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Racial disparities in initiation of adjuvant endocrine therapy of early breast cancer

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Abstract

Endocrine therapy (ET) is the cornerstone of adjuvant therapy for hormone-receptor positive (HR+) breast cancer. The survival gap between African-American (AA) and white women with breast cancer is most pronounced in HR+ subtypes, and could be related to differences in ET use. The relationship between race and initiation of ET is not well defined. We investigated patterns of ET initiation by race in a diverse cohort of women covered by commercial health insurance. We identified 2,640 women with incident HR+ breast cancer in the North Carolina Central Cancer Registry whose records linked to commercial insurance claims using the Integrated Cancer Information and Surveillance System (ICISS) database. The sample included women age<65 years diagnosed with stage I–III HR+ cancers between 2004 and 2009. We used multivariate Poisson regression to examine the effect of race on likelihood of initiating ET. 14 % of women did not initiate ET within 12 months of diagnosis. AA women were 17 % less likely to initiate ET than

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whites (aRR 0.83, 95 % CI 0.74–0.93). When analyzed by subset, racial disparities persisted among women who received chemotherapy (aHR 0.67, 95 % CI 0.56–0.80) but not among women who did not receive chemotherapy (aHR 0.96, 95 % CI 0.76–1.21). AA women in our sample were less likely to initiate ET than whites, and this disparity was concentrated among chemotherapy-treated women. ET under-utilization may contribute to the racial survival gap in HR + breast cancer, and represents an opportunity for intervention to reduce breast cancer disparities.

Keywords

Breast cancer; Health care disparities; Tamoxifen; Aromatase inhibitors; Medication adherence

Background

African-American women with hormone-receptor positive breast cancer have higher rates of recurrence and poorer survival compared to their white counterparts, and this pattern has been disturbingly stable over the past 30 years even as overall breast cancer outcomes have improved [1, 2]. Despite an overall favorable prognosis for estrogen-sensitive breast tumors, African-American women with hormone-receptor positive breast cancer experience a greater disparity in recurrence and survival outcomes than in any other breast cancer phenotype including aggressive variants such as triple negative breast cancer [3]. Although this disparity is partially explained by advanced stage at presentation and under-treatment [4], the racial survival gap persists after controlling for presenting stage and receipt of adjuvant therapies including chemotherapy and radiation. [5].

Endocrine therapy (ET) is an essential element of treatment for hormone-receptor positive breast cancer. Taken as an oral medication daily for 5 to 10 years, oral anti-estrogen medications including tamoxifen and aromatase inhibitors decrease the risk of breast cancer recurrence by an estimated 40 % and the risk of death by one-third [6]. Despite their impressive efficacy, not all breast cancer survivors initiate endocrine therapy medications. Previous studies suggest that 10–30 % of women eligible for endocrine therapy, depending on the population studied, never initiate treatment [7, 8]. Of those who initiate, many discontinue treatment early or skip a significant number of doses [9, 10]. Altogether, approximately half of women are not taking their endocrine therapy effectively by the end of 5 years of treatment [11]. This under-utilization of endocrine therapy has been tied to worse breast cancer recurrence and survival outcomes [12].

Under-utilization of endocrine therapy by African-American women may contribute to the survival gap in hormone-receptor positive breast cancer, but potential disparities in endocrine therapy utilization have not been well studied. Under-treatment of minority women compared to their white peers has been a tragic and consistent pattern across other breast cancer therapies, including definitive surgery, chemotherapy, and radiation [13, 14]. However, racial disparities in use of endocrine therapy have not been as well explored for several reasons. Data regarding oral medication use in cancer registries and other large observational databases have historically been limited or unavailable. Previous studies broadly examining racial disparities in adjuvant treatment have had incomplete information

regarding ET use, while studies specifically examining patterns of ET utilization using claims data have been limited by small African-American samples or have examined only uniformly underserved populations such as Medicaid patients [8, 15, 16]. One study by Short and colleagues examining medical records of commercially insured health plans in the Southern United States found a significantly lower rate of ET prescription for hormone-receptor positive disease among African-Americans compared to whites, but was not able to examine whether the prescriptions were filled or continued [17]. A second study using data from the Women's Health Initiative did not find racial differences in self-reported use of adjuvant endocrine therapy, but was limited by lack of objective data to con-firm self-reported medication taking behavior [18].

In the current study, our objective was to analyze racial differences in endocrine therapy initiation patterns among a racially diverse cohort of women with newly diagnosed breast cancer in the Integrated Cancer Information and Surveillance System (ICISS) database. ICISS links clinical information from the North Carolina Central Cancer Registry to claims data from a variety of insurance payers across the state. We leveraged the racial diversity of North Carolina and the strengths of registry-claims linked data, including pharmacy claims for oral medications, to examine the association between race and ET initiation.

Methods

Data

We utilized three linked data sources from the Integrated Cancer Information and Surveillance System (ICISS). ICISS is a data resource developed by the University of North Carolina Lineberger Comprehensive Cancer Center. It includes cancer case data from the North Carolina Central Cancer Registry and administrative and claims data for North Carolinians from Medicare, Medicaid, and beneficiaries in privately insured health plans. The registry-claims linked data in their entirety cover approximately 85 % of the North Carolina population with cancer through 2009. For the current study, we identified patients in the NC cancer registry whose files linked to insurance claims from privately insured health plans with reliable pharmacy claims data. Data from public insurers including Medicare and Medicaid were not used for this analysis due to lack of reliable pharmacy claims data during the study period. Cancer registry data were available for all incident cancer cases diagnosed from 2004 to 2009. The insurance administrative data include monthly enrollment data, inpatient and outpatient medical claims, and outpatient prescription drug claims.

Study Sample

We included women ages 64 and under who were identified in the North Carolina Central Cancer Registry as having a first and only diagnosis of stage I–III breast cancer between 2004 and 2009 and who had linked insurance claims from a commercial or SHP plan (N = 9,586). We excluded women who did not have continuous enrollment in the health plan in the month prior to and the 12 months following their breast cancer diagnosis date (N = 5,131) because the outcome of interest (initiation of endocrine therapy within 1 year) could not be ascertained in this group. Due to lack of specificity in registry data regarding the

identification of second breast cancers as recurrences, second primaries or distant metastases, we excluded women who had a second breast cancer diagnosis in the cancer registry after their index diagnosis ($N = 91$). To ensure that included women had claims adequately reflective of their health care utilization, we excluded women who had no evidence of medical or pharmacy benefits use in the year following diagnosis ($N = 295$). We also excluded patients who did not receive definitive breast cancer surgery (i.e., mastectomy or breast-conserving surgery) within 9 months of diagnosis ($N = 57$). We excluded women who had initiated endocrine therapy prior to their primary surgery ($N = 18$) due to uncertainty regarding palliative versus curative intent of treatment, and those with missing county information ($N = 4$). We also excluded women who were identified as Hispanic or "Other" race ($N = 125$) given our focus on differences between African-American and white women, and due to the relatively small percentage (3 %) of women in these categories within the private insurance groups in the state. Finally, we excluded women whose estrogen receptor status was negative or unknown ($N = 1,226$) because they would be not be appropriate candidates for endocrine therapy (Fig. 1). There were 2,640 women who met all study inclusion and exclusion criteria.

Ascertainment of endocrine therapy initiation

Initiation of endocrine therapy was measured in two ways. First, we defined initiation as a dichotomous variable as having at least one drug claim for tamoxifen or an aromatase inhibitor (anastrozole, letrozole, or exemestane) within 12 months of diagnosis. Second, among those who started on endocrine therapy, we calculated the time in days from diagnosis to the first dispensing for endocrine therapy to identify time until therapy initiation.

Covariates

Using data reported to the North Carolina Central Cancer Registry, we identified the following control variables measured at the time of the patient's diagnosis: patient age, race, year of diagnosis, cancer stage, tumor grade, and county of residence. For patients who had a full year of insurance enrollment prior to diagnosis, we used linked administrative insurance claims data to characterize medical comorbidity using the Klabunde modification of the Charlson index [19] and a separate algorithm for depression using the methods of Dusetzina et al. [20]. Women who did not have a full year of insurance enrollment prior to diagnosis (7 %) were assigned an "unknown" value for comorbidity score. We measured receipt of primary therapy, including breast-conserving surgery (BCS) or mastectomy, receipt of chemotherapy and receipt of radiation therapy during the 9 months post-diagnosis for surgery, and the 12 months post-diagnosis for radiation and chemotherapy.

Analytic strategy

First, we estimated the likelihood of receiving endocrine therapy during the 12 month period in the entire cohort. We used generalized estimating equations with a log link and Poisson distribution to generate the average risk of endocrine therapy initiation by race, adjusting for other measured covariates.

Next, we estimated hazard ratios for endocrine therapy initiation by race using Cox Proportional Hazard Models. When testing proportional hazards assumptions for our primary analysis, we found that these assumptions were not met for the indicator addressing receipt of chemotherapy. Because of this, we stratified the Cox Proportional Hazards analyses by chemotherapy receipt when evaluating racial differences in initiation over time, adjusting for all other measured covariates. We used SAS 9.3 (Cary, NC) for analyses.

Sensitivity analyses

Because of concerns that African-American women may be more likely to have delays in treatment initiation than whites, pre-specified sensitivity analyses were performed to measure endocrine therapy initiation and time to initiation in an 18 month (versus 12 month) window.

Results

Of the 2,640 women included in our sample, 295 (11 %) were African-American and 2,345 (89 %) were white. African-American women were more likely than white women to have poorly differentiated tumors, to have chemotherapy within the year following their diagnosis, and to be public employees within the state (Table 1). Overall, 79.7 % of African-American women and 86.7 % of white women initiated endocrine therapy within 1 year of diagnosis. As compared to white women, African-American women were 17 % less likely to initiate endocrine therapy during the 12 months following their diagnosis (adjusted risk ratio [aRR]: 0.83, 95 % Confidence Interval [CI]: 0.74–0.93) (Table 2). Factors associated with a higher likelihood of endocrine therapy initiation in our multivariate model included having stage I (versus Stage III disease), and having well-or moderately differentiated tumors (versus poorly differentiated tumors). Conversely, receipt of chemotherapy within the year following diagnosis was associated with lower likelihood of initiating endocrine therapy (Table 2).

When estimating the time to endocrine therapy initiation stratified by chemotherapy receipt, we found that among women treated with chemotherapy ($N = 1515$), African-American women were significantly less likely than white women to initiate ET within 12 months of diagnosis (adjusted hazard ratio [aHR]: 0.67, 95 % Confidence Interval [CI]: 0.56–0.80). However, there was no difference in endocrine therapy initiation by race among women who did not receive chemotherapy ($N = 1125$)(aHR: 0.96, CI: 0.76–1.21) (Table 3, Fig. 2). Other factors associated with likelihood of ET initiation in chemotherapy-treated women, but not in non-chemotherapy-treated women, included stage, tumor grade, and receipt of mastectomy without radiation. However, the subset of non-chemotherapy-treated women who received breast conserving surgery without radiation as their primary local therapy was markedly less likely to initiate (aHR: 0.37, CI: 0.20–0.65).

Due to concerns that delays in primary therapies might push the initiation of endocrine therapy beyond 12 months post-diagnosis, we performed sensitivity analyses extending our follow-up time for identifying initiation of endocrine therapy from 12 to 18 months (data not shown). These results were similar to our primary analyses, specifically in that there did not

appear to be a “catch-up” phenomenon among African-American women in ET initiation between 12 and 18 months.

Discussion

In our analysis of commercially insured North Carolina women with early stage hormone-receptor positive breast cancer, African-American race was associated with a significantly lower likelihood of endocrine therapy initiation. Further, the racial gap in endocrine therapy initiation appeared to be limited to women receiving more intensive overall treatment including chemotherapy. This finding adds to previous research documenting treatment disparities in other aspects of breast cancer care, and raises significant concerns regarding whether African-American women at high risk of cancer recurrence are receiving one potentially efficacious treatment only to miss out on another.

We found that among women whose treatment did not include chemotherapy, African-American women were as likely as their white counterparts to initiate endocrine therapy. To our knowledge, our study is the first to note this relationship among race, chemotherapy receipt, and endocrine therapy utilization. Several potential explanations exist for this finding. Vulnerable women may have a better chance to initiate endocrine therapy if it is offered closer to the time of diagnosis before loss to follow-up can occur. Intervening chemotherapy complications may make certain women less likely to pursue further treatment or risk further side effects, particularly if their social support or financial resources have already been strained by earlier treatments. Alternatively, receipt of chemotherapy may reassure women that their risk has been eliminated, decreasing their perceived need for ET, and this perception may vary by race. Finally, the additional stresses to social support and financial resources brought on by chemotherapy may pose barriers to accessing ET, such as lack of transportation to appointments or pharmacies, or lack of ability to afford co-payments, and these stresses may differentially impact minority women.

We found that women with stage III disease are less likely to initiate endocrine therapy independent of their race. We also noted that women with high grade tumors were less likely to initiate. While the association of higher risk disease with lower likelihood of ET initiation is counter-intuitive, it follows the pattern of prior work by Hershman et al. showing that women with lymph node-positive breast cancers were more likely to be non-adherent (taking <80 % of prescribed doses) to ET after initiation than women with earlier stage disease. [11] While our analysis did not examine specific chemotherapy regimens, it is possible that women with more biologically aggressive disease received more intensive chemotherapy regimens, adding to the barriers to initiation posed by chemotherapy-related complications, or that less attention was focused on education regarding endocrine therapy due to competing needs related to other treatments. Alternatively, it is possible that women who present with more advanced disease, perhaps as a result of screening non-adherence, poor access to health care or low health literacy, are also less likely to follow recommendations for ET.

This study had several limitations. We are unable to determine whether patients received prescriptions for ET that were never filled, or whether no ET was prescribed. While we did

control for availability of oncology services and income differences at the census tract level, we were unable to measure individual patient differences in socioeconomic status or access to care that may affect initiation behavior. In a claims-based analysis, we are also unable to examine factors such as social support, patient beliefs, and attitudes, or provider communication that may be key determinants of initiation behavior. Our findings come from a relatively young cohort of breast cancer survivors and may not apply to women over 65 and uninsured or publicly insured women. However, the finding of a significant race disparity in this cohort of relatively healthy and well-insured women raises significant concerns regarding ET initiation in populations such as the elderly and women in poverty, where race effects may be compounded by other vulnerabilities. Further exploration of ET utilization in minority women from these doubly vulnerable populations is urgently needed. Evaluation of the relationship between race and ET uses after initiation, including persistence (continuing to take medication) and adherence (taking ET at the prescribed dose and schedule), was not within the scope of this analysis, but is planned in future work.

Future research will be most useful if it builds on these observational findings to explore attitudes, beliefs, and barriers that prevent women from utilizing appropriate, safe, and relatively inexpensive endocrine therapies to decrease their risk of breast cancer recurrence and death. A variety of research methods including the collection of qualitative and quantitative patient-reported data regarding ET medication taking behaviors, as well as the development of culturally sensitive interventions to increase ET utilization, hold promise for narrowing the survival gap among African-American women with hormone-receptor positive breast cancer.

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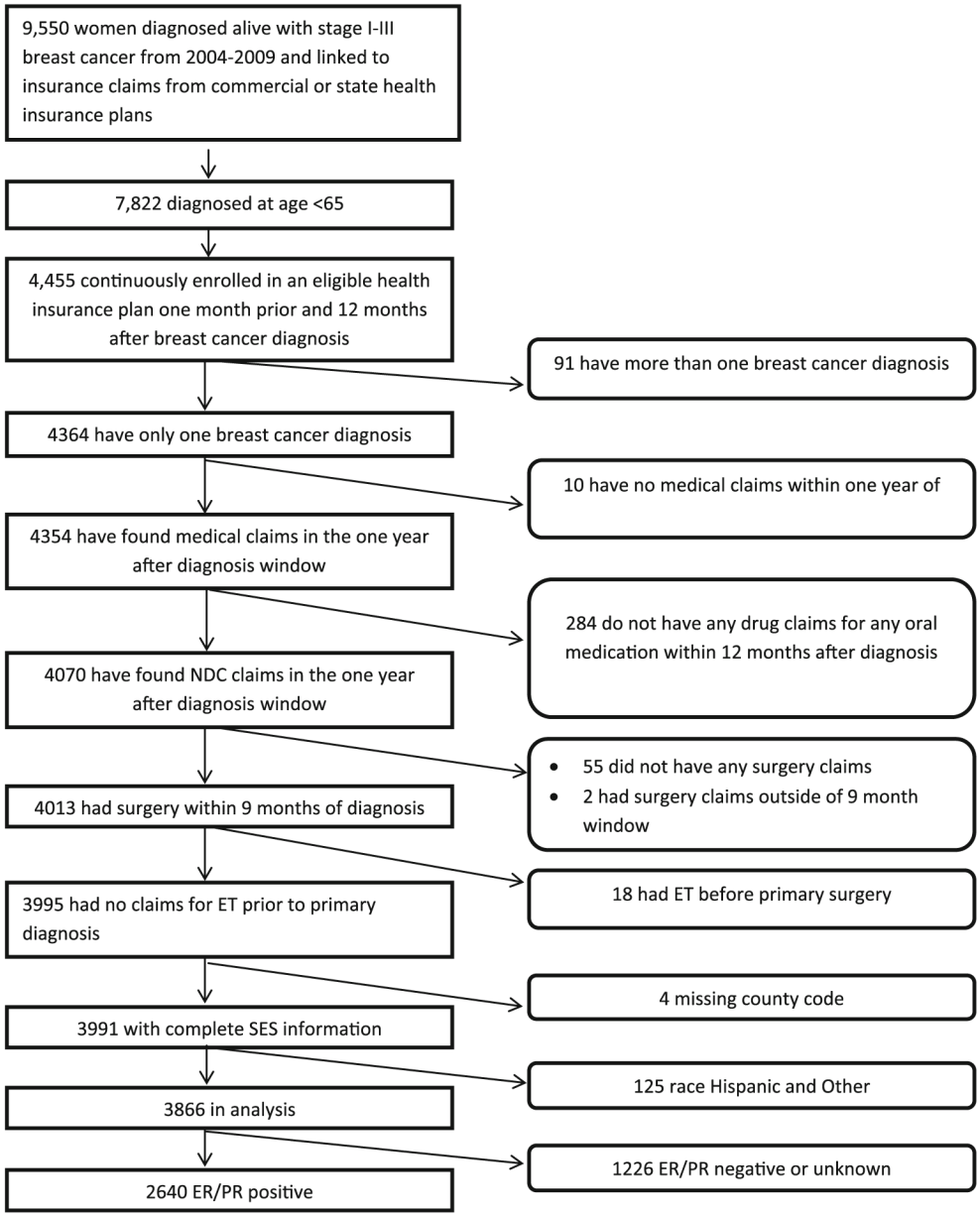

Fig. 1.
Cohort diagram

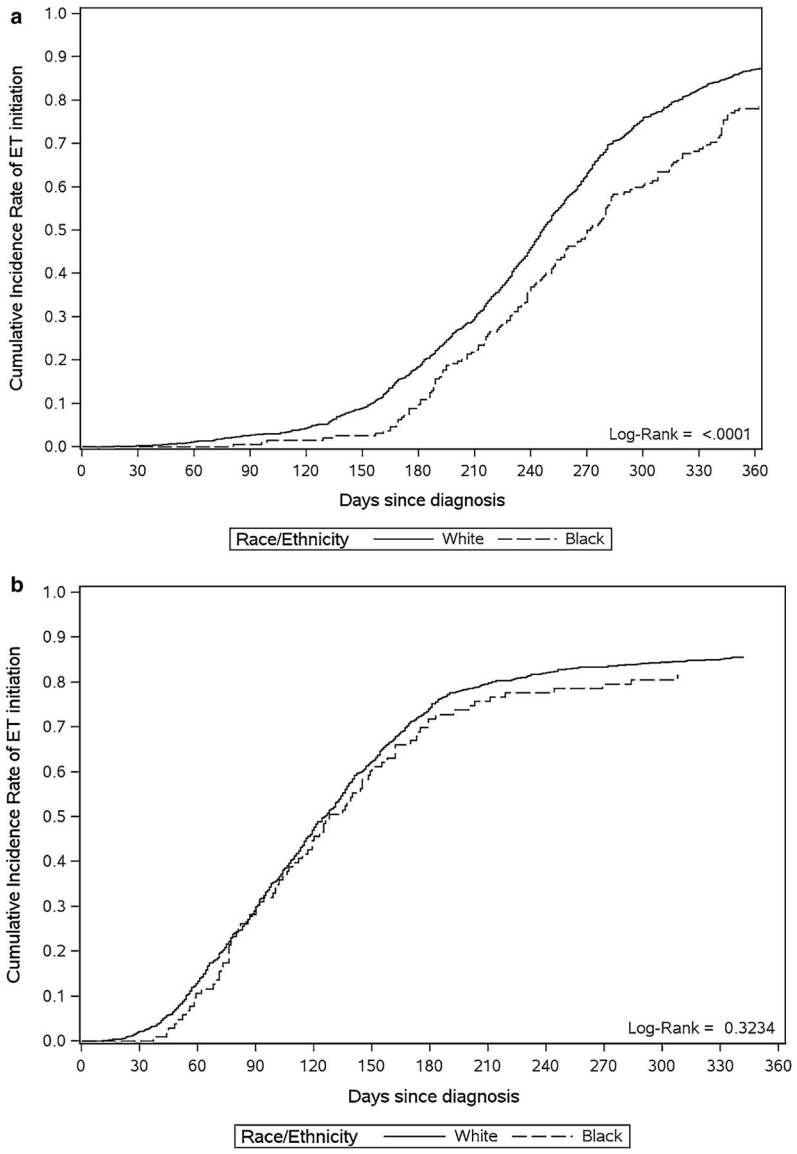

Fig. 2.

Cumulative rates of endocrine therapy initiation by race at 12 months post-diagnosis among chemotherapy-treated women (panel a) and women who did not receive chemotherapy (panel b)

Table 1

Characteristics of study population

Variable		Total (*N* = 2640) (%)	Black (*N* = 295) (%)	White (*N* = 2345) (%)	*P* value*
Age at diagnosis	<40	200 (8)	23 (8)	177 (8)	0.459
	40–49	745 (28)	87 (29)	658 (28)	
	50–59	1,193 (45)	134 (45)	1,059 (45)	
	60–64	502 (19)	51 (17)	451 (19)	
Year of diagnosis	2004	205 (8)	15 (5)	190 (8)	0.371
	2005	373 (14)	41 (14)	332 (14)	
	2006	457 (17)	43 (15)	414 (18)	
	2007	526 (20)	79 (27)	447 (19)	
	2008	500 (19)	59 (20)	441 (19)	
	2009	579 (22)	58 (20)	521 (22|)	
Stage at diagnosis	Stage I	1,350 (51)	139 (47)	1,211 (52)	0.685
	Stage II	1,000 (38)	131 (44)	869 (37)	
	Stage III	290 (11)	25 (8)	265 (11)	
Local therapy	BCS, no radiation	50–60 (2)[a]	<11 (2)[a]	40–50 (2)[a]	0.535
	BCS + radiation	1,546 (59)	175 (59)	1,371 (58)	
	Mastectomy, no radiation	632 (24)	71 (24)	561 (24)	
	Mastectomy + radiation	400–410 (15)[a]	40–50 (14)[a]	360–370 (16)[a]	
Tumor grade	Well differentiated	632 (24)	45 (15)	587 (25)	0.002
	Moderately differentiated	1,217 (46)	124 (42)	1,093 (47)	
	Poorly differentiated	693 (26)	113 (38)	580 (25)	
	Unkown/not assessed	98 (4)	13 (4)	85 (4)	
Chemo within 1 Year	Yes	1,515 (57)	192 (65)	1,323 (56)	0.005
	No	1,125 (43)	103 (35)	1,022 (44)	
NCI combined comorbidity index[b]	0	2,084 (79)	213 (72)	1,871 (80)	0.326
	1+	245 (9)	44 (15)	201 (9)	
	Unable to assess	311 (12)	38 (13)	273 (12)	
Pre-existing depression[b]	Yes	170–180 (7)[a]	<11 (2)[a]	170–180 (7)[a]	<.001
Insurance plan type	state health plan	1,186 (45)	195 (66)	991 (42)	<.001

Variable		Total (*N* = 2640) (%)	Black (*N* = 295) (%)	White (*N* = 2345) (%)	*P* value*
	other	1,454 (55)	100 (34)	1,354 (58)	
# hospitals with oncology services in county of residence	Lowest quartile	565 (21)	55 (19)	510 (22)	0.789
	Low-mid quartile	718 (27)	89 (30)	629 (27)	
	High-mid quartile	711 (27)	91 (31)	620 (26)	
	Highest quartile	646 (24)	60 (20)	586 (25)	
% poverty in county of residence	Lowest quartile	527 (20)	61 (21)	466 (20)	0.043
	Low-mid quartile	812 (31)	80 (27)	732 (31)	
	High-mid quartile	636 (24)	51 (17)	585 (25)	
	Highest quartile	665 (25)	103 (35)	562 (24)	

*Mantel–Haenszel Chi Square

[a]To assure protection of individual identities, exact numbers are suppressed and prevented from being derivable in accordance with Data Use Agreement requirements

[b]Calculated using claims from 12 months prior to diagnosis. Patients enrolled for <12 months prior to diagnosis were designated ‘unable to assess’

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Table 2

Results of incidence proportion model for overall cohort

Variable		RR	95 % CI
Race	Black	0.83**	(0.74–0.93)
	White	1.00	–
Age at diagnosis	<40	1.00	(0.85–1.18)
	40–49	1.06	(0.95–1.19)
	50–59	1.07	(0.96–1.19)
	60–64	1.00	–
year of diagnosis	2004	1.00	–
	2005	0.88	(0.72–1.08)
	2006	1.13	(0.95–1.36)
	2007	1.04	(0.86–1.25)
	2008	1.02	(0.85–1.23)
	2009	1.11	(0.93–1.33)
Stage at diagnosis	Stage I	1.16*	(1.02–1.32)
	Stage II	1.09	(0.97–1.21)
	Stage III	1.00	–
Local therapy	BCS, no radiation	0.48**	(0.33–0.70)
	BCS + radiation	1.00	–
	Mastectomy, no radiation	1.05	(0.96–1.16)
	Mastectomy + radiation	1.00	(0.90–1.10)
Tumor grade	Well differentiated	1.19**	(1.06–1.32)
	Moderately differentiated	1.17**	(1.08–1.27)
	Poorly differentiated	1.00	–
	Unkown/not assessed	0.99	(0.81–1.21)
Chemo within 1 year	Yes	0.67**	(0.61–0.74)
	No	1.00	–
NCI combined comorbidity index[a]	0	1.00	–
	1+	1.01	(0.89–1.14)
	Unable to assess	0.97	(0.87–1.08)
Pre-existing depression[a]	Yes	0.99	(0.86–1.13)
	No/unable to assess	1.00	–
Insurance plan type	public employee	1.00	–
	Other	0.94	(0.87–1.01)
# hospitals with oncology services in county of residence	Lowest quartile	1.00	–
	Low-mid quartile	0.89*	(0.79–1.00)
	High-mid quartile	1.01	(0.92–1.12)
	Highest quartile	0.97	(0.88–1.08)
% poverty in county of residence	Lowest quartile	1.00	–
	Low-mid quartile	0.89*	(0.80–0.99)

Variable		RR	95 % CI
	High-mid quartile	0.91	(0.81–1.03)
	Highest quartile	0.95	(0.84–1.07)

Significance:

* .05;

** .01

[a] Calculated using claims from 12 months prior to diagnosis. Patients enrolled for <12 months prior to diagnosis were designated ‘unable to assess’

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Table 3

Results of cox proportional hazards models stratified by receipt of chemotherapy

Variable		Chemotherapy		No chemotherapy	
		Hazard Ratio	95 % CI	Hazard Ratio	95 % CI
Race	Black	0.67**	(0.56–0.80)	0.96	(0.76–1.21)
	White	1.00	–	1.00	–
Age at diagnosis	<40	1.10	(0.88–1.38)	0.84	(0.52–1.36)
	40–49	1.10	(0.92–1.32)	0.97	(0.80–1.17)
	50–59	1.05	(0.88–1.24)	1.05	(0.90–1.23)
	60–64	1.00	–	1.00	–
Year of diagnosis	2004	1.00	–	1.00	–
	2005	0.93	(0.73–1.17)	0.68*	(0.49–0.94)
	2006	0.98	(0.78–1.23)	1.14	(0.84–1.55)
	2007	0.94	(0.75–1.18)	0.90	(0.66–1.22)
	2008	0.99	(0.79–1.24)	0.79	(0.58–1.07)
	2009	0.88	(0.71–1.10)	1.01	(0.75–1.36)
Stage at diagnosis	Stage I	1.35**	(1.12–1.62)	1.90	(0.87–4.16)
	Stage II	1.10	(0.94–1.29)	1.76	(0.80–3.89)
	Stage III	1.00	–	1.00	–
Local therapy	BCS, no radiation	0.68	(0.43–1.08)	0.37**	(0.20–0.65)
	BCS + radiation	1.00	–	1.00	–
	Mastectomy, no radiation	1.46**	(1.27–1.68)	1.02	(0.88–1.19)
	Mastectomy + radiation	1.03	(0.89–1.20)	0.95	(0.63–1.44)
Tumor grade	Well differentiated	1.38**	(1.16–1.64)	1.13	(0.90–1.40)
	Moderately differentiated	1.24**	(1.10–1.40)	1.12	(0.91–1.39)
	Poorly differentiated	1.00	–	1.00	–
	Unkown/not assessed	0.99	(0.71–1.38)	0.85	(0.59–1.22)
NCI combined comorbidity index[a]	0	1.00	–	1.00	–
	1+	0.97	(0.80–1.19)	0.97	(0.78–1.21)
	Unable to assess	0.96	(0.81–1.14)	0.86	(0.68–1.08)

Variable		Chemotherapy		No chemotherapy	
		Hazard Ratio	95 % CI	Hazard Ratio	95 % CI
Pre-existing depression[a]	Yes	0.88	(0.70–1.11)	1.07	(0.83–1.36)
	No/unable to assess	1.00	–	1.00	–
Insurance plan type	public employee	1.00	–	1.00	–
	other	0.90	(0.80–1.01)	0.94	(0.82–1.07)
# hospitals with oncology services in county of residence	Lowest quartile	1.00	–	1.00	–
	Low-mid quartile	1.07	(0.89–1.28)	0.78*	(0.63–0.96)
	High-mid quartile	1.22*	(1.03–1.45)	0.92	(0.76–1.11)
	Highest quartile	1.03	(0.87–1.22)	0.92	(0.76–1.11)
% poverty in county of residence	Lowest quartile	1.00	–	1.00	–
	Low-mid quartile	0.81*	(0.68–0.96)	0.84	(0.69–1.03)
	High-mid quartile	0.91	(0.76–1.09)	0.86	(0.69–1.06)
	Highest quartile	1.03	(0.85–1.26)	0.89	(0.71–1.13)

Significance:

* .05;

** .01

[a] Calculated using claims from 12 months prior to diagnosis. Patients enrolled for <12 months prior to diagnosis were designated ‘unable to assess’