Geographic variations in adherence to and persistence with adjuvant hormonal therapy for the privately insured women aged 18-64 with breast cancer in Texas

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Research Article

Keywords: adjuvant hormonal therapy, breast cancer, treatment adherence and persistence

Posted Date: April 19th, 2021

DOI: https://doi.org/10.21203/rs.3.rs-224248/v1

TITLE PAGE

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Abstract

Purpose: Objective of this study is to examine the geographical patterns of adjuvant hormonal therapy adherence and persistence and the associated factors in insured women aged 18-64 with early breast cancer in Texas. Methods: A retrospective cohort study was conducted by using claims data for population insured by Blue Cross Blue Shield of Texas (BCBSTX) from the year 2008 to 2013. Women diagnosed with early breast cancer who were taking tamoxifen or aromatase inhibitors (AIs) for adjuvant hormonal therapy with at least one prescription claim, from January 1, 2008 to December 31, 2012, and were enrolled through 2013, were identified. Adherence to adjuvant hormonal therapy and persistence on adjuvant hormonal therapy were calculated as outcome measures. Women without a gap between two consecutive dispensed prescriptions of at least 90 days in medication were considered as persistently taking the medications. Patient-level multivariate logistic regression models with repeated regional-level adjustments were used to determine the geographical variations and patient-level, provider-level, and area-level factors that were associated with adjuvant hormonal therapy adherence. Results: Of the 938 women in the cohort, 627 (66.8%) initiated adjuvant hormonal therapy. Most of the smaller HRRs have significantly higher or lower rates of treatment adherence and persistence rates relative to the median regions. The use of AHT varies substantially from one geographical area to another, especially for adherence, with an approximately two-fold difference between the lowest and highest areas and area-level factors were found to be significantly associated with the compliance of AHT. Conclusions: There are geographical variations in AHT adherence and persistence in Texas. Patient-level and area-level factors have significant associations explaining these patterns.

Geographic variations in adherence to and persistence with adjuvant hormonal therapy for the privately insured women aged 18-64 with breast cancer in Texas

INTRODUCTION

Breast cancer is the most commonly diagnosed cancer and second leading cause of death in women in Texas, representing 29.5% of all new malignant cancers diagnosed in women [1]. An average of 2,849 Texas women with breast cancer died annually from 2012-2016 [1]. In 2019, the expected breast cancer deaths were 3,213 and the total hospital charges for breast cancer hospitalizations were approximately $252 million, and the estimated total expenditure for breast cancer care was highest for physician care at about $29.9 million compared to inpatient or outpatient hospital care [1].

Significant variations in breast cancer care, including non-adherence to hormonal therapy, and/or early discontinuation of hormonal therapy, arise frequently and may impact survival [2, 3, 4]. Many patients fail to take the prescribed drug on a daily basis (non-adherence), or to continue of taking medication over a long-term period (persistence of use). Lack of compliance with prescribed adjuvant hormonal medication frequently results in treatment failure [3, 4, 5]. Adjuvant systemic hormonal therapy is a crucial procedure for maximizing the benefits of treatment. Guideline-concordant optimal adherence to, and persistence with therapy increases the likelihood that patients with hormonal sensitive breast cancer can expect better outcomes.

This study examines rates of adjuvant hormonal therapy compliance for patients with breast cancer aged between 18-64 across regions of Texas. Some studies have addressed regional variation in breast cancer initial treatment type [6-12]. However, no study has compared adjuvant hormonal therapy adherence and persistence rates to determine whether geographical variations are seen among regions. Further, the primary predictors for observed patterns of quality adjuvant hormonal therapy have not been determined. There are mixed findings among studies for various individual and clinical characteristics, with estimates of geographic variation and provider/area level factors frequently missing. It is unclear whether similar factors affect hormonal therapy use among younger population as among older patients [13-22].

We compare actual endocrine therapy compliance rates by Hospital Referral Regions across Texas. Texas is a particularly useful state in which to examine regional variation, because it is large and diverse demographically

and geographically. It is the second most populous U.S. state, with 27 million people in 2014 [23]. The state has several large urban and extensive rural areas and an ethnically diverse population. Some regions have access to large teaching hospitals, while many do not.

The purpose of this study is to explore the geographic variation by Hospital Referral Region in Texas in adherence to and persistence with adjuvant hormonal therapy use among privately insured women with breast cancer and its predictors.

METHODS

Data

This study employed a retrospective population-based cohort using enrollment and claims data for the population insured by Blue Cross Blue Shield of Texas (BCBSTX) from the year 2008 to 2013. The dataset includes a claims file with all the claims (institutional, professional and pharmacy claims) processed by the BCBSTX and a member enrollment file for approximately 5.6 million BCBSTX members from the year 2008 to 2013. This is approximately one-third of the private insurance population in Texas. The data were obtained through the University of Texas School of Public Health/ BCBSTX Research Program in Payment Systems and Policy. The socioeconomic status of the areas where patients reside was obtained from the Census 2010 summary file 3 (SF3). Area-level characteristics were obtained from the 2012-2013 Health Resources and Services Administration's Area Resource File (ARF).

Study cohort description

The study cohort includes all women aged between 18 to 64 and diagnosed with primary breast cancer (ICD-9 code, 174.x) and/or in situ breast cancer (ICD-9 code, 233.x) between June 1, 2008, and December 31st, 2012. All women in the target population were continuously enrolled after the index date and followed for at least one and up to five years after their diagnosis.

Patients were included if they were enrolled in preferred provider organizations (PPO and PPO+) plan type, had drug benefits with the BCBSTX during the study period, and resided in a Texas Hospital Referral Region (HRR). We included patients who received at least one prescription claim for oral hormonal therapy such as tamoxifen, anstrozole, exemestane, or letrozole after the index date and before disenrollment. We used the generic

product index (GPI) code to identify all the maintenance adjuvant hormonal therapy (AHT) medications of interest from the pharmacy claims data.

Outcome

This study examined the rates of adherence and persistence of adjuvant hormonal therapy for treating breast cancer by hospital referral regions in Texas.

Adherence was determined using a medication possession ratio (MPR), defined as the ratio of days covered by the amount of medication supplied, of 80% or greater during a defined period by year [14-22, 24-28].

Persistence was defined as the absence of a gap of 90 or more days between two consecutive dispensed prescriptions during the time from initiation to discontinuation of the AHT therapy. The use of 90 days for defining persistence will be primary gap definition in this study [18]. To account for potential variation in persistence, sensitivity analysis was conducted for the different gaps (60 and 180 days) in therapy defining the persistence measure [18, 22, 26-28].

Patient-level, Provider-level and Area-level characteristics

Patient-level variables included age at diagnosis, education, poverty, percent Hispanic and Latino population, year of diagnosis, whether initiating the therapy within a year of breast cancer diagnosis, health care utilization (a total number of outpatient visits and inpatient days during 6 months prior breast cancer diagnosis and each subsequent year of therapy), Charlson comorbidity that weights a range of comorbid conditions for a patient with a total of 22 conditions including heart disease, kidney disease, lung disease, AIDS, or cancer [27-29] as well as distance to care. Age was categorized into the intervals <40, 40–44, 45–49, 50–54, 55-59, and 60-64.

Patient socioeconomic status was measured at the zip code level, which includes the level of poverty in the area, level of educational attainment, and percent of the population which is non-white. Each of four equal groups was divided according to the distribution of values of those variables. Zip code level variables were measured at the Zip Code Tabulation Area (ZCTA) level and assigned to the patient using the patient zip code and the zip code to ZCTA crosswalk available on the Dartmouth Atlas of Health Care website. Health care utilization was coded as “0”

or “1” with “1” indicating any number of outpatient visits or inpatient stays during the study period of each individual.

We determined the hospital referral region (HRR) that each patient resided in. Hospital Referral Region (HRR) represents the regional health care markets for their respective tertiary medical centers [30]. HRR unit analysis was conducted to describe geographic variation of adjuvant hormonal therapy adherence and persistence in Texas. The U.S. is divided into 306 HRRs, and 22 are in Texas.

For provider-area characteristics (defined as County), the total number of hospitals, the number of hospital admissions, and hospital beds as a proxy of volume of hospital were estimated from the area resource file, with the most recent years of data were used. The county-level data from the ARF file was converted to HRR-level using county-HRR crosswalk that weights the population in each county. Area level characteristics also include numbers of oncology subspecialty (radiologists) from the ARF and numbers of oncology providers in area. The number of oncologists in area were calculated over the one calendar year for each hospital.

Statistical Analysis

Patient, provider, and area characteristics were summarized using percentages for categorical variables and means and standard deviations (SDs) for continuous variables. To examine geographic variation in adherence and persistence to the adjuvant hormonal therapy, we reported the mean and median adherence and persistence rates for breast cancer adjuvant hormonal therapy in our study across in Texas, as well as the lowest and highest compliance rates by HRR.

The adherence rates for each HRR were calculated by dividing the number of people who were already defined whether they were adhere or not adhere to the treatment by the number of adherence counts in the HRR.

We calculated the coefficient of variation and the index of variation to examine variation in adherence to guideline recommended care among HRRs in Texas.

The adherence by HRR were described in Table 2. For persistence by HRR, various lengths of treatment gaps were applied in Table 3. We listed the name of the HRR associated with each reported rate, so that we can look for similarities and differences in patterns of endocrine therapy care across regions in Texas.

To examine regional variation of adherence to and persistence of the hormonal therapy, we used patient-level logistic regression models with region of residence as a 22-level fixed effect. Differences were tested between each region and the median region for each outcome (adherence and persistence of therapy).

RESULTS

A total of 938 patients who had incident early breast cancer between the years 2008 to 2012 were identified. More than half of women had breast-conserving surgery (58.74%) and received radiation (97.12%). Most women were 45-59 years old at diagnosis, lived regions with neighborhood had a high school education, where people with below poverty line (Table 1). Of the 938 women with breast cancer, 627 (66.8%) initiated adjuvant hormonal therapy. Figure 1 addresses steps of the study inclusion and exclusion criteria.

Table 1 Descriptive statistics for the study cohort

Characteristic	**N (%)**
Adjuvant hormonal therapy	
Initiated therapy	627 (66.77)
Tamoxifen only	332 (52.95)
Aromatase inhibitor only	295 (47.05)
Did not initiate therapy	311 (33.23)
Cancer Treatment	
Breast conserving surgery	551 (58.74)
Mastectomy	317 (33.80)
Chemotherapy	565 (60.23)
Radiation therapy	911 (97.12)

Year of diagnosis	
2008	225 (23.99)
2009	223 (23.77)
2010	199 (21.22)
2011	170 (18.12)
2012	121 (12.90)
Age at diagnosis	
<40	45 (4.80)
40-44	82 (8.74)
45-49	176 (18.76)
50-54	234 (24.95)
55-59	312 (33.26)
60-64	89 (9.49)
Neighborhood, % nonwhite population	
<10%	108 (11.51)
10-24%	461 (49.15)
25-50%	273 (29.10)
≥50%	96 (10.23)
Percent of population ages 25 and older without a high school education	
<25%	733 (78.14)
≥25%	205 (21.86)
Neighborhood, % below poverty level	
<20%	705 (75.16)
≥20%	233 (24.84)
Distance to health services facilities	

less than 5 mile	273 (29.10)
5-10 mile	160 (17.06)
10-35 mile	292 (31.13)
35-100 mile	129 (13.75)
>100 mile	84 (8.96)
Comorbidity at diagnosis, mean (SD)	1.27 (1.96)
Health care utilization at diagnosis	
Outpatient visits in prior 6 months, mean (SD)	1.73 (2.69)
Inpatient days in prior 6 months, mean (SD)	1.45 (1.39)

Figure 1 Step of Inclusion/Exclusion Criteria

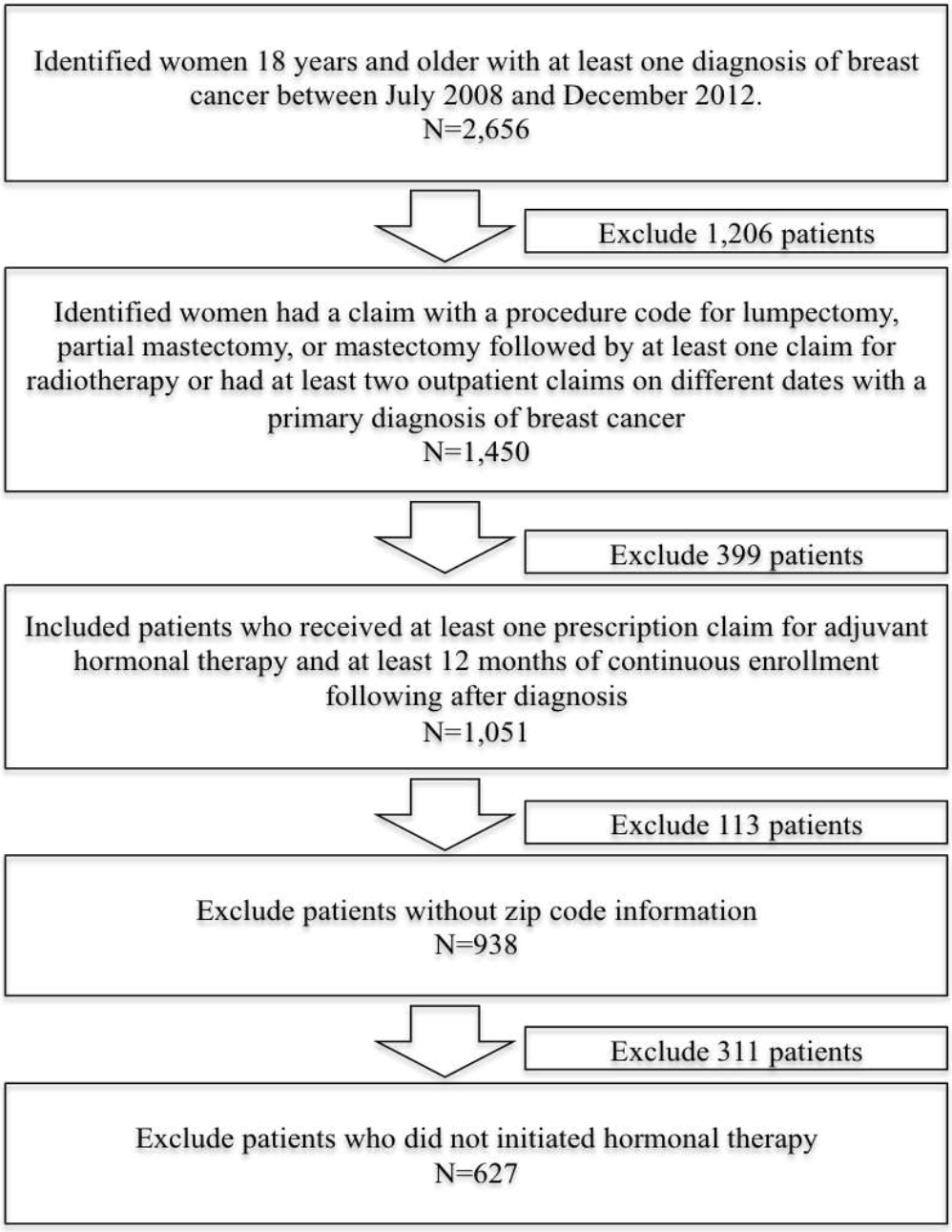


Table 2 provided descriptive statistics on mean adjuvant hormonal therapy adherence and persistence rates by the HRRs, as well as information with median, minimum, and maximum therapy adherence and persistence rates. We reported the number of people who received endocrine therapy in each HRR in the table.

The adherence rate is lowest in women from the HRR of San Angelo (54%) and highest in women from Victoria (100%). The median region of the adherence rate is Dallas (79%) and the mean rate for Texas was 79%. The median rate of persistence for 90-day gap in therapy is 81% in Dallas, the mean rate for Texas was 75%. The persistence rate is lowest in the HRR of Beaumont (50%) and highest in Bryan, San Angelo, Temple, and Victoria (100%). Figure 2 and 3 show the Texas maps with HRRs color-coded based on the adherence and persistence rates. The darker the color the higher the compliance to the treatment.

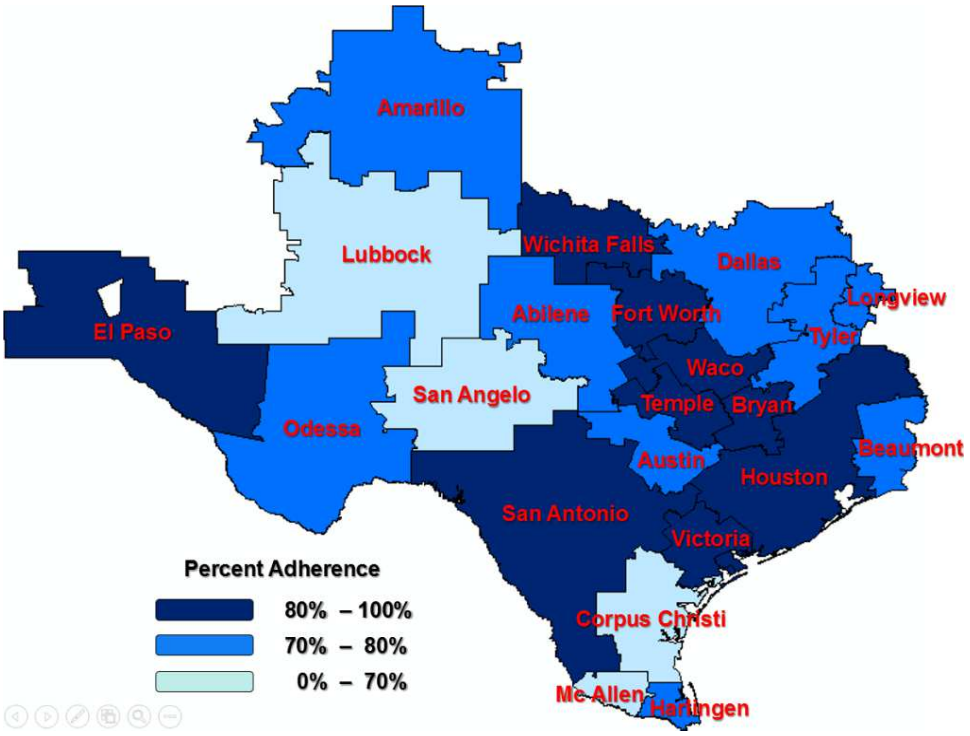
Table 2. Mean AHT adherence and persistence rates by HRR

	N	**Adherence by HRR**		**90-day gap persistence by HRR**	
Hospital Referral Region					
Abilene	13	0.7		0.89	
Amarillo	18	0.78		0.80	
Austin	78	0.77		0.86	
Beaumont	13	0.73		0.50	**Minimum region**
Bryan	12	0.94		1	**Maximum region**
Corpus Christi	6	0.61		0.6	
Dallas	244	**0.79**	**Median region**	**0.81**	**Median region**
El Paso	15	0.82		0.78	
Fort Worth	74	0.83		0.80	
Harlingen	12	0.71		0.88	
Houston	243	0.81		0.80	
Longview	19	0.77		0.87	
Lubbock	29	0.68		0.89	
McAllen	16	0.66		0.67	
Odessa	31	0.71		0.90	

San Angelo	9	**0.54**	**Minimum region**	1	**Maximum region**
San Antonio	66	0.84		0.73	
Temple	2	0.8		1	**Maximum region**
Tyler	25	0.76		0.78	
Victoria	1	**1**	**Maximum region**	1	**Maximum region**
Waco	10	0.96		0.80	
Wichita Falls	3	0.93		1	**Maximum region**

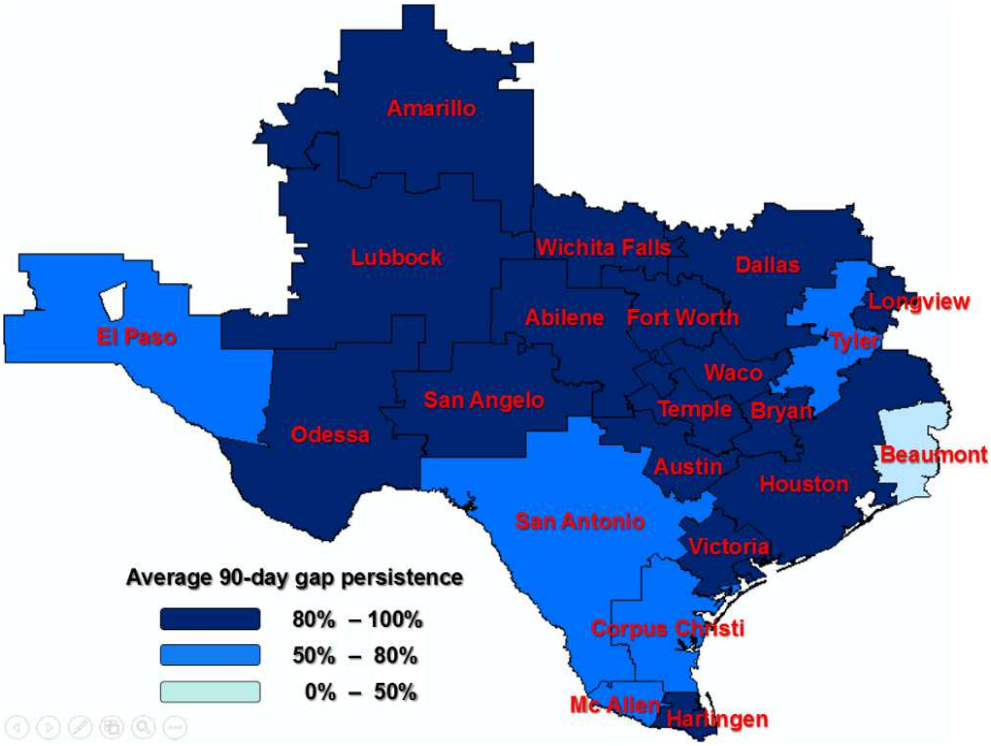
*Mean of TX=0.79;0.75

Figure 2 Adherence among Texas Hospital Referral regions (HRRs)



HRRs out of Texas regions were not considered in the study

Figure 3. 90-day persistence among Texas Hospital Referral regions (HRRs)



HRRs out of Texas regions were not considered in the study

Sensitivity analyses were conducted to see whether the 60-day or 180-day gaps in therapy affected the persistence rates across the regions. The median regions of the 60-day gap in therapy persistence rate and the 180-day gap in therapy persistence are Tyler (78%) and Lubbock (94%), respectively (Appendix Table A). The Texas mapping with HRRs to address variations in persistence of AHT across the regions can be found in the Appendix.

Adherence. In the adjusted regression models for adherence to hormone therapy (Table 3), the patients who received BCS ($p<0.011$) or chemotherapy ($p<0.032$) were more likely to adhere to the AHT, whereas patients who resided in the places where more non-white population live ($p<0.0001$), which had higher rates of poverty ($p<0.014$), and more Hispanics or Latinos ($p<0.009$) were less likely to adhere to the treatment. The number of outpatient visits ($p<0.035$) and days of inpatient stay ($p<0.04$) were associated with AHT adherence positively and negatively, respectively. The number of oncologists in the area ($p<.0001$) was significant factor of adherence and patients who initiated the hormonal therapy within a year of diagnosis as recommended ($p<.0001$) were more likely to adhere to the hormone therapy.

Regional variation in adherence. Five out of 22 HRRs in Texas (Brian, El Paso, Longview, Lubbock and San Antonio) had unadjusted rates of AHT adherence that were significantly different from the median regions of Dallas (Table 4). After controlling for other factors, four out of 22 HRRs in Texas had rates of AHT adherence that were significantly different from the median regions of Dallas. Bryan and El Paso remained significant after adjusting other factors and Austin and McAllen became significant in the adjusted model.

Persistence. In the adjusted models for persistence of adjuvant hormonal therapy (Table 3), patients who were diagnosed breast cancer in later year were more likely to continue the hormone therapy ($p<0.005$), patients who were further away from the health care services from the provider where they had the index treatment ($p<0.012$) and who had more outpatient visits ($p<0.02$) were less likely to persist in the treatment. Patients who initiated the hormonal therapy within a year of diagnosis as recommended ($p<.04$) were less likely to experiencing more gaps in therapy. The number of hospital admissions ($p<0.04$), the number of hospital beds ($p<0.04$), and the number of oncology in the area ($p<0.02$) were associated with less and more experiencing gaps in therapy, respectively.

Regional variation in persistence. Two regions, Amarillo and Houston, showed statistically significant unadjusted differences compared to median region of Dallas for 90-day gap persistence in therapy (Table 4). In the adjusted regression, three regions, Amarillo, Harlingen, and Odessa were statistically significantly different from the

median region of Dallas. Amarillo remained significant and Harlingen and Odessa became significant in the adjusted model.

Since gaps in therapy of other durations (60-day and 180-day) have also been used in the literature, we ran sensitivity analyses to see if regional variations in persistence differed by length of the gaps (see Appendix). One region (Amarillo) found to be significantly different compared to median region for average 180-day gap persistence in therapy. No significant differences in regional variation was found using a 60-day gap persistence in therapy.

Table3. Predictors of adherence to and persistence of the adjuvant hormonal therapy

Characteristics	Adherence	Persistence of 90-day gap in therapy
	OR (CI)	HR (CI)
Patient-level characteristics		
Cancer Treatment		
Surgery (referent: no cancer-directed surgery)		
Breast-conserving surgery	**2.04 (1.18, 3.54)**	1.69 (0.94, 3.04)
Mastectomy	1.30 (0.73, 2.33)	1.42 (0.76, 2.67)
Chemotherapy (referent: no chemotherapy)		
Yes	**1.61 (1.04, 2.48)**	1.17 (0.95, 1.45)
Radiation therapy (referent: no radiation therapy)		
Yes	1.10 (0.20, 6.17)	**0.39 (0.15, 0.97)**
Year of diagnosis (referent: 2008)		
2009	1.53 (0.87, 2.71)	**0.48 (0.27, 0.85)**
2010	1.18 (0.66, 2.09)	1.11 (0.60, 2.05)
2011	1.54 (0.86, 2.75)	1.29 (0.67, 2.48)
2012	1.54 (0.80, 2.98)	**2.54 (1.13, 5.74)**
Therapy initiation (referent: did initiated ATH within 1yr of BC diagnosis)		
Not-Initiated	**0.02 (0.009, 0.04)***	**0.87 (0.53, 0.98)**
Age at diagnosis, (referent: <40 years)		
40-44	2.28 (0.81, 6.37)	1.25 (0.46, 3.46)

45-49	1.54 (0.60, 3.98)	1.43 (0.56, 3.67)
50-54	2.07 (0.82, 5.23)	2.57 (0.99, 6.60)
55-59	2.49 (0.99, 6.30)	1.98 (0.78. 5.01)
60-64	1.12 (0.39, 3.21)	**3.44 (1.13, 10.52)**
Neighborhood, % nonwhite (referent: first quartile)		
Second quartile	0.56 (0.30, 1.02)	**0.79 (0.39, 1.62)**
Third quartile	**2.47 (1.27, 4.81)**	**1.41 (0.64, 3.11)**
Fourth quartile	1.16 (0.57, 2.38)	1.87 (0.80, 4.35)
Percent Hispanic and Latino population	**0.57 (0.39, 0.84)**	1.03 (0.84, 1.25)
Neighborhood, % more than high school education (referent: first quartile)		
Second quartile	1.64 (0.79, 3.39)	0.54 (0.22, 1.34)
Third quartile	1.55 (0.67, 3.67)	**0.23 (0.08, 0.72)**
Fourth quartile	1.48 (0.57, 3.86)	**0.21 (0.06, 0.72)**
Neighborhood, % below poverty level (referent: first quartile)		
Second quartile	**0.34 (0.16, 0.70)**	2.12 (0.85, 5.30)
Third quartile	**0.32 (0.13, 0.78)**	**3.06 (1.02, 9.14)**
Fourth quartile	0.55 (0.21, 1.43)	3.27 (0.91, 11.75)
Comorbidity score	0.92 (0.83, 1.02)	0.98 (0.88, 1.09)
Outpatient visits	**1.13 (1.00, 1.26)**	**0.84 (0.72, 0.98)**
Inpatient visits	**0.85 (0.72, 0.997)**	0.88 (0.75, 1.03)
Distance to health services facilities (referent: less than 5 mile)		
5-10 mile	0.68 (0.38, 1.22)	0.53 (0.28, 1.03)
10-35 mile	0.96 (0.55, 1.65)	0.72 (0.38, 1.34)
35-100 mile	1.81 (0.93, 3.50)	**0.80 (0.59, 1.12)**
>100 mile	1.03 (0.48, 2.22)	0.80 (0.35, 1.81)
Provider-level characteristics		

Total number of hospitals, 2012	1.02 (0.91, 1.15)	0.93 (0.82, 1.05)
Hospital admissions, 2012	1.00 (1.00, 1.001)	**1.00 (1.00, 1.001)**
Hospital beds, 2012	1.001 (0.99, 1.003)	**0.998 (0.995, 1.00)**
Area-level characteristics		
Total Subspecialty, 2013	1.00 (0.992, 1.007)	1.00 (0.991, 1.009)
Number of oncology providers in area	**0.99 (0.984, 0.991)***	**0.99 (0.992, 0.999)**

Bold numbers indicate statistically significant results (P <0.05)
Bold and asterisk numbers indicate statistically significant results (P <0.001)

Table 4. Unadjusted and adjusted odds of receiving AHT by hospital referral region

	N	Adherence		90-day gap persistence	
		Unadjusted	adjusted	Unadjusted	Adjusted
Abilene	9	1.65	2.15	0.76	0.91
Amarillo	15	1.02	2.28	**0.22[a] (0.003)[b]**	**0.14 (0.02)**
Austin	57	1.56	**2.94 (0.018)**	1.70	0.99
Beaumont	9	1.17	0.86	0.33	0.57
Bryan	10	**5.28 (0.008)**	**6.83 (0.02)**	-	-
Corpus Christi	5	2.64	7.98	0.33	0.55
Dallas	169	Ref	Ref	Ref	Ref
El Paso	13	**7.27 (0.001)**	**11.96 (0.013)**	0.80	0.87
Fort Worth	55	0.79	0.99	1.21	0.48
Harlingen	8	0.24	0.45	0.98	**3.03 (0.005)**
Houston	165	1.14	1.09	**0.50 (0.003)**	1.05
Longview	15	**2.94 (0.03)**	1.82	1.74	1.43
Lubbock	18	**0.20 (0.03)**	0.32	1.52	2.04
McAllen	12	2.64	**9.25 (0.026)**	0.48	1.15

Odessa	21	1.08	3.85	2.82	**10.29 (0.02)**
San Angelo	2	0.01	0.01	-	-
San Antonio	51	**2.07 (0.01)**	4.69	0.56	1.02
Temple	1	2.64	2.52	-	-
Tyler	18	0.83	0.78	0.76	0.33
Victoria	1	-	-	-	-
Waco	5	2.64	4.12	0.29	0.46
Wichita Falls	2	1.32	0.57	-	-

[a] Bolded coefficient have p-values less than 0.05.
[b] Numbers in parentheses are p-values. For ease of reading, p-values greater than 0.05 are not reported

DISCUSSION

Our findings explore regional variations in adherence to and persistence of AHT for those with early breast cancer across regions in Texas. We also examine what factors might have associated with those patterns.

We find at least some significant differences in AHT adherence and persistence rates across regions of Texas. Nine regions out of 22 HRRs adhere taking medications and 6 regions out of 22 showed discontinuing of taking the medication with less than 90-day gaps in therapy. 10 regions and 1 region out of 22 discontinued of taking the medication with less than 60-day gaps and 180-day gaps in therapy, respectively. Most of the smaller HRRs have significantly higher or lower rates of treatment adherence and persistence rates relative to the median regions.

The use of AHT varies substantially from one geographical area to another, especially for adherence, with an approximately two-fold difference between the lowest and highest areas. Areas in which the compliance rate is among the lowest quintile should be the focus of the policies or strategies to increase the use of recommended care.

Patient-level factors were found to be significantly associated with the compliance of AHT. For adherence, patients who reside in lower SES areas (the places where more non-white population live, higher rates of poverty, a lower proportion of the population receiving high school education, and more Hispanics or Latinos reside in) have lower probabilities of receiving AHT. Clinical factors including the patients who received BCS or chemotherapy, and the larger number of outpatient visits have positive effect on adherence. These findings are consistent with a

prior studies [33-35]. For persistence, patients who live in the areas where more non-white population reside and the further distance from the residential area to the health care services from the provider were less likely to persist in the treatment.

For both adherence and persistence, patients who initiated the hormonal therapy within a year of diagnosis as recommended were more likely to adhere and to continue to the hormone therapy. National guidelines and American Society of Clinical Oncology (ASCO) recommend that women with non-metastatic breast cancer should initiate adjuvant hormonal therapy within a year of diagnosis [36, 37]. Initiation of AHT medications and ensuring the continuity of care after the initiation should be emphasized since these interventions would reduce further exacerbation, recurrence.

Variation across geographical areas for adherence and persistence was partially explained by the number of hospital admissions and the number of hospital beds of the provider-level characteristics, and the number of oncologists in the area of the area-level characteristics. However, the larger number of oncologists in the area did not mean that higher adherence rates in this study. This could be due to the role of the patient in making the decision to refill prescription or have a follow up visit. Our data can only capture the patients who refilled their prescription and had a follow-up visit with their providers. We have no information on whether providers may emphasize the importance of taking the medications as prescribed and recommended. Therefore, we cannot test the hypothesis as to whether it is the patients who are primarily responsible for making the decision to get their prescription refilled or to take their medication as recommended, moreover, increased demand for specialist care such as oncologists may not be the most important factor in continuing their AHT for these breast cancer patients.

Our study has several limitations that need to be considered. Because administrative claims data are used in this study, we did not have clinical information, such as hormone-receptor status to justify the appropriateness of the initiation of AHT. However, we applied well-known algorithm that was specifically developed for claims data for identifying incident breast cancer cases [38], this algorithm has been approved of better performance of examining breast cancer cases using claims data. Examining adherence using prescription claims assumes that patients are taking medications as often as they fill prescriptions. Although using pharmacy records is the most accurate and validated estimate of actual medication use in large populations over periods of time [39, 40], future research should address whether patients are actually taking the medication continuously as prescribed for follow-up.

Finally, since our study population included only women aged less than 65 enrolled in private insurance in Texas, the results may not generalize to patients who have public, or no, coverage or the patients who reside in other states. However, no study has been conducted examining AHT compliance patterns of younger, privately insured women in Texas. This study helps to fill that gap.

In summary, we found substantial variations in the rates of adherence to and persistence with AHT for privately insured women with early breast cancer across the regions in Texas. Patient factors such as socioeconomic status are significantly associated with complying with treatment. System-level strategies, such as oncologists should explicitly recommend women about their medication use, and ask about barriers to compliance of the therapy, especially for those who reside in AHT underuse regions may improve the adherence to and persistence with the AHT and finally reduce further recurrence in patients with breast cancer.

Compliance with Ethical Standards:

Funding: This study was not funded.

Conflict of Interest: no conflict exists: all authors for this study declare that he/she has no conflict of interest.

Ethical approval: This article does not contain any studies with human participants performed by any of the authors.

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Appendix

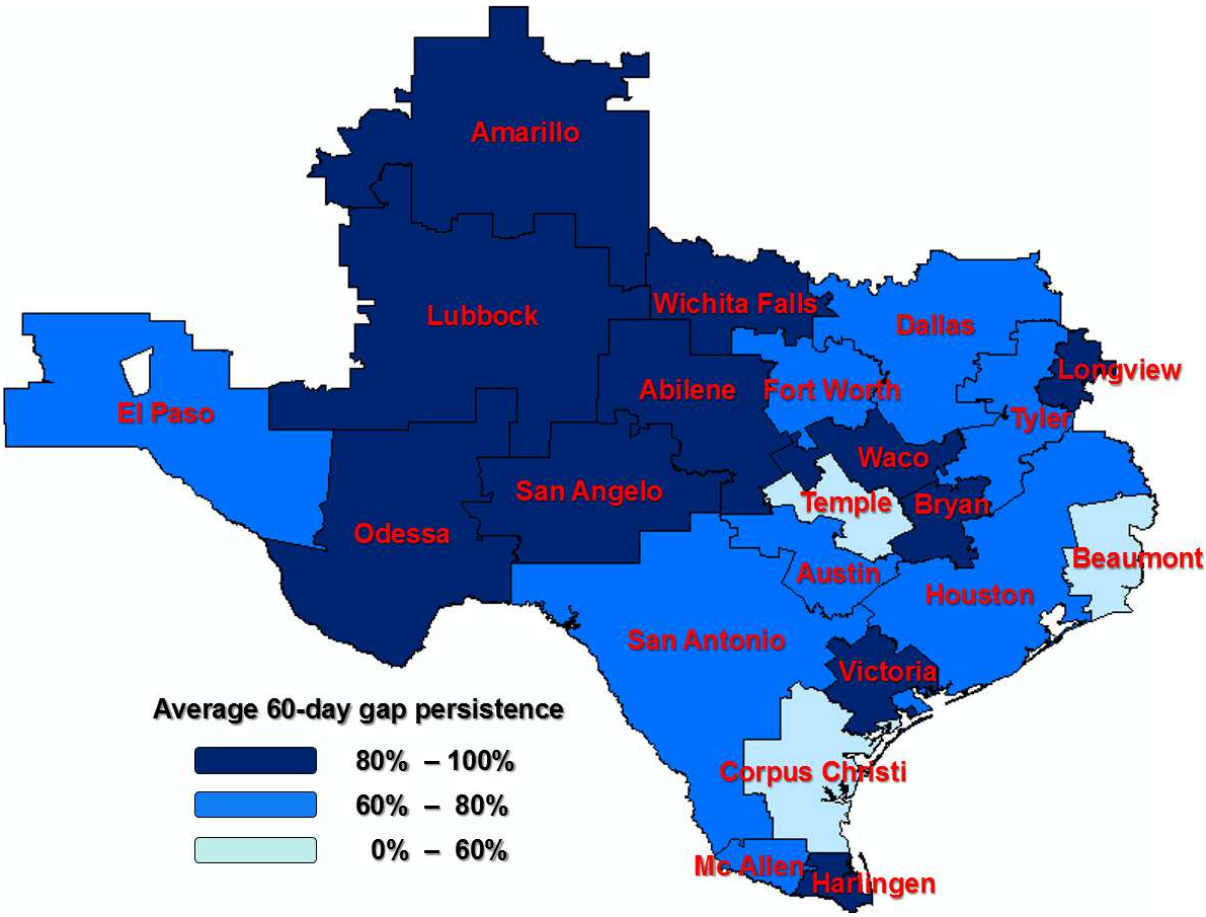
Table A. Mean AHT persistence by HRR, by length of treatment gap

	N	60-day gap persistence by HRR	180-day gap persistence by HRR
Hospital Referral Region			
Abilene	9	0.89	0.89
Amarillo	15	0.80	0.80
Austin	57	0.75	0.95
Beaumont	9	0.56	0.89
Bryan	10	1	1
Corpus Christi	*5*	*0.40*	1
Dallas	169	0.72	0.89
El Paso	13	0.77	0.85
Fort Worth	55	0.70	0.89
Harlingen	8	0.88	1
Houston	165	0.70	0.91
Longview	15	0.87	1
Lubbock	18	0.83	**0.94**
McAllen	12	0.67	0.67
Odessa	21	0.81	1
San Angelo	2	1	1
San Antonio	51	0.65	0.86
Temple	1	0	1
Tyler	18	**0.78**	0.83
Victoria	1	1	1

Waco	5	0.80	1
Wichita Falls	**2**	**1**	**1**

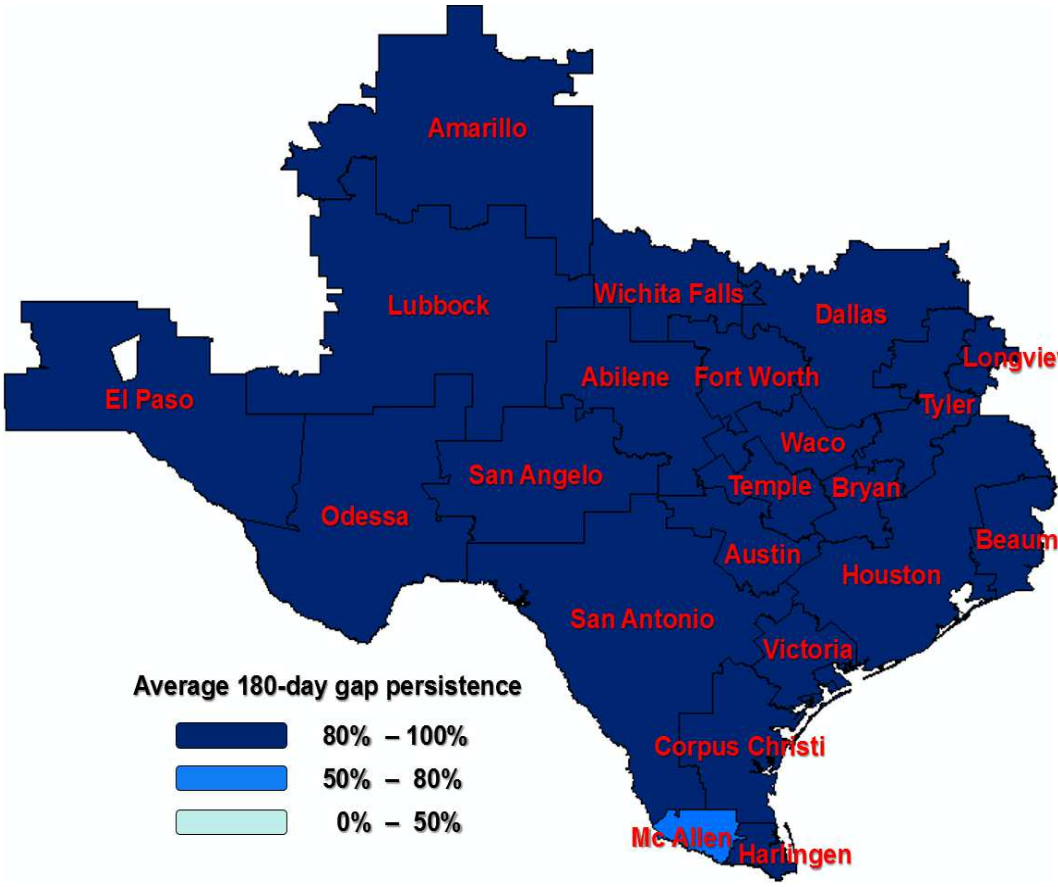
*Mean of TX=0.69;0.90

Figure a. 60-day persistence among Texas Hospital Referral regions (HRRs)



HRRs out of Texas regions were not considered in the study

Figure b. 180-day persistence among Texas Hospital Referral regions (HRRs)



HRRs out of Texas regions were not considered in the study

Table B. Unadjusted and adjusted odds of receiving AHT by hospital referral region

(by different days of gaps in therapy)

	N	60-day gap persistence		180-day gap persistence	
		Unadjusted	Adjusted	Unadjusted	Adjusted
Abilene	9	1.00	2.07	0.32	0.20
Amarillo	15	3.5	0.34	**0.09[a] (0.006)[b]**	**0.03 (0.0003)**
Austin	57	0.93	1.56	2.73	1.08
Beaumont	9	5.25	0.33	0.36	0.21

Bryan	10	0.01	-	-	-
Corpus Christi	5	*5.25*	*0.79*	-	-
Dallas	169	1.18	1.51	0.83	0.21
El Paso	13	0.96	3.99	0.55	0.73
Fort Worth	55	1.42	0.75	1.11	0.18
Harlingen	8	0.78	7.46	-	-
Houston	165	2.27	0.90	1.28	0.27
Longview	15	0.44	2.19	-	-
Lubbock	18	0.70	4.44	1	
McAllen	12	1.60	4.70	0.2	0.47
Odessa	21	1.17	3.98	-	-
San Angelo	2	0.01	-	-	-
San Antonio	51	2.04	1.63	0.56	0.60
Temple	1	-	-	-	-
Tyler	18	1	-	0.46	0.12
Victoria	1	0.01	-	-	-
Waco	5	2.62	0.42	-	-
Wichita Falls	2	0.01	-	-	-

[a] Bolded coefficient have p-values less than 0.05.

[b] Numbers in parentheses are p-values. For ease of reading, p-values greater than 0.05 are not reported

Table C. Predictors of failure to continue with adjuvant hormonal therapy by length of gap

Characteristics	Duration of gap in therapy	
	60 days	180 days
Patient-level characteristics		
Cancer Treatment (referent: no mastectomy no BCS no chemo no rad)		
Mastectomy	0.91 (0.72, 1.16)	0.89 (0.72, 1.10)

BCS	1.04 (0.84, 1.3)	1.003 (0.82, 1.22)
Chemotherapy	**1.3 (1.04, 1.62)**	1.19 (0.82, 1.22)
Radiation therapy	0.39 (0.14, 1.1)	0.42 (0.17, 1.01)
Year of diagnosis (referent: 2008)		
2009	**1.39 (1.02, 1.89)**	**1.37 (1.04, 1.80)**
2010	**2.36 (1.71, 3.25)***	**2.46 (1.86, 3.27)***
2011	**3.95 (2.85, 5.49)***	**3.80 (2.82, 5.11)***
2012	**6.49 (4.5, 9.36)***	**6.67 (4.75, 9.35)***
Therapy initiation (referent: did not initiated ATH within 1yr of BC diagnosis)		
Initiated	**0.49 (0.31, 0.78)***	**0.29 (0.19, 0.44)***
Age at diagnosis, (referent: <40 years)		
40-44	**0.58 (0.34, 0.99)**	0.69 (0.43, 1.11)
45-49	0.69 (0.43, 1.1)	0.75 (0.49, 1.14)
50-54	0.74 (0.47, 1.18)	0.69 (0.45, 1.03)
55-59	0.77 (0.48. 1.23)	0.77 (0.51. 1.17)
60-64	0.8 (0.48, 1.34)	0.76 (0.48, 1.22)
Neighborhood, % nonwhite (referent: <10%)		
10-24%	1.38 (0.99, 1.89)	**1.37 (1.03, 1.82)**
25-50%	1.31 (0.89, 1.93)	1.30 (0.91, 1.84)
≥50%	1.71 (1.03, 2.84)	1.35 (0.86, 2.13)
Percent Hispanic and Latino population	0.94 (0.76, 1.16)	**1.01 (0.84, 1.22)**
Neighborhood, % less than high school education (referent: <25%)		
≥25%	0.86 (0.64, 1.16)	0.88 (0.67, 1.16)
Neighborhood, % below poverty level (referent: <20%)		
≥20%	1.21 (0.90, 1.62)	1.12 (0.86, 1.48)
Comorbidity	**0.95 (0.90, 1.0)**	0.96 (0.92, 1.006)
Outpatient visits	0.99 (0.91, 1.09)	1.01 (0.94, 1.09)
Inpatient visits	0.98 (0.91, 1.07)	0.93 (0.93, 1.07)

Distance to health services facilities (referent: less than 5 mile)		
5-10 mile	0.67 (0.49, 0.91)	**0.71 (0.54, 0.94)**
10-35 mile	0.80 (0.62, 1.04)	0.92 (0.72, 1.16)
35-100 mile	0.78 (0.56, 1.09)	0.89 (0.66, 1.19)
>100 mile	0.82 (0.57, 1.19)	0.93 (0.66, 1.30)
Provider-level characteristics		
Total number of hospitals, 2012	1.02 (0.98, 1.06)	1.02 (0.98, 1.06)
Hospital admissions, 2012	1.0 (.99, 1.001)	1.0 (.99, 1.001)
Hospital beds, 2012	1.0 (1.00, 1.001)	1.0 (1.00, 1.001)
Area-level characteristics		
Total Subspecialty, 2013	0.99 (0.996, 1.002)	0.99 (0.998, 1.001)
Number of oncology providers in area	0.99 (0.997, 1.001)	0.99 (0.998, 1.003)

Bold numbers indicate statistically significant results (P <0.05)

Bold and asterisk numbers indicate statistically significant results (P <0.001)

Figures

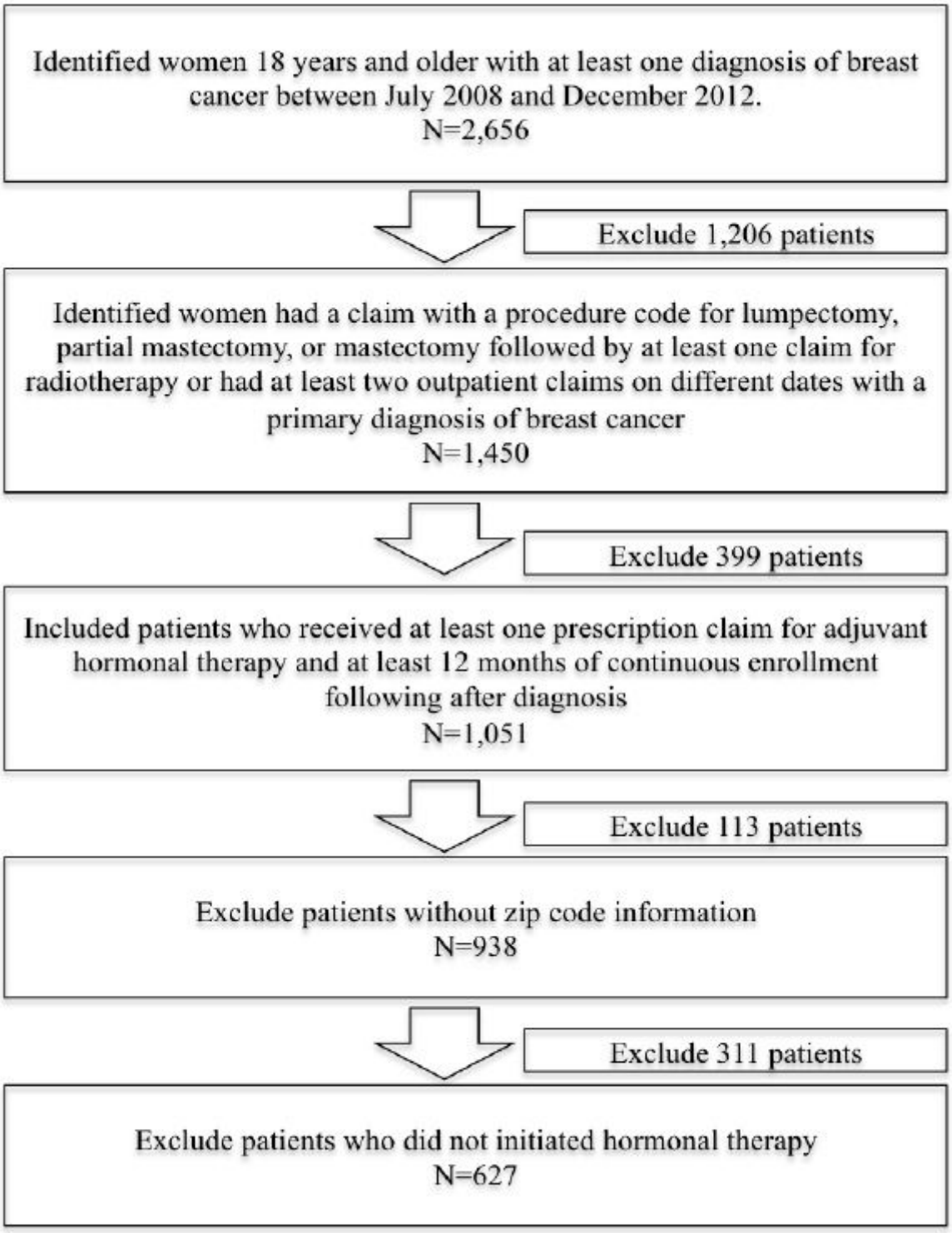


Figure 1

Step of Inclusion/Exclusion Criteria

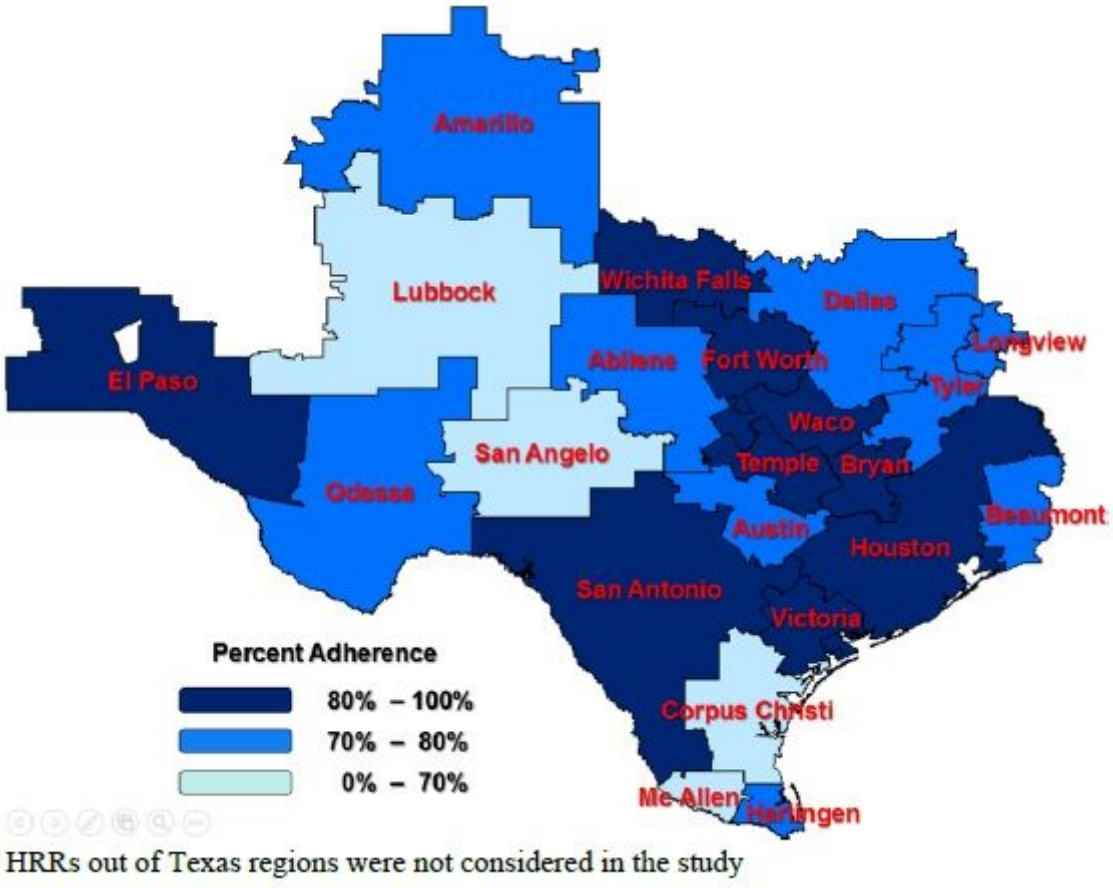


Figure 2

Adherence among Texas Hospital Referral regions (HRRs)

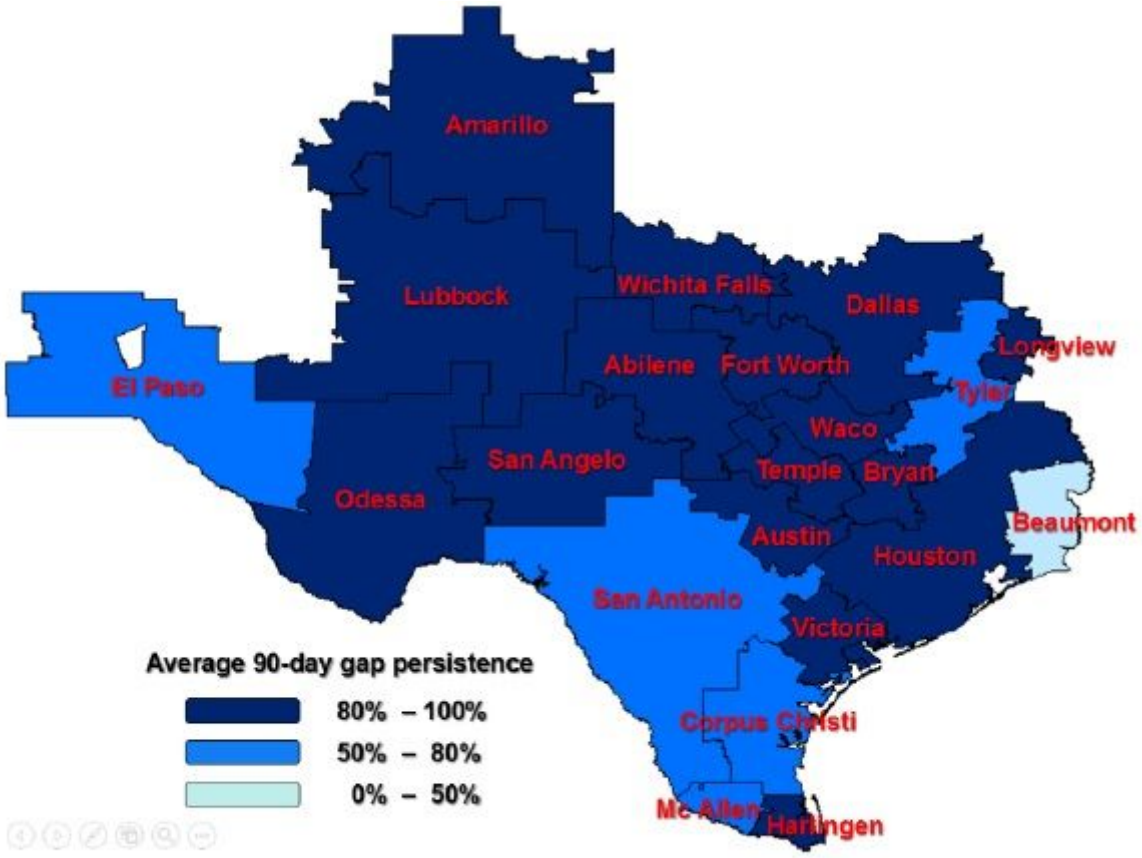


Figure 3

90-day persistence among Texas Hospital Referral regions (HRRs)