

Determinants of the receipt of guideline-concordant breast cancer treatment

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ABSTRACT

Patient and facility level determinants of non-concordance with recommended breast cancer treatment

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Background: Guidelines for the management of early stage invasive breast cancer include locoregional and systemic treatments that, on average, prolong disease-free and overall survival. Yet, a considerable proportion of women do not receive some or all of the guideline recommended breast cancer care. Disparities in the receipt of radiation therapy, chemotherapy, and endocrine therapy by patient and treatment facility characteristics may contribute to demographic differences in breast cancer survival.

Methods: This population-based cohort study enrolled women aged 20 – 69 years, diagnosed with stage I, II, or IIIA breast cancer in the Seattle-Puget Sound area between 2004 and 2011, who were identified through the local Surveillance Epidemiology and End Results cancer registry. Concordance with National Comprehensive Cancer Network (NCCN) guideline recommendations and American Society of Clinical Oncology (ASCO)/NCCN Quality Measures (QMs) was assessed for 1,344 women using data collected from cancer registry records and patient self-report. Multivariable logistic regression was used to estimate the association between patient and facility characteristics and non-concordance with NCCN guidelines and QMs.

Results: Compared to women with uninterrupted insurance coverage, women who did not have insurance at some point during their breast cancer treatment had a 3.5-fold (95% CI: 1.0-10.5) higher likelihood of non-concordance with NCCN guidelines for radiation therapy, and a 3.5-fold (95 % CI 1.2-10.5) higher likelihood of non-concordance with NCCN guidelines for chemotherapy. Low income was consistently associated with risk of non-concordance, with multivariate odds ratios of 2.3 (95% CI: 1.0-4.9) for radiation therapy guidelines, 4.6 (95% CI: 1.8-11.6) for chemotherapy guidelines, and 3.7 (95% CI: 1.4-9.7) for endocrine therapy guidelines associated with an annual family income of <\$50,000 relative to that of ≥\$90,000.

Conclusions: Economic factors were associated with non-receipt of most forms of recommended treatment. Interventions, such as patient navigation, may help remove individual-level barriers to the receipt of guideline-concordant breast cancer treatment in uninsured, underinsured, and low-income women.

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DEDICATION

For my parents, James McDougall and Denise Galloway, for their unconditional love and for demonstrating the rewards of a life of science.

CHAPTER 1: A brief study introduction, detailed description of the methods and materials used, and discussion of the study's limitations

INTRODUCTION

The clinical benefits of radiation therapy, chemotherapy, and endocrine therapy, for the treatment of breast cancer are well-documented, and these therapies have been incorporated into guidelines for breast cancer management.¹ However, a substantial proportion of patients do not receive all of the guideline recommended breast cancer treatment and disparities in the receipt of individual therapies have been observed by race, ethnicity, insurance, and marital status. Out of concern that “cancer patients may be getting the wrong care, too little care, or too much care”, the 1999 Institute of Medicine report, Ensuring Quality Cancer Care, called for national quality monitoring of cancer care.² Numerous prior studies have responded to this call, providing evidence that not all breast cancer patients are getting appropriate care by studying Medicaid,³⁻⁷ or Medicare populations,⁸⁻¹¹ single institutions,¹² National Comprehensive Cancer Network (NCCN) institutions,¹³⁻¹⁵ and other hospital or health system based studies.¹⁶⁻²⁵ Other studies have used data sources on geographically-defined populations to investigate the receipt of breast cancer care.²⁶⁻³⁰

The objective of this population-based study was to identify patient and facility level characteristics associated with the failure to receive guideline recommended breast cancer treatment. We evaluated non-concordance with National Comprehensive Cancer Network (NCCN) treatment guidelines for early stage breast cancer¹ and with 3 American Society of Clinical Oncology (ASCO)/NCCN Quality Measures (QMs) for breast cancer

METHODS

Study sample and data collection

To investigate concordance with breast cancer treatment recommendations, we assembled a cohort of breast cancer cases participating in an ongoing population-based study of risk factors for various subtypes of breast cancer. The parent study enrolled women aged 20 – 69 years without a history of in-situ or invasive breast cancer who were diagnosed with invasive breast cancer in the Seattle-Puget

Sound area (King, Pierce, or Snohomish county) between July 1, 2004 and December 31, 2011 identified from the Cancer Surveillance System (CSS), a population-based tumor registry that participates in the Surveillance, Epidemiology and End Results (SEER) program of the National Cancer Institute. Potential study subjects were sampled on the basis of age at diagnosis, estrogen receptor (ER) status and progesterone receptor (PR) status. All women with ER-negative/PR-negative tumors who met the specified age and stage criteria were eligible for enrollment. A random sample of women with ER-positive tumors (regardless of PR status) was also selected and was frequency matched on the basis of age (within 5 years) and year of diagnosis, for a 1:1 ratio of ER-positive to ER-negative/PR-negative cases. This sampling scheme resulted in a study population that was both younger and more likely to have ER-negative/PR-negative breast cancer than the general population of breast cancer cases in the United States.³¹ The Fred Hutchinson Cancer Research Center Institutional Review Board approved the study protocol, and all study subjects gave informed consent.

CSS Cancer Registry Data

CSS staff abstract data on patient demographics and tumor characteristics from medical records from hospitals, outpatient surgical centers, pathology laboratories, radiotherapy centers and selected clinician offices. We conducted a centralized review of all pathology reports available electronically from CSS to verify ER and PR status and ascertain HER2 status and testing method for all study participants. The facility where the breast cancer case was diagnosed, as recorded in CSS, was characterized using publically available data from the Joint Commission. Annual breast cancer patient load and availability of radiation therapy or chemotherapy were abstracted from the Joint Commission website for the most recent year data was available (2009 for most facilities, range 2007 – 2009).

Telephone Interviews

After being identified from CSS, eligible study participants were mailed a study introduction letter, a calendar, and set of show-cards. All participants had to have access to a telephone for the interview, which was conducted only in English. A trained study interviewer followed-up the mailing with a telephone call to answer questions and schedule an appointment for the interview. The calendar was used during

the interview to facilitate data collection of exposures and outcomes that occurred in relation to specific dates. Show-cards contained the names of surgical procedures, the generic and brand names of endocrine therapies, and lists of potential problems faced and support services used during treatment. Interviewers used a computer assisted telephone interview (CATI) written in Blaise (©Blaise – Statistics Netherlands – 2011) to ascertain information on start dates and types of treatment received. Dates of tumor recurrences were collected and used as a conditional check in the CATI program to ensure that only therapies to treat the initial diagnosis and not for a recurrence was used to classify non-concordance. The interview was also used to ascertain self-reported data on socioeconomic position, including highest level of education achieved, occupation, annual household income, total assets, total debt, home-ownership, financial security (measured as the number of months a woman estimated she could have remained in her place of residence with the same lifestyle, had she lost her regular source of income), type of insurance, whether she experienced a period of no insurance during treatment, and marital status. In addition, basic demographic data including age and race was verified and information on health history, including history of smoking and depression, and known or suspected breast cancer risk factors, including height and weight in the year prior to diagnosis, were collected during the interview.

Definition and classification of non-concordance with recommended breast cancer treatment

NCCN guidelines are continuously revised as new evidence from randomized controlled trials and observational studies of breast cancer interventions becomes available. All recommendations are categorized into ordered levels of evidence based on the degree of agreement between members of the NCCN expert panel that the intervention is appropriate. Category 1 and Category 2A recommendations are those for which there is NCCN consensus that the intervention is appropriate, whereas Category 2B and Category 3 recommendations may reflect some disagreement between NCCN panel members. We restricted our assessment of guideline concordance to Category 2A or higher recommendations and focused specifically on receipt of radiation therapy, adjuvant chemotherapy, and adjuvant endocrine therapy (Table 1.1). The continuous review process employed by NCCN results in an average of 2 versions of guidelines per year, however the Category 1 and 2A recommendations specifying who should receive radiation, chemotherapy, and endocrine therapy did not change across different versions of the

NCCN guidelines in use from July 1, 2004 to December 31, 2011. Therefore, all women in this study were assessed for concordance with guidelines that applied at the time of their breast cancer diagnosis.

In addition to investigating factors associated with non-concordance with NCCN guidelines, we were interested in how patient and facility level characteristics may be associated with the timing of breast cancer therapies. The 3 American Society of Clinical Oncology (ASCO)/NCCN Quality Measures (QMs) for breast cancer use the same evidence base as the NCCN guidelines but restrict the denominator for quality assessment to those women most likely to benefit from the therapy and specify a time interval from the date of diagnosis within which the therapy must be received in order to be considered concordant (Table 1.2).

Data on tumor characteristics, including tumor size, lymph node involvement, ER, PR, and HER2 status ascertained from CSS was used to determine eligibility for assessment with NCCN guidelines and ASCO/NCCN QMs. In addition to tumor characteristics, self-reported prior surgical management of the tumor was used to determine whether radiation was indicated. Women whose tumors met the criteria outlined in the denominator columns of tables 1.1 and 1.2 were included in the respective analyses of radiation therapy, chemotherapy, and endocrine therapy and each corresponding QM. In the telephone interview we asked "What types of surgery were performed as part of the diagnosis and/or treatment of your breast cancer?" Participants were referred to mailed show-cards for a list of common surgical procedures. The mailed calendar was then used to ascertain the date of each reported procedure. Participants were also asked "Have you received chemotherapy for your breast cancer?" Women who stated that they did were then asked about the date they began therapy and where the therapy was received. An identical set of questions were used to ascertain data about the receipt of radiation therapy and endocrine therapy. Women who stated that they did not receive radiation, chemotherapy, or tamoxifen or an aromatase inhibitor in the interview were classified as non-concordant with the respective NCCN guidelines if Category 1 or Category 2A recommendations indicated that therapy based on their individual tumor characteristics and prior surgical management. To be concordant with QMs, radiation therapy and endocrine therapy had to be received within 365 days of diagnosis and chemotherapy had to be received within 120 days of diagnosis.

A total of 1,890 potential study participants were identified from CSS; of whom 97 could not be located and 499 refused (Figure 1.1). A total of 1,344 women were interviewed (response of 71%). NCCN guidelines recommended radiation therapy for 701 women who were surgically treated with lumpectomy (n=649) or were surgically treated with mastectomy and had ≥ 4 positive axillary nodes (n=52). NCCN guidelines recommended chemotherapy for 753 of the 1,344 study subjects, and endocrine therapy was recommended for 449 study subjects. Of the 1,344 study subjects, 684 received lumpectomy and were eligible for assessment for concordance with QM1, 551 ER/PR-negative cases were eligible for assessment for concordance with QM2 and 415 ER/PR-positive cases were eligible for assessment for concordance with QM3.

Statistical analysis

Non-concordance was calculated by dividing the total number of women with a given characteristic by the number of women with that characteristic that did not receive the indicated therapy. Multivariable logistic regression was used to estimate the odds ratio (OR) and Wald based 95% confidence interval (CI) for each exposure of interest. Age at diagnosis, year of diagnosis, tumor stage, body mass index (BMI), smoking status at diagnosis, and history of depression were selected as a priori confounders and were included in all multivariable models given their assumed associations with the exposures of interest and with receipt of treatment. Compared to null models containing only the exposure of interest, the addition of age modeled continuously changed the estimated ORs by $>10\%$ for all exposures of interest. Year of diagnosis and tumor stage did not change the ORs by $>10\%$ but were included because of their clinical significance. Body mass index (BMI), smoking status at diagnosis, and history of depression were included as a group in an attempt to control for differences in general health status of the participants. The addition of these three covariates as a group changed the ORs for some, but not all models in comparison to the respective null model. Race and smoking history were also assessed as potential confounders but were not included in final models, as they did not change the risk estimates of any of the ORs of interest by $>10\%$. Effect modification by ER/PR/HER2 status was assessed given the sampling design of the parent study, but significant heterogeneity in OR estimates was not observed by HR status. Finally, sensitivity analyses were performed to assess the impact of

using Category 2A or higher NCCN recommendations to define guideline concordance. When the criteria for guideline concordance were modified to include category 2B recommendations, more women were eligible for assessment with each guideline recommended therapy and the overall percentage of women who were non-concordant increased. However, the addition of more women did not substantially alter our conclusions for the associations between patient and facility level characteristics and non-concordance, so we decided to use the more conservative guidelines based on the recommendations for which there is unanimous agreement of benefit. Data was analyzed using STATAv.12.1 (STATA® College Station, Texas).

LIMITATIONS

This study has several important limitations, warranting cautious interpretation of the results. First, 100% concordance with NCCN guidelines or QMs is not expected. Quality breast cancer care involves joint decision making by patients and providers as they weigh the risks and benefits of therapy. Risks that may tip the balance towards an appropriate deviation from guideline recommendations include comorbidities and a patient's general health. Unfortunately, the prevalence of poor health is likely to be greater in women with low socioeconomic position and may be especially high among women with public or no insurance. We attempted to control our estimates for this confounding effect of poor health by including BMI, smoking status, and depression as covariates in all models. Given the strong relationship between having a high BMI or being a current smoker and many of the comorbid conditions included in the Charlson comorbidity index,^{32,33} we expect that by controlling for these factors some of the confounding by comorbidity was lessened. However, we cannot rule out the possibility that residual confounding may contribute to the observed associations. Second, while our interview facilitated the collection of dynamic data on socioeconomic position and numerous treatments, we could only conduct the survey in English and we were not able to contact women whose telephone numbers had changed since their last date of contact with a treatment provider. Consequently, we may have disproportionately not enrolled women with low medical literacy that may have been at highest risk of not receiving treatment, potentially leading to an underestimate of non-concordance in comparison to the underlying population of breast cancer cases. Finally, although we interviewed over 1,300 women, the sample size

was inadequate for investigating the relative contributions of correlated variables to non-concordance or to detect associations between uncommon exposures and non-concordance. For uncommon exposures, such as having a period of no insurance, the width of the CIs range over 20-fold demonstrating a lack of precision due to limited power.

SUMMARY

This study was designed to identify factors at the patient and facility level that contribute to non-concordance with recommended breast cancer treatment. It overcomes some limitations of prior studies that have focused on non-geographically defined populations with restricted generalizability, or were population-based studies relying on incomplete cancer registry data, by using a detailed telephone interview of a population-based sample of women with breast cancer. Despite improving data collection in some respects, our use of a telephone interview also limited our ability to include all women and could not be used to collect data on reasons why providers may have recommended against or discontinued treatment. Future studies could overcome some of the limitations of using re retrospectively collected data from English-only telephone interviews, as presented here, by enrolling women at diagnosis and following them for 5-years. Such a study could collect longitudinal data on a number of outcomes and time varying exposures, and with proper funding data collection could be tailored to meet the needs of a more diverse population than we were able to include.

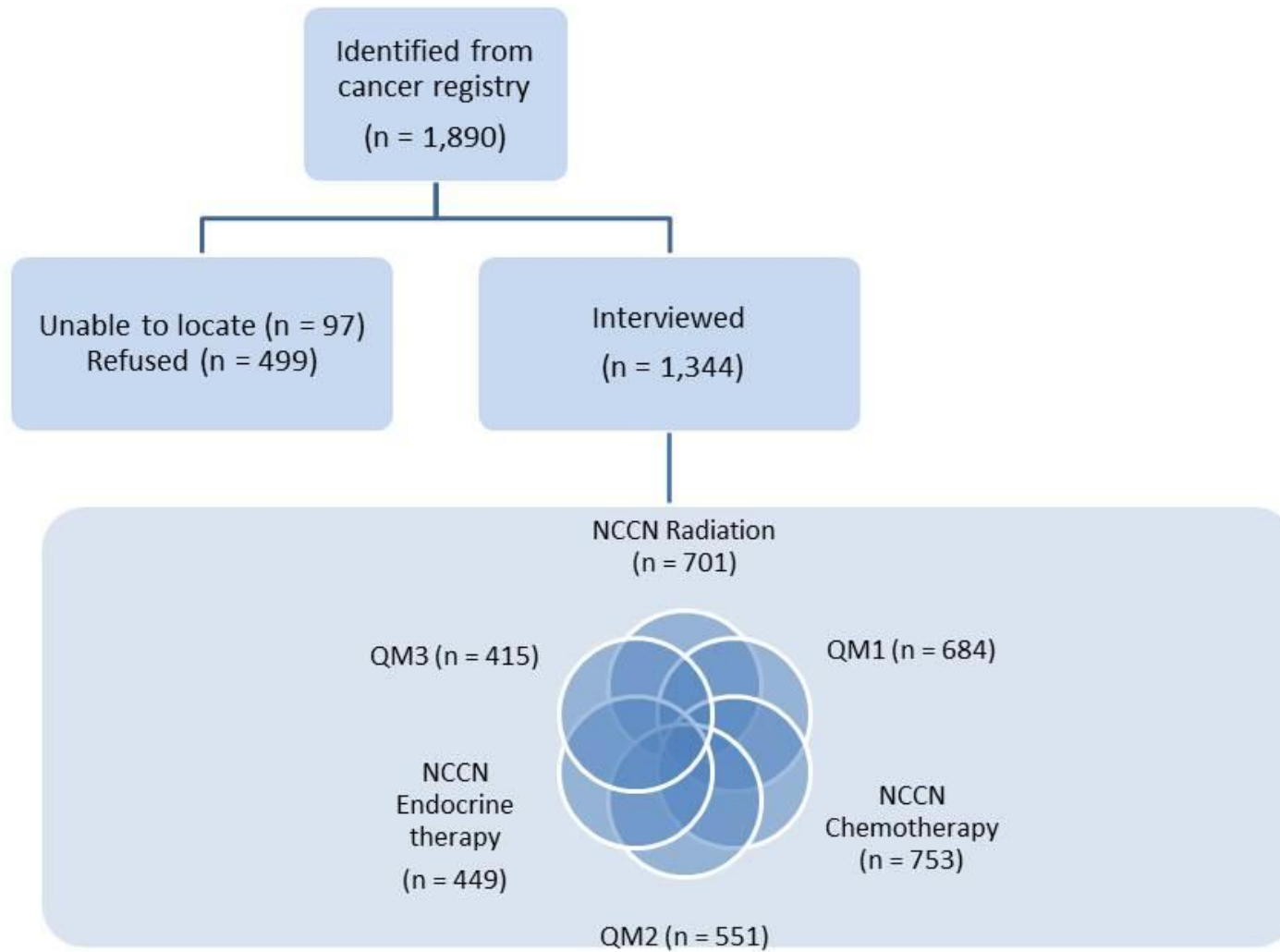
Table 1.1 National Comprehensive Cancer Network Category 1 or 2A Recommendations for Radiation Therapy, Chemotherapy, and Endocrine Therapy

NCCN guideline recommendations for the use of radiation therapy to treat women with clinical stage I, II, or IIIA disease	
Numerator (non-concordant)	Denominator
<ul style="list-style-type: none"> Participant did not receive radiation therapy 	<ul style="list-style-type: none"> Surgically treated by breast conservation surgery (lumpectomy) OR Surgically treated with mastectomy AND participant had ≥ 4 positive axillary nodes
NCCN guideline recommendations for the use of chemotherapy to treat women with clinical stage I, II, or IIIA disease	
Numerator (non-concordant)	Denominator
<ul style="list-style-type: none"> Participant did not receive chemotherapy 	<ul style="list-style-type: none"> Tumor was ER+/PR+/HER2+, ER-/PR-/HER2+ or ER-/PR-/HER2- and tumor was ≥ 1cm or node-positive OR Tumor was ER+/PR+/HER2- and node positive
NCCN guideline recommendations for the use of endocrine therapy to treat women with clinical stage I, II, or IIIA disease	
Numerator (non-concordant)	Denominator
<ul style="list-style-type: none"> Participant did not receive tamoxifen or aromatase inhibitor 	<ul style="list-style-type: none"> Tumor was ER+ or PR+ AND Tumor was > 0.5cm

Table 1.2 American Society of Clinical Oncology/National Comprehensive Cancer Network Quality Measures for Breast Cancer

QM.1 Radiation therapy is administered within 1 year (365 days) of diagnosis for women under age 70 receiving breast conserving surgery for breast cancer.	
Numerator (non-concordant)	Denominator
<ul style="list-style-type: none"> Participant did not receive radiation Radiation was administered >365 days after diagnosis 	<ul style="list-style-type: none"> Surgically treated by breast conservation surgery (surgical excision less than mastectomy) Interviewed >365 days post-diagnosis
QM.2 Combination chemotherapy is administered or considered within 4 months (120 days) of diagnosis for women under 70 with AJCC T1cN0M0, or Stage II or III hormone receptor negative breast cancer.	
Numerator (non-concordant)	Denominator
<ul style="list-style-type: none"> Participant did not receive chemotherapy Chemotherapy was administered >120 days after diagnosis 	<ul style="list-style-type: none"> AJCC T1c, or Stage II or III tumor Primary tumor is ER- and PR- Interviewed >120 days post-diagnosis
QM.3 Tamoxifen or third generation aromatase inhibitor is administered or considered within 1 year (365 days) of diagnosis for women with AJCC T1cN0M0, or Stage II or III hormone receptor positive breast cancer.	
Numerator (non-concordant)	Denominator
<ul style="list-style-type: none"> Participant did not receive tamoxifen or aromatase inhibitor Tamoxifen or aromatase inhibitor was administered >365 days after diagnosis 	<ul style="list-style-type: none"> AJCC T1cN0M0, or Stage II or III Primary tumor is ER+ or PR+ Interviewed >365 days post-diagnosis

Figure 1.1 Study sample schematic



CHAPTER 2: The relationship between patient and treatment facility characteristics and non-concordance with radiation therapy guidelines for the treatment of Stage I to IIIA breast cancer

ABSTRACT

Background: Radiation therapy is an essential component of the treatment of many women with invasive breast cancer. However, not all women with breast cancer receive guideline-recommended radiation therapy and disparities have been documented by demographic factors.

Results: After adjustment for clinical and demographic factors, women who were uninsured had a 3.3-fold (95% CI 1.1-10.5) increased likelihood of non-concordance with NCCN guidelines, compared to women with continuous insurance coverage. Compared to women with an annual household income \geq \$90,000, women with an income $<$ \$50,000 had a 2.3-fold (95% CI 1.0-4.9) increased likelihood of non-concordance with NCCN guidelines. We also observed consistent associations between financial insecurity and both NCCN radiation therapy guidelines and QM. We did not observe associations between education or facility characteristics and non-concordance with radiation recommendations.

Conclusion: Lack of insurance, low income, and financial insecurity were associated with an increased likelihood of non-concordance with radiation recommendations. These results were consistent with those of several previous studies documenting disparities in the receipt of radiation by insurance, and provide the first evidence of an association between other measures of socioeconomic position and non-concordance with radiation recommendations. Our results and those of previous studies documenting socioeconomic disparities in the receipt of guideline recommended radiation therapy warrant further study of the root causes of these inequities, and of the effectiveness of interventions designed to improve guideline concordance among uninsured, underinsured, and low-income women.

INTRODUCTION

Radiation therapy is an essential component of the treatment of clinical Stage I – IIIA breast cancer for all women under age 70 surgically treated with lumpectomy and for women treated with mastectomy with ≥ 4 positive axillary lymph nodes.¹ Postsurgical radiation in these women has been shown to prolong disease-free and overall survival in numerous clinical trials.³⁴⁻³⁶ However, older women,^{3,28,37,38} African American women,^{9,16,39} women with public or no insurance,^{13,16,26,27,38} women who have not graduated from high school,¹³ and low-income women,^{13,28} have all been observed to have increased risks of non-concordance with radiation therapy guidelines.

Although numerous studies have described disparities in the receipt of radiation by demographic characteristics, the majority of these studies are not population-based. Studies of radiation receipt in National Comprehensive Cancer Network (NCCN) centers have access to high quality medical records, but tend to find substantially higher concordance (94% post-lumpectomy,¹² 84% post-mastectomy¹⁵) with radiation recommendations than studies of Medicare and Medicaid-enrolled women, averaging ~70%.^{3,5-7,9,39,40} Two of the three recent population-based studies investigating disparities in the receipt of radiation use data from cancer registries to ascertain receipt of treatment^{26,27} which may substantially underestimate the receipt of recommended treatment.⁴¹⁻⁴³ The remaining population-based study of radiation receipt linked data from the Detroit and Los Angeles SEER sites and interviewed patients to collect self-reported receipt of radiation, and found that 79% of women receiving lumpectomy and 60.2% of women receiving mastectomy had started radiation.²⁸

The objective of this population-based study was to identify patient and facility level characteristics associated with non-concordance with radiation therapy recommendations for the treatment of breast cancer. We collected detailed data on patient socio-demographics and treatment from interviews with patients identified from a population-based cancer registry and evaluated concordance with both NCCN radiation therapy guidelines and American Society for Clinical Oncology (ASCO)/NCCN Quality Measure 1 for Breast Cancer.^{1,44}

RESULTS

Of the 701 women for whom radiation therapy was indicated, 48 (7%) did not receive treatment. Eighty-six percent of women with indications for radiation were Non-Hispanic white and 27% were obese (BMI ≥ 30 mg/kg²) (Table 2.1). Non-concordant women tended to be younger, were more likely to have a history of depression, and were more likely to be ER-positive/PR-positive than the overall population with indications for radiation therapy.

There was no difference in the likelihood of non-concordance with NCCN radiation therapy guidelines comparing publically and privately insured women (Table 2.2). However, among women assessed for concordance with QM1, 9 (16%) of 56 publically insured women were non-concordant compared to 60 (10%) of 614 privately insured women (Table 2.3). The multivariable OR for the association between insurance type and non-concordance with QM1 suggested a 1.9-fold (95% CI 0.8-4.5) increased likelihood of non-concordance comparing publically to privately insured women. Experiencing a period without insurance coverage was associated with a 3.3-fold (95% CI 1.0-10.5) higher likelihood of non-concordance compared to women with uninterrupted insurance coverage (Table 2.2). There was also a suggestion that experiencing a period without insurance coverage was associated with non-concordance with QM1 (OR 1.9, 95% CI 0.6-6.0).

Of 211 women who were not employed at the time of diagnosis, only 7 (3%) of 211 were non-concordant with NCCN radiation therapy guidelines compared to 39 (8%) of 487 employed women; women who were not employed at diagnosis had an OR of 0.4 (95% CI 0.2-0.9) compared to women who were employed (Table 2.2). No association was observed between employment and concordance with QM1.

Women with an annual household income $< \$50,000$ (OR 2.3, 95% CI 1.0-4.9) and women who estimated that they could stay in their home ≤ 2 months had they lost their regular source of income (OR 2.2, 95% CI 1.0-4.5) had an approximately 2-fold increased likelihood of non-concordance with NCCN radiation therapy guidelines compared to women with a household income $\geq \$90,000$ or who estimated they could have stayed > 6 months (Table 2.2). Similar associations between income and financial security were observed for QM1 (Table 2.3). We did not observe associations between assets, debt, or

homeownership and non-concordance with either NCCN guidelines or QM1. Education was not clearly associated with non-concordance with either NCCN radiation therapy guidelines or QM1.

There was a suggestion of moderate associations with being divorced, widowed or separated and non-concordance with both NCCN guidelines (OR 1.7, 95% CI 0.8-3.6; Table 2.2) and QM1 (OR 1.6, 0.9-2.9; Table 2.3), as compared to being married or living with a partner. No increased likelihood of non-concordance was observed for never married women in either analysis.

Patients who sought a second opinion had a slightly higher probability of non-concordance with both NCCN radiation therapy guidelines and QM1 than women who did not seek a second opinion. However, in multivariable analyses the ORs comparing women who did and did not seek a second opinion did not differ substantially for either NCCN guidelines (OR 1.2, 95% CI 0.6-2.4; Table 2.2) or QM1 (OR 1.2, 0.6-2.1; Table 2.3). No associations were observed for the facility characteristics investigated in this study and non-concordance with NCCN guidelines or QM1.

DISCUSSION

The results of this study are indicative of substantial inequalities in the receipt of radiation by insurance, employment, income, and financial security. We observed 3.3-fold (95% CI 1.0-10.5) higher odds of non-concordance with NCCN radiation therapy guidelines comparing women who were uninsured at some point during their breast cancer treatment to women with continuous insurance coverage. Previous studies have reported mixed results, with some studies finding no association,^{13,27,28} and others reporting moderate, significantly lower odds of radiation use among uninsured women with estimates ranging from 0.7-0.9.^{26,45} Differences in the underlying reasons for not being insured and the services available to uninsured women may have varied across study populations, contributing to variation in the association between insurance and receipt of radiation across studies. Another reason our results may differ from previous studies is our combination of women who were uninsured at diagnosis (n=11) and women who were insured at diagnosis but lost coverage during their treatment (n=12). This latter group of women is an important, understudied group experiencing changes in marital status, employment, and other life issues and events that may contribute jointly to interruptions in insurance coverage and non-

concordance. Separating the effects of disruptions in insurance from the effects of these other events was not possible in our analysis. However, identifying uninsured women as a high-risk group regardless of the causal mechanism may be helpful if patient-level interventions, such as navigation that can address both insurance issues and other life stresses,⁴⁶ are made available. In addition, public insurance has been associated with lower receipt of radiation in two previous studies,^{13,26} yet we found no evidence that women with public insurance had a higher likelihood of non-concordance with NCCN radiation therapy guidelines. We did observe a difference in the probability of non-concordance with QM1 between public (16%) and privately (10%) insured women, though this observed difference was within the limits of chance. The possible association of insurance type with QM1 but not NCCN guidelines suggests that if insurance type does affect the receipt of radiation, it may be in the timing of administration.

Several prior studies have investigated associations between markers of socioeconomic position and receipt of radiation. In our study, women in the lowest income category of <\$50,000 had a 2.3-fold (95% CI 1.0-4.9) higher likelihood of non-concordance than women with an annual household income of \geq \$90,000. This relationship has not been documented previously. In the only other study with individual-level income data, Jagsi et al, found no association for the receipt of radiation (OR 1.1, 0.8-1.7) comparing women with incomes \geq \$70,000 to women with incomes <\$20,000.²⁸ However, the estimate presented by Jagsi et al, comes from a model that includes the correlated effects of education and insurance status. We also observed evidence of an association between income and non-concordance with QM1 (OR 1.9, 95% CI 1.0-3.5 comparing women with incomes <\$50,000 to \geq \$90,000). Financial insecurity was strongly associated with non-concordance with both NCCN guidelines and QM1. Ours is the first study to use this alternative measure of wealth, which has yet to be examined in other populations. While we did not observe an association between education and non-concordance with recommended radiation therapy, higher education has been associated with a higher likelihood of radiation receipt among women treated at NCCN centers,^{13,15} but not in the population-based study by Jagsi et al.²⁸ Selection bias in our study and the study by Jagsi et al, both of which had a substantial fraction of nonresponse, may be responsible for the difference in findings from population-based surveys and NCCN databases. On the other hand, it is possible that the effect of patient education on concordance is more pronounced at NCCN centers than in other care settings. Women who were not

employed at diagnosis, which includes a heterogeneous group of women who were unemployed, chose not work, or were retired, were less likely to receive non-concordant radiation therapy in our study, which has not been observed in prior studies. It is possible that women who are not employed at diagnosis face fewer barriers with scheduling appointments, contributing to the low probability of non-concordance in this group.

The results of this study, together with results from previous studies, document inequalities in the receipt of radiation by insurance status, with uninsured women having a higher risk of non-concordance with both NCCN guidelines. Low-income and financial insecurity were also associated with non-concordance with NCCN radiation therapy guidelines while financial insecurity was the only characteristic that was significantly associated with non-concordance with QM1. We did not observe associations for treatment facility characteristics in this study. A main strength of this study is the use of a population-based cohort and our results suggest that identifying patients at high-risk of not receiving radiation is possible by collecting basic demographic information including income and insurance. In addition, these support the use of evidence-based interventions such, as patient navigation, designed to improve adherence to treatment recommendations. As the Affordable Care Act is implemented in 2014, new opportunities for the way that women enroll in and maintain insurance coverage are on the horizon. Patient navigation may be effective in removing individual-level barriers,⁴⁶ and could be utilized to work with women of low socioeconomic position to women to take advantage of new insurance options. Further study of the root causes of the socioeconomic inequities in the receipt of guideline recommended radiation observed in this study, and of the effectiveness of interventions designed to improve concordance, are important future directions in the pursuit of quality breast cancer care.

Table 2.1 Description of women for whom radiation therapy was recommended by NCCN guidelines, N = 701

	Overall		Non-concordant	
	n	%	n	%
Age at diagnosis				
24 - 39	77	11%	11	23%
40 - 49	234	33%	17	35%
50 - 59	227	32%	12	25%
60 - 69	163	23%	8	17%
Race/ethnicity				
Non-Hispanic White	603	86%	39	81%
Black or African American	34	5%	1	2%
Other	61	9%	8	17%
Body mass index (m/kg ²)				
<18.5	11	2%	2	4%
18.5 - 24.9	297	42%	26	54%
25.0 – 29.9	201	29%	9	19%
≥30	189	27%	11	23%
Smoker at diagnosis				
Yes	65	9%	6	13%
No	635	91%	42	88%
History of depression				
Yes	191	27%	16	33%
No	510	73%	32	67%
Tumor stage				
Stage I	361	52%	18	38%
Stage IIA	217	31%	20	42%
Stage IIB	96	14%	7	15%
Stage IIIA	16	2%	0	0%
Unknown	11	2%	3	6%
Hormone receptor (HR)/HER2 status				
HR+/HER2+	27	4%	4	8%
HR+/HER2-	268	38%	20	42%
HR-/HER2+	86	12%	10	21%
HR-/HER2-	314	45%	13	27%
HER2 unknown	6	1%	1	2%

Table 2.2 Relationship between patient and treatment facility characteristics and non-concordance with NCCN radiation therapy guidelines (N=701)

	Overall n	Non- concordant n	%	OR ^a	95% CI
Patient characteristics					
Insurance type					
Private	627	41	7%	1.0	(ref)
Public	59	4	7%	1.0	(0.3-3.6)
Period of no insurance					
Yes	23	4	17%	3.3	(1.0-10.5)
No	671	43	6%	1.0	(ref)
Education (highest level achieved)					
≤ High school	187	11	6%	0.8	(0.4-1.9)
Some college	176	13	7%	0.9	(0.4-1.9)
College graduate	212	18	8%	1.0	(ref)
Graduate study	125	6	5%	0.4	(0.2-1.2)
Employed at diagnosis					
Yes	487	39	8%	1.0	(ref)
No	211	7	3%	0.4	(0.2-0.9)
Annual household income					
<\$50,000	159	15	9%	2.3	(1.0-4.9)
\$50,000 - \$89,999	220	14	6%	1.3	(0.6-2.8)
≥\$90,000	283	17	6%	1.0	(ref)
Total assets					
<\$200K	247	21	9%	1.7	(0.9-3.2)
\$200K+	381	21	6%	1.0	(ref)
Total debt ^b					
<\$2,000	245	13	5%	1.0	(ref)
\$2,000 - \$9,999	175	13	7%	1.4	(0.6-3.3)
≥\$10,000	230	17	7%	1.3	(0.6-2.9)
Home owner					
Yes	602	41	7%	1.0	(ref)
No	94	6	6%	0.8	(0.3-2.1)
Time participant could stay in home if regular source of income was lost (months)					
≤ 2	165	17	10%	2.2	(1.0-4.5)
3 - 6	176	11	6%	1.2	(0.5-2.6)
>6	326	18	6%	1.0	(ref)

Table 2.2 continued						
Marital status						
Married, living as married	525	33	6%	1.0	(ref)	
Divorced/widowed/separated	129	12	9%	1.7	(0.8-3.6)	
Single, never married	47	3	6%	0.8	(0.2-2.9)	
Pt. sought a 2nd opinion						
Yes	151	13	9%	1.2	(0.6-2.4)	
No	547	34	6%	1.0	(ref)	
Treatment facility characteristics						
Annual breast cancer patient load						
<200	75	6	8%	2.0	(0.6-6.4)	
200 - 299	130	7	5%	0.9	(0.3-2.6)	
300 - 399	156	11	7%	1.5	(0.6-4.1)	
≥400	136	8	6%	1.0	(ref)	
Radiation oncology						
On-site	552	37	7%	1.0	(ref)	
Referral only	86	7	8%	1.4	(0.6-3.3)	

a: Odds ratios adjusted for age at diagnosis, year of diagnosis, tumor stage, BMI, smoking status at diagnosis, and history of depression

b: Excludes mortgage on a home

Table 2.3 Relationship between patient and treatment facility characteristics and non-concordance with ASCO/NCCN QM1, post-lumpectomy radiation therapy within 1 year of diagnosis (N= 684)

	Overall n	Non- concordant n	%	OR ^a	95% CI
Patient characteristics					
Insurance type					
Private	614	60	10%	1.0	(ref)
Public	56	9	16%	1.9	(0.8-4.5)
Period of no insurance					
Yes	22	4	18%	1.9	(0.6-6.0)
No	655	66	10%	1.0	(ref)
Education (highest level achieved)					
≤ High school	185	19	10%	1.0	(0.5-2.0)
Some college	172	23	13%	1.3	(0.7-2.4)
College graduate	204	21	10%	1.0	(ref)
Graduate study	122	9	7%	0.6	(0.3-1.4)
Employed at diagnosis					
Yes	474	53	11%	1.0	(ref)
No	207	17	8%	0.7	(0.4-1.3)
Annual household income					
<\$50,000	156	23	15%	1.9	(1.0-3.5)
\$50,000 - \$89,999	216	17	8%	0.9	(0.5-1.7)
≥\$90,000	273	26	10%	1.0	(ref)
Total assets					
<\$200K	243	29	12%	1.4	(0.8-2.5)
\$200K+	368	32	9%	1.0	(ref)
Total debt ^b					
<\$2,000	240	17	7%	1.0	(ref)
\$2,000 - \$9,999	172	17	10%	1.5	(0.7-3.1)
≥\$10,000	221	28	13%	1.9	(1.0-3.6)
Home owner					
Yes	586	59	10%	1.0	(ref)
No	93	12	13%	1.2	(0.6-2.5)
Time participant could stay in home if regular source of income was lost (months)					
≤ 2	162	26	16%	2.1	(1.1-3.8)
3 - 6	172	14	8%	1.0	(0.5-1.9)
>6	316	27	9%	1.0	(ref)

Table 2.3 continued					
Marital status					
Married, living as married	510	49	10%	1.0	(ref)
Divorced/widowed/separated	128	19	15%	1.6	(0.9-2.9)
Single, never married	46	4	9%	0.8	(0.3-2.3)
Pt. sought a 2nd opinion					
Yes	146	17	12%	1.2	(0.6-2.1)
No	535	53	10%	1.0	(ref)
Treatment facility characteristics					
Annual breast cancer patient load					
<200	72	6	8%	1.0	(0.4-3.0)
200 - 299	128	15	12%	1.3	(0.6-2.9)
300 - 399	153	13	9%	0.9	(0.4-2.1)
≥400	130	12	9%	1.0	(ref)
Radiation oncology					
On-site	539	59	11%	1.0	(ref)
Referral only	83	7	8%	0.8	(0.3-1.6)

a: Odds ratios adjusted for age at diagnosis, year of diagnosis, tumor stage, BMI, smoking status at diagnosis, and history of depression

b: Excludes mortgage on a home

CHAPTER 3: Non-concordance with recommended adjuvant chemotherapy in a population-based cohort of breast cancer patients

ABSTRACT

Background: There is substantial evidence documenting the benefit of adjuvant chemotherapy for the treatment of breast cancer, and clinical practice guidelines recommend chemotherapy for the adjuvant treatment of many women. However, not all women receive recommended chemotherapy, and variation in guideline concordance has been reported by numerous demographic factors. Despite variation between groups of patients, little is known about the individual-level factors that may influence receipt of chemotherapy in population-based settings.

Results: A total of 751 women required chemotherapy to be concordant with National Comprehensive Cancer Network (NCCN) guidelines. 55 (7%) of these women did not receive chemotherapy. Compared to women with uninterrupted insurance, women with a period of no insurance while they were being treated for breast cancer had 3.5-fold (1.2-10.5) higher odds of non-concordance with NCCN chemotherapy guidelines. There were 551 women with estrogen receptor (ER)-negative/progesterone receptor (PR)-negative breast cancer who were available for assessment for concordance with Quality Measure 2 (QM2), 70 (13%) of whom did not receive chemotherapy within 120 days of diagnosis. Compared to private insurance, the OR for the association of public insurance and non-concordance with QM2 was 3.3 (95% CI 1.5-7.0). The OR for uninsured women was 3.8 (95% CI 1.5-9.7). Low income, few assets, and lack of home ownership were also significantly associated with non-concordance with QM2.

Conclusions: In this study, lack of insurance, low income, and other markers of low socioeconomic position were associated with an increased likelihood of non-concordance with chemotherapy recommendations. Our results and those of previous studies documenting socioeconomic disparities in the receipt of guideline recommended chemotherapy warrant further study of the root causes of these inequities, and of the effectiveness of interventions designed to improve guideline concordance among uninsured, underinsured, and low-income women.

INTRODUCTION

There is substantial evidence documenting the benefit of adjuvant chemotherapy for the treatment of breast cancer.⁴⁷ However, the considerable toxicity of chemotherapeutic agents requires that patients and providers weigh the benefits and risks of therapy. National Comprehensive Cancer Network (NCCN) Clinical Practice Guidelines recommend chemotherapy for all women <70 years of age who are node-positive and for most women with tumors ≥ 1 cm in size.¹ For women with estrogen receptor (ER)-negative/progesterone receptor (PR)-negative, human epidermal growth factor 2 (HER2)-negative tumors, chemotherapy is the only recommended adjuvant systemic therapy, and the timely administration of chemotherapy to women with ER-negative/PR-negative tumors is the focus of the second American Society of Clinical Oncology (ASCO)/NCCN Quality Measure.

Demographic inequalities in the receipt and timing of chemotherapy have been observed in several previous studies. Older women,^{19,30,48,49} African American women,^{19,21,30,37,49} Hispanic women,³⁷ women with Medicare,³⁷ Medicaid-enrolled women,^{16,30} obese women,²⁰ and women with less than a high school education^{19,20} have all been identified as having an increased likelihood of receiving less than optimal chemotherapy. However, these prior studies have been limited in their ability to investigate why individual women have not received chemotherapy.

The aim of this population-based study was to investigate possible associations between patient and facility level characteristics and non-concordance with chemotherapy recommendations for the treatment of breast cancer. Patient socio-demographic and treatment data were ascertained from interviews with patients identified from a population based cancer registry and concordance with both NCCN chemotherapy guidelines and ASCO/NCCN Quality Measure 2 for Breast Cancer was evaluated.^{1,44} In addition, women were interviewed about factors hypothesized to influence the receipt of chemotherapy, including problems experienced communicating with treatment providers, scheduling and getting to appointments, social support, and use of patient services.

RESULTS

Chemotherapy was indicated for a total of 751 women according to NCCN guidelines. Fifty-five (7%) of these women did not receive chemotherapy. Table 3.1 describes the characteristics of all women with guideline indicated chemotherapy (N = 753) and of non-concordant women (n=43). 85% of the study population was Non-Hispanic white and 26% of the population was obese (BMI ≥ 30 m/kg²). 69% of the population had stage II tumors and more than half had a triple negative phenotype (ER-/PR-/HER2-). Non-concordant women were more likely to be older, to smoke and to have stage I or IIA tumors compared to the overall study population. There were 551 women with ER-/PR-negative breast cancer who were available for assessment for concordance with QM2, 70 (13%) of whom did not receive chemotherapy within 120 days of diagnosis.

Although 7 (10%) of 69 publically insured women were non-concordant with NCCN chemotherapy guidelines compared to 33 (5%) of 661 privately insured women, the multivariable OR for the association between insurance type and NCCN guideline concordance was not indicative of a significant difference (Table 3.2). There was, however, a strong association between insurance type and QM2, with publically insured women having a 3.3-fold (95% CI 1.5-7.0) higher likelihood of non-concordance than privately insured women (Table 3.3). Women who experienced a period of no insurance had an approximately 3.5-fold increased likelihood of non-concordance with both NCCN guidelines (OR 3.5, 95% CI 1.2-10.5; Table 3.2) and QM2 (OR 3.8, 95% CI 1.5-9.7; Table 3.3), compared to women with uninterrupted insurance.

No association between education and NCCN chemotherapy guidelines was observed (Table 3.2). However, 27 (17%) of 163 women with \leq a high school education were non-concordant with QM2 compared to 12 (14%) of 87 women with a college degree and 12 (8%) of 153 women who attended graduate school (Table 3.3). The multivariable OR comparing high school or below educated women to college graduates of 1.9 (95% CI 0.9-4.0) was suggestive of a higher likelihood of non-concordance with QM2 among less educated women.

Twenty-one (12%) of 120 women with an annual household income $<$ \$50,000 were non-concordant with NCCN chemotherapy recommendations, compared to 12 (5%) of women with an income

between \$50,000 and \$89,000 and 7 (2%) of women with an income \geq \$90,000; the multivariable OR for non-concordance with NCCN guidelines comparing low to high income women was 4.6 (95% CI 1.8-11.6) (Table 3.2). Compared to high income women, low-income women had a 2.5-fold (95% CI 1.3-4.9) increased likelihood of non-concordance with QM2 (Table 3.3). Non-concordance with both NCCN guidelines (Table 3.2) and QM2 (Table 3.3) was also >2-times as high among women with <\$200,000 in assets and women who did not own their home compared to women with \geq \$200,000 in assets and homeowners, respectively. In contrast, no associations were observed for non-concordance with NCCN guidelines or QM2 for employment, debt, or financial insecurity.

While 20 (4%) of 566 married women were non-concordant with NCCN chemotherapy guidelines, 19 (14%) of 133 women who were divorced, widowed, or separated were non-concordant and 4 (8%) of 53 never married women were non-concordant (Table 3.2). Compared to married women, divorced, widowed, or separated women and never married women had 3.5-fold (95% CI 1.7-7.0) and 3.6-fold (95% CI 1.1-11.8) higher likelihood of non-concordance, respectively. A similar disparity in the probability of non-concordance with QM2 was observed between divorced, widowed, or separated women and married women (OR 2.3, 95% CI 1.3-4.1), though similar proportions of never married and currently married women were non-concordant with QM2 (Table 3.3).

Sixteen (8%) of 192 patients who sought a second opinion for the treatment of their breast cancer were non-concordant with NCCN chemotherapy guidelines; this group had a 2.8-fold (95% CI 1.4-5.6) higher likelihood of non-concordance with chemotherapy guidelines than women who did not seek a second opinion (Table 3.2). No such association was observed with QM2 (Table 3.3).

We also observed a suggestion of increased probability of non-concordance with NCCN guidelines among 67 women diagnosed at treatment facilities that offered chemotherapy by referral only (OR 2.3, 95% CI 0.9-5.9) (Table 3.2). This suggested difference was less apparent for QM2 (Table 3.3). Annual breast cancer patient load of the treatment facility did not appear to be associated with non-concordance with NCCN chemotherapy guidelines (Table 3.2) or QM2 (Table 3.3).

Factors influencing non-concordance with NCCN recommended chemotherapy

We observed differences in non-concordance with NCCN chemotherapy guidelines by several hypothesized factors. Seven (12%) of 57 women who stated that talking to doctors or their staff when they had questions or problems was a problem were non-concordant with NCCN recommended chemotherapy compared to 34 (5%) of 688 women who stated this was not a problem (OR 2.7, 95% CI 1.1-6.4) (Table 3.4). Nine (10%) of 86 women who said that they did not have someone to help them with daily chores and care for them if they were sick or tired were non concordant with NCCN recommended chemotherapy compared to 34 (5%) of 663 women who did have someone to do this (OR 2.2, 95% CI 1.0-4.7). Also, 7 (15%) of 46 women who stated that they did not have someone to go with them to appointments and drive them home were non-concordant with NCCN recommended chemotherapy compared to 36 (5%) of 702 women who stated that they did have someone who could do this (OR 3.3, 95% CI 1.4-7.9). Only 5 (2%) of women who visited a patient and family resource center were non-concordant with chemotherapy guidelines compared to 38 (7%) of 510 women who did not visit a resource center (OR 0.3, 95% CI 0.1-0.7).

DISCUSSION

We found substantial differences in non-concordance with NCCN chemotherapy guidelines and QM2 by insurance and socioeconomic factors including income, assets, and homeownership. In a recent population-based study of women in Los Angeles and Detroit SEER registries, Griggs et al, reported that Medicaid-enrolled women were 40% less likely to receive chemotherapy, compared with Medicare enrolled women (OR 0.6, 95% CI 0.4-1.0) while women with no insurance were 77% more likely than Medicare-enrolled women to receive chemotherapy (OR 1.8, 95% CI 1.0-3.1).³⁰ In that same study, no association with income and receipt of chemotherapy was observed (though 17% of participants were missing income data). Similar to Griggs et al, we observed that women with public insurance were much more likely to be non-concordant with QM2 than privately insured women, while insurance type was not associated with non-concordance with NCCN guidelines in our study. It is possible that publically insured women may have to wait longer than privately insured women for their chemotherapy to be covered by insurance, causing delays of >120 days. Vandergrift et al recently reported that at NCCN centers, women

with Medicaid had a 2.8 week delay (95% CI 2.3-3.3) in the receipt of chemotherapy compared to women with commercial insurance³⁷. Women enrolled in Medicare in that study had 0.7 week delay (95% CI 0.2-1.2). Our finding of a higher likelihood of non-concordance among women with a period of no insurance contrasts with the higher likelihood of receiving chemotherapy among women with no insurance reported by Griggs et al. However, this may be due to differences in reasons for non-insurance across study populations or to our inclusion of both women who were uninsured at diagnosis (n=18) and women who lost coverage at any point while be treated for breast cancer (n=17). This latter group of women is an important, understudied group experiencing changes in marital status, employment, and other life issues and events that may contribute jointly to interruptions in insurance coverage and non-receipt of therapy.

Our finding that women who were not married, or living as married, were more likely to be non-concordant with chemotherapy guidelines contrasts with the null associations reported by two previous studies.^{30,50} However, the higher non-concordance in women who were not married or living as married in our study is consistent with the important role that social support seemed to play in our study. Women who reported that they did not have someone to help them with daily chores and care for them if they were sick or tired and women who reported that they did not have someone to go with them to appointments and drive them home were much more likely to be non-concordant than women who did have someone to do these things. Social support may be a crucial factor for ensuring that patients get to the clinic and have help managing the side effects of chemotherapy. However it is also likely to be related to socioeconomic position and marital status. Additional research to tease apart the causal mechanisms behind these correlated exposures is warranted.

We observed a suggestion of an association between chemotherapy availability at the treatment facility listed in CSS and non-concordance, although the difference did not reach statistical significance. Women diagnosed at facilities that offered chemotherapy by referral only seemed to be more likely to be non-concordant with chemotherapy guidelines. We also found an association between communication with providers and non-concordance with NCCN recommended chemotherapy. In the interviews conducted by Griggs et al, women were asked to report a reason why they did not receive chemotherapy and the most common response was "My physician said I did not need it".³⁰ Future studies investigating

the role of patient-provider communication in non-concordance may identify common failures in communication that contribute to unintended non-concordance.

In conclusion, differences in the receipt of chemotherapy described here and previously by insurance availability are of public health importance, as new opportunities for the way that women enroll in and maintain insurance coverage are on the horizon with the Affordable Care Act. However, overhauling insurance may not eliminate disparities in the receipt of guideline concordant breast cancer care, as we also observed substantial variation in non-concordance with chemotherapy recommendations by income and other markers of socioeconomic position, marital status and by whether or not a woman sought a second opinion. Communication with providers and social support may be important avenues for interventions designed to improve chemotherapy guideline concordance.

Table 3.1 Description of women for whom chemotherapy was recommended by NCCN guidelines (N = 753)

	Overall		Non-concordant	
	n	%	n	%
Age at diagnosis				
24 - 39	126	17%	1	2%
40 - 49	271	36%	8	19%
50 - 59	218	29%	18	42%
60 - 69	138	18%	16	37%
Race/ethnicity				
Non-Hispanic White	640	85%	38	88%
Black or African American	40	5%	3	7%
Other	69	9%	2	5%
Body mass index (m/kg ²)				
<18.5	14	2%	0	0%
18.5 - 24.9	317	42%	21	49%
25.0 – 29.9	220	29%	10	23%
≥ 30	197	26%	11	26%
Smoker at diagnosis				
Yes	86	11%	9	21%
No	667	89%	34	79%
History of depression				
Yes	206	27%	9	21%
No	547	73%	34	79%
Tumor stage				
Stage I	187	25%	15	35%
Stage IIA	306	41%	22	51%
Stage IIB	209	28%	4	9%
Stage IIIA	41	5%	0	0%
Unknown	10	1%	2	5%
Hormone receptor (HR)/HER2 status				
HR+/HER2+	50	7%	1	2%
HR+/HER2-	150	20%	14	33%
HR-/HER2+	128	17%	5	12%
HR-/HER2-	414	55%	20	47%
HR or HER2 unknown	11	1%	3	7%

Table 3.2 Relationship between patient and treatment facility characteristics and non-concordance with NCCN chemotherapy guidelines (N= 753)

	Overall	Non-concordant			
	n	n	%	OR ^a	95% CI
Patient characteristics					
Insurance type					
Private	661	33	5%	1.0	(ref)
Public	69	7	10%	1.8	(0.7-5.0)
Period of no insurance					
Yes	35	5	14%	3.5	(1.2-10.5)
No	707	38	5%	1.0	(ref)
Education (highest level achieved)					
≤ High school	197	12	6%	0.9	(0.4-2.3)
Some college	204	12	6%	1.4	(0.6-3.5)
College graduate	224	10	4%	1.0	(ref)
Graduate study	126	9	7%	1.7	(0.6-4.6)
Employed at diagnosis					
Yes	518	28	5%	1.0	(ref)
No	230	15	7%	0.8	(0.4-1.5)
Annual household income					
<\$50,000	180	21	12%	4.6	(1.8-11.6)
\$50,000 - \$89,999	229	12	5%	2.3	(0.9-6.0)
≥\$90,000	314	7	2%	1.0	(ref)
Total assets					
<\$200K	288	20	7%	2.5	(1.2-5.2)
\$200K+	403	16	4%	1.0	(ref)
Total debt ^b					
<\$2,000	245	14	6%	1.0	(ref)
\$2,000 - \$9,999	188	6	3%	0.6	(0.2-1.8)
≥\$10,000	272	17	6%	1.5	(0.7-3.4)
Home owner					
Yes	631	31	5%	1.0	(ref)
No	118	12	10%	2.6	(1.2-5.4)
Time participant could stay in home if regular source of income was lost (months)					
≤ 2	199	13	7%	1.6	(0.7-3.6)
3 - 6	200	9	5%	1.2	(0.5-2.8)
>6	325	17	5%	1.0	(ref)

Table 3.2 continued					
Marital status					
Married, living as married	566	20	4%	1.0	(ref)
Divorced/widowed/separated	133	19	14%	3.5	(1.7-7.0)
Single, never married	53	4	8%	3.6	(1.1-11.8)
Pt. sought a 2nd opinion					
Yes	192	16	8%	2.8	(1.4-5.6)
No	556	27	5%	1.0	(ref)
Treatment facility characteristics					
Annual breast cancer patient load					
<200	78	6	8%	1.3	(0.4-4.3)
200 - 299	123	4	3%	0.5	(0.1-1.7)
300 - 399	202	11	5%	1.0	(0.4-2.7)
≥400	141	8	6%	1.0	(ref)
Medical oncology - chemotherapy					
On-site	634	33	5%	1.0	(ref)
Referral only	67	6	9%	2.3	(0.9-5.9)

a: Odds ratios adjusted for age at diagnosis, year of diagnosis, tumor stage, BMI, smoking status at diagnosis, and history of depression

b: Excludes mortgage on a home

Table 3.3 Relationship between patient and treatment facility characteristics and non-concordance with ASCO/NCCN QM2, chemotherapy within 120 days of diagnosis for ER/PR-negative tumors (N= 551)

	Overall n	Non- concordant n	%	OR ^a	95% CI
Patient characteristics					
Insurance type					
Private	480	49	10%	1.0	(ref)
Public	55	17	31%	3.3	(1.5-7.0)
Period of no insurance					
Yes	26	8	31%	3.8	(1.5-9.7)
No	518	62	12%	1.0	(ref)
Education (highest level achieved)					
≤ High school	163	27	17%	1.9	(0.9-4.0)
Some college	146	19	13%	1.6	(0.7-3.6)
College graduate	87	12	14%	1.0	(ref)
Graduate study	153	12	8%	1.6	(0.7-3.9)
Employed at diagnosis					
Yes	380	43	11%	1.0	(ref)
No	168	27	16%	1.2	(0.7-2.1)
Annual household income					
<\$50,000	126	29	23%	2.5	(1.3-5.0)
\$50,000 - \$89,999	172	19	11%	1.3	(0.7-2.6)
≥\$90,000	230	19	8%	1.0	(ref)
Total assets					
<\$200K	212	37	17%	2.5	(1.4-4.3)
\$200K+	297	26	9%	1.0	(ref)
Total debt ^b					
<\$2,000	175	21	12%	1.0	(ref)
\$2,000 - \$9,999	142	15	11%	1.1	(0.5-2.2)
≥\$10,000	200	27	14%	1.5	(0.8-2.8)
Home owner					
Yes	461	48	10%	1.0	(ref)
No	88	22	25%	3.3	(1.8-6.1)
Time participant could stay in home if regular source of income was lost (months)					
≤ 2	154	23	15%	1.6	(0.7-3.0)
3 - 6	146	18	12%	1.4	(0.7-2.7)
>6	232	28	12%	1.0	(ref)

Table 3.3 continued					
Marital status					
Married, living as married	420	42	10%	1.0	(ref)
Divorced/widowed/separated	98	24	24%	2.3	(1.3-4.1)
Single, never married	32	4	13%	1.5	(0.5-4.6)
Pt. sought a 2nd opinion					
Yes	133	20	15%	1.6	(0.9-2.9)
No	415	50	12%	1.0	(ref)
Treatment facility characteristics					
Annual breast cancer patient load					
<200	61	8	13%	1.7	(0.6-5.2)
200 - 299	95	9	9%	0.9	(0.3-2.6)
300 - 399	143	16	11%	1.3	(0.5-3.3)
≥400	98	8	8%	1.0	(ref)
Medical oncology - chemotherapy					
On-site	465	55	12%	1.0	(ref)
Referral only	47	7	15%	1.7	(0.7-4.1)

a: Odds ratios adjusted for age at diagnosis, year of diagnosis, tumor stage, BMI, smoking status at diagnosis, and history of depression

b: Excludes mortgage on a home

Table 3.4 Relationship between factors hypothesized to influence receipt of chemotherapy and non-concordance with NCCN chemotherapy guidelines

	Overall	Non-concordant		OR [*]	95% CI
	n	n	%		
When you were being treated for breast cancer how much of a problem was ...					
Talking to your doctors or their staff when you had questions or problems					
A big problem/somewhat of a problem	57	7	12%	2.7	(1.1-6.4)
Not a problem	688	34	5%	1.0	(ref)
Scheduling and finding time for your appointments					
A big problem/somewhat of a problem	46	3	7%	1.2	(0.3-3.9)
Not a problem	704	40	6%	1.0	(ref)
Transportation to and from appointments					
A big problem/somewhat of a problem	53	3	6%	1.0	(0.3-3.3)
Not a problem	696	40	6%	1.0	(ref)
Arranging care for a dependent					
A big problem/somewhat of a problem	83	3	4%	0.6	(0.2-1.9)
Not a problem	666	40	6%	1.0	(ref)
The amount of money you paid for doctor visits, treatments, and medications					
A big problem/somewhat of a problem	232	11	5%	0.8	(0.4-1.5)
Not a problem	515	32	6%	1.0	(ref)
Any of the above problems	329	18	5%	1.0	(0.5-1.8)
None of the above problems	417	24	6%	1.0	(ref)

Table 3.4 continued					
When you were being treated for breast cancer did you have ...					
Someone you could talk to about your diagnosis, your needs, your problems, or your fears					
Yes	708	41	6%	1.0	(ref)
No	40	2	5%	0.9	(0.2-3.7)
Someone to help you with daily chores and care for you if you were sick or tired					
Yes	663	34	5%	1.0	(ref)
No	86	9	10%	2.2	(1.0-4.7)
Someone to go with you to appointments and drive you home					
Yes	702	36	5%	1.0	(ref)
No	46	7	15%	3.3	(1.4-7.9)
When you were being treated for breast cancer did you use ...					
A patient and family resource center					
Yes	239	5	2%	0.3	(0.1-0.7)
No	510	38	7%	1.0	(ref)
Patient guides, navigators, or social workers					
Yes	208	10	5%	0.8	(0.4-1.6)
No	541	33	6%	1.0	(ref)
Financial services or counselors					
Yes	99	4	4%	0.7	(0.2-1.9)
No	650	38	6%	1.0	(ref)
Symptom management or physical therapists					
Yes	289	14	5%	0.8	(0.4-1.5)
No	460	28	6%	1.0	(ref)
Cancer support group					
Yes	150	5	3%	0.5	(0.2-1.3)
No	600	38	6%	1.0	(ref)
Any of the above services	525	21	4%	0.4	(0.2-0.7)
None of the above services	225	22	10%	1.0	(ref)

* Unadjusted Odds Ratio

CHAPTER 4: Relationship between patient and treatment facility characteristics and non-concordance with endocrine therapy recommendations for the treatment of hormone receptor positive breast cancer

ABSTRACT

Background: There is substantial evidence documenting the benefit of adjuvant endocrine therapy for the treatment of hormone receptor (HR) positive breast cancer, and the receipt of appropriate endocrine therapy has been identified as a marker of high quality breast cancer care. However, not all women receive recommended endocrine therapy and variation in guideline concordance has been reported by demographic factors. Previous studies have been limited in their ability to investigate the association between socioeconomic position and initiation of endocrine therapy.

Results: In this cohort of women with HR-positive breast cancer (N=449), 37 (8%) women did not receive any endocrine therapy. Non-concordance with endocrine therapy guidelines (OR 3.7, 95% CI 1.4-9.7) and Quality Measure 3 (QM3) (OR 2.0, 95% CI 1.0-3.9) was higher among women with an annual household income <\$50,000 than women with a household income ≥\$90,000. Non-concordance with QM3 was also higher among never married women than women who were married or living as married (OR 3.4, 95% CI 1.6-7.4), and was lower among women diagnosed at treatment facilities with an annual breast cancer patient load <200 compared to ≥400 (OR 0.2, 95% CI 0.1-0.8).

Conclusions: This study identified low income, never having been married, and high patient load of the treatment facility to be associated with non-concordance with endocrine therapy recommendations. Patient navigation, communication with providers, and improved access to affordable medications may remove barriers to concordance with endocrine therapy.

INTRODUCTION

Adjuvant endocrine therapy as a treatment for hormone receptor (HR) positive breast cancer improves a woman's chances of both disease-free and overall survival, and lowers the risk of contralateral breast cancer.⁴⁷ Guidelines for the treatment of HR-positive breast cancer recommend 5 years of tamoxifen for premenopausal women, or aromatase inhibitors (AIs) for postmenopausal women for up to 5 years.^{1,51} Initiation of endocrine therapy is included in efforts to monitor the quality of cancer care and has been included in the American Society of Clinical Oncology (ASCO)/National Comprehensive Cancer Network (NCCN) Quality Measures.⁵²

Variation in concordance with endocrine therapy guidelines has been described by race,^{23,45} marital status,⁵³⁻⁵⁵ area-level poverty,^{16,54} and size or affiliation of treatment facilities.^{16,55} Previous studies of concordance with endocrine therapy guidelines have been limited in their ability to investigate associations between insurance, income, and other markers of socioeconomic position and initiation of treatment. Several studies have found that women living in low-income or high poverty census tracts are less likely to be concordant with endocrine therapy,^{23,44} but a recent study found no association between concordance and area-level education poverty and income.¹⁶ Given that endocrine therapy may or may not be covered by insurance, must be taken for several years before any benefit is realized, has side-effects that may lead to management with additional medications, and is not administered in the clinic, women with limited resources may decide against starting therapy. The aim of this population-based study was to investigate possible associations between patient and facility level characteristics and non-concordance with endocrine therapy recommendations for the treatment of HR-positive breast cancer. Patient socio-demographic and treatment data were ascertained from interviews with patients identified from a population based cancer registry and concordance with both NCCN endocrine therapy guidelines and ASCO/NCCN Quality Measure 3 (QM3) for Breast Cancer was evaluated.^{1,44}

RESULTS

Endocrine therapy was indicated for 449 women with HR-positive tumors that were ≥ 0.5 cm for concordance with NCCN Category 1 or 2A recommendations.¹ Table 4.1 describes the characteristics of women with indications for endocrine therapy according to NCCN guidelines (N=449) and those of non-concordant women (n=37). 86% of the study population was Non-Hispanic white and 21% of the population was obese (BMI ≥ 30 m/kg²). 59% of the population had stage I tumors. Non-concordant women were more likely to be of normal weight (BMI 18.5-24.9 m/kg²) than women in the overall study population.

Of the 449 HR-positive women with NCCN guideline indications for adjuvant endocrine therapy 37 (8%) did not receive endocrine therapy. A total of 415 women were available for assessment for concordance with QM3. 72 women (17%) did not start endocrine therapy within 365 days of diagnosis.

No differences in the likelihood of non-concordance with NCCN guidelines were observed by insurance status (Table 4.2). In contrast, there was a suggestion of an association between insurance type and non-concordance with QM3 with 9 (35%) of 26 publically insured women being non-concordant compared to 59 (16%) of 376 women with private insurance (OR 1.9, 95% CI 0.7-5.0) (Table 4.3). Non-concordance with QM3 was somewhat lower among women with a period of no insurance (2 (11%) of 19) than among women with uninterrupted insurance (68 (17%) of 391); the multivariable OR was 0.6 (95% CI 0.1-2.5) (Table 4.3).

Fourteen (13%) of 104 women with an annual household income $< \$50,000$ were non-concordant with NCCN endocrine therapy recommendations, compared to 12 (9%) of 136 women with a household income between $\$50,000$ and $\$89,000$ and 8 (4%) of 189 with an income $\geq \$90,000$ (Table 4.2). In multivariable models, women with an annual household income $< \$50,000$ had a 3.7-fold (95% CI 1.4-9.7) increased likelihood of non-concordance with endocrine therapy guidelines, compared to women with a household income $\geq \$90,000$. Similarly, women with a household income $< \$50,000$ were twice as likely to be non-concordant with QM3 (OR 2.0, 95% CI 1.0-3.9), compared to women with a household income $\geq \$90,000$ (Table 4.3).

We observed some evidence that women with \leq a high school education (OR 1.9, 95% CI 0.8-4.9) and those who sought a second opinion for the treatment of their breast cancer (OR 1.5, 95% CI 0.7-3.2) had a higher likelihood of non-concordance with NCCN endocrine therapy guidelines than women with a college degree and women who did not seek a second opinion, respectively (Table 4.2). However, there was no association between education or having sought a second opinion and non-concordance with QM3 (Table 4.3). Other markers of socioeconomic position, including employment, assets, debt, homeownership, and financial security did not appear to be associated with non-concordance with either the NCCN guidelines (Table 4.2) or with QM3 (Table 4.3).

Compared to 47 (15%) of 310 women who were married or living with a partner, 13 (34%) of 38 never married women were non-concordant with QM3 (OR 3.4, 95% CI 1.6-7.4) (Table 4.3). There was also a suggestion of an increased likelihood of non-concordance with NCCN guidelines comparing never married women to married women (OR 2.0, 95% CI 0.7-5.8). However, this association did not reach statistical significance (Table 4.2).

Three (8%) of 36 women diagnosed at breast cancer facilities with an annual breast cancer patient load <200 were non-concordant with QM3 (OR 0.2, 95% CI 0.1-0.8), compared to 19 (23%) of 81 women diagnosed at facilities with a patient load ≥ 400 (Table 4.3). This inverse association was not observed between treatment facility size and non-concordance with NCCN guidelines.

DISCUSSION

We observed substantial differences in non-concordance with NCCN endocrine therapy and QM3 by income. Women with an annual household income $< \$50,000$ had a nearly 4-fold (OR 3.7, 95% CI 1.4-9.7) likelihood of non-concordance with NCCN guidelines and 2-fold (OR 2.0, 95% CI 1.0-3.9) odds of non-concordance with QM3, compared to women with a household income of $\geq \$90,000$. Several prior studies have examined receipt of endocrine therapy by area-level income and reported null or modest associations between residence in a low-income area and non-concordance.^{16,23,31,44} We did not observe clear relationships for other markers of socioeconomic position, including education, employment, assets, debt, homeownership, or financial security, and receipt of endocrine therapy. Adjuvant endocrine therapy

is initiated after a woman has already undergone surgery and potentially radiation and/or chemotherapy. By the time endocrine therapy is recommended, financial resources may already be depleted, and women may be starting to feel better as they are further removed from the cancer diagnosis, surgery, and toxic therapies. Recent evidence suggests that the amount of prescription copay significantly affects the likelihood that a woman will continue endocrine therapy.⁵⁶ For low-income women, cost may be enough of a financial deterrent to prevent them from starting therapy.

We also observed high non-concordance with QM3 among never married women (35%). Ours is the first study that we are aware of to present separate results for the association with non-concordance with recommended endocrine therapy for never married women and divorced, widowed or separated women. Livaudais et al, recently reported that women who were married or living with a partner were more likely to receive endocrine therapy than single, widowed or divorced women (OR 1.3, 95% CI 1.2-1.4).¹⁶ Married women have similarly been found to be more likely to adhere to and continue recommended endocrine therapy in two other previous studies.^{53,55} Kimmick et al, suggested that this difference might be explained by a higher level of social support among married women.⁵⁵ It is also possible that, compared to married women, never married women are more likely to be low-income or have public insurance, which were both associated with non-concordance in this study.

Our finding that women treated at facilities with an annual breast cancer patient load <200 had a reduced odds of non-concordance is comparable to the finding of Kimmick et al, that low-income women treated at hospitals with <100 beds were more likely to fill a prescription for endocrine therapy (OR 1.5, 1.1-2.1). In contrast, a recent population-based study reported that women treated at Commission on Cancer affiliated hospitals, which tend to be larger facilities, were found to be more likely to be concordant with NCCN guideline recommended endocrine therapy.³¹ Future studies may help to elucidate the role that facility characteristics contribute to concordance with endocrine therapy recommendations.

In conclusion, this study identified income and marital status as patient-level characteristics associated with non-concordance with endocrine therapy recommendations. In addition, we found evidence that women diagnosed at treatment facilities with a small annual breast cancer patient load were less likely to be non-concordant with QM3 than patients at facilities with ≥ 400 breast cancer patients

annually. Patient navigation,⁴⁶ communication with providers,⁵⁷ and improved access to affordable medications,⁵⁶ may improve concordance with endocrine therapy.

Table 4.1 Description of women for whom endocrine therapy was recommended by NCCN guidelines (N = 449)

	Overall		Non-concordant	
	n	%	n	%
Age at diagnosis				
24 - 39	77	17%	9	24%
40 - 49	201	45%	14	38%
50 - 59	98	22%	5	14%
60 - 69	73	16%	9	24%
Race/ethnicity				
Non-Hispanic White	388	86%	31	84%
Black or African American	9	2%	1	3%
Other	50	11%	5	14%
Body mass index (m/kg ²)				
<18.5	8	2%	1	3%
18.5 - 24.9	222	49%	24	65%
25.0 – 29.9	121	27%	5	14%
≥ 30	95	21%	6	16%
Smoker at diagnosis				
Yes	48	11%	5	14%
No	318	71%	26	70%
History of depression				
Yes	131	29%	11	30%
No	318	71%	26	70%
Tumor stage				
Stage I	212	47%	22	59%
Stage IIA	132	29%	11	30%
Stage IIB	80	18%	3	8%
Stage IIIA	20	4%	0	0%
Unknown	5	1%	1	3%

Table 4.2 Relationship between patient and treatment facility characteristics and non-concordance with NCCN endocrine therapy guidelines (N = 449)

	Overall n	Non- concordant n	%	OR ^a	95% CI
Patient characteristics					
Insurance type					
Private	407	34	8%	1.0	(ref)
Public	30	2	7%	0.4	(0.1-3.5)
Period of no insurance					
Yes	18	1	6%	0.8	(0.1-6.1)
No	427	36	8%	1.0	(ref)
Education (highest level achieved)					
≤ High school	92	11	12%	1.9	(0.8-4.9)
Some college	101	9	9%	1.4	(0.6-3.6)
College graduate	170	12	7%	1.0	(ref)
Graduate study	85	5	6%	0.8	(0.3-2.5)
Employed at diagnosis					
Yes	326	26	8%	1.0	(ref)
No	121	11	9%	1.2	(0.6-2.7)
Annual household income					
<\$50,000	104	14	13%	3.7	(1.4-9.7)
\$50,000 - \$89,999	136	12	9%	2.3	(0.9-5.8)
≥\$90,000	189	8	4%	1.0	(ref)
Total assets					
<\$200K	154	14	9%	1.2	(0.6-2.5)
\$200K+	248	18	7%	1.0	(ref)
Total debt ^b					
<\$2,000	176	16	9%	1.0	(ref)
\$2,000 - \$9,999	106	9	8%	1.0	(0.4-2.4)
≥\$10,000	135	10	7%	0.8	(0.3-1.8)
Home owner					
Yes	390	30	8%	1.0	(ref)
No	56	7	13%	1.5	(0.6-3.8)
Time participant could stay in home if regular source of income was lost (months)					
≤ 2	89	9	10%	1.3	(0.5-3.3)
3 - 6	112	5	4%	0.6	(0.2-1.7)
>6	224	16	7%	1.0	(ref)

Table 4.2 continued

Marital status						
Married, living as married	342	29	8%	1.0		(ref)
Divorced/widowed/separated	71	3	4%	0.3		(0.1-1.3)
Single, never married	35	5	14%	2.0		(0.7-5.8)
Pt. sought a 2nd opinion						
Yes	113	13	12%	1.5		(0.7-3.2)
No	334	24	7%	1.0		(ref)
Treatment facility characteristics						
Annual breast cancer patient load						
<200	40	3	8%	1.0		(0.3-4.4)
200 - 299	76	6	8%	1.2		(0.4-4.0)
300 - 399	98	7	7%	1.1		(0.3-3.3)
≥400	91	7	8%	1.0		(ref)

a: Odds ratios adjusted for age at diagnosis, year of diagnosis, tumor stage, BMI, smoking status at diagnosis, and history of depression

b: Excludes mortgage on a home

Table 4.3 Relationship between patient and treatment facility characteristics and non-concordance with ASCO/NCCN QM3, endocrine therapy within 1 year of diagnosis for HR-positive tumors (N = 415)

	Overall	Non-concordant		OR ^a	95% CI
	n	n	%		
Patient characteristics					
Insurance type					
Private	376	59	16%	1.0	(ref)
Public	26	9	35%	1.9	(0.7-5.0)
Period of no insurance					
Yes	19	2	11%	0.6	(0.1-2.5)
No	391	68	17%	1.0	(ref)
Education (highest level achieved)					
≤ High school	80	16	20%	0.9	(0.4-1.9)
Some college	98	16	16%	0.9	(0.4-1.7)
College graduate	160	27	17%	1.0	(ref)
Graduate study	76	13	17%	1.0	(0.5-2.0)
Employed at diagnosis					
Yes	301	49	16%	1.0	(ref)
No	111	21	19%	1.1	(0.6-1.9)
Annual household income					
<\$50,000	96	26	27%	2.0	(1.0-3.9)
\$50,000 - \$89,999	132	21	16%	1.2	(0.6-2.3)
≥\$90,000	170	23	14%	1.0	(ref)
Total assets					
<\$200K	144	23	16%	0.8	(0.5-1.5)
\$200K+	232	43	19%	1.0	(ref)
Total debt ^b					
<\$2,000	166	25	15%	1.0	(ref)
\$2,000 - \$9,999	101	19	19%	1.5	(0.8-3.0)
≥\$10,000	123	26	21%	1.6	(0.9-3.1)
Home owner					
Yes	357	59	17%	1.0	(ref)
No	55	11	20%	1.2	(0.6-2.6)
Time participant could stay in home if regular source of income was lost (months)					
≤ 2	90	19	21%	1.7	(0.9-3.3)
3 - 6	98	17	17%	1.5	(0.8-2.9)
>6	205	28	14%	1.0	(ref)

Table 4.3 continued					
Marital status					
Married, living as married	310	47	15%	1.0	(ref)
Divorced/widowed/separated	66	12	18%	0.9	(0.4-1.8)
Single, never married	38	13	34%	3.4	(1.6-7.4)
Pt. sought a 2nd opinion					
Yes	109	19	17%	1.1	(0.6-1.9)
No	303	52	17%	1.0	(ref)
Treatment facility characteristics					
Annual breast cancer patient load					
<200	36	3	8%	0.2	(0.1-0.8)
200 – 299	74	12	16%	0.7	(0.3-1.5)
300 – 399	92	15	16%	0.6	(0.3-1.3)
≥400	81	19	23%	1.0	(ref)

a: Odds ratios adjusted for age at diagnosis, year of diagnosis, tumor stage, BMI, smoking status at diagnosis, and history of depression

b: Excludes mortgage on a home

CONCLUSION

In this population-based cohort study, low-income women were consistently less likely to receive recommended breast cancer therapies. Although some of the association between income and non-concordance may be explained by appropriate deviations from guideline recommendations in women with comorbid conditions, it is also likely that the financial burden of cancer treatment inhibits some otherwise healthy low-income cancer patients from receiving treatment.

Associations between other patient and facility characteristics and non-concordance were not consistent across therapies. For example, having a period of no insurance appeared to increase the likelihood of non-concordance for receipt of radiation and chemotherapy, but there was a weak suggestion of an inverse association between having a period of no insurance and non-concordance with endocrine therapy. Such inconsistency could be due to several factors. First, only 22, 26, and 19 women assessed for concordance with QM1, QM2, and QM3 were uninsured at some point during their treatment, respectively, resulting in limited precision to investigate this exposure. Moreover, the small number of women available for assessment with QM3 further limits the power of the analysis. However, it is possible that the difference in the association between having a period of no insurance differs for endocrine therapy compared to radiation or chemotherapy because of the timing of treatment. Women who do not have insurance coverage at the time of diagnosis may become insured through Medicaid or other state-sponsored programs; while they may not go back and get radiation or chemotherapy once they have insurance they may be more likely to start endocrine therapy. Another theory is that some women may delay or avoid endocrine therapy while trying to conceive. If these women who are trying to conceive are more likely to have uninterrupted insurance coverage then this could also help explain the different relationship between having a period of no insurance with non-concordance across outcomes. However, these theories only apply if the seeming difference in effect is real and not due to a lack of power.

Future studies with larger sample sizes and more diverse patient populations may help to disentangle the effects of correlated socioeconomic exposures and could be powered to test whether associations truly differ across different therapies.

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