The Role of Human Epidermal Growth Factor Receptor 2 in the Survival of Women With Estrogen and Progesterone Receptor-negative, Invasive Breast Cancer

The California Cancer Registry, 1999–2004

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BACKGROUND. Breast cancers that are negative for estrogen receptor (ER), progesterone receptor (PR), and human epidermal growth factor receptor 2 (HER2) (triple negative [TN]) have been associated with high-grade histology, aggressive clinical behavior, and poor survival. It has been determined that breast cancers that are negative for ER and PR but positive for HER2 (double negative [DN]) share features with TN breast cancers. In this report, the authors quantified the contribution of HER2 as well as demographic and tumor characteristics to the survival of women with TN tumors, DN tumors, and other breast cancers (OBC).

METHODS. In total, 61,309 women who were diagnosed with invasive breast cancer between 1999–2004 were identified in the California Cancer Registry. Demographic and tumor characteristics of women with TN tumors were compared with those from women with DN tumors and women with OBC. A compound proportional hazards regression analysis (PHPH) (a generalization of the Cox proportional hazards model) was used to model these characteristics.

RESULTS. Women with TN tumors were younger, African American, Hispanic, and of lower socioeconomic status (SES), whereas women with DN tumors were slightly older; African American, and Asian/Pacific Islander. Women with TN and DN tumors presented with larger, higher grade, and higher stage than women with OBC. Survival among women with TN tumors was poorer compared with that among women with OBC but was nearly the same as that of women with DN tumors. Results of the regression analysis indicated that disease stage, tumor grade, SES, and race/ethnicity were significant risk factors for survival. Negative ER and PR status was associated with an increased risk of death. There was a small but significant difference in both long-term and short-term survival patients who had TN tumors compared with patients who had DN tumors.

CONCLUSIONS. Patients with TN tumors shared many clinical, demographic, and tumor features and had survival that was very similar survival to that of patients with DN tumors, and survival for both groups contrasted greatly with survival for

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patients with OBC. Disease stage, tumor grade, SES, race/ethnicity, negative ER and PR status, rather than negative HER2 status, were risk factors for survival. ***Cancer* 2008;112:737–47.** © *2008 American Cancer Society.*

KEYWORDS: breast neoplasms, receptors, estrogen, receptors, progesterone, human epidermal growth factor receptor 2/*neu*, ethnic groups, health disparities, survival analysis.

Breast cancer is the most common cancer among women in California. Despite decreased mortality, breast cancer remains a significant cause of cancer death.[1] Breast cancer incidence and mortality vary greatly according to demographic factors, such as age, race/ethnicity, and socioeconomic status (SES).[2–4] These demographic factors produce wide disparities in survival, including lower rates for younger women,[5–9] ethnic minority women,[10,11] and less affluent women.[12,13] Breast cancer survival depends on prognostic factors like tumor size, histologic grade, and tumor receptor status, regardless of treatment.[14] These prognostic factors are distributed differentially in the population by age and race/ethnicity.[15–19]

Human epidermal growth factor (HER), estrogen, and progesterone regulate cell growth, apoptosis, and differentiation. Tumor cell expression for receptors of HER2 is considered a prognostic factor in breast cancer[19–21] and is one of the risk-stratification features of the St. Gallen International Consensus Guidelines.[22] Overexpression of HER2 is associated with worse clinical outcomes in both patients with lymph node-negative cancer and patients with lymph node-positive cancer.[23,24] These patients tend to have more aggressive disease, which leads to shortened overall survival.[25] However, it has not been demonstrated that HER2-negative tumors predict a poor prognosis in women with breast cancer in the absence of other tumor marker data.[26] Endocrine sensitivity, as assessed by the expression of estrogen receptor (ER) and/or progesterone receptor (PR), is an important prognostic and predictive factor. Patients who are negative for these receptors have a worse prognosis, at least in the first 5 to 10 years after treatment.[27,28] However, these tumor markers are invaluable as predictors of response to therapy: ER and PR predict response to endocrine therapy,[27] such as tamoxifen, aromatase inhibitors, and ovarian suppression; and HER2 overexpression predicts for response to targeted anti-HER2 therapy.[29,30]

Breast cancer is a heterogeneous disease with a wide spectrum of clinical, pathologic, and molecular features.[31–33] Gene-expression profiling studies have identified at least 4 categories of breast cancer.[31,33] These molecular categories correlate with biomarker phenotypes (luminal A is ER-positive and/or PR-positive/HER2-negative, luminal B is ER-positive and/or PR-positive/HER2-positive, HER2 overexpression is ER-negative/PR-negative/HER2-positive, and basal-like is ER-negative/PR-negative/HER2 negative)[33,34] and have distinct differences in disease progression, prognosis, and survival.[33] Specifically, the basal-like subtype, known as triple-negative (TN), is associated with aggressive histology, poor clinical outcomes,[33,35] and BRCA1-related breast cancer.[36,37] TN breast cancer is more prevalent among young, premenopausal, African-American,[33,38,39] and Hispanic women[39] and is a strong contributing factor to the poor clinical outcomes in these women.

In an earlier investigation, we observed that patients with ER-negative/PR-negative/HER2-negative (TN) breast tumors or TN breast cancers had demographic, clinical/pathologic features, and survival that were similar to those of patients with ER-negative/PR-negative/HER2-positive breast cancers, that is, the HER2-overexpressed molecular subtype or double negative [DN].[40] We observed that overall survival was nearly identical for women with the TN and DN phenotypes, suggesting that HER2 played a minimal role in survival. The current study extends our earlier observations by quantifying the contribution of HER2, along with clinical, demographic, and other tumor characteristics, to the survival of women with TN and DN tumors and of women with other breast cancers (OBC).

MATERIALS AND METHODS

Patient Identification

Patients who were included in the current analyses were identified by using the California Cancer Registry (CCR), a population-based registry composed of 8 regional registries that collect cancer incidence and mortality data for the entire population of California. In 1985, California state law mandated the reporting of all newly diagnosed cancers in California, and statewide implementation began January 1, 1988. Cases are reported to the Cancer Surveillance Branch of the California Department of Health Services from hospi-

tals and any other facilities that provide care or therapy to cancer patients who reside in California.[41] For this study, women with primary, invasive breast cancer (*International Classification of Diseases for Oncology, 3rd edition* [ICDO-3] sites C50.0-C50.9)[42] who were diagnosed between January 1, 1999 and December 31, 2004 and were reported to the CCR as of October 2006 were included.

The CCR requires the collection of tumor marker information from the medical record on the ER and PR status of breast cancers diagnosed on or after January 1, 1990 and requires data on the HER2 status of breast cancers diagnosed on or after January 1, 1999.[41] Issues associated with the collection and recording of hormone receptor data have been described elsewhere.[43] ER and PR status are recorded according to the pathologist's interpretation of the assays. ER and PR are considered negative if immunoperoxidase staining of tumor cell nuclei is <5%. ER and PR status also may be determined by examining cytosol protein. ER is considered negative if there is <3 fmol/mg of cytosol protein, and PR is considered negative if there is <5 fmol/mg of cytosol protein.[44] HER2 is assessed through immunohistochemistry (IHC) or fluorescence in situ hybridization (FISH). IHC is scored on a qualitative scale from 0 to 3+, based on interpretation of staining intensity, with 0 and 1+ classified as negative, 2+ classified as borderline, and 3+ classified as positive.[45] FISH is scored on a quantitative scale with <2 copies of the HER2 gene classified as negative and with ≥2 copies classified as positive.[46]

Patients were categorized into distinct groups based on their tumor marker status. Patients who had tumors that were negative for ER, PR, and HER2 were referred to as TN, patients who had tumors that were classified as negative for ER and PR but positive for HER2 were referred to as DN, and patients who had tumors that were classified as neither TN nor DN were referred to as OBC. Patients who had at least 1 unknown tumor marker and those with borderline results were excluded from these analyses.

Variables

Race/ethnicity was classified into 4 mutually exclusive categories of Asian-Pacific Islander (API), Hispanic, non-Hispanic black, and non-Hispanic white. Race/ethnicity was based on information obtained from the medical record, which can be derived from patient self-identification, assumptions based on personal appearance, or inferences based on the race/ethnicity of the parents, birthplace, surname, or maiden name. Hispanic ethnicity was based on information from the medical record and computerized comparisons to the 1980 United States Census List of Hispanic Surnames. Patients who were identified as Hispanic on the medical record or patients who were identified as white, black, or of unknown race with a Hispanic surname were classified as Hispanic.[47] Patients with unknown race/ethnicity, age, or sex were excluded from these analyses.

SES was assigned based on patient's census block group (2000 United States Census) derived from their address at the time of initial diagnosis as reported in the medical record. This SES variable is an index that uses education, employment characteristics, median household income, proportion of the population living 200% below the Federal Poverty Level, median rent, and median housing value of census tract of residence for case and denominator population. A principal components analysis was used to identify quintiles of SES ranging from 1 (the lowest) to 5 (the highest).[48]

Stage at diagnosis was collected from the patient's medical record and was coded according to the American Joint Commission on Cancer (AJCC) *Cancer Staging Manual, 6th edition*.[49] The CCR collected Surveillance, Epidemiology, and End Results (SEER) Extent of Disease (EOD) data for breast cancer cases diagnosed from 1988 through December 2003[50] and, in 2004, began collecting Collaborative Staging data items.[51] EOD was converted to AJCC stage at diagnosis by using SEER guidelines.[52] For some of these analyses, stages III and IV at diagnosis were combined, and patients who had unknown disease stage at diagnosis were omitted. Tumor grade was collected from the medical record and was coded according to ICDO-3.[42]

Statistical Analysis

Statistical significance for pairwise comparisons was determined by using the Wilcoxon signed-rank test (to compare medians) and the test for independent proportions.[53] Comparisons of survival among patients' tumor marker phenotypic groups and stage at diagnosis were performed by using the 5-year cumulative relative survival of all available years of data. Counts, 5-year cumulative relative survival, and 95% confidence intervals (95% CIs) were calculated by using SEER*Stat software (version 6.2.4; Silver Spring, Md).

Because previous studies indicated that the proportional hazards (PH) model is positioned poorly to reproduce the effects of ER and PR status on breast cancer survival, a more general survival model was selected for the current analysis.[54] Survival was modeled using a compound regression analysis method (PHPH) regression model, a generalization of the Cox PH model that was developed for use when data

indicate a possibility of long-term survival and nonproportional hazards. Departures from the proportionality assumption indicate that hazard ratios (HRs) vary with time and are introduced in the form of short-term effects.[55] A pure short-term effect corresponds to survival curves that converge with time and long-term survivors who have no differences with respect to variables included in the model. The PHPH model is constructed by a composition of 2 separate PH models: long-term hazard and short-term hazard. Both models are defined by using limiting behavior of survival and hazard functions; hence, there is no sharp cutoff point between short-term and long-term survival. The PHPH model[55] describes the survival function $S(t|z)$ as follows:

$$(St|z) = \exp\{-\theta(z)[1 - F(t)^{\eta(z)}]\}, \quad (1)$$

where F(t) is a baseline survival function ("proper" means 1 with zero chance of long-term survival), and $\theta(z)$ and $\eta(z)$ are predictors that depend on the variables of interest z (covariates). In the equation above, $\eta(z)$ describes the short-term survival effects. Thus $\theta(z)/\theta(0)$ and $\eta(z)$ represent the relative risks (RR) for long- and short-term survival, respectively. The diversity of responses reproduced by the PHPH model includes crossing survival curves characterized by counteracting short-term and long-term effects. A universal estimation algorithm, the so-called quasi-EM procedure, has been developed to provide inference for such models.[56] It should be stressed that "long-term" survival in the semiparametric model[1] is a mathematical term used to define risks operating at the end of the follow-up range. The follow-up range in the current study is 6 years, which, by the standards of breast cancer, cannot be identified with the time when the risk becomes negligible, because many 6-year survivors still are expected to fail.

RESULTS

We identified 110,163 incident cases of invasive breast cancer from 1999 to 2004 from the CCR. Of these selected cases, 61,309 had definitive results for all 3 tumor markers on record. A comparison of the cases that were included in these analyses with cases that were omitted has been discussed elsewhere. We observed no significant differences in results when omitted cases were added to the analyses.[39]

Table 1 compares the demographic and tumor characteristics of TN patients with both OBC patients and DN patients. The median age at diagnosis of patients with TN tumors was significantly younger than the median age of OBC patients (54 years vs 60 years; $P \leq .001$). Patients with TN tumors were significantly more likely to reside in areas of lower SES than OBC patients ($P < .001$). A significantly higher proportion of non-Hispanic black and Hispanic patients had tumors that were TN ($P \leq .001$ for both). TN tumors were significantly more likely to be larger ($P \leq .001$), poorly differentiated ($P \leq .001$), or anaplastic ($P \leq .01$), and they were significantly more likely to present as stage II or III disease ($P \leq .001$ and $P \leq .01$, respectively).

Patients with DN tumors and patients with TN tumors were very similar and had few differences that reached statistical significance. The median age of patients with DN tumors was only slightly older than the median age of patients with TN tumors. There were no significant differences in SES between these 2 groups. Race/ethnicity was distributed similarly, with the exception of API women, who were significantly more likely to have DN tumors ($P \leq .05$). Both DN tumors and TN tumors tended to be approximately the same size and tended to be poorly differentiated at diagnosis, and significantly fewer DN tumors presented as grade 3 ($P \leq .001$). Although the distribution by stage of diagnosis was similar for DN tumors and TN tumors, a significantly larger proportion of patients with DN tumors presented with stage III disease ($P \leq .01$).

The 5-year cumulative relative survival rates by tumor maker status were 76.2% (95% CI, 74.4–78%) for women with TN tumors, 75.9% (95% CI, 73.6–78.3%) for women with DN tumors, and 94.2% (95% CI, 93.6–94.8%) for women with OBC (data not shown). Figure 1 illustrates 5-year cumulative relative survival by tumor marker status and by stage. Relative survival patterns of patients with TN tumors and patients with DN tumors appeared to be similar, and both were in sharp contrast to the survival patterns in patients with OBC. Overall, relative survival among women with TN tumors generally was poorer than that for women with OBC but was nearly the same as that for women with DN tumors. Among patients with stage I disease, the relative survival of patients with TN tumors was significantly shorter than that for patients with OBC ($P = .0032$) but did not differ significantly from that of DN patients. Among patients with stage II and III/IV disease, the relative survival of patients with TN tumors was significantly shorter than the relative survival both for patients with OBC ($P < .001$ for both) and for patients with DN tumors ($P = .01$ and $P < 0.001$, respectively).

The relative contribution of demographic and tumor characteristics were modeled by using PHPH regression (Table 2). In the PHPH models, breast cancer survival data were fit with disease stage; tu-

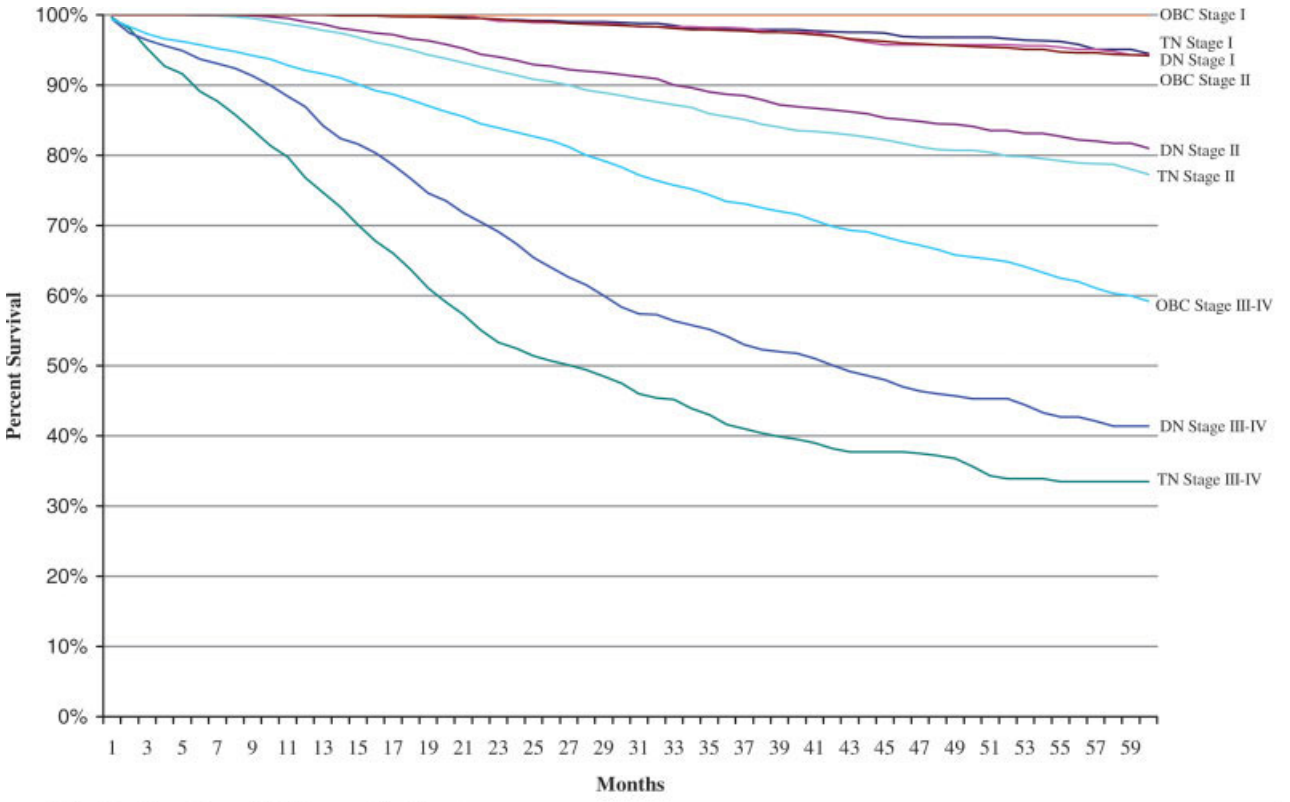
TABLE 1
Selected Demographic and Tumor Characteristics, Female Invasive Breast Cancers by Tumor Marker Status, California, 1999–2004

	OBC		TN			DN		
Characteristic	**No.**	**%**	**No.**	**%**	***P***	**No.**	**%**	***P***
Total no of patients	48,851	100	8022	100		4436	100	
Median age at diagnosis, y	60		54		≤.001	55		
Age group at diagnosis, y								
≤49	11,735	24	2870	35.8	≤.001	1474	33.2	
>50	37,116	76	5152	64.2	≤.001	2962	66.8	≤.05
SES								
1 (Low)	4651	9.5	1077	13.4	≤.001	596	13.4	
2	7388	15.1	1470	18.3	≤.01	832	18.8	
3	9874	20.2	1687	21		933	21	
4	12,059	24.7	1866	23.3		985	22.2	
5 (High)	14,879	30.5	1922	24	≤.001	1090	24.6	
Race/ethnicity								
Non-Hispanic white	35,776	73.2	4922	61.4	≤.001	2700	60.9	
Non-Hispanic black	2094	4.3	860	10.7	≤.001	318	7.2	≤.05
Hispanic	6219	12.7	1493	18.6	≤.001	830	18.7	
Asian-Pacific Islander	4447	9.1	690	8.6		563	12.7	≤.05
Other/unknown	315	0.6	57	0.7		25	0.6	
Median tumor size, mm	16		22		≤.001	23		≤.05
Histologic grade								
1	12,180	24.9	238	3	≤.001	91	2.1	
2	21,550	44.1	1267	15.8	≤.001	866	19.5	≤.05
3	11,081	22.7	5744	71.6	≤.001	3003	67.7	≤.001
4	672	1.4	390	4.9	≤.01	207	4.7	
Unknown	3368	6.9	383	4.8		269	6.1	
AJCC stage at diagnosis								
I	23,133	47.4	2599	32.4	≤.001	1234	27.8	≤.01
II	18,835	38.6	3827	47.7	≤.001	1946	43.9	≤.01
III	3452	7.1	942	11.7	≤.001	751	16.9	≤.01
IV	1468	3	333	4.2		279	6.3	
Other/unknown	1963	4	321	4		226	5.1	

OBC indicates other breast cancers; DN, double negative (estrogen receptor [ER] negative, progesterone receptor [PR] negative, and HER2 positive); TN, triple negative (ER negative, PR negative, and HER2 negative); SES, socioeconomic status; AJCC, American Joint Committee on Cancer.
Red lines present a comparison of TN and OBC. Blue lines present a comparison of TN and DN.

mor grade; ER, PR, and HER2 status; SES; and race/ethnicity as explanatory variables for both long-term and short-term probability of death while controlling for age at diagnosis. In the full model, not surprisingly, the long-term probability of death increased significantly with progressive stage at diagnosis and tumor histology ($P < .0001$). High SES was associated with better long-term survival. For SES level 3 versus 1, the long-term difference was characterized by an RR of 0.82 ($P = .038$); and, for SES level 5 versus 1, the difference was characterized by an RR of 0.75 ($P = .003$). Similar effects were observed for short-term survival, although only SES level 5 versus 1 demonstrated a significant difference (HR, 0.8; $P = .003$).

Non-Hispanic black women had worse survival compared with non-Hispanic white women (long-term RR, 1.32; $P = .0005$). The effect of race followed the PH assumption, indicating no short-term departures ($P = .865$). Although that may be meaningful to patient survival, differences in many of demographic and tumor characteristics were not statistically significant for short-term survival. The exception was disease stage at diagnosis, which maintained a pattern similar to that observed in long-term survival but with a reduced effect. Most important, negative receptor status for each of the tumor markers (ER, PR, and HER2) was associated with an adverse effect on both long- and short-term survival with the exception of long-term survival on HER2 (RR, 0.98; $P = .715$). Negative ER status (RR, 1.48; $P < .0001$) and negative PR status (RR, 1.20; $P = .030$) were associated with an increase in the long-term risk of death, whereas short-term effects were even stronger



Median Duration of Follow-up for Survivors

	Other Breast Cancers (OBC)			Triple Negative (TN)			Double Negative (DN)		
	Stage I	Stage II	Stage III-IV	Stage I	Stage II	Stage III-IV	Stage I	Stage II	Stage III-IV
Survivors	21,470	13,992	4,868	2,361	2,421	976	1,121	1,273	647
Median Follow-up, months	32.3	37.4	10.6	29.7	34.7	9.7	29.1	36.4	13.1

FIGURE 1. Five-year relative cumulative survival for invasive female breast cancers by tumor marker phenotype and American Joint Committee on Cancer stage at diagnosis: California, 1999–2004. Double negative (DN) indicates tumors that were estrogen receptor (ER) negative, progesterone receptor (PR) negative, and human epidermal growth factor receptor 2 (HER2) positive; triple negative (TN), tumors that were ER negative, PR negative, and HER2 negative.

(ER-negative tumors: RR, 1.70; $P < .0001$; PR-negative tumors: RR, 1.41; $P = .001$). Negative HER2 status had little effect on long-term survival (RR, 0.98; $P = .715$) but increased the short-term risk of death (RR, 1.18; $P = .038$).

Next, the phenotypic combinations TN and DN were used as explanatory variables in the full model rather than individual tumor makers, whereas all other variables remained the same. In this model, nearly identical patterns were observed in both long-term and short-term survival for stage at diagnosis, tumor histology, race/ethnicity, and SES, similar to what was observed in the first model. Patients with TN tumors and patients with DN tumors had a clear survival disadvantage in long-term and short-term survival compared with patients who had OBC. Patients who had TN tumors showed 1.74 times higher long-term risk ($P < .0001$) compared with patients who had OBC; whereas the short-term risk had a greater effect (HR, 2.27; $P < .0001$). Patients who had DN tumors had 1.48 times higher long-term risk compared with patients who had OBC ($P < .0001$) and had an HR of 1.78 ($P < .0001$) for the short-term effect compared with patients who had OBC. TN tumors were compared with DN tumors in the full model, which was rerun with a different coding for the phenotype variable (all other variables remained the same; DN was the assumed baseline category of the phenotype variable). There was a small but significant difference in both long-term survival (HR, 1.17) and short-term survival (HR, 1.29) for patients who had TN tumors compared with patients who had DN tumors.

DISCUSSION

In this large, population-based cohort study, we described the demographic, clinical, and tumor char-

TABLE 2
Compound Proportional Hazards (Long-term Hazard and Short-term Hazard) Regression Analysis of Survival by Selected Tumor and Demographic Characteristics in Women With Invasive Breast Cancer, California, 1999 to 2004

	Model 1			Model 2		
Characteristic	**HR**	**95% CI**	***P***	**HR**	**95% CI**	***P***
Long-term risk						
Stage at diagnosis						
Regional vs localized	3.27	2.83–3.78	<.0001	3.31	2.86–3.83	<.0001
Distant vs localized	14.90	12.50–17.76	<.0001	15.73	13.17–18.78	<.0001
Tumor histology (differentiation)						
Moderate vs well	1.97	1.42–2.73	<.0001	1.92	1.39–2.66	<.0001
Poor vs well	3.69	2.68–5.06	<.0001	3.76	2.74–5.16	<.0001
Undifferentiated vs well	3.45	2.36–5.05	<.0001	3.39	2.32–4.94	<.0001
SES						
2 vs 1 (Low)	1.03	0.85–1.25	.745	1.03	0.85–1.24	.789
3 vs 1 (Low)	0.82	0.68–0.99	.038	0.82	0.68–0.98	.031
4 vs 1 (Low)	0.86	0.71–1.05	.132	0.88	0.72–1.07	.214
5 vs 1 (Low)	0.75	0.62–0.91	.003	0.75	0.62–0.91	.004
Race/ethnicity						
NH black vs NH white	1.32	1.09–1.60	.005	1.32	1.09–1.61	.005
Hispanic vs NH white	0.95	0.76–1.18	.630	0.97	0.77–1.21	.767
API vs NH white	1.11	0.94–1.30	.216	1.10	0.93–1.29	.265
Tumor receptor status						
ER negative vs positive	1.48	1.26–1.73	<.0001			
PR negative vs positive	1.20	1.02–1.41	.030			
HER2 negative vs positive	0.98	0.87–1.10	.715			
Phenotype						
DN vs OBC				1.48	1.26–1.73	<.0001
TN vs OBC				1.74	1.52–2.00	<.0001
TN vs DN				1.17	1.00–1.37	.045
Short-term risk						
Stage at diagnosis						
Regional vs localized	1.31	1.08–1.58	.006	1.29	1.07–1.56	.009
Distant vs localized	3.04	2.41–3.83	<.0001	2.89	2.28–3.65	<.0001
Tumor histology (differentiation)						
Moderate vs well	0.98	0.65–1.49	.928	1.05	0.69–1.59	.819
Poor vs well	1.08	0.72–1.61	.709	1.16	0.78–1.71	.476
Undifferentiated vs well	1.28	0.78–2.08	.332	1.45	0.89–2.34	.132
SES						
2 vs 1 (Low)	0.97	0.76–1.25	.830	0.97	0.75–1.25	.812
3 vs 1 (Low)	1.06	0.83–1.35	.641	1.09	0.85–1.38	.507
4 vs 1 (Low)	0.82	0.64–1.06	.134	0.79	0.61–1.03	0.078
5 vs 1 (Low)	0.80	0.62–1.03	.087	0.80	0.62–1.03	.080
Race/ethnicity						
NH black vs NH white	0.98	0.76–1.26	.865	0.98	0.75–1.26	.846
Hispanic vs NH white	0.83	0.62–1.11	.219	0.82	0.61–1.10	.178
API vs NH white	0.87	0.71–1.08	.207	0.89	0.72–1.10	.272
Tumor receptor status						
ER negative vs positive	1.70	1.38–2.08	<.0001			
PR negative vs positive	1.41	1.14–1.73	.001			
HER2 negative vs positive	1.18	1.01–1.38	.038			
Phenotype						
DN vs OBC				1.78	1.45–2.19	<.0001
TN vs OBC				2.27	1.90–2.72	<.0001
TN vs DN				1.29	1.04–1.58	.018
Log (-log) of baseline probability of long-term survival*	0.04		<.0001	0.03	0.02–0.04	<.0001

HR indicates hazard ratio; 95% CI, 95% confidence interval; SES, socioeconomic status; NH, non-Hispanic; API, Asian-Pacific Islander; ER, estrogen receptor; PR, progesterone receptor; HER2, human epidermal growth factor receptor 2; TN, triple negative (ER negative, PR negative, and HER2 negative); DN, double negative (ER negative, PR negative, and HER2 positive).

* For all variables combined (stage at diagnosis, histology, SES, race/ethnicity, receptor status, and phenotype), the log (-log) of baseline probability of long-term survival was 0.03; for all subgroups combined, the log (-log) of baseline probability of long-term survival was 0.02.

acteristics of patients with invasive breast cancer in California who had either TN tumors or DN tumors and compared them with all other invasive breast cancer phenotypes. We observed that patients who had TN tumors and patients who had DN tumors shared many clinical, demographic, and tumor features; had very similar survival; and contrasted greatly with women who had OBC.

In agreement with other studies, we demonstrated that important risk factors for the women with TN tumors were younger age, race/ethnicity (significant differences for non-Hispanic black and Hispanic women), and lower SES.[33,38,39] Women with TN breast cancers were diagnosed with larger tumors, more aggressive histology, and at a more advanced stage,[33,39] which contributes to faster progression to metastasis and poorer prognosis.[57–59] Risk factors for DN tumors and TN tumors were slightly older age and race/ethnicity (significant differences for non-Hispanic black and API); however, it is noteworthy that SES played no role. Women with DN and breast cancer presented with larger tumors, more aggressive histology, and more advanced disease stage.

Patients with TN tumors and patients with DN tumors had very similar survival that was significantly shorter than the survival of patients who had OBC regardless of disease stage at diagnosis.[33,39] Modeling data for individual tumor markers suggested that the shortened survival of women with TN tumors and women with DN tumors was caused primarily by the negative ER and PR status and that receptor negativity affected long-term survival more than short-term survival. The statistically insignificant contribution of HER2 to the lethality of these phenotypes requires further study.

Poor outcomes in women with breast cancer have been associated with negative ER and PR status without regard to HER2 status.[28,60] Some investigators have postulated that all ER-negative tumors carry a relatively poor prognosis, irrespective of the cytokeratin composition or the gene expression signature.[26] Tumors that are HER2 positive have been associated for some time with worse clinical outcomes.[24,61] The survival of women with TN tumors is almost identical to the survival of women with DN tumors, as reported previously.[26,32,33,62,63] Jumppanen et al. concluded that, within the ER-negative tumor entity, there was no difference in survival between nonbasal tumors and basal-like tumors as classified by IHC or gene expression.[26] Previous studies were focused principally on defining gene expression-based classification of breast cancers[32,62,63] or specifically on characterizing the basal-like phenotype among young African-American women,[33] and they did not discuss the relative importance of HER2, perhaps because small sample sizes may have precluded further investigation.

In the current study, patients who had TN tumors had a small but significantly increased risk for long-term and short-term earlier death compared with patients who had DN tumors. We observed that African-American women consistently were at significantly greater risk of death than women of other ethnicities. Bivariate analyses indicated that Hispanic women were at greater risk of having TN tumors, and API women were at greater risk of having DN tumors. Unlike African-American ethnicity, Hispanic and API ethnicity were not identified as independent contributors to early death in multivariate analyses. Although SES was prominent in the bivariate analysis for patients with TN tumors, it played a limited role in short-term survival; however, it had significant long-term survival effects in multivariate analyses.

Racial, ethnic, and SES disparities in breast cancer incidence and mortality are well documented in the medical literature. Numerous studies have demonstrated that African-American women have a lower incidence of breast cancer but worse survival compared with non-Hispanic white women.[2,60,64–67] Fewer studies have described the risk for Hispanic women, but those studies indicated that, similar to African-American women, Hispanic women had lower incidence but worse survival.[10,68,69] It is believed that breast cancer survival among African-American and Hispanic women is compromised, in that these women are younger at the time of diagnosis,[5,70–72] their tumors more often are ER-negative,[64,71,73] and they present at higher stages,[74] perhaps because of issues associated with access to healthcare.[12,75–78] In studies that adjusted for clinical and SES factors, African-American women continued to have slightly but significantly poorer survival compared with white women, whereas the differences in survival among Hispanic and Asian women compared with white women were ameliorated.[79–81]

The current study included a large number of patients from an ethnically diverse population, thus allowing us to compare the clinical, demographic, and tumor features of women with TN breast cancer, DN breast cancer, and OBC. Nevertheless, this study was not without limitations. The data were taken from a population-based cancer registry and were not supplemented with other clinical data or gene-expression analyses. Population-based cancer registry data derive from many sources. Histologic grading of tumors and tests for ER, PR, and HER2 were performed by a wide variety of laboratories without cen-

tral review. In addition, almost 50% of the initial study population lacked information about ER, PR, and HER2 status, with the latter constituting the bulk of missing data. In 1999, the CCR began collection of HER2 results; however, >50% of newly diagnosed breast cancers lacked this test result. By 2003, HER2 testing of primary breast cancer was more common, and >70% of patients with breast cancer included HER2 data.[43] HER2 testing was not recommended for all women with invasive breast cancer until 2007[82]; thus an increase in testing and improvements in documentation over time are expected. Finally, adjuvant therapy information in the CCR was considered limited, so we did not include it in the survival models. Therefore, we made no attempt to attribute overall survival to any specific form of therapy. The omission of therapies may confound the correlation between overall breast cancer survival and phenotypic group.

In summary, the current results indicate that patients with TN tumors share many clinical, demographic, and tumor features and have survival that is almost identical to that of patients with DN tumors. We also observed that disease stage, tumor grade, SES, race/ethnicity, and negative ER and PR status remained as significant and independent risk factors for long-term survival. In addition, we demonstrated that negative ER and PR status, rather than negative HER2 status, was the predominant factor contributing to poor survival. The TN phenotype, although it is a useful surrogate marker for the identification of basal-like breast cancers, may not explain all of the poor prognostic features of breast cancer in young African-American women. The correlations between race/ethnicity, SES, and breast cancer survival are provocative and difficult to untangle, and this difficulty underscores the need for more precise reporting of patient characteristics and tumor factors in future studies.

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