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Endocrine therapy initiation among Medicaid-insured breast cancer survivors with hormone receptor-positive tumors

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Abstract

Purpose—Hormone receptor positive (HR+) cancers account for most breast cancer diagnoses and deaths. Among survivors with HR+ breast cancers, endocrine therapy (ET) reduces 5-year risk of recurrence by up to 40%. Observational studies in Medicare and privately-insured survivors suggest under-utilization of ET. We sought to characterize ET use in a low-income Medicaid-insured population in North Carolina.

Methods—Medicaid claims data were matched to state cancer registry records for survivors ages 18–64 diagnosed with stage 0-II HR+ breast cancer from 2003–2007, eligible for ET, and enrolled in Medicaid for at least 12 of 15 months post-diagnosis. We used multivariable logistic regression

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Human Subjects and Animal Studies Statement

This research on human subjects was approved by the University of North Carolina at Chapel Hill Institutional Review Board. No animal studies were carried out by the authors for this article.

Conflict of Interest Statement

Dr. Stephanie Wheeler, Racquel Elizabeth Kohler, Dr. Katherine Elizabeth Reeder-Hayes, Ravi K. Goyal, Dr. Kristen Hassmiller Lich, Alexis Moore, Timothy W. Smith, Dr. Cathy L. Melvin, and Dr. Hyman Bernard Muss declare that they have no conflict of interest.

to model receipt of any ET medication during 15-months post-diagnosis controlling for age, race, tumor characteristics, receipt of other treatments, co-morbidity, residence, reason for Medicaid eligibility, involvement in the Breast and Cervical Cancer Control Program (BCCCP), and diagnosis year.

Results—Of 222 women meeting inclusion criteria, only 50% filled a prescription for ET. Involvement in BCCCP and earlier year of diagnoses were associated with significantly higher odds of initiating guideline-recommended ET (Adjusted Odds Ratio [AOR] for BCCCP: 3.76, 95%CI: 1.67–8.48; AOR for 2004 relative to 2007: 2.80, 95%CI: 1.03–7.62; AOR for 2005 relative to 2007: 2.11, 95%CI: 0.92–4.85).

Conclusions—Results suggest substantial under-utilization of ET in this population. Interventions are needed to improve timely receipt of ET and to better support survivors taking ET.

Implications of cancer survivors—Low-income survivors should be counseled on the importance of ET and offered support services to promote initiation and long-term adherence.

Keywords

Endocrine Therapy; Breast Cancer; Medicaid; Survivorship

Introduction

Over the past 20 years major advances in the treatment of breast cancer have led to earlier diagnoses, improved outcomes, and more survivors. Among the estimated 13.7 million cancer survivors currently alive in the US, 41% are female breast cancer survivors.[1] As treatment options become more sophisticated and prognosis continues to improve, supporting ongoing surveillance to address identified gaps in breast cancer survivorship care will become increasingly important in further reducing the burden of cancer. From the health system perspective, monitoring cancer survivors closely can ensure long-term care needs are managed, result in earlier detection of recurrences, improve patient satisfaction, and safeguard high quality survivorship care.[2]

An important component of high quality breast cancer survivorship care is long-term use of endocrine therapy (ET), the cornerstone of adjuvant treatment to prevent recurrence among hormone receptor positive (HR+) (defined as estrogen or progesterone receptor positive) breast cancer survivors. HR+ breast cancer is the most common breast cancer phenotype, affecting approximately 70% of breast cancer patients, and is the leading cause of breast cancer mortality.[3] Five years of treatment with either tamoxifen or an aromatase inhibitor (AI) reduces risk of HR+ breast cancer recurrence by 40% and risk of death by one-third.[4] Unfortunately, many women do not experience the full benefits of ET due to underuse.[5–9] Percentages of HR+ breast cancer survivors who never initiate ET range from 18% in women seen at academic medical centers to 36% in low-income women.[10–13] Overall, half of women who do initiate ET discontinue or do not take ET as prescribed after five years.[7, 6]

Observational studies show the high prevalence of ineffective ET use, document its potential impact, and offer insight into how drivers of ET underuse may vary among subgroups.

Patient-level factors associated with ET non-initiation in observational studies include minority race/ethnicity, competing co-morbidities, more advanced disease,[13, 12] and prevalence of reported side effects of ET. Some women report confusion about the hormonal nature and actions of tamoxifen, and considerable distress caused by hot flashes, weight gain, cessation of menses, and loss of fertility.[14] Similarly, AI have been associated with arthralgia, musculoskeletal problems, and gynecologic effects, resulting in underuse of this ET medication.[15] Most of the data on ET use come from privately insured or single institution or single health plan studies.[16, 17, 13] We need additional data from vulnerable populations, such as low-income, Medicaid enrollees, to better understand whether these populations are at higher risk for ET underuse and correspondingly worse outcomes. One study conducted in New York's Medicaid population found that only 39% received optimal ET including prompt initiation and adherence during the first year post-diagnosis and that comorbidity and more advanced disease were associated with failure to initiate.[12] Another study conducted in the North Carolina (NC) Medicaid population found that women who were older, not married, taking more prescription medications, higher stage, being treated at a small hospital, and not receiving chemotherapy or radiation therapy were more likely to initiate ET.[11] That study, however, included women with unknown hormone receptor status and used Medicaid data from 1998–2002.[11] Providers and decision makers need updated data from states like NC (i.e., large, socioeconomically and racially diverse, largely rural states with access to care challenges) reflecting more recent trends in ET use in low-income populations. The purpose of this paper is to update the literature by examining initiation of ET among Medicaid-insured HR+ breast cancer survivors diagnosed in 2003–2007 to understand more clearly how to improve cancer survivorship care in this population.

Methods

Data Sources

Our data include 2003–2007 Medicaid claims and enrollment data for women diagnosed with breast cancer in NC in the same years, according to NC Central Cancer Registry (NCCCR) records. The database contains paid claims for emergency, inpatient, and outpatient services and prescription drug claims, as well as administrative data tracked at the patient level longitudinally.

Study Population

We restricted our analyses to women ages 18–64 who had stage 0, I, or II, breast disease (Figure 1). We further limited our patient sample to exclude women with stage 0 disease who received mastectomy, as ET is not clinically indicated in this group. Eligible women were enrolled in Medicaid for at least one month before their initial diagnosis and had no evidence of a cancer diagnosis prior to that time according to NCCCR records. To ensure that all claims for cancer treatments, hospitalizations, emergency department visits, prescriptions, and regular care were recorded in our data, but recognizing that Medicaid enrollment can sometimes be transient, we required that women be enrolled in Medicaid for at least 12 of the 15 months following the index breast cancer diagnosis, consistent with a previously published methodology.[18] We also excluded women who were dually insured by Medicare during our study period because we did not have access to Medicare claims;

failure to exclude this group would have likely missed relevant claims. Other exclusions were based on the same previously published methodology.[18] HR+ status was taken from biomarker measures reported in the NCCCR data; we coded positive or elevated estrogen and progesterone receptor status as positive.

Dependent Variables

American Society of Clinical Oncology (ASCO) quality metrics for breast cancer surveillance for survivors (2006) state that coordination of care, including adjuvant ET for women with HR+ disease, should be ensured.[19] National Comprehensive Cancer Network (NCCN) guidelines recommend that ET be prescribed for most HR+ patients with stage I-II disease and considered for those with HR+, stage 0, ductal carcinoma in situ (DCIS) to reduce risk of recurrence and development of a new primary tumor in the contralateral breast (Version 3.2013). In accordance with these guidelines, we developed the following binary quality of care measure: receipt of any ET (Tamoxifen, Femara/Letrozole, Aromasin/Exemestane, or Arimidex/Anastrozole) in the 15-month period post-diagnosis, among women with HR+ disease. National drug codes used to identify ET in the claims are detailed in Supplemental Table 1 (Appendix).

Independent Variables

Based upon published literature, we selected factors associated with quality of survivorship care to include in multivariate models.[18] Specifically, independent variables included age at diagnosis, race, urban/rural residence at diagnosis, reason for Medicaid eligibility, involvement in the Breast and Cervical Cancer Control Program (BCCCP), year of diagnosis, co-morbidities, stage at diagnosis, and receipt of breast cancer treatments other than ET. We used Medicaid race/ethnicity information, when available, because it is based on Social Security information; when it was not available, we used NCCCR race/ethnicity. County codes of patient's residence at diagnosis were used to assign rural or urban categories, as determined from the 2003 US Department of Agriculture Economic Research Service. We included indicators for ever being classified as blind or disabled for Medicaid eligibility and ever being enrolled in BCCCP. Diagnosis year was recorded based upon NCCCR data.

Clinical independent variables included presence of co-morbid conditions and cancer stage at diagnosis. Presence of co-morbid conditions was determined using the National Cancer Institute (NCI) combined index with modification as described elsewhere.[18] Stage at diagnosis (stage 0, stage I, and stage II) was derived from the 6th edition American Joint Committee on Cancer (AJCC) grouping. Surveillance, Epidemiology and End Results (SEER) summary stage was used for the remaining patients when AJCC was not available. If neither AJCC nor summary stage were available, we used Tumor, Node, and Metastasis (TNM) information to classify into stages. Therapeutic characteristics included receipt of breast cancer surgery, radiation therapy, and chemotherapy, which were identified using relevant diagnostic and procedural codes, following previously published methodology.[18]

Statistical Analysis

We used descriptive statistics and bivariate analyses to explore distributions of all variables and to characterize the study population. Multivariable logistic regression was used to examine initiation of ET as a function of all independent variables. We tested the specification and functional form of variables such as age, co-morbidity, and year of diagnosis and ultimately used the continuous form of age and co-morbidity and categorical specifications of year of diagnosis based upon model fit statistics. We considered and tested several interaction terms of interest, but due to lack of improvement of model fit and considering our relatively small sample size, we elected not to include interaction terms in final model estimations. All statistical analyses were conducted using STATA (Stata 12; StataCorp, College Station, TX).

We also conducted a secondary analysis restricting the sample to only include women who received primary therapy within 15 months of diagnosis (n=147) and examining ET use in the next 15 months post-primary therapy completion, because many women do not begin ET until after primary treatment (surgery, radiation therapy, and/or chemotherapy) is complete.

Results

Of 1,264 women with stage 0-II or unstaged breast cancer enrolled in Medicaid in the initial sample, 222 met inclusion criteria and were included in our final primary analysis. Of these, the mean age was 49 years, 47% were white, the majority (67%) lived in urban versus rural areas, most women were stage 1 (57%), and 21% participated in BCCCP. More than half of our sample received mastectomy (52%), and 26% of our sample received breast conserving surgery (BCS), leaving 22% who received no surgical procedure at all during the 15 month study period, the majority of whom had stage I or II disease (80%). Only half (50%) had a pharmacy claim for ET within 15 months of diagnosis, suggesting significant failure to initiate in this population. Among women receiving adjuvant ET (n=111), tamoxifen was the most commonly used ET medication (57%), anastrozole was the most commonly used AI (50% of AI users), and 7% of women switched among types of ET prescriptions during our study period. The mean time to first ET prescription fill was 267 days post-diagnosis. In general, as expected, women filling tamoxifen prescriptions were younger than women filling AI prescriptions ($p<0.001$)

In bivariate analyses (Table 1), women who received guideline-recommended ET were more likely to have had any surgery (85% versus 71%, $p<0.01$), more likely to have received radiation therapy (67% versus 50% of those who did not get ET, $p=0.01$) and more likely to have been enrolled in BCCCP (31% compared to 12%, $p<0.001$). Women who did not receive any primary therapy (surgery, radiation therapy, and/or chemotherapy) were much less likely to receive ET ($p<0.004$).

Table 2 presents results from the multivariable logistic regression for receipt of ET at any time during the 15-month period post-diagnosis among all women with HR+ breast cancer. Participation in BCCCP was a highly significant predictor of ET initiation (adjusted odds ratio (AOR): 3.76; 95% CI: 1.67–8.48; $p<0.01$). In addition, earlier year of diagnosis (2004 or 2005) was associated with higher odds of ET initiation, compared to 2007 (2004 AOR:

2.80; 95% CI: 1.03–7.62; $p < 0.05$; 2005 AOR: 2.11, 95% CI: 0.92–4.85; $p < 0.10$). Black women had lower odds of ET initiation (AOR: 0.84), but this effect was not statistically significant.

Our secondary analysis limited to the women receiving primary therapy during the first 15 months post-diagnosis ($n=147$) indicated that 72% of women initiated ET during the 15 months after primary treatment completion (results not shown).

Discussion

In this study, we sought to describe patterns of ET initiation among low-income, Medicaid-insured women diagnosed with HR+ breast cancer. ET is the cornerstone of adjuvant treatment for HR+ cancers, yet only 50% of women with HR+ cancers initiated ET within a reasonable time period post-diagnosis. The literature suggests that even fewer adhere to ET for the full recommended 5 years.[17, 7] We also observed another concerning problem: 22% of our sample did not receive any surgical intervention in the 15 months post-diagnosis. Although some women may have forgone these treatments for clinically valid reasons, the overall high rates of under-utilization of both ET and surgery may indicate that this low-income population remains particularly underserved, despite having access to health insurance.

Our estimates of ET initiation were lower than those reported in other settings (e.g., older women in academic medical centers;[10] privately insured women;[23, 13] and New York Medicaid patients[12]), perhaps reflecting particular vulnerabilities of younger and Medicaid-insured patients in North Carolina, such as poor access to care. Our results are also different from a previous study conducted in NC Medicaid patients in an earlier time period, 1998–2002,[11] but a number of methodological differences between the two studies may account for the difference in findings (i.e., that study included women older than 65, whereas ours did not, due to our focus on understudied younger women; that study included all women who were HR+ or had unknown HR status and received BCS, whereas ours examined only HR+ women receiving any type of surgical intervention or no surgical intervention). Despite slight differences in methodological approach and time period of observation, our study and others suggest that ET initiation is substantially lower than it should be.

Taking ET is accompanied by many known side effects (e.g., hot flashes and other menopausal symptoms; joint pain) that likely influence whether women decide to initiate the medication.[24, 10, 15, 25, 26] Additionally, adherence to a daily medication that causes uncomfortable side effects to prevent recurrence—a silent health condition for which patients may feel they are not particularly at risk—may be difficult for many women, particularly those who are already socioeconomically vulnerable or have poor access to supportive care. As such, interventions that focus on education, outreach, and support may help low-income women better understand their personal risk for recurrence and make more evidence-informed decisions about whether and how to take ET for the recommended time duration.

In our study, BCCCP enrollment was significantly associated with receipt of ET. The reasons for this may be multifactorial: BCCCP-enrolled women, who were previously uninsured and whose breast cancer was detected through free screening provided by BCCCP, may have been previously quite disconnected from health care services, and enrollment in BCCCP may empower them to become more connected to health services. In addition, certain health providers or systems may be more likely to facilitate BCCCP enrollment and may also provide better quality of care. It is possible that ‘safety net’ and assistance programs like BCCCP have the potential to improve quality of survivorship and follow-up care in particularly underserved, hard-to-reach populations. If this is true, then the policies and procedures associated with BCCCP should be studied in more depth to better understand the nature of support that is provided, as it may be leveraged further.

Several explanations may account for the fact that 22% of women in our sample did not undergo surgery. First and foremost, it is possible that women were lost to clinical follow-up, but still enrolled in Medicaid. Indeed, 10% of the total study sample did not receive any primary therapy at all within 15 months, which may mean that these women declined or delayed treatment intentionally or that they were interested in receiving treatment, but were not able to do so due to poor access to care or ineffective navigation through the treatment and referrals process. This finding is consistent with other studies which have reported treatment disparities in lower income breast cancer populations.[27–29] It is also possible that treating providers made a clinical decision not to perform surgery in an otherwise curable patient, perhaps due to other serious co-morbid illnesses which may be more common among lower income patients.[30] Lastly, women initially reported as having early stage disease may have been determined later to have metastatic disease, leading to other non-surgical treatments.

One potential implication for these findings pertains to the role of the oncologist and primary care provider (PCP) in managing breast cancer survivors during the 5 years they are supposed to be taking ET. Research shows that PCPs may be able to help coordinate breast cancer survivorship care.[31, 2] Given oncology specialist shortages and increasing demand for breast cancer follow-up care resulting from growing numbers of survivors, PCPs may be vital agents in helping patients seek consultation and follow-up from a medical oncologist so that adjuvant ET may be prescribed, if indicated.[32–34]

A number of important limitations accompany our analysis. First and foremost, we focused on initiation of ET as measured by prescription fills of ET in pharmacy claims data. Such data cannot provide information about (a) whether women actually swallowed the first pill after filling the prescription; or (b) whether providers wrote prescriptions for ET that were never filled by patients. We also were unable to measure in claims or registry data some important factors that may influence ET initiation, such as patient perceptions and concerns about taking medication every day and patient-provider communication. Given the observational nature of our data, we also are unable to say whether associations between certain independent variables such as BCCCP enrollment and ET initiation are causal. Second, Medicaid prescription claims data may be incomplete if women pay out of pocket for low-cost ET. This is more likely the case in later years, as cheaper, generic ET medications became available on the market and may help explain our study’s finding that

earlier year of diagnosis was associated with higher odds of ET receipt. Nonetheless, we expect that most low-income, Medicaid-insured women with pharmacy benefits would rather have Medicaid pay for their ET than to pay out of pocket. Third, because our analysis was conducted in a NC population insured by Medicaid, findings may not be generalizable to other states' Medicaid programs or to other non-Medicaid populations. Nevertheless, results from this research may help inform other state-based and private sector initiatives in NC and elsewhere to improve the quality of care for breast cancer survivors. Finally, our small sample size prevented us from having sufficient power to detect whether important disparities in ET use exist by race/ethnicity, rural/urban residence, unemployment status, and social isolation. Nonetheless, because all women in our sample were Medicaid-insured, they are all vulnerable socioeconomically, and some studies suggest that socioeconomic status is a greater predictor of health and healthcare behavior than race and other indicators of vulnerability.[35, 36]

These findings suggest an urgent need for improvement. Qualitative research may help elucidate why women fail to initiate this important medication and how to improve ET in underserved populations. Interventions aimed at improving adjuvant ET initiation and sustaining adherence in the long-term, particularly in underserved populations like Medicaid patients, are necessary to address sub-optimal survivorship care and improve breast cancer outcomes. Policies and programs that emphasize the benefits of long-term adherence to ET and reduce structural barriers to care (such as lack of oncology providers who accept Medicaid insurance) are recommended. In turn, optimizing the delivery of ET will eventually lead to fewer breast cancer recurrences and improvements in mortality in underserved populations. 11

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Figure 1.

Inclusion and exclusion criteria applied to identify the analytic sample

Notes: * Includes stage 0 women receiving breast conserving therapy or no surgery; **

Excludes women who did not receive primary therapy

Table 1

Descriptive Summary of HR+ Breast Cancer Survivors

N=222			
Patient Characteristics	Received ET % (n)	No Receipt of ET % (n)	p-value
	50.0 (111)	50.0 (111)	
<i>Clinical Characteristics</i>			
NCI Combined Comorbidity Index mean (SD) [†]	0.27 (0.41)	0.27 (0.44)	
Tumor Stage			
Stage 0	9.9 (11)	12.6 (14)	
Stage 1 (reference category)	61.3 (68)	52.3 (58)	
Stage 2	28.8 (32)	35.1 (39)	
<i>Socio-demographic Characteristics</i>			
Age mean (SD)	49.0 (8.6)	50.2 (9.1)	
Race			
White (reference category)	49.5 (55)	45.0 (50)	
Black	34.2 (38)	40.5 (45)	
Other	16.2 (18)	14.4 (16)	
Urban Residence	64.9 (72)	68.5 (76)	
Blind/Disabled classification	45.9 (51)	52.3 (58)	
BCCCP participation	30.6 (34)	11.7 (13)	p<0.001
Year of Diagnosis			
2004	15.3 (17)	9.9 (11)	
2005	27.0 (30)	24.3 (27)	
2006	25.2 (28)	27.9 (31)	
2007 (reference category)	32.4 (36)	37.8 (42)	
<i>Therapeutic Characteristics</i>			
Chemotherapy	58.6 (65)	50.5 (56)	
Radiation	66.7 (74)	50.5 (55)	p=0.01
Surgery			
Mastectomy (reference category)	55.0 (61)	48.6 (54)	
BCS	29.7 (33)	22.5 (25)	
No Surgery	15.3 (17)	28.8 (32)	p=0.01
No Primary Treatment	4.5 (5)	16.2 (18)	p=0.004
<i>Endocrine Therapy Outcomes</i>			
Tamoxifen only	56.8 (63)	--	
Aromatase Inhibitors only	36.0 (40)	--	
Anastrozole [‡]	50.0 (20)	--	
Letrozole [‡]	32.5 (13)	--	
Exemestane [‡]	7.5 (3)	--	
Switched Endocrine Therapy prescriptions [§]	7.2 (8)	--	

N=222			
Patient Characteristics	Received ET % (n)	No Receipt of ET % (n)	p-value
Mean days to first prescription fill	267 (104)	--	

Notes: HR+, Hormone Receptor Positive; ET, Endocrine Therapy; SD, Standard Deviation; BCCCP, Breast and Cervical Cancer Control Program; BCS, Breast Conserving Surgery; NCI, National Cancer Institute; AI, Aromatase Inhibitor;

[†] NCI Combined Comorbidity Index for cancer site-specific conditions in claims data (Klabunde et al, 2007);

[‡] among women filling AI prescriptions;

[§] women switching between any prescription class

Table 2

Logistic Regression Estimation of Receipt of Endocrine Therapy in Primary Analytic Sample

Patient Characteristics	Endocrine Therapy OR	95% CI
<i>Clinical characteristics</i>		
Comorbidity Score	1.042	(0.504 – 2.156)
Tumor Stage (Stage 1 reference category)		
Stage 0	0.869	(0.309 – 2.438)
Stage 2	0.716	(0.370 – 1.387)
<i>Socio-demographic</i>		
Age	0.977	(0.939 – 1.016)
Race (White reference category)		
Black	0.84	(0.439 – 1.609)
Other	1.434	(0.584 – 3.518)
Urban Residence	0.894	(0.478 – 1.673)
Blind/Disabled classification	1.234	(0.595 – 2.557)
BCCCP participation	3.759 ***	(1.666 – 8.480)
Year of Diagnosis (2007 reference category)		
2004	2.805 **	(1.032 – 7.622)
2005	2.110 *	(0.918 – 4.849)
2006	1.398	(0.623 – 3.137)
<i>Therapeutic Characteristics</i>		
Chemotherapy	1.013	(0.497 – 2.064)
Radiation	1.463	(0.743 – 2.880)
Surgery (Mastectomy reference category)		
BCS	1.183	(0.481 – 2.911)
No Surgery	0.574	(0.262 – 1.260)
Constant	1.538	(0.183 – 12.96)
Observations	222	

Notes: BCCCP, Breast and Cervical Cancer Control Program; BCS, Breast Conserving Surgery

p<0.01,**
p<0.05,*
p<0.1