitors	1,925	774	40.2	149	19.2	625	80.8	0.762	339	43.8	435	56.2	0.628
Tamoxifen		1,151	59.8	228	19.8	923	80.2		517	44.9	634	55.1	

Note: P value was obtained from chi-square test (categorical data) or t-test (continuous data).

[a] *P < 0.01.*

[b] *P < 0.05.*

[c] *P < 0.001.*

AET = adjuvant endocrine therapy; C% = column percentage; HMO = health maintenance organization; HR = hormone receptor; PDC = proportion of days covered; R% = row percentage; SD = standard deviation; SES = socioeconomic status.

women tended to have BC at a later stage (8.9% vs. 6.4%, *P* < 0.001), higher tumor grade (32.3% vs. 20.6%, *P* < 0.01), larger proportion of smaller tumors (44.7% vs. 37.7%, *P* < 0.05), and more comorbid conditions (27.6% vs. 22.1%, *P* = 0.007). There were no differences by race in lymph node status or the type of AET.

TABLE 2 Multivariable Logistic and Zero-Inflated Negative Binomial Regression Models for Adherence Outcomes

Statistically Selected Variables	Model 1: PDC ≥ 80 OR (95% CI)	Model 2: ≤ 10-Day Gap OR (95% CI)	Model 3: Total Gap OR (95% CI)
Race (black vs. white)	0.72 (0.57-0.90)[a]	0.65 (0.54-0.79)[b]	0.46 (0.34-0.63)[b]
Age, years (25-49 vs. 65-93)	0.65 (0.48-0.87)[a]	0.73 (0.57-0.93)[a]	0.61 (0.42-0.88)[a]
Age, years (50-64 vs. 65-93)	0.88 (0.67-1.15)	0.94 (0.76-1.15)	0.89 (0.67-1.18)

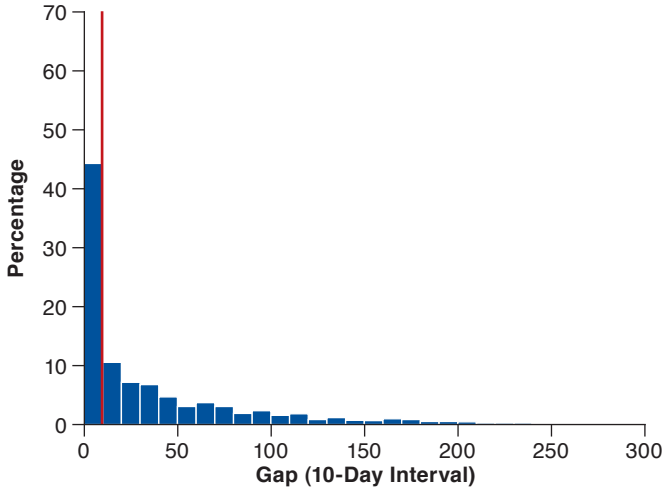
Note: Site is controlled for in the model. Based on logistic regression, Model 1 is fitted on the probability of having 80% of PDC, and Model 2 is fitted on the probability of having less than 10 days of gap. Based on zero-inflated negative binomial regression, Model 3 estimated the probability of having an excess of 0 days of gap (completely adherent, as well as the expected number of gap days.

[a]*P* < 0.01.

[b]*P* < 0.001.

CI = confidence interval; OR = odds ratio; PDC = proportion of days covered.

FIGURE 2 Distribution of Medication Adherence: 10-Day Interval Gap



Note: Figure 2 shows the cutoff (red line) of dichotomization for prescription gap. There were 56% of women who had a medication gap of > 10 days.

Patterns of AET Adherence

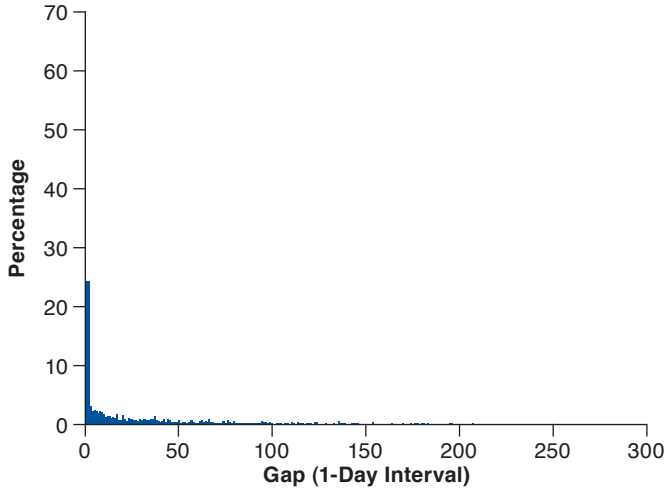
PDC Adherence. A total of 80% of women presented a PDC ≥ 80%, thus being considered adherent (Figure 1). Factors associated with PDC ≥ 80% in bivariate analyses were age, race, tumor size, and enrollment in an HMO plan (Table 1). A higher proportion of women aged 65-93 years had PDC ≥ 80% than younger women (83.2% vs. 79.0%, *P* = 0.027). A higher proportion of white women had PDC ≥ 80% than black women (82.5% vs. 76.8%, *P* = 0.008). A higher proportion of women who resided in the Midwest had a PDC ≥ 80% compared with women residing in the Southeast (84.3% vs. 75.3%, *P* < 0.001). A higher proportion of women diagnosed with smaller tumors (i.e., < 2 cm) had a PDC ≥ 80% (82.8% vs. 78.8%, *P* = 0.033). A higher proportion of women who were not enrolled in an HMO plan had PDC ≥ 80% than those enrolled in an HMO plan (86% vs. 80%, *P* = 0.013). In the logistic regression model for PDC adherence, race and age remained statistically significant. Black women were less likely to be adherent than white women (odds ratio [OR] = 0.72, 95% confidence interval [CI] = 0.57-0.90, *P* < 0.01). Compared with the oldest age group (65-93 years), younger women (25-49 years) were less likely to be adherent (OR = 0.65, 95% CI = 0.48-0.87, *P* < 0.01; Table 2). The Hosmer and Lemeshow goodness-of-fit test indicated that the model provided a good fit to the data (*P* = 0.75).

Medication Gaps (≤ 10 Days). When examining smaller increments of medication gaps (≤ 10-day interval), more than half of the sample (55.5%) were without their medications for 10 days or more (Figure 2). In bivariate analyses, only age and race were significant (*P* < 0.05; Table 1). The results of logistic regression models indicated that black women were less likely to have a ≤ 10-day gap than their white counterparts (OR = 0.65, 95% CI = 0.54-0.79, *P* < 0.01). Younger women (25-49 years) were less likely to have a ≤ 10-day gap (OR = 0.73, 95% CI = 0.57-0.93, *P* < 0.01) compared with those belonging to the older age group (65-93 years; Table 2). The Hosmer and Lemeshow goodness-of-fit test showed that the logistic regression model with race and age as covariates provided a good fit to the data (*P* = 0.95).

A sensitivity analysis of the cutoff points of medication gap is provided in Appendix B (available in online article). For 10-day and 60-day intervals, black and younger women had significantly lower odds of having those gaps. However, black women were more likely to have more than 30 days without taking medication, compared with white women, and younger women were more likely to have more than 90 days without taking medication when compared with older women. For some cutoffs, there is no evidence of a difference.

Total Days of AET Medication Gaps. The number of days women were without their medication over a 12-month period ranged from 0 to 330 days (median = 15; 25% quantile = 1; 75% quantile = 54; Figure 3). The median medication gap for black women was 23.5 days (25% quantile = 4; 75% quantile = 63) and 11.0 for white women (25% quantile = 0; 75% quantile = 45; *P* < 0.0001). Results of the ZINB regression model identified that race and age were associated with the probability of being adherent without missing a single refill. The odds of having zero days without taking medication for black women were 0.46 times lower (95% CI = 0.34-0.63, *P* < 0.0001) compared with white women. Women between 25-49 years were less likely to be adherent (OR = 0.61, 95% CI = 0.42-0.88, *P* = 0.008) than the oldest age group of women (65-93 years; Table 2).

FIGURE 3 Distribution of Medication Adherence: Total Medication Gap (Days)



Note: Figure 3 shows that 24% of women had zero days with medication gaps (perfect adherence).
PDC = proportion of days covered.

Discussion

This study focused on insured women and examined 3 methods to estimate AET adherence and describe a range of adherence patterns. All methods yielded similar results, suggesting that the identified predictors of race and age were robust. The influence of clinical and health care factors diminished after controlling for covariates. To our knowledge, our study had among the largest samples of black women with HR+BC outside of a Medicare setting. The inclusion of a substantial proportion of black insured women (37%) allowed for greater statistical power to detect racial differences in adherence. Finally, the ZINB statistical approach enabled the evaluation of the full range of adherence with regard to medication gaps by modeling excess probability of being zero and predicting the expected days without medication from the NB model.

It was reassuring that most of the sample had >80% medication adherence based on PDC and that black insured women in our sample had higher PDC rates (76%) than some previous studies.[35,36] However, our findings suggest that while all women were insured, disparities were still noted by race. Black women (vs. white women) were without their medication for longer periods of time (23.5 days vs. 11.0), were less likely to have perfect adherence, and were less likely to have a PDC ≥ 80% (OR = 0.72, $P < 0.05$).

These data suggest that black women may experience more short-term interruptions with filling their prescriptions compared with their counterparts. Short-term interruptions have been associated with a greater likelihood to prematurely discontinue therapy.[37] The lower adherence in black patients is particularly concerning given the proven effectiveness of AET as a targeted therapy to improve BC outcomes and disparities in BC mortality in black women with HR+BC.[38] Despite the growing number of studies regarding adherence to AET, black patients continue to be underrepresented, and several studies have lacked statistical power to examine differences by race/ethnicity.

Potential reasons for lower adherence patterns in black women include medication costs,[35] pharmacy type (e.g., mail vs. retail),[39] physician recommendation,[40,41] age,[5,42] SES, and longer prescription refill intervals.[5] Our finding is noteworthy given that cost and access have been shown to be potential explanations for racial differences in AET adherence.[8] The persistence of racial differences among this group of insured women may underscore differences in plan structure and out-of-pocket costs that may be more of a burden for many black women with BC that have health insurance.[35] For example, in a sample of insured women, younger black women reported financial barriers to initiation of AET.[43] On the other hand, Hershman et al. (2010) noted that differences in adherence diminished after controlling for financial net worth.[44] While not significant, we did note that black women in this study were more likely to be in non-HMO plans, which may suggest more variation in out-of-pocket health care and medication costs even within the system of care. In bivariate analyses, women covered via an HMO were more likely to be adherent. Because black women were more likely to have a non-HMO plan (22% vs. 15%), they may be more at risk of having greater out-of-pocket costs.

Mixed results have been produced in studies that have examined the relationship between age and AET adherence, with studies reporting lower adherence in older women (vs. younger; e.g., 40-45 years).[42] These mixed results may be due in part to differences in age cutoffs and sample settings (e.g., Medicare, HMO, and clinical). Our finding that older women were more likely to be adherent than their younger counterparts is in concert with some previous research in HMO settings.[5,9,36] Hershman et al. (2011) found higher rates of nonadherence and discontinuation among younger women (aged <40 years).[5] In another study, the majority of younger women in the sample were more likely to be nonadherent than older women.[44] The lower adherence among the youngest age group may underscore financial barriers, given that the oldest age group of women may have supplemental insurance that assists with medication costs.[45] While many of the AETs are likely available in generic form, it is possible that younger women may face additional financial burden such as job disruptions.[46] In a study of initiation of AET, financial burden was highest among the youngest patients.[43]

Additionally, tolerance of side effects may be more problematic for the younger women who might be facing consequences

of systemic treatment, including but not limited to menopausal symptoms, fertility issues, and sexual dysfunction, while taking AET.[47,48] For example, in a qualitative study by Wen (2017), a main concern for younger women was the effect of their AET on fertility; women were apprehensive about taking AET for up to 10 years without knowing the effects it may have on their ability to reproduce.[49] Our study did not include information about side effects, so we cannot detect this from our data. Because of the mixed reports regarding age, more research is needed to understand that sample composition, contextual issues relevant to the study, and detailed patient-reported data to help elucidate experiences of women taking AET.

While there is no gold standard for assessing medication adherence, pharmacy records are recognized as a reliable source of adherence with regard to women getting their prescriptions filled.[50,51] Our approach of investigating various methods of measuring adherence suggests that employing strategies that examine the total days that patients are without their medication may be useful instead of relying solely on dichotomized variables that have somewhat arbitrary cutoffs. Furthermore, capturing nonadherence early on might better enable providers, particularly pharmacists, to intervene. Future efforts to capture patient-reported experiences may aid in the identification of important variables.

Small increments of nonadherence may be important as they likely increase the risk of problematic adherence. The clinical significance of smaller increments, such as the 10-day increment in the study, has not been linked to recurrence or mortality. However, observing smaller gaps offers an opportunity to address the risk of nonadherence (i.e., longer gaps and PDC) earlier and more in line with real time rather than identifying women as nonadherent after they have been without their medication for an extended period of time.

Limitations

Despite the strengths of this study's approach, some limitations should be noted. The sample of women who self-identified as either black or white were all insured and receiving care from 2 integrated health systems. While we recognize this as a strength, sampling in this manner limited our ability to generalize findings to uninsured populations across the United States. Underinsured patients may be less likely to remain adherent because of their plan's limited coverage of medications relative to patients' ability to pay.[35,52,53]

It is probable that patients may have filled prescriptions for their AET outside of the integrated health systems network, which may justify the gap in prescription refills. This study was limited in assessing multiple dimensions of individual-level SES variables, such as income, assets, and coinsurance, that may provide information about the potential financial burden among women.[54]

The current analysis was limited to the first year of medication; following women for a longer time frame may elucidate patterns of persistence. Further, other factors (e.g., costs, aggregation of multiple plan designs, and radiation receipt) may have affected our findings. There is no gold standard to measure adherence; however, we recognize that other measures, including a continuous measure of medication acquisition, or a combination of measures, may provide additional information about patterns of adherence.[51,55]

Conclusions

Treatment disparities in adherence to AET have been reported for black and younger BC patients and attention to these groups is warranted. Findings from this study highlight potential intervention targets, such as focusing on decreasing the number of gap days, thereby contributing to improved adherence in these populations. Further work is needed to understand reasons and to address nonadherence within an integrated health setting. Insurers have a unique ability to reach populations at various entry points, including physician visits and via pharmacists. Few interventions exist to address adherence overall, but it will be imperative to develop interventions to support adherence in black women with HR+BC. Such interventions may contribute to reducing disparities in mortality in the future.

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APPENDIX A Generic Names of Drugs Pulled in Data Abstraction

We pulled drugs by their generic and brand names. We included drugs that had the following text strings in them:
TAMOX
LETRO
RALOX
TOREM
EXEME
ANAST
FEMARA
EVISTA
ARIMIDEX
AROMASIN
FARESTON
NOLVADEX
SOLTAMOX

APPENDIX B Logistic Regression Model Selected Variable Based on Different Cutoff Points of Medication Gap

Statistically Selected Variables	10 Days, OR (95% CI)	30 Days, OR (95% CI)	60 Days, OR (95% CI)	90 Days, OR (95% CI)
Race (black vs. white)	0.65 (0.54-0.79)[a]	0.61 (0.50-0.73)[a]	0.73 (0.58-0.90)[a]	–
Age (25-49 years) vs. (65-93)	0.73 (0.57-0.93)[b]	–	0.70 (0.53-0.93)[c]	0.58 (0.41-0.82)[b]
Age (50-64 years) vs. (65-93)	0.94 (0.76-1.15)	–	0.92 (0.71-1.18)	0.76 (0.56-1.04)

Note: For different cutoff points—10 days, 30 days, 60 days, and 90 days—the variables were selected by logistic regression model.

[a]*P < 0.001.*

[b]*P < 0.01.*

[c]*P < 0.05.*

CI = confidence interval; OR = odds ratio.