

## Survival Analysis of Women with Triple Negative Breast Cancer Using EMR-Linked Cancer Registry Data in Florida

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### Abstract

**Background:** Triple negative breast cancer (TNBC) is an aggressive tumor phenotype which has limited therapeutic options. Epidemiological studies suggested a number of risk factors that are associated with the prognosis of TNBC. Survival difference exists among patients diagnosed with TNBC after adjusting these risk factors. This study aims to investigate the survival of women with triple negative phenotype breast cancer (BC).

**Methods:** Electronic medical records from a network of 9 hospitals were linked to female BC patients diagnosed between 2007 and 2010 in Florida. Cox proportional hazards model was used.

**Results:** Two-year survival of the BC patients was 95.1%. Median follow-up time for those who died due to BC was 569 days. Survival functions between Blacks and non-Blacks were significantly different over time ( $p < 0.0001$ ). Survival probability among Blacks was lower than that of non-Blacks. Hazard of BC death among patients with TNBC and patients with unknown status were 4.34 and 2.35 times that of non-TNBC patients, respectively. Death rate among Blacks was 1.6 times that of non-Blacks. Other factors associated with increased hazard were: unmarried, Medicare recipients, diagnosis of regional stage or unknown stage, poorly or un-differentiated tumor, larger tumor size, and more positive nodes detected. Immediately after diagnosis, distant stage and more comorbidity conditions were associated with an elevated risk, and more lymph nodes examined was associated with reduced risk of BC death. However these effects gradually attenuated over time.

**Conclusions:** Women with triple negative BC have the worst survival outcome. This study highlights the importance of improvement of care for patients with TNBC biomarkers.

**Keywords:** Breast cancer; Triple negative; Survival; Electronic medical records

## Introduction

Breast cancer (BC) is the most common malignancy affecting women and the second common cause of cancer-related death among women in the United States [1]. It is estimated that 246,660 new cases of invasive breast cancer will be diagnosed in women, and 40,450 women will die from this disease in the United States in 2016 [1]. Breast cancer disproportionately affects minority racial/ethnic and economically disadvantaged groups [1]. Black women are more likely to be diagnosed at a later stage and to experience higher breast cancer mortality compared with White women [1]. Breast cancer is a heterogeneous disease, comprising multiple entities associated with distinctive histological and biological features. Breast cancers that have estrogen receptors are often referred to as ER-positive (or ER+) cancers while those containing progesterone receptors are called PR-positive (or PR+) cancers.

Triple-negative breast cancer (TNBC) is a subtype of breast cancer that is estrogen receptor negative (ER-), progesterone receptor negative (PR-), and human epidermal growth factor receptor 2 (HER2) negative. TNBC accounts for 12% of overall breast cancer [1]. TNBC carries a particularly unfavorable prognosis and has limited therapeutic options [2,3]. Black women are more likely to be diagnosed with TNBC, compared to women of other ethnic groups [4,5] and coincidentally they have the worse survival from BC among all women with BC [5]. However, it is unclear whether triple-negative phenotype is a significant contributing factor to the survival of Black women [6-8]. It is also unknown whether survival differences persist after adjusting for disparities in comorbidity, access to treatment, disease and socioeconomic status.

Population-based cancer registry data are widely used for breast cancer survival analysis. However, most of cancer registry data, if not all, do not contain tumor phenotype of individual patients and/or do not have a long follow-up period. Therefore individual based long-term breast cancer outcomes research is hindered. To overcome this data limitation, we linked BC phenotype information in the hospital electronic medical records with the Florida cancer registry data through a partnership between the Florida Department of Health, the Florida Cancer Data System (FCDS) and a large Florida hospital network [9]. The linked dataset allows a comprehensive analysis of BC survival in relation to individual women's tumor phenotype.

## Methods

### Study population and data sources

Women who were diagnosed and/or treated in any of the 9 hospitals of the hospital network were included in this study. The hospital network's electronic medical records (EMRs) contain detailed patient medical and demographic information. Invasive breast cancer patients were identified among patients whose principal diagnosis or a secondary diagnosis code was International Classification of Diseases (ICD-9-CM) code between 174.0 and 174.9. The EMR records of invasive breast cancer patients were then linked to the state cancer registry data using unique patient identifiers.

Study subjects were restricted to female breast cancer patients with diagnosis and/or treatment within the partner hospital system between 2007 and 2010. This study was approved by the Florida Department of Health Institutional Review Board (#H11163).

### Statistical analyses

This study focused on time from diagnosis of breast cancer to death due to breast cancer. Patients who died due to other reasons during the study period were censored at death, and patients who did not die were censored at end of study. Sample mean and sample proportion were utilized to summarize patient characteristics. Associations between categorical variables were tested using  $\chi^2$  tests, and group means were compared using T-tests. The Kaplan-Meier method was used to estimate survival probabilities and create survival curves. The Log-rank test was applied to compare survival probability over time between Black and non-Black patients. Multivariate Cox proportional hazards model was used to assess effects of factors in multivariable setting. While total comorbidity and triple negative status were kept in model, forward stepwise model selection procedure was adopted to detect other variables that were associated with breast cancer survival. Statistical analyses for this study were performed using SAS/STAT® software, Version 9.3 of the SAS System for Windows (Cary, North Carolina).

## Results

Patient characteristics by race are summarized in Table 1. Among all patients, 6.87% died from breast cancer and 4.98% died from other causes during study period. The majority of the patients were age of over 50 years at diagnosis (75.62%). Most of the patients were White (89.16%), non-Hispanic (93.30%), while Blacks made up 9.07% of the study patients. Distribution of socioeconomic status shows that the majority of patients came from areas where 10%-20% population living in poverty (34.19%) or areas where 5%-10% of population living in poverty (30.31%), while 14.15% came from areas where over 20% of population living in poverty and 19.17% were from areas where less than 5% of population living in poverty. About half of the patients were married (51.40%), and 46.40% of patients were unmarried. Over half of patients (52.58%) had medical insurance other than Medicaid or Medicare. Among the study population, 35.92% patients were Medicare recipients, 7.11% were Medicaid beneficiaries, and 2.61% without an insurance. On average, each patient had one comorbidity.

Race was associated with all patient characteristic variables. Specifically, percentage of Blacks among those who died from breast cancer was the highest (21.45%), while the percentages among people who were alive by end of study and people who died from other causes during study period were around the same (8.16% and 8.10%, respectively). The proportion of Black patients diagnosed at age 50 or below was higher (12.88%) than that among patients diagnosed at age of over 50 (7.84%). Blacks counted for 9.54% of non-Hispanic patients, while only 2.86% of Hispanic patients.

**Table 1:** Patient characteristics and relation with race (N = 4,220)

Variable		Percentage	Non-Black*	Black*	p-value
Vital status	Alive	88.15	91.84	8.16	<.0001
	Dead due to breast cancer	6.87	78.55	21.45	
	Dead due to other reasons	4.98	91.90	8.10	
Age at dx	Age at dx ≤ 50	24.38	87.12	12.88	<.0001
	Age at dx > 50	75.62	92.16	7.84	
Race	White	89.16			
	Black	9.07			
	Other	1.76			
Hispanic	No	93.30	90.46	9.54	0.0002
	Yes	6.70	97.14	2.86	
Social economic status	> 20% living below poverty line	14.15	68.30	31.70	<.0001
	Between 10% and <20% of population living in poverty	34.19	91.45	8.55	
	Between 5% and <10% of population living in poverty	30.31	96.62	3.38	
	< 5% of population living in poverty	19.17	96.90	3.10	
	Unknown	2.18	97.80	2.20	
Married	Unmarried	46.40	87.93	12.07	<.0001
	Married	51.40	93.76	6.24	
	Unknown	2.20	87.18	12.82	
Insurance	Not insured	2.61	88.99	11.01	<.0001
	Medicaid	7.11	76.92	23.08	
	Medicare	35.92	94.17	5.83	
	Other insurance	52.58	90.48	9.52	
	Unknown	1.78	97.33	2.67	
Total comorbidity		0.99 (1.45)	0.96 (1.41)	1.31 (1.80)	0.0003

\* row % or mean (std. dev.)

The proportion of Blacks was much higher among patients coming from areas where over 20% of population lived in poverty (31.70%), from areas where 10%-20% of population lived in poverty (8.55%) than among patients living in affluent areas where 5%-10% of population lived in poverty (3.38%) or areas where less than 5% of population lived in poverty (3.10%). The percentage of Blacks was lower among married patients (6.24%), than among unmarried patients (12.07%) and among patients with unknown marital status (12.82%). Among patients with a health insurance, the proportion of Blacks was the highest among Medicaid beneficiaries

(23.08%), followed among patients without insurance (11.01%), among patients with other insurance (9.52%) and Medicare recipients (5.83%). On average, a Black patient had more comorbidity conditions (1.31) than a non-Black patient (0.96). Two-year survival was estimated to be 95.1%. The median follow-up time for those who died due to breast cancer was 569 days. Table 2 presents the distributions of tumor characteristic and treatment by race.

Table 2: Tumor characteristics, treatment, and relation with race (N = 4,220)

Variable		Percentage	Non-Black*	Black*	p-value
ER	-	19.55	85.52	14.48	<.0001
	+	72.87	92.28	7.72	
	Unknown	7.58	91.85	8.15	
PR	-	34.27	87.98	12.02	<.0001
	+	57.89	92.67	7.33	
	Unknown	7.84	90.91	9.09	
HER2	-	17.94	89.23	10.77	0.2082
	+	4.91	91.26	8.74	
	Unknown	77.16	91.29	8.71	
Triple Negative	No	74.91	92.24	7.76	<.0001
	Yes	2.61	72.22	27.78	
	Unknown	22.49	88.71	11.29	
Breast surgery	No surgery	1.49	88.89	11.11	0.0009
	Mastectomy	38.70	89.78	10.22	
	Other surgery	51.68	92.49	7.51	
	Unknown	8.13	86.76	13.24	
Hormone	No	78.20	90.71	9.29	0.2581
	Yes	20.78	91.41	8.59	
	Unknown	1.02	97.62	2.38	
Radiation	No	68.27	91.11	8.89	0.6310
	Yes	31.02	90.62	9.38	
	Unknown	0.71	86.67	13.33	
Chemo	No	62.04	92.78	7.22	<.0001
	Yes	35.38	87.42	12.58	
	Unknown	2.58	94.50	5.50	
Stage	Localized	62.42	92.86	7.14	<.0001
	Regional	28.63	88.69	11.31	
	Distant	4.93	81.16	18.84	
	Unknown/un-staged	4.03	88.82	11.18	
Grade	Well-differentiated	20.45	95.33	4.67	<.0001
	Moderately-differentiated	38.51	92.97	7.03	
	Poorly- or un-differentiated	41.04	86.82	13.18	
Histology	Ductal	83.29	90.79	9.21	0.0094
	Lobular	10.69	94.00	6.00	
	Other	6.02	87.25	12.75	
Tumor Size (mm)		21.98 (19.93)	21.37 (19.42)	28.34 (23.80)	<.0001
Number of positive nodes examined		1.14 (2.97)	1.07 (2.88)	1.77 (3.77)	0.0004
Total number of nodes examined		6.11 (7.36)	5.97 (7.28)	7.50 (8.06)	0.0004

\* row % or mean (std. dev.)

The majority of patients had ER+ results (72.87%), PR+ results (57.89%), unknown HER2 status (77.16%), and were not diagnosed with triple negative (74.91%). Most patients had some type of surgery where 38.70% had mastectomy and 51.68% had other surgery. Most patients were not given hormone therapy (78.20%), or radiation therapy (68.27%), or chemotherapy (62.04%). A large proportion of patients had localized diagnosis stage (62.42%), followed by regional diagnosis stage (28.63%). Only 4.93% of patients who were diagnosed with distant stage. In the study sample, 41.04% of patients had poorly- or un-differentiated tumor, while 38.51% had moderately differentiated tumor and 20.45% had well differentiated tumor at diagnosis. Most patients had ductal histology (83.29%), followed by lobular histology (10.69%). The mean tumor size was 21.98 mm. On average 6.11 nodes were examined in total for each patient, where average number of positive nodes identified was 1.14. The proportion of Blacks was higher in the groups of ER negative (14.48%), PR negative (12.02%), and triple negative (27.78%) than that in the positive groups. Black patients counted for 11.11% of patients who did receive any surgery, 10.22% of patients who received mastectomy, 7.51% of patients who had other surgery, and 13.24% of patients with unknown surgery status. The proportion of Blacks was higher among patients who received chemotherapy (12.58%) than among patients who did not receive chemotherapy (7.22%). The percentage of Black patients was the highest among patients with distant diagnosis stage (18.84%) and the lowest among patients with localized stage (7.14%) among patients by cancer stage at diagnosis.

Among patients by cancer grades, the proportion of Blacks was the highest (13.18%) among patients with poorly- or un-differentiated tumor, and was the lowest (4.67%) among patients with well-differentiated tumor. Among groups by histology, the proportion of Blacks was the highest among patients with other histology (12.75%), followed by 9.21% among patients who had ductal histology and 6.00% for patients with lobular histology. In addition, compared to non-Black patients, Black patients on average had larger tumor size, more positive nodes identified, and more nodes examined in total.

The Kaplan Meier survival curves for Black and non-Black patients are shown in Figure 1. The Log-rank test indicates survival functions for Black and non-Black patients were significantly different over time, with a p value of less than 0.0001. Figure 1 suggests survival probability for Blacks was always lower than that of non-Blacks after diagnosis.

The results of multivariate survival analysis from the time of diagnosis to death from breast cancer are shown in Table 3 below. The hazard of breast cancer death for women diagnosed with triple negative breast cancer and those with unknown triple negative status during study period were 4.34 and 2.35 times that of non-triple negative women, respectively. Death rate was 1.6 times for Blacks compared to that for non-Blacks over time.

Figure 1: Kaplan-Meier survival estimates by race category (N=4220, p< 0.0001)

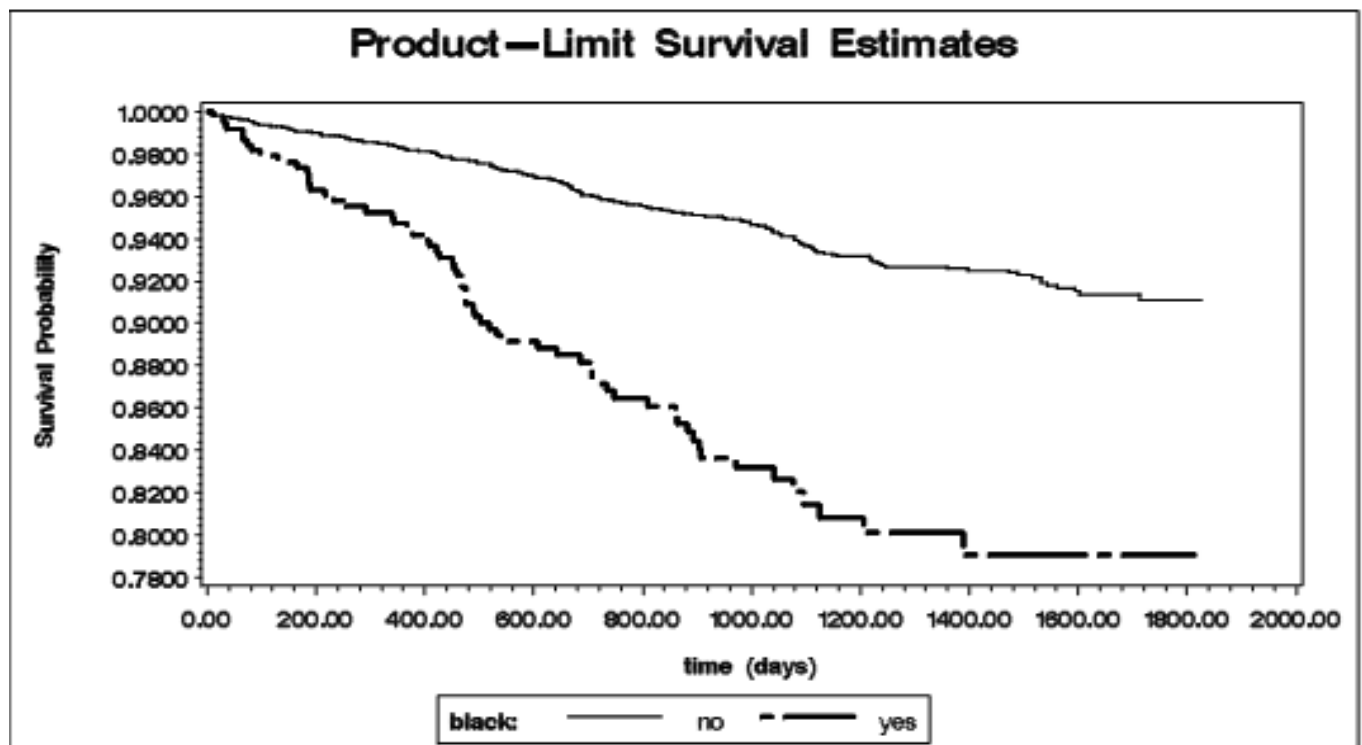


Table 3: multivariate survival analysis of time to breast cancer death (N = 4,124)

Variable		Estimate	Std. Err.	p-value	Hazard Ratio
Triple Negative	Triple negative vs Non-triple negative	1.47	0.32	<.0001	4.34
	Unknown vs Non-triple negative	0.86	0.13	<.0001	2.35
Comorbidity		0.47	0.13	0.0003	1.59*
Race	Black vs Non-Black	0.46	0.16	0.0030	1.59
Diagnosis stage	Distant vs Localized stage	4.93	0.98	<.0001	138.95*
	Regional vs Localized stage	1.08	0.20	<.0001	2.96
	Unknown vs Localized stage	1.70	0.25	<.0001	5.46
Tumor grade	Moderately-vs Well-differentiated	0.61	0.32	0.0532	1.85
	Poorly-/un-vs Well-differentiated	0.91	0.31	0.0034	2.49
Tumor size (mm)		0.01	0.00	<.0001	1.01
Number of + nodes		0.10	0.02	<.0001	1.10
Number of nodes		-0.22	0.08	0.0054	0.81*
Breast surgery	Mastectomy vs No surgery	0.06	0.32	0.8539	1.06
	Other surgery vs No surgery	-0.27	0.34	0.4333	0.77
	Unknown vs No surgery	0.49	0.30	0.1041	1.64
Insurance	No insurance vs Other insurance	0.49	0.26	0.0619	1.63
	Medicaid vs Other insurance	0.34	0.19	0.0729	1.41
	Medicare vs Other insurance	0.50	0.14	0.0004	1.66
Marital status	Unmarried vs Married	0.32	0.13	0.0150	1.37
	Unknown vs Married	-0.80	0.60	0.1800	0.45
Interactions with time					
Comorbidity x ln(time)		-0.06	0.02	0.0051	
Distant stage x ln(time)		-0.41	0.16	0.0095	
Number of nodes x ln(time)		0.03	0.01	0.0288	

\* HR at day 1 after diagnosis

Other identified factors associated with an increased hazard over time were being diagnosed in regional stage or having unknown diagnosis stage, having moderately-, poorly- or un-differentiated tumor, being a Medicare recipient, being unmarried, with larger tumor size, and with more positive nodes detected. There were also factors whose effects changed over time. Diagnosis of distant stage was associated with a dramatically elevated risk of breast cancer death immediately after diagnosis compared to diagnosis of localized stage. Right after diagnosis, more comorbidity conditions were associated with higher hazard of breast cancer death. In addition, having more nodes examined in total was associated with a reduced risk of breast cancer death closely after diagnosis. However, interactions with time suggest the adverse effects of diagnosis of distant stage and more comorbidity conditions, as well as the positive effect of more nodes examined in total, were greatest instantly after diagnosis, then gradually attenuated over time.

## Discussion

This study investigated the impact of triple negative phenotype on survival of patients with breast cancer using Florida statewide cancer registry data linked with hospital EMR data. The key findings were that women with TNBC had poorer survival compared to non-TNBC patients. Black women had worse BC survival compared to non-Black women. Distant stage at diagnosis was associated with the worst survival. Medicare recipients had the worst survival outcome compared with patients with other insurance. Married women had a better outcomes across the board compared to unmarried women. Having more nodes examined was associated with a reduced risk of BC death closely after diagnosis.

Our results confirmed the findings of previous studies and revealed that survival outcome in women with TNBC is significantly poorer compared to that of women with non-TNBC of breast cancer [10-12]. TNBC is potentially clinically relevant, as they differ in their underlying biology and clinical outcome and, consequently, requires different treatment strategies [3,13]. TNBC is more likely to spread to other organs and recur. This touches on the broader issue of developing strategies for identifying high-risk populations, including younger women, Black women, and breast cancer genes 1 mutation carriers. There is also a concerted effort to achieve improvement in survival in women with TNBC with implication for both clinical practice and clinical trial design [14,15]. These efforts have been directed towards developing new locoregional and systemic treatment strategies for patients with this aggressive subtype [16-18].

Our findings of poorer TNBC survival in Black women compared to non-Black women are in lines with those of other investigations [12,19]. Previous studies have also shown that racial disparity in TNBC survival persists even after adjustment for variables such as age, stage, socioeconomic status, insurance status, and, in some studies, pathologic characteristics [7,19,20].

Factors that contribute to the Black-White disparities in TNBC survival may include differences in early detection and treatment. Black women have historically been less likely than Whites to be screened for breast cancer. Additionally, among Black women who undergo screening, delay in the timing of treatment initiation remains a consequence for increased recurrence and lower survival [21-23].

Our observation that distant stage at diagnosis was associated with the worst survival is similar across all malignancies. In fact, the extent of disease at diagnosis is the most important prognostic factor for cancer patients' survival. In fact, a study using the population-based California Cancer Registry data found that regardless of stage at diagnosis, women with TNBC had poorer survival than those with other breast cancers [12]. Previous findings indicate that women with TNBC tended to be diagnosed at advanced stage than those with non-TNBC [12,24,25]. When it comes to TNBC, disparity in stage at diagnosis may not totally be a consequence of socioeconomic factors such as low educational attainment, living in poverty, and lack of health insurance. Disparity in stage at diagnosis may partly be explainable by inherent biological differences. Research to determine whether there is a genetic component to the often aggressive and have a poorer prognosis in TNBC and race/ethnicity is ongoing. Nonetheless, thus far, the most consistent findings reveal specific genetic alterations that appears to impact prognosis factors, and treatment among Black women, ultimately contributing to survival rates [26-28]. The genetic risk factors that predispose Black women to TNBC is observed irrespectively of tumor size, stage, grade, presence of axillary lymph node metastasis, and age. Our findings show that Medicare recipients had worst survival. The poor health outcome in Medicare recipients could be explained by diagnosis at old age, comorbid conditions that are commonly present in elderly patients, and the non-receipt of standard therapy [29,30]. The diagnosis of cancer in the Medicare population, is often made amidst the diagnosis or treatment of other medical conditions. Comorbidity is a determinant of treatment selection, and adversely affects breast cancer survival [31-33]. Elderly patients with comorbidity do not receive standard cancer therapy because aging often involves a decline in tumor aggressiveness and a corresponding decline in the effectiveness of treatment such as chemotherapy [34-36]. The chance of completing the course of treatment is also lower among these patients [37]. Large randomized trials usually exclude elderly patients with breast cancer, as well as people with comorbidities, thus there is an insufficient evidence for the treatment of such patients [38-41].

Marital status has been associated with outcomes in several cancer sites [42-44]. The potentially significant impact that social support can have on breast cancer detection, treatment, and survival has been well described [45-47]. Married women are also more likely to participate in breast cancer screening compared to their unmarried counterparts [48-50].

Married women receive more spousal support and more likely than the unmarried to consult a healthcare provider at occurrence of symptoms, thus possibly detecting tumors at an earlier stage. After diagnosis with breast cancer, differences in receipt of treatments and adherence to treatment are paramount, with married women having a higher probability of complementing their course of treatment compared to those that are not married [51,52]. Married women are also more likely to have access to emotional support, financial support, physical care, and practical help, such as transportation to medical appointments or assistance [52]. Limitations of this study include the challenges that are inherent in using a cancer registry as a source of data. There were patients excluded because of missing information including cancer stage and receptor status. The data source also lacks other useful individual-level and area-level characteristics such as family history, lifestyle and environmental factors. In spite of these limitations, our results lend insight into the source of disparities and prognostic factors for TNBC survival. Most previous studies investigating breast cancer survival have been hampered by a lack of inclusion of women from Hispanic ethnic groups, a fast-growing population, a lack of information on ER/PR/HER2 status, and inconsistent assessment of other key factors such as treatment, socioeconomic status, body, and comorbid conditions. By linking the statewide cancer registry data with hospital EMR, we were able to capture cancer diagnosis and treatment data more quickly and flexibly than was possible with traditional methods of cancer reporting, and the expanded data capacity provided invaluable potential for comparative effectiveness research on cancer treatments. Specifically, this study took advantage of patient data including detailed treatment. The linked dataset also allowed the investigators to obtain more in-depth information on a subtype of breast cancer than has been available in past studies. A key strength of the study is large sample size of 4,220 women diagnosed with breast cancer in Florida, during 2007–2010, with complete follow-up for vital status and causes of death.

## Conclusion

This study is one of the first to use a comprehensive dataset to investigate survival in women with TNBC using a state population-based cancer registry. The study highlights the usefulness of EMRs in relation to cancer registries. Our findings indicate that despite the progress that has been made towards cancer prevention and control, not all segments of the population have benefitted equally from improvements in breast cancer. Women with triple negative breast cancer deserve special attention in clinical practice because of the uniqueness of this population. Future studies should examine the role of other factors that were not included in the present study, including the quality of care and particularly the benefit of treatment. There is an urgent need for clinicians, patients, researchers, and regulatory agencies to work together to facilitate research in triple-negative breast cancer populations.

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