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Adherence to adjuvant hormonal therapy and its relationship to breast cancer recurrence and survival among low income women

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Abstract

Objectives—Although clinical trials have demonstrated the benefit of adjuvant hormonal therapy for hormone receptor positive breast cancer, it is not known whether poor medication adherence might impact outcomes, particularly in the context of a low-income population traditionally under-represented in clinical trials. We explored the relationship between adherence to tamoxifen or selective aromatase inhibitors with cancer recurrence and death in a low-income, Medicaid-insured population.

Methods—Using a Medicaid claims-tumor registry and National Death Index data (NDI), we evaluated adherence to adjuvant hormonal therapy [defined by the Medication Possession Ratio (MPR)], cancer recurrence, and cancer-specific survival for female breast cancer diagnosed from 1998–2002, in North Carolina. Multivariate Cox Proportional Hazards models and logistic regression models were used to examine the role of adherence on cancer recurrence and survival.

Results—The sample consisted of 857 cases, mean age 67.7 years, 56.9% Caucasian, 60.9% local stage, with a mean follow-up of 4.4 years. Mean first year MPR was 77%. MPR adherence was not significantly associated with cancer-related death [adjusted HR =1.18 (95% CI 0.54 – 2.59)], or recurrence [adjusted OR= 1.49 (95% CI 0.78–2.84)]. There was also no significant interaction between adherence and use of concurrent CYP2D6 enzyme inhibitors.

Discussion—Hormonal therapy adherence was not associated with breast cancer outcomes in this low-income population with relatively poor adherence. Although suboptimal adherence is considered to be an important clinical problem, its effects on breast cancer outcomes may be masked by patient genetic profiles, tumor characteristics, and behavioral factors.

Keywords

adherence; adjuvant hormonal therapy; breast cancer; recurrence; survival

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Authors' Disclosure of Potential Conflicts of Interest

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INTRODUCTION

Endocrine therapy is a crucial component of adjuvant treatment for women with hormone receptor positive breast cancer [1–10]. However, oncology patient adherence to daily oral therapy is increasingly recognized as a challenge [11;12]. For adjuvant hormonal therapy, reported adherence rates range from 50% to 75%[11;13–16], with discontinuation rates particularly high during the first year [17–20]. It has been estimated that half of breast cancer patients discontinue adjuvant endocrine treatment before the recommended five year treatment period[21]. At least two cohort studies have now linked poor hormonal therapy adherence with adverse outcomes for breast cancer patients including recurrence[22] and mortality[23].

One factor that has been hypothesized to modify the effect of hormonal therapies on breast cancer outcomes is concomitant use of medications that interfere with the activity of the cytochrome P450 2D6 (CYP2D6) enzyme that metabolizes tamoxifen[24]. It has been suggested that concurrent use of CYP2D6 inhibitor medications and tamoxifen may result in reductions in plasma tamoxifen metabolites[25] and possibly reduced treatment efficacy[26]. Thus, concurrent use of CYP2D medications might be expected to moderate observed associations between adjuvant hormonal medication adherence and breast cancer outcomes. However, several recent studies failed to find an association between use of CYP2D6 inhibitor medications and poorer breast cancer outcomes in the context of adjuvant hormonal therapy[22;27;28]. Although Dezentje and colleagues[22] did not find evidence of interactions between tamoxifen adherence and use of CYP2D6 inhibitor medications this possibility needs to be examined in a more diverse sample of women and for additional clinical endpoints.

We previously reported low adherence, with only 60% reporting with medication possession ratios (MPR) greater than 80%, to adjuvant hormonal therapy for early stage breast cancer[29] among low income women identified from a linked database of North Carolina (NC) Medicaid and NC Central Cancer Registry (CCR)[30;31]. In this report, we describe the relationship of adherence to adjuvant hormonal therapy to breast cancer recurrence and death.

METHODS

This study was approved by the Institutional Review Boards at Wake Forest University School of Medicine and at Duke University Medical Center.

Database

Methods used to create the NC CCR-Medicaid linked dataset have been previously described[32]. In NC, Medicaid is almost entirely fee-for service with one small managed care program (<10,000 covered lives), thus exclusions for incomplete utilization data from HMO enrollees is minimal. Health care claims for persons enrolled in Medicaid with dual Medicare insurance (for those legally blind/disabled or 65+ years) are ‘crossed over’ to the Medicaid claims processing contractor, such that Medicaid pays the deductible and coinsurance for these individuals. As a result, our dataset includes detailed claims for both Medicaid and Medicare for the dually insured. For simplicity, we refer to all study claims as ‘Medicaid’ claims regardless of source of reimbursement.

Study Population

We used the NC CCR-Medicaid administrative database to identify 3207 women diagnosed with nonmetastatic, invasive breast cancer between 1998 and 2002 who had local or regional staging, and a confirmed breast conserving surgery or mastectomy after diagnosis. The

sample was further limited to women whose tumors were hormone receptor positive, defined as estrogen receptor (ER) and/or progesterone receptor (PR) positive, or unknown, and who filled at least one prescription for tamoxifen or an aromatase inhibitor within a year of first cancer diagnosis, along with additional criteria summarized in Table 1. The final analytic sample was n=857.

Definition of Variables

Medication possession ratio (MPR)—Adherence is defined as the extent to which a medication is taken as prescribed[33]. One commonly used index for measuring medication adherence, the medication possession ratio (MPR), is defined as the ratio of the total days covered by the medication (using total day supply) divided by the days needing the medication[34;35]. MPR can be expressed as following: MPR = (p/d) × 100. Where p = total day supply minus surplus day supply, and d = total number of days (365) minus the number of days the patient spent in the hospital. As in a previous study of hormonal therapy adherence[22], we focused on adherence during the first year of treatment to allow adherence to be treated as a time invariant predictor.

Medication persistence—Medication persistence was defined as continuous medication use during the year after start of adjuvant hormonal therapy. For our purpose, discontinuity was indicated if a gap of more than 3 months was found between medication refill date/end of therapy year and previous medication refill date plus day supply.

Medications—For the purposes of this study, adjuvant hormonal therapy included the following medications: tamoxifen, anastrozole (ArimidexTM), letrozole (FemaraTM), and exemestane (AromasinTM). In order to calculate adherence and persistence, these medications were treated as indistinguishable from each other if a patient switched to or concurrently took any of the medications. Additionally, a variable for the number of unique prescriptions for all conditions was calculated and defined as the unique number of medications (as defined by the first 9 digits of the National Drug Code) during the year after study medication start date, not limited to the study medications.

Sociodemographic and disease variables—Other independent variables, including breast cancer stage, hormone receptor status, tumor grade, urban/rural residence, and patient race/ethnicity, were obtained from the cancer registry, through which information was abstracted from medical charts by hospital registrars following North American Association of Central Cancer Registries (NAACCR) guidelines[36]. Staging was calculated by categories from Surveillance Epidemiology and End Results (SEER) summary stages[37]. SEER stages 1 and 2 defined local stage, and SEER stage 3, 4, or 5 comprised regional stage. ER and PR status were obtained from the registry. Race was defined as white or non-white. Medicare/Medicaid claims data consistent to the National Cancer Institute's International Classification of Diseases 9th revision grouping methods for comorbidity[38] were used to construct the Charlson Comorbidity Index, a weighted score of comorbidity. This index was calculated over the first two years after cancer diagnosis to better identify underlying conditions and distinguish cancer treatment related complications.

CYP2D6 inhibitor medications—To explore the possible effect of other medications that might decrease the efficacy of tamoxifen, which was used in 88.8% of these women, we identified concomitant use of drugs that were CYP2D6 inhibitors. We focused on medications used in a prior study[27], including fluoxetine (Prozac), paroxetine (Paxil, Seroxat) cimetidine (Tagamet), and sertraline (Zoloft, Lustral), celecoxib, citalopram, escitalopram, levomepromazine, metoclopramide, levomepromazine, mirtazapine, amitriptyline, timolol, propranolol, venlafaxine, and zuclopenthixol.

Recurrence algorithm—A study specific algorithm was developed to detect cancer recurrence. Recurrence was assumed if a patient had a cancer restaging procedure, followed in time by the presence of codes related to breast cancer directed surgery, radiation, or chemotherapy. A complete list of Current Procedural Terminology (CPT)/Healthcare Common Procedure Coding System (HCPCS), National Drug Code (NDC), International Classification of Diseases (ICD)-9, and Diagnosis Related Groups (DRG) codes used to identify treatment is available in Supplemental Digital Content 1. In addition, patients who were identified from the Master Death File as having died of cancer related causes after surgery were assumed to have had a recurrence.

Death Data—We linked these data to the U.S. Social Security Master Death File to record the event of death from all causes through the period of December 31, 2005. The Master Death File has been shown to be highly accurate, and inclusive of 93 percent to 96 percent of deaths occurring to members of the Social Security retirement benefits program when compared to data from the National Center for Health Statistics' National Death Index, the most authoritative source of death information for the U.S. population[39]. Upon locating a match by Social Security Number, we verified the match based on first and last name contained in the registry. Only those matches with exact Social Security Numbers and names were classified as having the outcome of death. After we identified death from the Master Death File, cause of death was determined by the North Carolina Department of Health Statistics vital records database. Cancer-related deaths were defined as those deaths that had cancer listed as the underlying cause coded from the death certificate.

Data Analysis

The SAS system v9.2 was used for all statistical analyses. We first conducted bivariate and multivariate analyses to examine the relationship between adherence (measured by MPR and persistence) and both survival and recurrence. The relationship between adjuvant hormonal therapy adherence and cancer-related death starting one year after initiation of therapy was examined by fitting bivariate and multivariate Cox Proportional Hazard models to the data with cancer- related death treated as the outcome and adherence (MPR and persistence, in different models) as the predictor. The following variables were included as covariates in the multivariate analysis: index medication (Tamoxifen only, AI only, concurrent), age group (0–<45,45–<55,55–<65,65–<75,75+), race (white vs non-white), Charlson comorbidity (continuous), number of unique prescriptions (continuous), concurrent use of medication that decreases CYP2D6 activity (yes vs no), stage (local versus regional), hormone receptor status (positive or unknown), positive lymph nodes (0, 1–3, 4–9,10+), tumor grade using the Facility Oncology Registry Data Standards (FORDS) coding system (I, II, III, IV, and undetermined), type of surgery [breast conserving surgery or mastectomy], use of chemotherapy after diagnosis [yes vs no], use of radiation after diagnosis, urban residence, and year of therapy start (continuous 1998–2003).

Several model assumptions were checked. The proportional hazards assumption for both adherence models was checked by testing for the interactions with the log of follow-up time. The assumption of a linear relationship between the log hazard with MPR was examined using a likelihood ratio test which compared a model with additive splines for MPR to the original linear model.

The relationship between recurrence after one year of therapy initiation and adherence was then examined by use of a logistic regression where the dependent variable was patient recurrence one year after start of therapy and the independent variables were adherence plus the covariates described above. Non-linearity of MPR adherence was assessed as before.

Finally, a subgroup analysis was conducted by testing the interaction of CYP2D6 enzyme inhibitor medication use with MPR adherence. The interaction effect was entered into the multivariate model separately and tested using Type 3 Wald Chi square test.

RESULTS

Sociodemographic and Disease-related Characteristics

Characteristics of the 857 eligible women with nonmetastatic, hormone receptor positive or unknown, invasive breast cancer who had a filled prescription for adjuvant hormonal therapy within one year of diagnosis are shown in Table 2. Hormone receptor status was positive in 75.9% of the sample, and tumor grade was intermediate (grade two) or high (grade 3/4) in 40.5% and 24.2% of cases, respectively. The tumor was local stage in 60.9% of cases. With regard to other treatments, 67.0% had mastectomy, 43.1% radiation, and 33.3% chemotherapy. Mean age was 67.7 years and 56.9% of the sample was white, with 54.1% living in urban areas.

Cancer Survival and Recurrence

During the study period, cancer-related death occurred in 113 (13.2%) of patients and 281 (32.8%) had tumor recurrence. follow-up in the sample starting from initiation of therapy was 1617 days (4.4 years), ranging from 401 days (1.1 years) to 2860 days (7,8 years) after initiation of hormonal therapy.

Hormonal Therapy Adherence

Mean MPR (ranging from 0 to 100) was 77% during the year after initiation, 71% at 2 years, 70% at 3 years, 65% at 4 years, and 58% at 5 years, restricted to patients with continuous enrollment during each year. The proportion of patients who achieved MPR at 80% from year 1 to 5 was 63%, 62%, 60%, 55% and 46% respectively. During the first year of treatment, 82% of the patients were found to be persistent.

Hormonal Therapy Adherence and Cancer Outcomes

Higher MPR adherence to adjuvant hormonal therapy during the first year was not significantly associated with cancer recurrence (unadjusted OR = 1.21, 95%CI 0.70–2.06; adjusted OR = 1.49, 95%CI 0.78–2.84; Table 3) or to cancer-related death (unadjusted HR= 1.37, 95% CI 0.67–2.82; adjusted HR = 1.18, 95% CI 0.54–2.59; Table 3). Persistence during the first year was also not significantly associated with recurrence (unadjusted OR = 1.04, 95% CI 0.72–1.51; adjusted OR = 1.18, 95% CI 0.76–1.82) or to cancer-related death (unadjusted HR 1.25, 95% CI 0.75–2.09; adjusted HR = 1.22, 95% CI 0.70–2.15). No violations of the proportionality assumption (for MPR and persistence) or assumption of linearity (for MPR) were found. There were no significant interactions between use of CYP2D6 enzyme inhibitors and either measure of medication adherence on breast cancer recurrence or death (all *p*-values >.40). Elimination of patients not taking tamoxifen did not change the interaction results.

DISCUSSION

Our finding of no association between hormonal therapy adherence and breast cancer outcomes contrasts with recent studies reporting significant associations between adherence and breast cancer event-free time[22] and all cause mortality[23]. Importantly, these studies included women from the Netherlands and Scotland with very different sociodemographic characteristics and generally better levels of adherence (means or medians of 93% compared to only 77% in our population). In addition, the reported hazards ratios in these positive studies were small (HR= .99 for continuous adherence and recurrence and HR= 1.10 for

poor adherence and mortality). Explanations for the lack of improvement in recurrence and survival with higher adherence rates in our sample may include factors unique to this population of patients and/or breast cancers that develop in this population, methodological limitations of claims data, and inability to detect what may have been a small effect.

Our measure of medical adherence, prescription refill data, was also used in prior studies of hormonal therapy and breast cancer outcomes, but has several limitations. First, it is possible that patients did not take their medications, even if they filled their prescription. Second, prescription refill data are subject to error introduced by receiving free samples of medications and use of discount medications ordered from other sources. We believe the later was unlikely to occur in this population because women in the cohort generally received prescription medications for free or at a very low cost ($1–$6).

There may be characteristics of this patient group that explain the lack of association between adherence and breast cancer recurrence and survival. Indeed, low socioeconomic status is known to be a risk factor for poorer outcomes after breast cancer generally[40]. Breast cancer treatment disparities, including underuse of adjuvant radiation following breast conserving surgery[41], have been previously documented in this sample. In addition, there are known lifestyle factors, such as smoking, obesity, and physical inactivity that impact outcomes after breast cancer that are more common among women of low socioeconomic status [42–46]. These factors may mask the effect of adherence to adjuvant hormonal therapies.

Tumor characteristics unique to this population may explain the lack of association between adherence and breast cancer outcomes. Similar to other registry studies[47], nearly a quarter of the women in the study did not have hormone receptor data recorded in the cancer registry. All were prescribed adjuvant hormone therapy, but if a significant number of these “unknown” patients were actually ER/PR negative then the actual effect of adjuvant endocrine therapy may have been masked in this population.

We defined hormone receptor positive as ER positive and/or PR positive. The importance of the PR to the tumor’s response to hormonal therapy has been debated in the literature. Tumors that are both ER and PR positive, termed luminal A, respond more often to hormonal therapy than tumors that are ER positive and PR negative, termed luminal B, or those that are ER negative and PR positive[48;49]. It is possible that this population of low income women has a higher prevalence of ER positive, PR negative tumors that are less responsive to hormonal therapy. It has been reported that the luminal A tumor type is less common among black women[50], who comprised 40.8% of this sample, Differences in the prevalence of breast cancer subtypes by socioeconomic status have not been described. The tumor registry data from 1998–2002 did not contain information on human epidermal growth factor receptor-2 (HER-2) status which distinguishes between the luminal subtypes. HER-2 positivity may indicate resistance to hormonal therapy[48;51], especially in ER+/PR− subtypes. Controlling for tumor grade in the analysis may have partially accounted for this effect, since most HER-2 positive tumors are high grade.

Patient characteristics that decrease efficacy of adjuvant hormonal therapy are another consideration. It has been reported that side effects are a major determinant of adherence to adjuvant hormonal therapy[11;15;17], such that patients who have less side effects are more adherent to therapy. Lack of side effects might be related to increased tolerance for certain side effects or to drug pharmacokinetics/pharmacogenetics. For instance, tamoxifen is metabolized by the cytochrome P450 system and patients who have low CYP2D6 enzyme activity or who are taking medications that interfere with the activity of this enzyme are less prone to side effects from tamoxifen because there are less active metabolites[24]. The “poor metabolizer” phenotype occurs in less than 10% of people and varies by ethnic group [52;53].

It is unlikely that the prevalence of low CYP2D6 metabolism is higher in this low socioeconomic population, but, if it is, it could explain why we observed no association between adherence and outcomes. There are also many medications that interact with CYP2D6 and thereby decrease metabolism of tamoxifen to its more active metabolites[24;52]. We examined this possibility in our dataset and found that use of CYP2D6 enzyme inhibitor medications was not independently associated with breast cancer outcomes and did not interact with hormonal therapy adherence.

Alternatively, it is possible that current hormonal therapy dosing regimens are robust to occasional nonadherence, particularly if it is sporadic rather than sustained (e.g. missing one or two days a week, rather than entire weeks). Tamoxifen has a relatively long half life (approximately 7 days) and studies have found blood tamoxifen levels consistent with clinical response up to 21 days after drug discontinuation[54]. Anastrozole, letrozole, and exemestane have shorter half lives (1–3 days)[55]. Future studies should try to characterize the patterns of nonadherence.

One limitation of the current study is the possible absence of some important confounding variable that would explain the lack of significant associations between adherence and breast cancer outcomes, as is common among administrative or claims data. In a recent paper, Giordano and colleagues [56] illustrate the difficulties of replicating results from randomized clinical trials using administrative data. In an effort to reduce selection bias, we limited our analysis to cancer-related outcomes, rather than all-cause mortality. Relying solely on clinical trials data is not an option when researchers study groups that have traditionally under-represented in trials, such as the elderly and individuals of low socioeconomic status.

Finally, the sample size and/or length of follow-up may have limited our ability to detect differences in breast cancer outcomes, particularly for cancer-free survival. In clinical trials, survival differences with adjuvant hormonal therapy are typically seen at 5–10 years[57], but cumulative reductions in mortality may be twice as big at 15 years[1]. It is more surprising that with a mean follow-up years, we also saw no association between adherence and breast cancer recurrence. The relatively poor adjuvant endocrine adherence observed in this population may limit our ability to detect difference in recurrence within the study time period. In addition, if the women in this study also had limited compliance with post-cancer treatment mammography surveillance, it is possible that detection of a breast cancer recurrence could have been delayed until after the follow-up period of this study.

In conclusion, in this database of low-income women with breast cancer who were enrolled in Medicaid, we did not observe a significant association between adherence to adjuvant hormonal therapies and breast cancer recurrence or death. Consistent with other recent studies [22;27], we also did not observe either an independent association between use of CYP2D6 enzyme inhibitor medications and breast cancer outcomes or an interaction with hormonal therapy adherence. Although suboptimal adherence is considered to be an important clinical problem, its effects on breast cancer outcomes may be masked by patient genetic profiles, tumor characteristics, and behavioral factors that may independently or interactively influence patient outcomes after breast cancer.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Table 1

Eligibility Criteria

Non-metastatic, invasive breast cancer, diagnosed between 1998-2002, local regional stage, confirmed breast cancer directed surgery after diagnosis (N = 3207)

⇩

ER/PR Positive or undetermined (N = 2440)

⇩

Initiated adjuvant hormonal therapy + no institutional visits during therapy year (N = 2331)

⇩

Continuously enrolled until death or December 2005 (N = 1015)

⇩

Survived during hormonal therapy year (N = 984)

⇩

Started therapy within one year after diagnosis (N = 857)

Table 2

Patient Characteristics

	Study Population ER/PR Positive or Unknown N = 857
Index Medications	
Tamoxifen only	702 (81.9%)
Tamoxifen concurrent with AI	59 (6.9%)
AI only	96 (11.2%)
Age (years)	
Mean (std) [min,max]	67.7 (13.2)[32,100]
<45	60 (7.0%)
45 – <55	90 (10.5%)
55 – <65	180 (21.0%)
65 – <75	227 (26.5%)
75 +	300 (35.0%)
Race	
Caucasian	488 (56.9%)
Other	369 (43.1%)
Comorbidity (Charlson)	
Mean(std)[min,max]	2.46 (2.25)[0,11]
0	207 (24.2%)
1	125 (14.6%)
2	155 (18.1%)
3	141(16.4%)
4+	229 (26.7%)
Number of unique prescription medications during study period	
Mean (Std)[min,max]	15.1 (9.2)[1,69]
None – 5	52 (6.1%)
5 – 10	205 (23.9%)
10 – 20	402 (46.9%)
20+	198 (23.1%)
Number of Positive Lymph nodes	
Negative	410 (47.8%)
1–3	209 (24.4%)
4–9	86 (10.0%)
10+	39 (4.6%)
Not Examined	113 (13.2%)
Concurrent use of medication that decreases CYP2D6 activity	
Any	403 (47.02%)

	Study Population ER/PR Positive or Unknown N = 857
None	454 (53.0%)
Stage	
Local	522 (60.9.%)
Regional	335 (39.1%)
Hormone receptor status	
Positive	650 (75.9%)
Not determined	207 (24.2%)
Type of surgery	
BCS (Breast Conserving Surgery)	283 (33.0%)
Mastectomy	574 (67.0%)
Chemotherapy[1]	
No	572 (66.7%)
Yes	285 (33.3%)
Radiation[1]	
No	488 (57.0%)
Yes	369 (43.1%)
Urban residence	
No	393 (45.9%)
Yes	464 (54.1%)
Tumor Grade	
Low (grade 1)	136 (15.9%)
Intermediate (grade 2)	347 (40.5%)
High (grade 3/4)	208 (24.2%)
Undetermined	166 (19.4%)
Year Initiation of Therapy	
1998	85 (9.9%)
1999	163 (19.0%)
2000	164 (19.1%)
2001	204 (23.8%)
2002	185 (21.6%)
2003	56 (6.5%)
Survival in days [2] Mean (std) [min, max]	1617.11 (565.4) [401,2860]
Cancer Related Deaths	113 (13.2%)
Patient recurrence	
No	576 (67.2%)
Yes	281 (32.8%)

	Study Population ER/PR Positive or Unknown N = 857
Mean MPR Adherence (std); % with MPR Adherence > 80%	
Year 1 (N = 857)	77% (27); 63%
Year 2 (N = 812)	71% (32); 62%
Year 3 (N = 705)	70% (34); 60%
Year 4 (N = 489)	65% (37); 55%
Year 5 (N = 290)	58% (38); 46%
Persistence during 1st year (std)	82% (39)

*1*Chemotherapy and Radiation treatment as identified by codes in Table 2, with date of service within 6 months (chemotherapy) and 1 year (radiation) of diagnosis date.

*2*Survival until cancer related death/censoring event. Patients who died within a year after start of therapy were excluded

*3*Patients who recurred within a year after start of therapy were excluded.

Table 3

Multivariate Analysis of Hormonal Therapy Adherence and Cancer-Related Death and Cancer Recurrence.

	Outcome	
	Time to Cancer-Related Death Hazard Ratio (95% CI)	**Cancer Recurrence Odds Ratio (95% CI)**
MPR Adherence (0–100%)	1.18 (0.54–2.59)	1.49 (0.78–2.84)
Age (Years)		
<45	0.84 (0.41– 1.72)	2.89 (1.42–5.88)
45–54	0.69 (0.32–1.53)	2.26(1.26–4.06)
55–64	0.80 (0.44–1.43)	1.57 (0.98–2.52)
65–74	1.13(0.69–1.87)	1.17 (0.75–1.81)
75+	Reference	Reference
Race, other vs white	1.35 (0.89–2.03)	1.81 (1.28– 2.56)
Cancer Stage (Local vs Regional)	1.17 (0.30–4.58)	0.35 (0.08–1.56)
Adjuvant Hormonal Therapy Medications		
Tamoxifen only	0.38(0.20– 0.70)	0.89(0.47–1.67)
AI only	0.25 (0.09–0.69)	0.64 (0.29–1.39)
Tamoxifen concurrent with AI	Reference	Reference
Surgery Type, Breast-conserving vs mastectomy	0.88 (0.49–1.55)	1.86 (1.17– 2.95)
Adjuvant Cancer Treatment (yes vs no)		
Chemotherapy	1.40 (0.87–2.24)	1.27 (0.85–1.88)
Radiation	0.95(0.59–1.53)	1.56 (1.02–2.38)
Number of Positive Lymph nodes		
Negative	Reference	Reference
1–3	1.70 (0.41–7.10)	0.48 (0.10– 2.22)
4–9	2.78 (0.69–11.28)	0.92 (0.20– 4.24)
10+	6.54 (1.53–28.00)	3.44(0.62–19.06)
Not Examined	0.95 (0.44–2.08)	0.72 (0.42–1.25)
Tumor Grade		
Low	Reference	Reference
Intermediate	1.34 (0.58–3.11)	0.88 (0.53–1.43)
High	4.39 (1.95–9.87)	2.37 (1.40–4.00)
Undetermined	1.80 (0.75–4.30)	1.24 (0.71–2.17)
Hormone Receptor Status (positive vs undetermined)	0.85 (0.54, 1.34)	0.83 (0.57, 1.20)
Charlson Comorbidity Index	1.07 (0.97–1.18)	1.05 (0.97– 1.20)
Use of CYP2D6 Inhibitor Medications (yes vs no)	0.83 (0.54–1.25)	0.93 (0.66–1.30)

	Outcome	
	Time to Cancer-Related Death Hazard Ratio (95% CI)	**Cancer Recurrence Odds Ratio (95% CI)**
Number of Unique Prescription Medications	1.00 (1.00– 1.01)	1.00 (1.00–1.00)

MPR= Medication Possession Ratio; CYP2D6= Cytochrome P450 2D6 enzyme; Cox proportional hazard models were used to calculate the hazard ratio for time to cancer-related death from hormonal therapy initiation date. Logistic regression models were used to calculate the odds ratio for cancer recurrence. Multivariate analyses also controlled for year of initiation of hormonal therapy and urban vs non-urban residence.