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ORIGINAL REPORT

Adjuvant Hormonal Therapy Use Among Insured, Low-Income Women With Breast Cancer

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ABSTRACT

Purpose
Use of adjuvant hormonal therapy, which significantly decreases breast cancer mortality, has not been well described among poor women, who are at higher risk of cancer-related death. Here we explore use of adjuvant hormonal therapy in an insured, low-income population.

Methods
A North Carolina Cancer Registry–Medicaid linked data set was used. Women with hormone receptor–positive or unknown, nonmetastatic breast cancer, diagnosed between 1998 and 2002, were included. Main outcomes were (1) prescription fill within 1 year of diagnosis, (2) adherence (medication possession ratio), and (3) persistence (absence of a 90-day gap in prescription fills over 12 months).

Results
The population consisted of 1,491 women (mean age, 67 years). Sixty-four percent filled prescriptions. Predictors of prescription fill included the following: older age (odds ratio [OR], 1.01; $P = .017$), greater number of prescription medications (OR, 1.06; $P < .001$), nonmarried status (OR, 1.82; $P = .001$), higher stage (OR, 1.83; $P < .001$), positive hormone receptor status (positive *v* unknown, OR, 1.98; $P < .001$), not receiving adjuvant chemotherapy (OR, 1.74; $P = .001$), receipt of adjuvant radiation (OR, 1.55; $P = .004$), and treatment in a small hospital (OR, 1.49; $P = .024$). Adherence and persistence rates were 60% and 80%, respectively. Nonmarried status predicted greater adherence (OR, 1.90; $P = .006$) and persistence (OR, 1.75; $P = .031$).

Conclusion
Prescription fill, adherence, and persistence to adjuvant hormonal therapy among socioeconomically disadvantaged women are low. Improving use of adjuvant hormonal therapy may lead to lower breast cancer–specific mortality in this population.

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INTRODUCTION

Hormonal therapy is a crucial component of treatment for women whose breast cancer is hormone receptor positive.[1-8] It is delivered in pill form, by prescription, for at least 5 years. Patient adherence to oral therapy is an increasingly recognized challenge. For adjuvant hormonal therapy, reported adherence rates range from 50% to 75%,[9-13] with discontinuation rates particularly high during the first year after initial prescription.[14-17] Furthermore, low adherence to adjuvant hormonal therapy may result in lower survival.[18]

Low medication adherence may contribute to poor outcomes in low-income populations, where higher cancer fatality is seen.[19-25] For breast cancer, higher rates of recurrence and mortality are linked to less than standard therapy.[26-28] Medicaid, the health program for individuals and families with low income and resources,[29] is a rich data source for treatment and outcome information in a uniformly poor group, but data from Medicaid does not contain cancer stage designation.

To explore treatment patterns in poor women with early-stage breast cancer, we created a linked database of North Carolina (NC) Medicaid and NC Central Tumor Registry[30,31] and we found higher mortality in women who did not receive adjuvant radiation after breast-conserving surgery.[32] Because Medicaid provides prescription coverage to enrollees, we are also able to track prescription fills and adherence and persistence to adjuvant hormonal therapy over time.

METHODS

This study was approved by the institutional review boards at Wake Forest University School of Medicine, Winston-Salem, NC, and at Duke University Medical Center, Durham, NC.

Study Population

We used the NC Central Cancer Registry (CCR) and NC Medicaid Claims administrative database to identify 1,782 women diagnosed with nonmetastatic, invasive breast cancer between 1998 and 2002 who were continuously enrolled in Medicaid for the 24 months after diagnosis, had local or regional staging, a confirmed breast-conserving surgery or mastectomy after diagnosis, and consistent, nonmissing data on radiation status, age, and diagnosis hospital size. The sample was further limited to women with either hormone receptor–positive or unknown breast cancers who were, therefore, eligible for adjuvant hormonal therapy (n = 1,491).[1]

Methods used to create the NC CCR–Medicaid linked data set have been previously described.[33] In NC, Medicaid is almost entirely fee-for-service with one small managed care program (< 10,000 covered lives), thus exclusions for missing data from health maintenance organization enrollees is minimal. Health care claims for persons enrolled in Medicaid with dual Medicare insurance (for those legally blind/disabled or with age ≥ 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 data set 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.

Definition of Variables

The following dependent variables were constructed: prescription rates, medication possession ratio, and persistence. All acceptable adjuvant hormonal agents, including tamoxifen, anastrozole, letrozole, or exemestane, were included.

Prescription rate. The rate of use of hormonal therapy is defined as at least one pharmacy-filled prescription for an agent within 1 year of diagnosis. For the purposes of defining adherence and persistence, a prescription filled for any of the potentially acceptable agents was included in the denominator.

Medication possession ratio. Adherence is defined as the extent to which a medication is taken as prescribed.[34] 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.[35,36] The total number of days needing the medication is counted from the day the first prescription was filled up to the end of the observation period (365 days) minus the number of days the patient spent hospitalized. Surplus day supply exceeding the observation period was subtracted from the total day supply. This MPR can be expressed as follows: MPR = $(p/d) \times 100$, where p indicates total day supply minus surplus day supply, and d indicates total number of days (365) minus the number of days the patient spent in the hospital. Adherent is defined as an MPR greater than 80%, which is the most frequently used threshold.[37]

Persistence. The duration that a patient continues to fill prescriptions after the first prescription is termed persistence.[36,38] The most widely used method for measuring medication persistence relies on quantifying the gaps between prescription refills.[37,39,40] To minimize misclassifying an individual as nonpersistent because of a legitimate delay in medication refill, such as hospitalization, we used a 90-day gap in prescription fills to define nonpersistence. Other independent variables, including hospital size, breast cancer stage, hormone receptor status, urban/rural residence, and patient race/ethnicity, were obtained from the CCR, through which information was abstracted from medical charts by hospital registrars following North American Association of Central Cancer Registries guidelines.[41] Hospital size was classified by the tumor registry as large (> 100 beds) and small (< 100 beds) on the basis of the most current data from the American Hospital Directory (2007). Stage categories from Surveillance Epidemiology and End Results (SEER) summary stages,[42] as used by the CCR, were used. Local stage was defined as a combination of SEER stage 1 or 2 and regional stage was defined as SEER stages 3, 4, and 5. Status of estrogen receptor (ER) and progesterone receptor (PR) were defined by the CCR (two cases where ER was borderline and PR negative and were coded as hormone receptor negative). Race was defined as white or nonwhite. Charlson comorbidity index, which is a weighted score of comorbidity, was constructed using Medicare/Medicaid claims data consistent to the National Cancer Institute's International Classification of Diseases 9th revision grouping methods for comorbidity.[43] The number of unique prescriptions is defined as the unique number of medication prescriptions from the start date to 1 year after the start date.

Independent variables of number of oncology visits and having a mammogram within the adherence year were also considered, but were not significantly associated with adherence in univariate analysis, so were not included in the multivariate analyses.

Data Analysis

Multivariate logistic regression analyses were conducted to determine predictors of (1) prescription of adjuvant hormonal therapy and (2) adherence and (3) prescription to adjuvant hormonal therapy during the year after the first prescription was filled. In the first analysis, variables included age, race, Charlson comorbidity index, number of unique prescription medications during year since diagnosis, marital status, stage, hormone receptor status, type of surgery, adjuvant chemotherapy, radiation, urban/rural status, and small versus large hospital. For the second and third analyses, the sample was limited to patients initiating adjuvant hormonal therapy within 1 year from diagnosis. Variables were the same as in the first analysis, except that number of unique prescriptions was calculated during year from medication start.

RESULTS

The study sample consisted of 1,491 women with nonmetastatic, hormone receptor–positive or unknown invasive breast cancer. Of the 1,782 women with nonmetastatic, invasive breast cancer in the population, hormone receptor status was positive in 50% (899 of 1,782 patients), negative in 16% (291 of 1,782 patients), and unknown in 33% (592 of 1,782 patients).

Characteristics of the 1,491 women who were eligible for adjuvant hormonal therapy are described in Table 1. Mean age was 67 years (range, 29 to 102 years). Twenty-one percent were age 54 years and younger, 19% were age 55 to 64 years, 24% were age 64 to 75 years, and 35% were age 75 years and older. The majority (59%) were white. The average Charlson comorbidity index was 4.2, with a range of 0 to 15. The average number of unique medications prescribed within 1 year of diagnosis was 15.3 (range, 0 to 66 medications). The tumor was local stage in 65% and regional stage in 35% of patients. With regard to other treatments, most women (66%) had mastectomy, 39% received radiation, and 30% had adjuvant chemotherapy. Most women lived in urban areas (55%) versus rural and were treated at hospitals with more than 100 beds (86%).

Prescription Rate

Rate of prescription fill was 64% overall and 70% among women whose tumors were recorded as hormone receptor positive (Table 2). Tamoxifen was prescribed most commonly (88%). The mean number of days from cancer diagnosis to start of adjuvant hormonal therapy was 112 days.

In multivariate analysis (Table 3), the following predictors were associated with a higher likelihood of filling a prescription for adjuvant hormonal therapy: older age (odds ratio [OR], 1.01; $P = .017$), higher number of unique prescription medications taken from diagnosis date to one year (OR, 1.06; $P \leq .001$), not being married (OR, 1.82; $P = .001$), regional stage (OR, 1.83; $P \leq .001$), positive versus unknown hormone receptor status (OR, 1.98; $P < .001$), no receipt of chemotherapy (OR, 1.74; $P = .001$), receipt of radiation (OR, 1.55; $P = .004$), and small versus large hospital size (OR, 1.49; $P = .024$).

Table 1. Characteristics of Patients With Estrogen Receptor/Progesterone Receptor–Positive or Unknown Breast Cancer (N = 1,491)

Characteristic	No.	%
Age, years		
< 45	141	9
45-54	179	12
55-64	288	19
65-74	360	24
75+	523	35
Race		
White	884	59
Other	607	41
Charleson comorbidity index		
0	156	10
1	146	10
2	174	12
3	199	13
4+	816	55
No. of unique prescription medications		
0-5	158	11
5-10	257	17
10-20	673	45
20+	403	27
Marital status		
Married	164	11
Divorced/separated	164	11
Single/never married	154	10
Widow	357	24
Other	652	44
Stage		
Local	974	65
Regional	517	35
Hormone receptor status		
Positive	899	60
Not determined	592	40
Type of surgery		
BCS	507	34
Mastectomy	984	66
Adjuvant chemotherapy		
No	1,049	70
Yes	442	30
Radiation		
No	908	61
Yes	583	39
Urban residence		
No	674	45
Yes	817	55
Type of hospital		
Large	1,277	86
Small	214	14

Abbreviation: BCS, breast-conserving surgery.

Table 2. Rate of Prescription of Adjuvant Hormonal Therapy Medication in Medicaid-Insured Women With Hormone Receptor–Positive or Unknown Status Breast Cancer

Hormonal Agent	Rate of Use	%
None	540	36.2
Tamoxifen	837	56.1
Anastrozole	89	6.0
Letrozole	24	1.6
Exemestane	1	0.1

NOTE. Rate of prescription defined by first hormonal agent prescription filled within 1 year of diagnosis. Excluded patients not continuously eligible during 12 months from diagnosis. The list of National Drug Codes used to identify adjuvant hormonal therapy is available from the authors upon request.

Adherence

Of women who filled a prescription within 1 year after diagnosis, the mean MPR adherence rate was 0.75, with a range from 0.08 to 1.00 during the year after initial prescription. The median MPR adherence rate was 0.86. Only 60% of patients exceeded an MPR of 0.80.

Table 4 shows the results of the multivariate analysis of predictors of adherence. Marital status was significantly associated with adherence rate, with nonmarried being more likely to be adherent (OR, 1.90; $P = .006$). Age, race, stage at diagnosis, type of surgery, and receipt of adjuvant chemotherapy or radiation were not significantly associated with adherence rate.

Persistence

The persistence rate was 80%. Multivariate analysis of predictors of persistence to adjuvant hormonal therapy is shown in Table 5. Factors associated with higher likelihood of persistence were the following: nonmarried status (OR, 1.75; $P = .031$), having Charlson comorbidity index of 3 compared with 0 (OR, 2.09; $P = .037$), and regional versus local stage (OR, 1.48; $P = .046$).

We explored the relationship between adherence (with an 80% threshold in MPR, which, for the 1-year study period, is 73 days), and persistence (defined as 90 days without prescription refill, censored at 365 days). Although both measures were significantly correlated ($r = 0.81$), a cross-tabulation of persistent patients and adherent patients (n = 951) showed that 190 patients were both nonadherent and nonpersistent, 194 patients were nonadherent but persistent,

Table 3. Multivariate Analysis of Predictors of (any) Use of Prescription Hormonal Therapy in Women With Hormone Receptor Positive or Unknown Status Breast Cancer (N = 1,491)

Outcome: Hormone Prescription = 1	Odds Ratio	95% CI	*P*
Age	1.01	1.00 to 1.02	.017
Race, other *v* white	1.19	0.94 to 1.50	.140
Comorbidity			
1 *v* 0	0.84	0.52 to 1.37	.493
2 *v* 0	0.83	0.51 to 1.32	.430
3 *v* 0	0.90	0.56 to 1.45	.668
4 + *v* 0	0.70	0.47 to 1.06	.091
No. of prescription medications	1.06	1.05 to 1.08	< .001
Marital status, other *v* married	1.82	1.27 to 2.59	.001
Stage, regional *v* local	1.83	1.39 to 2.42	< .001
Hormone receptor status, positive *v* unknown	1.98	1.58 to 2.49	< .001
Type of surgery, mastectomy *v* BCS	1.17	0.87 to 1.58	.293
No adjuvant chemotherapy	1.74	1.26 to 2.39	.001
Radiation	1.55	1.15 to 2.09	.004
Urban residence	0.87	0.69 to 1.10	.244
Type of hospital, small *v* large	1.49	1.05 to 2.10	.024

Abbreviation: BCS, breast-conserving surgery.

Table 4. Predictors of Adherence to Adjuvant Hormonal Therapy During the Year After the First Prescription in Women With Hormone Receptor–Positive Breast Cancer Who Filled a Prescription Within 12 Months of Diagnosis (n = 951)

Outcome: MPR = 0.80	Odds Ratio	95% CI	*P*
Age	1.01	1.00 to 1.02	.098
Race, other *v* white	0.84	0.64 to 1.10	.196
Comorbidity			
1 *v* 0	1.31	0.71 to 2.40	.387
2 *v* 0	0.94	0.53 to 1.69	.833
3 *v* 0	1.62	0.90 to 2.90	.105
4 + *v* 0	0.86	0.52 to 1.41	.542
No. of prescription medications	1.01	0.99 to 1.02	.350
Marital status, other *v* married	1.90	1.20 to 3.00	.006
Stage, regional *v* local	1.24	0.92 to 1.69	.161
Hormone receptor status, unknown *v* positive	0.98	0.74 to 1.30	.897
Type of surgery, mastectomy *v* BCS	1.24	0.86 to 1.79	.240
Adjuvant chemotherapy	0.73	0.51 to 1.06	.098
Radiation	1.21	0.85 to 1.72	.286
Urban residence	0.90	0.68 to 1.19	.452
Type of hospital, small *v* large	1.16	0.79 to 1.70	.441

NOTE. Adherence defined as MPR > 80%; may include overlapping prescriptions for hormonal agents. Switching to another medication took place.
Abbreviations: MPR, medication possession ratio; BCS, breast-conserving surgery.

none were adherent but nonpersistent, and 567 patients were both adherent and persistent.

DISCUSSION

In this population-based study of low-income, continuously insured patients with breast cancer, we report low fill, adherence, and persistence rates to adjuvant hormonal therapy. Only 64% of women who were eligible filled any prescription for tamoxifen or an aromatase inhibitor within 12 months after diagnosis. In the year after first prescription fill, adherence (MPR > 80%) and persistence rates were 60% and 80%, respectively.

Table 5. Predictors of Persistence in Use of Adjuvant Hormonal Therapy in Women With Hormone Receptor–Positive Breast Cancer Who Filled a Prescription Within 12 Months of Breast Cancer Diagnosis (n = 951)

Outcome: Persistence = 1	Odds Ratio	95% CI	*P*
Age	1.01	0.99 to 1.03	.100
Race, other *v* white	0.82	0.59 to 1.15	.257
Comorbidity			
1 *v* 0	1.70	0.84 to 3.46	.142
2 *v* 0	1.16	0.60 to 2.25	.648
3 *v* 0	2.09	1.05 to 4.19	.037
4+ *v* 0	1.39	0.79 to 2.45	.265
No. of prescription medications	1.01	0.99 to 1.03	.339
Marital status, other *v* married	1.75	1.05 to 2.90	.031
Stage regional *v* local	1.48	1.01 to 2.18	.046
Hormone receptor status, positive *v* unknown	1.00	0.70 to 1.41	.983
Type of surgery, mastectomy *v* BCS	0.98	0.63 to 1.53	.931
Adjuvant chemotherapy	0.97	0.62 to 1.53	.904
Radiation	0.78	0.51 to 1.20	.259
Urban residence	0.88	0.63 to 1.24	.475
Type of hospital, small *v* large	1.02	0.64 to 1.64	.925

NOTE. Persistence defined as the absence of a break in prescriptions of 90 days or more during the year after the start date.
Abbreviation: BCS, breast-conserving surgery.

Predictors of a greater likelihood of filling a prescription for hormonal therapy were older age, more prescription medications, not being married, higher stage, having hormone receptor status of positive (*v* unknown), not receiving adjuvant chemotherapy, receiving adjuvant radiation, and receiving diagnosis in a small hospital. Except in the oldest old (85 to 92 years old), for which use of hormonal therapy has been reported lower,[44] other studies also found greater use with older age.[12,45] With regard to ER status, lower fills with ER unknown status may reflect appropriate prescribing, but this cannot be ascertained from registry/claims data. Finally, the inverse association of adjuvant hormonal therapy and chemotherapy is similar to that of prior reports.[12] We suspect that hormonal therapy is substituted for chemotherapy in cases where there is concern about toxicity. Adherence to adjuvant hormonal therapy, in these cases, would be particularly important.

Poor adherence to tamoxifen has been linked to increased risk of death from breast cancer.[18] In their retrospective cohort study of 2,080 patients with breast cancer, Thompson et al[18] reported tamoxifen prescription rate of 79%, median adherence of 93% (interquartile range, 84% to 100%), and reduced breast cancer survival with lower adherence. Furthermore, Thompson and other investigators reported that longer duration of tamoxifen use was associated with improved survival.[1,28]

In this low-income, insured population, the adherence rate (defined as MPR > 80%) of only 60% within the first year of adjuvant hormonal therapy is lower than rates reported in other studies.[14,16,17] Among women initiating tamoxifen for primary breast cancer and who were enrolled in New Jersey Medicaid or Pharmaceutical Assistance to the Aged and Disabled programs, nonadherence (defined as ≤ 80% of eligible days covered by prescription tamoxifen) within the first year after prescription was only 17%.[16] When interviewed, only 8% of women ≥ 65 years of age with hormone receptor–positive breast cancer from four regions in the United States reported nonadherence to tamoxifen within the first year after prescription.[14] In a study of three large commercial health programs, the nonadherence rate (defined as MPR < .80) to anastrozole within 12 months of prescription ranged from 12% to 18% among the health plans.[17] We suspect that the high nonadherence rate of 40% in our study, despite continuous insurance coverage that included prescriptions at a low copay rate, was related to the population—a uniformly low-income population in NC.

The nonpersistence rate of 20% within 1 year after initial prescription is also higher than that of most previous reports and is worrisome because it is likely that persistence to adjuvant hormonal therapy declines further over subsequent years of treatment. Rates of discontinuation, or nonpersistence, reported in clinical trials of adjuvant tamoxifen range from 16% to 32% at 5 years.[46-50] Persistence rates for patients not participating in clinical trials are typically lower.[10,12,14] These studies, however, primarily focused on older patients and used patient self-report as a measure of treatment discontinuation, a method that has considerable limitations and may significantly underestimate the true rate of nonpersistence.[13,51] There are two reports of persistence to tamoxifen therapy based on prescription fills.

The first is a study of women ≥ 65 years of age in six health care delivery systems in the United States describing discontinuation rates (defined as no tamoxifen for 60 days) of 15%, 24%, 33%, 40%, and 49% at 1, 2, 3, 4, and 5 years, respectively.[15] The second was a study of the Irish Health Service Executive Primary Care Reimbursement Services pharmacy database and reported a discontinuation rate at 1 year similar to that seen in our study (22%), but with a significantly more stringent definition of nonadherence (180 consecutive days with no tamoxifen or alternative hormonal therapy); at 3.5 years, 35% had discontinued.[52] Even in the Irish system of "equal" access, therefore, many women did not continue therapy through the full course. We project that the low rate of persistence to adjuvant hormonal therapy at 1 year among these low-income women only leads to lower rates in subsequent years and may contribute to the poor outcomes seen in this population.

In multivariate analyses, we found that not being married was positively associated with adherence and persistence. Higher comorbidity and stage were predictive of persistence but not of adherence. Age, race, and tumor management were not significantly associated with adherence or persistence. We are not aware of other studies reporting a relationship between marital status and adherence or persistence with adjuvant hormonal therapy for breast cancer. Conversely, in other chronic diseases, social support and being married were associated with greater medication adherence.[53] We lack a good explanation for this finding, but suspect that it reflects a different pattern of social support in this particular population.

There are three general strengths of this study. First, this database of Medicaid-insured women provides a uniformly low-income population for study. Second, linking Medicaid and NC CCR data allows accurate stage designation, which is otherwise not available from Medicaid claims alone. Third, Medicaid has a prescription plan, allowing for accurate tracking of prescription fills. As opposed to other databases, such as Surveillance, Epidemiology, and End Results, where prescription information is not available and reporting of hormonal therapy is limited by the ability of registrars to collect the information (κ of 0.52 for registry v medical chart review),[54] we are able to directly measure prescription fills. Of note, we included only women who were continuously covered by Medicaid insurance for 24 months, either as Medicaid only or as dually insured by Medicaid and Medicare, and thus provided information across age groups. Furthermore, with information about all filled prescriptions in the Medicaid database, we captured patients who switched to other, alternative, acceptable hormonal agents and included them as adherent or persistent, therefore presenting potentially more comprehensive information than has previously been possible.

We recognize that there are limitations to the study. First, we lack information about individual patient adverse effects or health literacy, which are known to be linked to treatment adherence and persistence.[9,10] Second, in this administrative data set, we cannot determine whether a prescription is not written, as well might be the case for women enrolled in Medicaid,[55] or whether it was written and not filled. Alternatively, medication provided as samples or through patient assistance programs is not captured, though use of patient assistance programs was unlikely, because there is nominal cost to prescriptions with Medicaid. Finally, we dichotomized medication adherence and persistence behaviors in our multivariate analyses, which may have limited our ability to find significant associations among variables. Sensitivity analyses were conducted using multivariate models treating these variables as continuous and time series, respectively, and we did not find any differences in the direction and significance of the estimates.

In summary, use of adjuvant hormonal therapy, as measured by prescription fill adherence and persistence, was low in this group of low-income, insured women who were eligible for adjuvant hormonal therapy for breast cancer. Given its impressive therapeutic efficacy[1] and low toxicity relative to adjuvant chemotherapy, consensus guidelines[56-58] recommend that adjuvant hormonal therapy be offered to women with hormone receptor–positive breast cancer. We propose that improving use of adjuvant hormonal therapy will improve breast cancer outcome in low-income and underserved populations. The next steps for this research will be to find modifiable risk factors for low use of adjuvant hormonal therapy in this low-income population and to design interventions. This will likely require study outside claims data. Factors such as care processes, patient-physician communication, reduced adherence owing to side effects, and patient knowledge or beliefs regarding treatment are not available in administrative data and will need to be explored. Whatever the method, a successful approach to this problem will likely lead to improved care for underserved patients in other areas as well.

AUTHORS' DISCLOSURES OF POTENTIAL CONFLICTS OF INTEREST

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