Cancer recurrence and survival in patients with early-stage triple-negative breast cancer

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Background: Triple-negative breast cancer (TNBC) has fewer treatment options and is associated with a poor prognosis in the metastatic and adjuvant setting.

Objective: To evaluate the impact of triple-negative (TN) status on disease recurrence and survival among stage I-III patients who were treated with adjuvant chemotherapy in a community-based clinical practice setting.

Methods: Data were extracted from the 2003-2008 Georgia Cancer Specialist Database. Stage I-III breast cancer patients who received adjuvant chemotherapy were followed from initial diagnosis until death, recurrence, or loss to follow-up. The influence of TN status on disease-free survival (DFS) and recurrence was assessed.

Results: The study included 1,572 patients, of whom 26.3% had TNBC. The 5-year DFS was 76.8% for TNBC patients and 89.0% for non-TNBC patients ($P < .001$); 5-year recurrence rates were 18.8% for TNBC and 11.2% for non-TNBC ($P < .001$). The adjusted likelihood for DFS was lower for TNBC patients (hazard ratio [HR], 0.37; $P < .001$), and risk for recurrence was higher (HR, 2.85; $P < .001$) compared with non-TNBC patients. In the subpopulation with confirmed race, the comparable adjusted HRs were 0.27 and 4.70 ($P < .001$, for both), respectively. African American race was an independent risk factor for worse outcome.

Limitations: Some potential confounding factors are not accounted for in this study, including accessibility to health care, differences in chemotherapy type, dose intensity, and socioeconomic status.

Conclusions: Patients with stage I-III TNBC had shorter DFS and higher recurrence risk, despite having received chemotherapy. The results emphasize the need for more effective treatments.

Breast cancer presents a major risk to American women, who have a 1 in 8 lifetime chance of developing the disease.[1] The estimated incidence of invasive breast cancer in the United States for 2010 was 207,090 women, making it the most common cancer after skin cancer in women. Although survival has improved because of advances in treatment and early diagnoses as a result of the increased use of mammographic screening, fatalities in 2010 have been put at 40,000.[1-3]

Among the reasons for the continuing mortality are that there are fewer treatment options for triple-negative breast cancer (TNBC), which accounts for 10%-17% of all breast cancers in the United States. Survival after treatments known to be effective in non-TNBC patients is lower.[4,5] The malignant cells that make up the triple-negative (TN) tumors lack hormone receptors; they are negative for the estrogen and progesterone receptors (ER and PR, respectively), and test negative for overexpression of human epidermal growth factor receptor 2 (HER2).[4,5] Thus, therapies such as tamoxifen (an ER antagonist), aromatase inhibitors (which decrease estrogen production), trastuzumab (an anti-HER2 antibody), and lapatinib (a tyrosine kinase inhibitor) lack a therapeutic rationale and efficacy in TNBC. However, anthracycline-, taxane- and platinum-based chemotherapies do seem to be beneficial in the neoadjuvant and adjuvant settings.[6-9]

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TNBC is more common in African American and Hispanic women. It is also more likely to occur in younger women. A retrospective analysis of California Cancer Registry data concluded that African American women with breast cancer were more likely to have TN disease (odds ratio, 1.77), compared with white women with breast cancer.[5] TNBC has a particularly aggressive disease course, with the tumors tending to be larger at diagnosis, and there is a higher risk of recurrence or death in the first 5 years after diagnosis.[4,5] In the California Cancer Registry data, 77% of women with TNBC survived 5 years after diagnosis, compared with 93% of women with other types of breast cancers.[5]

A variety of demographic, disease, and therapeutic factors likely interact in patients with TNBC. In this study, we have tried to characterize the impact of TN status on disease recurrence and survival among early-stage patients treated with adjuvant chemotherapy in a community-based clinical practice setting.

Materials and methods

Data source and study population

Data for this study were derived from the electronic medical records (EMRs) in the Georgia Cancer Specialists Database from 2003 to 2008 and were supplemented by chart review. The practice records 160,000 cancer patient visits annually.

The database includes patient demographics (eg, age, sex, and race), disease diagnosis, staging at diagnosis, chemotherapy protocols (eg, protocol name, line of therapy, start and end dates of the protocol), longitudinal records of infusion drugs (chemotherapy and nonchemotherapy), outpatient services, outpatient prescriptions, laboratory results, insurance information, and survival status. We reviewed supplementary chart reviews to extract additional information on smoking status, body mass index (BMI), surgery, radiation therapy, and disease recurrence on selected patients.

The study population was selected from EMRs of patients with a diagnosis of stage I, II, or III primary breast cancer who received adjuvant chemotherapy between January 1, 2003, and December 31, 2008. The date of initial diagnosis was designated as the index event. Patients included in the study had confirmed TNBC or non-TNBC based on ER, PR, and HER2 status, as evaluated by local laboratory results. Specifically, ER and PR positivity is defined as any positivity $\geq$ 1%; HER2 positivity is defined as 3+ by immunohistochemistry or $>$ 2.2 by fluorescent in situ hybridization test. The eligible patients all received adjuvant chemotherapy. They were followed from the time of initial diagnosis through the earliest date of recurrence, then to loss to follow-up or death. All of the analyses were performed on a deidentified database. The study was exempt from internal review board approval, and was compliant with the 1996 Health Insurance Portability and Accountability Act.

Outcomes and covariates

The primary end point was disease-free survival (DFS), defined as time to the earliest of either death (all-cause), recurrence (local, regional, or distant metastasis; or new primary breast cancer), or last follow-up. A secondary end point was recurrence, as measured by the rate of or time to recurrence events. The follow-up period was defined as time to the earliest of either death (all-cause), recurrence (local, regional or distant metastasis; or a new primary breast cancer), or last follow-up.

The factor of primary interest was TN status (a dichotomous variable). Analyzed covariates included age and disease stage at diagnosis, race, overall comorbidity profile, baseline BMI (kg/m^2), smoking status, and surgery or radiation after diagnosis. Race was classified as white, African American, other, and unknown. Smoking status was divided into active, never, prior, and unknown categories.

Patient comorbidity profiles were scored according to the Charlson Comorbidity Index (CCI).[10] The version of the index applied here has been adapted to use International Classification of Diseases, 9th revision (ICD-9) codes in administrative databases.[11] The CCI was then categorized into a dichotomous variable (ie, 0 for patients with a CCI of 0, and 1 for those with a CCI of $>$ 0).

Statistical analysis

In the descriptive analysis, Kaplan-Meier curves plotted DFS and recurrence stratified by TN and non-TN status, with the log-rank test evaluating the differences between the two groups. Student's t-test determined the significance of observed differences in continuous variables, whereas differences in categorical variables (race, breast cancer stage, CCI, smoking status, and surgery or radiation after diagnosis) were evaluated using Chi-squared tests.

For the multivariate analysis, we used the Cox proportional hazards modeling to examine the association between outcomes and TN status, with adjustment of confounding covariates. The independent variables used in the Cox model were TN status, race, age, CCI, BMI, smoking status, stage, any surgery after diagnosis and any radiation after diagnosis. This analysis was performed both in the study population as a whole and in a subset that excluded patients without confirmed race.

TNBC is an aggressive form of breast cancer that displays poor survival. It is rational to propose that TNBC is associated with poor DFS and breast cancer recurrence in patients with early-stage disease who are treated with

TABLE 1 Patient characteristics at diagnosis

	Total	TNBC	Non-TNBC	*P* value
Number (%)	1,572 (100)	414 (26.3)	1,158 (73.7)	
Age at diagnosis, mean (SD), y	52.4 (10.6)	53.2 (11.8)	52.2 (10.2)	.132
Range, y	24-85	25-85	24-84	
CCI > 0, n (%)	100 (6.4)	36 (8.7)	64 (5.5)	.024
BMI, mean, kg/m^2 (SD)	28.7 (6.7)	29.5 (6.7)	28.4 (6.7)	.009
Smoking status, n (%)				.131[a]
Active smoker	161 (10.2)	45 (10.9)	116 (10.0)	
Never smoked	1,023 (65.1)	259 (62.6)	764 (66.0)	
Previous smoker	255 (16.2)	64 (15.5)	191 (16.5)	
Unknown	133 (8.5)	46 (11.1)	87 (7.5)	
Race, n (%)				< .001[a]
White	553 (35.2)	116 (28.0)	437 (37.7)	
African American	245 (15.6)	89 (21.5)	156 (13.5)	
Other	32 (2.0)	4 (1.0)	28 (2.4)	
Unknown	742 (47.2)	205 (49.5)	537 (46.4)	
Stage, n (%)				
I	494 (31.4)	150 (36.2)	344 (29.7)	.005
II	887 (56.4)	234 (56.5)	653 (56.4)	.005
III	191 (12.2)	30 (7.2)	161 (13.9)	.005
Surgery after diagnosis, n (%)	1,565 (99.6)	411 (99.3)	1,154 (99.7)	.32
Radiation therapy after diagnosis, n (%)	990 (63.0)	267 (64.5)	723 (62.4)	.457

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; SD, standard deviation; n, subsample size; TNBC, triple-negative breast cancer.
[a] Related to general comparison.

adjuvant chemotherapy, compared with women who have other breast cancers. A retrospective study such as ours, which used EMR data derived from a large pool of patients, is a useful way to study cancers such as TNC that have a relatively low incidence rate. To prevent sampling bias, we compiled a detailed oncology registry from a reliable source and designed it to include a comprehensive collection of population-based cancer patient data.

Results

Baseline characteristics

Of the total 1,572 patients, 414 (26.3%) had TNBC (Table 1). The average age of the overall sample was 52.4 years at diagnosis (standard deviation [SD], 10.6 years; range, 24-85 years). The mean follow-up time was 939 days (SD, 626 days) for TN patients and 913 days (SD, 576 days) for non-TN patients. There were no significant differences in age, smoking status, surgery, and radiation therapy between the TN and non-TN patients. All but 7 of the patients (3 TNBC, 4 non-TNBC) underwent surgery, and 64.5% of TN patients and 62.4% of non-TN patients received radiation therapy (P =.457).

Significant differences between the 2 groups included a higher BMI (29.5; SD, 6.7) in TN patients than in non-TN patients (28.4; SD, 6.7; P = .009; Table 1). In all, 6.4% of the patients exhibited major comorbidities (CCI > 0), but there was a significantly higher percentage of those among the TNBC patients than among the non-TNBC patients (8.7% and 5.5%, respectively; P = .024). TN patients also were more likely than non-TN patients to have stage I breast cancer (36.2% and 29.7%, respectively; P = .005), with a corresponding decrease in stage III (7.2% and 13.9%, respectively; P = .005).

For the 830 (52.8%) patients with confirmed race, 553 (66.6%) were white and 245 (29.5%) were African American (Table 1). A significantly higher proportion of African Americans had TNBC than did other confirmed races (white and others), at 36.3% and 20.5%, respectively, P < .001.

Disease-free survival and recurrence

The Kaplan-Meier curve showed that TN patients had significantly shorter period of DFS than did the non-TN patients, with respective 5-year DFS rates of 76.8% and

89.0% ($P < .001$; Figure 1). Triple-negative patients also had a higher 5-year recurrence rate than did non-TN patients (18.8% and 11.2%, respectively; $P < .001$; Figure 2).

The Cox proportional hazards model further evaluated the independent factors contributing to these differences (Table 2). The adjusted hazard ratio (HR) for TN patients' DFS compared with that of the non-TN patients was 0.37 ($P < .001$). TN patients' adjusted HR for recurrence was 2.85 ($P < .001$).

The presence of comorbidities (CCI > 0) also was shown to be independently associated with poor outcomes. The disease progression HR in those with comorbidity (a non-zero CCI) was 2.62 ($P < .001$), whereas the HR for recurrence was 2.58 ($P < .001$; Table 2). Similarly, the presence of higher-stage breast cancers at diagnosis predicted a worse outcome. Patients who were diagnosed with stage III breast cancer had an HR of 7.46 for disease progression ($P < .001$) and 7.68 for recurrence ($P < .001$).

A parallel Cox proportional hazards analysis was conducted in the subgroup of patients with confirmed racial data. TNBC remained an independent risk factor for shorter DFS and higher breast cancer recurrence (DFS-adjusted HR, 0.27; recurrence-free survival [RFS]–adjusted HR, 4.70; $P < .001$ for both comparisons; Table 3). In addition, African American race was independently associated with poorer outcomes. Compared with whites, African Americans' adjusted HR for disease progression was 2.43 ($P < .001$), and their adjusted HR for recurrence was 3.49 ($P < .001$). The calculated HRs associated with the presence of comorbidities and later disease stage were similar to those for the entire study population, but later disease stage was not statistically significant in this subgroup analysis (Table 3).

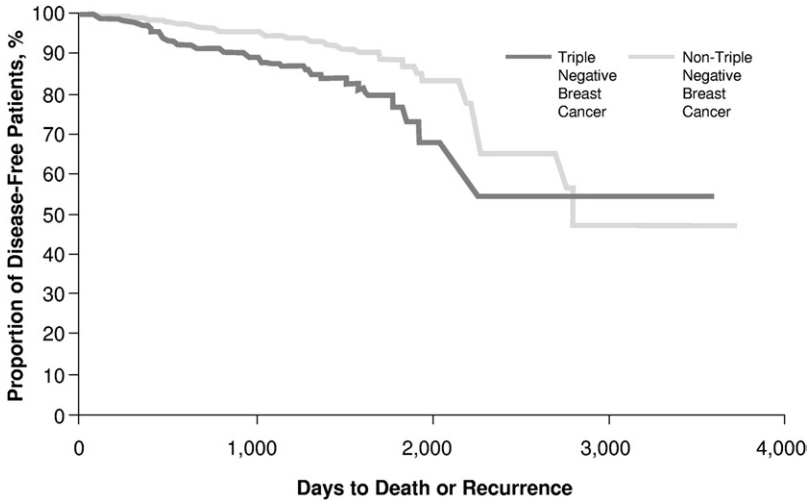

FIGURE 1 Disease-free survival for triple-negative and non–triple-negative groups.

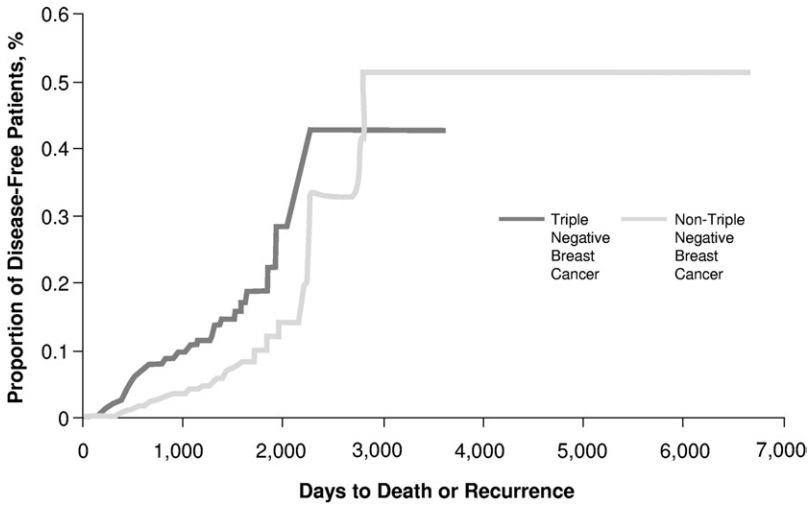

FIGURE 2 Risk of recurrence for triple-negative and non–triple-negative groups.

Discussion

This study shows that the 5-year DFS rate is lower for women with TNBC compared with women with other types of breast cancer. The rate of disease recurrence is higher for TNBC, but the curves begin to converge in the sixth year after diagnosis. Notwithstanding the higher prevalence of TNBC in African American women, this study's multivariate analysis indicated that both African American race and TN status independently confer greater risk of disease progression.

The association of TN status with earlier and more rapid disease progression agrees with findings in other studies. Gonzalez-Angulo and colleagues followed 965 patients who all had small (< 1 cm), node-negative breast tumors at diagnosis; 79.6% were white and 7.3% were African American.[12] Patients who received adjuvant chemotherapy or trastuzumab were excluded from the study. The 5-year rate of recurrence-free survival in the TN patients (13% of the total) was 85.2%. The comparative rates were 95.2% in hormone receptor–positive, HER2-negative patients, and 77.1% in HER2-positive patients.[12] The TN patients' increased risk of recurrence occurred in the first 3 years after diagnosis.[12] In a follow-up study, the TN patients had a twofold higher risk of distant recurrence over 5 years than did hormone receptor–positive patients (adjusted HR, 2.08; 95% confidence interval [CI], 1.04-4.17; $P =$

TABLE 2 Multivariate analysis for the entire study population

Characteristic	Adjusted hazard ratio (*P* value)	
	Disease-free survival	Recurrence
Triple-negative status	0.37 (< .001)	2.85 (< .001)
Age	1.00 (.696)	0.99 (.307)
CCI > 0	2.62 (< .001)	2.58 (< .001)
BMI	0.99 (.675)	0.99 (.483)
Smoking status		
Active smoker	Reference	Reference
Never smoked	0.85 (.585)	0.80 (.488)
Previous smoker	0.98 (.956)	0.95 (.882)
Unknown	0.45 (.075)	0.49 (.117)
Stage		
Stage I	Reference	Reference
Stage II	2.55 (.002)	2.55 (.003)
Stage III	7.46 (< .001)	7.68 (< .001)
Surgery after diagnosis	0.25 (.085)	0.21 (.054)
Radiation therapy after diagnosis	0.77 (.202)	0.96 (.837)

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index.

TABLE 3 Multivariate analysis for the study subpopulation with confirmed racial data (n = 830)

Characteristic	Adjusted hazard ratio (*P* value)	
	Disease-free survival	Recurrence
Triple-negative status	0.27 (< .001)	4.70 (< .001)
Age	0.98 (.256)	0.98 (.169)
CCI	1.55 (.28)	1.62 (.268)
BMI	0.98 (.3371)	0.96 (.098)
Smoking status		
Active smoker	Reference	Reference
Never smoked	1.58 (.408)	1.87 (.336)
Previous smoker	0.93 (.91)	0.90 (.894)
Unknown	1.37 (.667)	1.78 (.475)
Race		
White	Reference	Reference
African-American	2.43 (.004)	3.49 (< .001)
Other	1.04 (.98)	1.22 (.854)
Stage		
Stage I	Reference	Reference
Stage II	2.66 (.017)	2.98 (.019)
Stage III	12.7 (< .001)	14.3 (< .001)
Surgery after diagnosis	0.05 (.009)	0.03 (.003)
Radiation therapy after diagnosis	0.54 (.039)	0.75 (.391)

Abbreviations: BMI, body mass index; CCI, Charlson Comorbidity Index; n, subsample size.

.039).[13] Kaplan and colleagues have also reported that TN patients with T1N0 disease have a greater recurrence risk compared with those with hormone receptor–positive, HER2-negative breast cancer, despite the fact that they receive more frequent and more aggressive adjuvant chemotherapy.[14]

In 2008, Liedtke and colleagues reported on 1,118 breast cancer patients who were receiving neoadjuvant chemotherapy, of whom 23% were TN.[7] The TN patients had increased risk of disease progression or death during the first 3-5 years after surgery, with decreased overall 3-year survival, compared with the non-TNBC patients (74% and 89%, respectively; $P < .0001$).[7] That was despite a higher pathological complete response rate on the part of TN patients compared with non-TN patients (22% and 11%, respectively; $P = .034$). The 3-year progression-free survival rate for TN and non-TN patients was 63% and 76%, respectively (HR, 1.86; $P < .001$). Findings from numerous studies have demonstrated that patients with TNBC can achieve pathological complete responses with a variety of chemotherapy-based regimens, including platinum agents.[15]

A study population similar to the cohort described here was based on EMRs from a Midwestern community oncology practice.[16] The 1,134 stage I-III patients in the Midwestern study were almost entirely white (97.43%), the prevalence of TNBC was lower than in our cohort (13.4%), and the mean age (62.7 years) was 10 years older than in our cohort. In contrast with our cohort, which included only patients who were receiving adjuvant chemotherapy, 45.8% of the Midwestern patients received such therapy. The subpopulation with TNBC had poorer overall survival and DFS, compared with those with hormone receptor–positive breast cancer.[16] Relative to hormone receptor–positive, HER2-negative patients, the TN patients also had an HR for disease progression of 1.83 (95% CI, 1.06-3.17). For overall mortality, HR was 1.75 (95% CI, 1.01-3.03).[16]

The general agreement between our results and those of other studies demonstrates the validity of extracting breast cancer outcomes data from electronic medical records. EMRs are applicable to other breast cancer studies in which community-based outcome data are desired. Such studies bridge the gap between research and clinical practice, and provide the basis for rapidly testing hypoth-

eses and highlighting areas for further clinical and translational research.[17]

The main limitation of the present study arises from the possibility that undetected, confounding factors may affect the results.[18] For example, accessibility to health care, differences in chemotherapy type, and dose intensity were not taken into account. The BMIs of patients with TNBC were significantly greater than they were in non-TNBC patients, and it is possible that dose attenuations were made as a result. Recently, guidelines have been published recommending that full-dose therapy be given using actual body weight,[19] but clearly this has not always been the case. The specific dose calculations are not available, so dose intensity cannot be compared. There is however, no evidence that the observed differences in DFS and recurrence rates can be explained by differences in chemotherapy type. Taken together, our results and the findings in the other studies described here suggest that the worse outcomes experienced with TNBC are independent of chemotherapy. A recent study proposed that the differential survival patterns of clinically stratified breast cancer subtypes, including TNBC, may be attributed in part to their molecular heterogeneity.[20] Other authors counter by noting the good prognosis of those TNBC patients who obtain a pathological complete response to neoadjuvant chemotherapy.[8]

Another factor that is not accounted for is socioeconomic status, which has been found to independently affect outcome.[5] These and other covariates could be included as refinements in future investigations.

In conclusion, the results described here demonstrate that TNBC is associated with increased recurrence and mortality despite the use of current adjuvant chemotherapies. This study could be refined by examining more independent covariates, such as specific treatment protocols. It also could be extended to different populations. Most immediately, however, it illustrates the feasibility of applying EMR databases to outcomes research. Furthermore, it confirms the need for additional therapeutic strategies to manage TNBC. Fortunately, this is an area of active investigation.[6,21]

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References

1. National Cancer Institute. SEER stat fact sheets: breast. http://seer.cancer.gov/statfacts/html/breast.html. Accessed November 9, 2010.

2. Sprague BL, Trentham-Dietz A, Remington PL. The contribution of postmenopausal hormone use cessation to the declining incidence of breast cancer. *Cancer Causes Control*. 2011;22(1):125-134.

3. Rosso S, Gondos A, Zanetti R, et al. Up-to-date estimates of breast cancer survival for the years 2000-2004 in 11 European countries: the role of screening and a comparison with data from the United States. *Eur J Cancer*. 2010;46(18):3351-3357.

4. Reis-Filho JS, Tutt AN. Triple negative tumours: a critical review. *Histopathology*. 2008;52(1):108-118.

5. Bauer KR, Brown M, Cress RD, Parise CA, Caggiano V. Descriptive analysis of estrogen receptor (ER)–negative, progesterone receptor (PR)–negative, and HER2-negative invasive breast cancer, the so-called triple-negative phenotype: a population-based study from the California Cancer Registry. *Cancer*. 2007;109(9):1721-1728.

6. Santana-Davila R, Perez EA. Treatment options for patients with triple-negative breast cancer. *J Hematol Oncol*. 2010;3:42.

7. Liedtke C, Mazouni C, Hess KR, et al. Response to neoadjuvant therapy and long-term survival in patients with triple-negative breast cancer. *J Clin Oncol*. 2008;26(8):1275-1281.

8. Carey LA, Dees EC, Sawyer L, et al. The triple negative paradox: primary tumor chemosensitivity of breast cancer subtypes. *Clin Cancer Res*. 2007;13(8):2329-2334.

9. Jacquin JP, Jones S, Magné N, et al. Docetaxel-containing adjuvant chemotherapy in patients with early stage breast cancer. Consistency of effect independent of nodal and biomarker status: a meta-analysis of 14 randomized clinical trials. *Breast Cancer Res Treat*. 2012 Jan. 24 (doi:10.1007/s10549-011-1933-0).

10. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. *J Chronic Dis*. 1987;40(5):373-383.

11. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. *J Clin Epidemiol*. 1992;45(6):613-619.

12. Gonzalez-Angulo AM, Litton JK, Broglio KR, et al. High risk of recurrence for patients with breast cancer who have human epidermal growth factor receptor 2–positive, node-negative tumors 1 cm or smaller. *J Clin Oncol*. 2009;27(34):5700-5706.

13. Litton JK, Chen H, Mittendorf EA et al. Outcomes differences in tumors < 1 cm by age and breast cancer subtype [ASCO abstract 580]. *J Clin Oncol*. 2010;28(15;suppl).

14. Kaplan HG, Malmgren JA, Atwood M. T1N0 triple negative breast cancer: risk of recurrence and adjuvant chemotherapy. *Breast J*. 2009;15(5):454-460.

15. Amos KD, Adamo B, Anders CK. Triple-negative breast cancer: an update on neoadjuvant clinical trials. *Int J Breast Cancer*. 2012;2012:385978.

16. Onitilo AA, Engel JM, Greenlee RT, Mukesh BN. Breast cancer subtypes based on ER/PR and HER2 expression: comparison of clinicopathologic features and survival. *Clin Med Res*. 2009;7(1-2):4-13.

17. Atreja A, Achkar JP, Jain AK, Harris CM, Lashner BA. Using technology to promote gastrointestinal outcomes research: a case for electronic health records. *Am J Gastroenterol*. 2008;103(9):2171-2178.

18. Hershman DL, Unger JM, Barlow WE, et al. Treatment quality and outcomes of African American versus white breast cancer patients: retrospective analysis of Southwest Oncology studies S8814/S8897. *J Clin Oncol*. 2009;27(13):2157-2162.

19. Griggs JJ, Mangu PB, Anderson H, et al. Appropriate chemotherapy dosing for obese adult patients with cancer: American Society of Clinical Oncology clinical practice guideline. *J Clin Oncol*. 2012;30(13):1553-1561.

20. Blows FM, Driver KE, Schmidt MK, et al. Subtyping of breast cancer by immunohistochemistry to investigate a relationship between subtype and short and long term survival: a collaborative analysis of data for 10,159 cases from 12 studies. *PLoS Med*. 2010;7(5):e1000279.

21. Anders CK, Carey LA. Biology, metastatic patterns, and treatment of patients with triple-negative breast cancer. *Clin Breast Cancer*. 2009;9(suppl 2):S73-S81.