Original Article

Clinicopathologic Features, Patterns of Recurrence, and Survival Among Women With Triple-Negative Breast Cancer in the National Comprehensive Cancer Network

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BACKGROUND: The objective of this study was to describe clinicopathologic features, patterns of recurrence, and survival according to breast cancer subtype with a focus on triple-negative tumors. **METHODS:** In total, 15,204 women were evaluated who presented to National Comprehensive Cancer Network centers with stage I through III breast cancer between January 2000 and December 2006. Tumors were classified as positive for estrogen receptor (ER) and/or progesterone receptor (PR) (hormone receptor [HR]-positive) and negative for human epidermal growth factor receptor 2 (HER2); positive for HER2 and any ER or PR status (HER2-positive); or negative for ER, PR, and HER2 (triple-negative). **RESULTS:** Subtype distribution was triple-negative in 17% of women (n = 2569), HER2-positive in 17% of women (n = 2602), and HR-positive/HER2-negative in 66% of women (n = 10,033). The triple-negative subtype was more frequent in African Americans compared with Caucasians (adjusted odds ratio, 1.98; $P < .0001$). Premenopausal women, but not postmenopausal women, with high body mass index had an increased likelihood of having the triple-negative subtype ($P = .02$). Women with triple-negative cancers were less likely to present on the basis of an abnormal screening mammogram (29% vs 48%; $P < .0001$) and were more likely to present with higher tumor classification, but they were less likely to have lymph node involvement. Relative to HR-positive/HER2-negative tumors, triple-negative tumors were associated with a greater risk of brain or lung metastases; and women with triple-negative tumors had worse breast cancer-specific and overall survival, even after adjusting for age, disease stage, race, tumor grade, and receipt of adjuvant chemotherapy (overall survival: adjusted hazard ratio, 2.72; 95% confidence interval, 2.39-3.10; $P < .0001$). The difference in the risk of death by subtype was most dramatic within the first 2 years after diagnosis (overall survival for 0-2 years: OR, 6.10; 95% confidence interval, 4.81-7.74). **CONCLUSIONS:** Triple-negative tumors were associated with unique risk factors and worse outcomes compared with HR-positive/HER2-negative tumors. ***Cancer*** **2012;118:5463-72.**

KEYWORDS: triple-negative, basal-like, breast cancer, outcomes, brain metastases, obesity, race.

INTRODUCTION

Breast cancer is comprised of multiple biologic subtypes that can be approximated using standard immunohistochemical (IHC) markers.[1] The majority of triple-negative tumors (that is, tumors that are negative for estrogen receptor [ER], progesterone receptor [PR], and human epidermal growth factor receptor 2 [HER2]) cluster with the basal subset and are associated with a high rate of distant relapse.[2,3]

Several studies have examined characteristics associated with the triple-negative subtype.[4-7] Triple-negative cancers comprise a greater proportion of breast cancers in African American women.[4,7] Other associations with the triple-negative subtype include higher parity and lack of breast feeding; reports on associations with obesity have been inconsistent.[5,8-13] Patients with triple-negative cancers tend to present at a younger age and with more advanced cancer; however, the contribution of tumor subtype to the risk of lymph node involvement is less well defined.[4,6,14] With respect to patterns of recurrence, central nervous system (CNS) disease is a concern.[15,16]

The identification of factors associated with the triple-negative subtype is hampered by the absence of data on large populations. With few exceptions, population and hospital cancer registries, key sources of such data, did not routinely

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collect tumor HER2 status until recently. Since 1997, the National Comprehensive Cancer Network (NCCN) Breast Cancer Outcomes Database has collected data on women with newly diagnosed breast cancer who presented to many of its member institutions across the United States. HER2 status determined by IHC was added to the NCCN data as a routine element in 1999; HER2 status determined by fluorescence in situ hybridization (FISH) was added in 2001. Demographic, treatment, and outcome information also is available. Although it is not a population-based cohort, the large size of the database and the varied patient population allows for the investigation of clinical predictors of triple-negative cancer and a detailed description of its behavior.

MATERIALS AND METHODS

Data Source

Data are collected prospectively within the NCCN database primarily through review of medical records and institutional tumor registries by trained abstractors. Vital status and cause of death are ascertained from medical records and confirmed using the Social Security Death Index and the National Death Index. If cause of death is unknown based on the medical record, then information from the National Death Index is used in its place. Data are subjected to rigorous quality assurance.[17] Institutional review boards from each center approved the study, data collection, transmission, and storage protocols. At centers where institutional review boards require signed informed consent for data collection, only patients who consented are included in the database.

Patient Selection

Patients were included if they presented with newly diagnosed, stage I through III, unilateral, invasive breast cancer between January 1, 2000 and December 31, 2006 at 1 of 8 NCCN institutions: Arthur G. James Cancer Hospital at Ohio State University (Columbus, Ohio), City of Hope Comprehensive Cancer Center (Duarte, Calif), Dana-Farber Cancer Institute (Boston, Mass), Fox Chase Cancer Center (Philadelphia, Pa), H. Lee Moffitt Cancer Center (Tampa, Fla), Roswell Park Cancer Institute (Buffalo, NY), The University of Texas M. D. Anderson Cancer Center (Houston, Tex), and the University of Michigan Comprehensive Cancer Center (Ann Arbor, Mich). From 17,510 potentially eligible patients, we excluded patients with previous malignancies (n = 1336); with unknown ER, PR, and HER2 status (n = 868); or who did not have invasive cancer within the breast (n = 102), leaving an analysis cohort of 15,204 patients.

Variables of Interest

Tumor characteristics

The database contains information on tumor size, lymph node status, tumor grade, lymphovascular invasion, extensive intraductal component, ER and PR status, and HER2 status, as abstracted from pathology reports. Disease stage is assigned according to the version of the American Joint Committee on Cancer (AJCC) Cancer Staging Manual that was applicable at the time of diagnosis. For the current analysis, tumor grade was categorized as high (according to histologic grade, or, if not available, by nuclear grade) or low-intermediate.

Data collected on HER2 status have changed over time. Before March 1, 2001, the only information recorded was the IHC result, which was categorized as positive or negative. Since March 2001, both IHC results (recorded on a scale from 0 to 3+) and FISH results (recorded as positive or negative) have been collected. We used FISH results, if available. If only IHC results were available, then 3+, "high positive," and "positive not otherwise specified" results were considered HER2-positive; whereas 2+, 1+, 0, and "negative" results were considered HER2-negative. It is noteworthy that only approximately 2% of patients in the database had IHC results coded as 2+ without available FISH results.

Patient characteristics

The following variables were collected by chart review: age at diagnosis, height and weight, sites of recurrence, treatment types, and vital status. Body mass index (BMI) was calculated as weight in kilograms/height in meters squared (kg/m^2) and was grouped according to categories defined by the National Heart, Lung, and Blood Institute as follows: underweight, <18.5 kg/m^2; normal, 18.5 to 24.9 kg/m^2; overweight, 25.0 to 29.9 kg/m^2, and obese, ≥ 30 kg/m^2.

Data on race, ethnicity, and menopausal status came from patient surveys that were conducted at the time of initial presentation to the NCCN center. Patients were considered postmenopausal if they were amenorrheic for >6 months before breast cancer diagnosis, were taking hormone replacement therapy, or were aged ≥ 50 years without a documented menopausal status in their medical record or baseline patient survey.

Definition of Breast Cancer Subtypes

Triple-negative tumors were defined as tumors that were ER-negative, PR-negative, and HER2 negative. HER2-positive tumors included both ER-positive and ER-negative tumors. HR-positive/HER2 negative tumors were defined as ER-positive and/or PR-positive, *and* HER2 negative.

Statistical Analyses

Clinicopathologic variables were tabulated by tumor subtype, and proportions across subtypes were compared using chi-square tests. We constructed univariate followed by multivariable logistic regression models to identify the factors associated with triple-negative subtype and the risk of lymph node positivity. Univariate logistic regression estimated the risk of sites of recurrence among those diagnosed with a recurrence. Follow-up for survival analysis was defined as the time in years from tumor diagnosis to the date of death or last known vital status date. Breast cancer-specific survival was determined by identifying breast cancer as the cause of death based on International Statistical Classification of Disease codes. Kaplan-Meier analysis was used to compare OS and breast cancer-specific survival between triple-negative tumors versus HR-positive/HER2 negative tumors. Cox proportional hazards regression was used to calculate hazard ratios and their associated 95% confidence interval (95% CI) to estimate the risk of any death and breast cancer-specific death for triple-negative versus HR-positive/HER2 negative tumors adjusting for age (<50 years, ≥50 years), stage (I, II, III), race (Caucasian, African American, other), adjuvant chemotherapy (yes/no), tumor size (≤2 cm, >2 cm), histologic grade (low/intermediate, high, unknown), and lymph node status (positive, negative). It is known that the risk of death over time in these tumor subtypes is nonproportional. Several techniques were applied to verify the nonproportionality of tumor subtype and to assess the proportionality of each of the model covariates. Because the risk of death between tumor subtypes was not proportional, hazard ratios were calculated for the entire follow-up period in addition to the following time windows: birth to 2 years from diagnosis, 2 to 6 years, and ≥6 years from diagnosis to the end of the follow-up period. These time points were chosen based on a review of Kaplan-Meier survival curves comparing tumor subtypes. All statistical analyses were performed using the SAS statistical software package (version 9.2; SAS Institute, Inc., Cary, NC).

RESULTS

Description of Study Cohort

We identified 15,204 women who were eligible for inclusion. Subtype distribution was: triple-negative, 17% (n = 2569); HER2-positive, 17% (n = 2602); and HR-positive/HER2-negative, 66% (n = 10,033). Table 1 indicates that 82% of patients identified themselves as Caucasian/non-Hispanic, 8% identified themselves as African American, 7% identified themselves as Hispanic, and 3% identified themselves as Asian/Pacific Islander. The mean follow-up was 3.06 years (median, 2.6 years; range, 0-8.5 years).

Presenting Characteristics

Compared with patients who had HR-positive/HER2-negative tumors, patients who had triple-negative tumors were less likely to present on the basis of an abnormal screening mammogram (48% vs 29%; $P < .0001$) (Table 1). Greater than 66% of patients with triple-negative tumors presented initially with symptoms, most commonly a self-detected breast mass. Patients with triple-negative tumors were also less likely to present with T1 disease (46% vs 67% for HR-positive/HER2-negative tumors; $P < .001$). Lymphovascular invasion and extensive intraductal component were less common in triple-negative tumors and were more frequent in association with HER2-positive tumors.

Predictors of Triple-Negative Subtype

On univariate analysis, African American race, premenopausal status, and obesity were associated independently with a greater risk of having the triple-negative subtype. The triple-negative subtype comprised 33% of tumors in premenopausal African American women and 26% of tumors in postmenopausal African American women, compared with 17% and 15% of breast cancers in premenopausal and postmenopausal Caucasian women, respectively ($P < .001$ for the association of tumor subtype and menopausal status within Caucasians; $P = .04$ for African Americans).

When race and BMI were entered into a logistic regression model that included disease stage and menopausal status (Table 2), African American race retained a significant association with the triple-negative subtype (adjusted odds ratio, 1.98; 95% CI, 1.72-2.27; $P < .0001$). BMI retained borderline significance overall ($P = .052$); however, there was a significant interaction between BMI and menopausal status ($P_{interaction} = .02$). Among obese premenopausal women, 24% of breast tumors were triple-negative compared with 16% of normal-weight premenopausal women; there was no apparent effect of BMI on the risk of having the triple-negative subtype for postmenopausal women (Table 3).

Relation Between Lymph Node Status and Tumor Subtype

To explore the correlation between tumor subtype and lymph node status, we constructed a logistic regression model to control for tumor size. For patients who received neoadjuvant chemotherapy, we used clinical tumor classification at initial presentation. For patients who did not

Table 1. Patient Demographics and Clinicopathologic Characteristics

Characteristic	No. of Patients (%)[a]				*P*
	All Patients	Triple Negative	HER2+	HR+/HER2−	
Total	15,204	2569 (17)	2602 (17)	10,033 (66)	
Age: Mean±SD, y	55±12	52±12	52±12	56±12	<.001
Length of follow-up after presentation: Mean±SD, y	3.1±2.0	2.9±2.0	3.1±2.0	3.1±2.1	<.001
Race/ethnicity					<.001
Caucasian	12,406 (82)	1953 (76)	2059 (79)	8394 (84)	
African-American	1142 (8)	330 (13)	174 (8)	618 (6)	
Hispanic	995 (7)	185 (7)	209 (8)	601 (6)	
Asian/Pacific Islander	443 (3)	67 (3)	97 (4)	279 (3)	
Other/unknown	218 (1)	34 (1)	43 (2)	141 (1)	
Menopausal status					<.001
Premenopausal	6175 (41)	1137 (44)	1216 (47)	3822 (38)	
Postmenopausal	9029 (59)	1432 (56)	1386 (53)	6211 (62)	
BMI at presentation, kg/m^2					<.001
Underweight: <18.5	228 (1.5)	34 (1)	36 (1)	158 (2)	
Normal: 18.5 to <25	5606 (37)	879 (34)	1019 (39)	3708 (37)	
Overweight: 25 to <30	4442 (29)	740 (29)	736 (28)	2966 (30)	
Obese: ≥30	4366 (29)	835 (33)	713 (27)	2818 (28)	
Missing	562 (4)	81 (3)	98 (4)	383 (4)	
Method of detection					<.001
Abnormal screening mammogram	6472 (43)	735 (29)	883 (34)	4854 (48)	
Symptoms	8158 (54)	1745 (68)	1591 (61)	4822 (48)	
Other	466 (3)	67 (3)	107 (4)	292 (3)	
Unknown	108 (<1)	22 (<1)	21 (<1)	65 (<1)	
Tumor size: Mean±SD, cm	1.9±1.6	2.2±1.8	2.0±1.8	1.8±1.5	<.001
Tumor classification					<.001
T1	9258 (61)	1187 (46)	1338 (51)	6733 (67)	
T2	4504 (30)	1036 (40)	892 (34)	2576 (26)	
T3	818 (5)	192 (7)	196 (8)	430 (4)	
T4	613 (4)	151 (6)	171 (7)	291 (3)	
Unknown	11 (<1)	3 (<1)	5 (<1)	3 (<1)	
Lymph node status					<.001
Positive	5953 (39)	975 (38)	1162 (45)	3816 (38)	
Negative	9233 (61)	1593 (62)	1438 (55)	6202 (62)	
Lymph nodes not assessed	18 (<1)	1 (<1)	2 (<1)	15 (<1)	
AJCC stage					<.001
I	6688 (44)	840 (33)	883 (34)	4965 (49)	
II	6306 (41)	1274 (50)	1146 (44)	3886 (39)	
III	2210 (15)	455 (18)	573 (22)	1182 (12)	
Histology					<.001
Invasive ductal	11,942 (79)	2379 (93)	2359 (91)	7204 (72)	
Invasive lobular	1379 (9)	59 (2)	91 (3)	1229 (12)	
Mixed ductal/lobular	1260 (8)	47 (2)	118 (5)	1095 (11)	
Other (tubular, colloid, medullary, adenocystic)	623 (4)	84 (3)	34 (1)	505 (5)	
Histologic grade					<.001
Low/intermediate	7896 (52)	347 (14)	704 (27)	6845 (68)	
High	6583 (43)	2123 (83)	1783 (69)	2677 (27)	
Other	5 (<1)	3 (<1)	1 (<1)	1 (<1)	
Unknown	720 (5)	96 (4)	114 (4)	510 (5)	
Presence of LVI					<.001
Yes	3755 (25)	663 (26)	933 (36)	2159 (22)	
No	11,031 (73)	1814 (71)	1591 (61)	7626 (76)	
Unknown	418 (3)	92 (4)	78 (3)	248 (2)	

(Continued)

Table 1. (Continued)

Characteristic	No. of Patients (%)[a] All Patients	Triple Negative	HER2+	HR+/HER2−	P
Presence of EIC					<.001
Yes	1861 (12)	235 (9)	482 (19)	1144 (11)	
No	13,343 (88)	2334 (91)	2120 (81)	8889 (89)	
Chemotherapy					<.001
Neoadjuvant only	1901 (13)	520 (20)	452 (17)	929 (9)	
Adjuvant only	6859 (45)	1457 (57)	1400 (54)	4002 (40)	
Both neoadjuvant and adjuvant	629 (4)	158 (6)	221 (8)	250 (2)	
None	5815 (38)	434 (17)	529 (20)	4852 (48)	

Abbreviations: AJCC, American Joint Committee on Cancer; EIC, extensive intraductal component; HER2+, positive for human epidermal growth factor receptor 2; HER2−, negative for human epidermal growth factor receptor 2; HR+, hormone receptor positive (positive for estrogen receptor and/or progesterone receptor); LVI, lymphovascular invasion; SD, standard deviation; triple negative, negative for all 3 hormone receptors (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2).
[a] Because of a rounding error, some of the percentages do not total 100%.

receive neoadjuvant therapy, we used pathologic tumor classification. Across all subtypes, the likelihood of positive lymph nodes increased with increasing tumor size (Table 4). Compared with HR-positive/HER2-negative tumors as the referent group, triple-negative tumors were associated with a lower risk of lymph node positivity, (adjusted odds ratio, 0.88; 95% CI, 0.80-0.97; $P < .001$) (Table 5). HER2-positive tumors were associated with the greatest risk of lymph node involvement.

Sites of Recurrence

At a median follow-up of 3.06 years, recurrences were recorded in 1389 women. Relative to women who had HR-positive/HER2-negative tumors, women who had triple-negative tumors were more likely to experience a first recurrence in brain, lung, or locoregional sites, and they were less likely to recur in bone (Table 6). The results were similar for first and subsequent sites of recurrence (data not shown). CNS comprised 62 of 589 sites of recurrence at the time of metastatic presentation among patients who had triple-negative breast cancer with documented recurrence. Overall, CNS comprised 174 of 1348 sites of involvement at initial or subsequent recurrence among patients with triple-negative breast cancer. Thus, the CNS was involved initially in 13% of patients (62 of 480) and was ever-involved in 36% of patients (174 of 480) who had documented recurrences of triple-negative breast cancer.

Survival Outcomes

Because of the various use of trastuzumab across the study period, we chose to limit our survival analysis to patients with either triple-negative or HR-positive/HER2-negative tumors. Among the 12,902 women who met these criteria, 1280 deaths occurred, of which 1025 were classified as breast cancer-specific. The triple-negative subtype was associated with worse breast cancer-specific survival (data not shown) and OS (Fig. 1) compared with HR-positive/HER2-negative tumors and retained its poor prognostic significance after adjustment for age, stage, race, receipt of adjuvant chemotherapy, tumor size, grade, and lymph node status (breast cancer-specific survival: hazard ratio, 2.99; 95% CI, 2.59-3.45; $P < .0001$; OS: hazard ratio, 2.72; 95% CI, 2.39-3.10; $P < .0001$). The inclusion of

Table 2. Results of an All Main Effects Logistic Regression Model to Test for the Risk of Triple-Negative Breast Cancer[a]

Variable	Sample Size	Adjusted OR (95% CI)	Type 3 P
Race			<.001
Caucasian	12,406	Baseline	
African American	1142	1.98 (1.72-2.27)	
Other	1656	1.05 (0.91-1.20)	
BMI, kg/m^2			.052
18.5 to <25	5606	Baseline	
25 to <30	4442	1.04 (0.94-1.16)	
≥30 kg/m^2	4366	1.16 (1.04-1.29)	
<18.5	228	0.94 (0.64- 1.36)	
Missing	562	0.92 (0.72-1.19)	
AJCC stage			<.001
I	6688	Baseline	
II	6306	1.70 (1.54-1.87)	
III	2210	1.66 (1.46-1.89)	
Menopausal status			.003
Premenopausal	6175	Baseline	
Postmenopausal	9029	0.88 (0.80-0.96)	

Abbreviations: AJCC, American Joint Committee on Cancer; BMI, body mass index; CI, confidence interval; OR, odds ratio; triple negative, negative for all 3 hormone receptors (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2).
[a] A model that included all main effects and an interaction term for menopausal status and BMI was statistically significant ($P = .02$ for interaction).

Table 3. Distribution of Breast Cancer Subtypes by Menopausal Status and Body Mass Index

BMI at Presentation, kg/m^2	No. of Patients (%)			*P*
	Total No. of Patients	Triple-Negative Subtype	All Other Tumors	
Premenopausal at diagnosis				<.001
<18.5	121	20 (17)	101 (83)	
18.5 to <25	2835	462 (16)	2373 (84)	
25 to <30	1643	298 (18)	1345 (82)	
≥30	1403	335 (24)	1068 (76)	
Missing	173	22 (13)	151 (87)	
Postmenopausal at diagnosis				.35
<18.5	107	14 (13)	93 (87)	
18.5 to <25	2771	417 (15)	2354 (85)	
25 to <30	2799	442 (16)	2357 (84)	
≥30	2963	500 (17)	2463 (83)	
Missing	389	59 (15)	330 (85)	

Abbreviations: BMI, body mass index; triple negative, negative for all 3 hormone receptors (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2).

Table 4. Frequency of Positive Lymph Node Status According to Tumor Size Stratified by Tumor Subtype (N = 15,168)

Tumor Size, cm	No. of Patients With at Least 1 Positive Lymph Node (%)[a]		
	Triple Negative Subtype	HER2+	HR+/HER2−
Missing	33	69	148
≤1	61 (17)	97 (20)	382 (14)
>1 to ≤2	258 (33)	324 (40)	1340 (34)
>2 to ≤5	485 (47)	542 (60)	1431 (56)
>5	247 (73)	269 (78)	477 (70)

Abbreviations: HER2+, positive for human epidermal growth factor receptor 2; HER2−, negative for human epidermal growth factor receptor 2; HR+, hormone receptor positive (positive for estrogen receptor and/or progesterone receptor); triple negative, negative for all 3 hormone receptors (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2).

[a] The sample INCLUDES patients who received neoadjuvant chemotherapy or neoadjuvant endocrine therapy (n = 2641 of a total N = 15,204) but EXCLUDES patients who did not have lymph nodes assessed or who had unknown clinical stage (n = 36), resulting in a sample size of 15,168.

race in the model did not appreciably alter the hazard ratio for death associated with triple-negative subtype. It is noteworthy that there was a dramatic increase in the risk of death within 2 years of diagnosis among the triple-negative group, even after adjusting for age, stage, race, receipt of adjuvant chemotherapy, tumor size, grade, and lymph node status (breast cancer-specific survival: hazard ratio for 0-2 years, 8.30; 95% CI, 6.23-11.05; OS: hazard ratio for 0-2 years, 6.10; 95% CI, 4.81-7.74); however, the magnitude of the risk increase declined substantially over time (Table 7).

DISCUSSION

In a cohort of >15,000 women with stage I through III breast cancer, we observed that presenting features, patterns of recurrence, and survival differed significantly by breast cancer subtype. Our findings are consistent with population-based data indicating a greater frequency of triple-negative tumors among African American women.[4,7] The extent to which this association explains racial differences in breast cancer mortality is an open question. In a neoadjuvant trial conducted among patients with triple-negative breast cancer, the likelihood of a pathologic response did not vary by race.[18] However, because the benefits of adjuvant chemotherapy are greater in triple-negative tumors than in HR-positive/HER2-negative tumors, racial differences in the receipt of appropriate therapy may further amplify baseline differences in prognosis.[19-21] It is noteworthy that including race in our models did not substantially alter our survival estimates by tumor subtype, suggesting that the poor prognosis of the triple-negative subtype we observed was not mediated by an effect of race, either biologically or indirectly through disparities in care.

The biologic basis of the association between race and triple-negative subtype is not well understood. Obesity has been proposed as a possible contributing factor.[9,10,12,14,22] We observed that race remained a significant predictor of triple-negative subtype, independent of BMI. With respect to the relation between BMI and tumor subtype, several smaller studies have yielded conflicting results.[5,8,12] Study of this issue has been limited, because data on BMI and HER2 status are not available in large population registries. Our study included >2500 women with triple-negative breast cancer. Therefore, we were able to assess the overall effect of BMI and to test for different effects within subgroups. The association between BMI and the triple-negative subtype did not quite reach statistical significance ($P = .052$). However, there was a significant interaction between BMI and menopausal status, such that triple-negative tumors were overrepresented in obese, premenopausal individuals. It is possible that this effect could be mediated by reproductive risk factors or by other modifiers of risk, including family history, alcohol consumption, or physical activity. Millikan et al noted that younger age at menarche, younger age at first full-term pregnancy, higher parity, and shorter duration of breastfeeding were associated with basal-type

Table 5. Results of All Main Effects Logistic Regression Models to Test for Predictors of Positive Lymph Nodes (N = 14,918)

Variable	Sample Size[a]	Adjusted OR (95% CI)	Type 3 *P*
Tumor subtype			<.001
HR+/HER2−	9864	Baseline	
Triple negative	2526	0.88 (0.80-0.97)	
HER2+	2528	1.35 (1.23-1.48)	
Tumor size, cm			<.001
≤1	3509	Baseline	
>1 to ≤2	5531	2.94 (2.64-3.28)	
>2	5878	7.83 (7.03-8.71)	

Abbreviations: CI, confidence interval; HER2+, positive for human epidermal growth factor receptor 2; HER2−, negative for human epidermal growth factor receptor 2; HR+, hormone receptor positive (positive for estrogen receptor and/or progesterone receptor); OR, odds ratio; triple negative, negative for all 3 receptors (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2).

[a] The sample INCLUDES patients who received neoadjuvant chemotherapy or neoadjuvant endocrine therapy (n = 2641), and EXCLUDES patients who did not have lymph nodes assessed (n = 36) or who were missing tumor size (n = 250), resulting in a sample size of 14,918.

Table 6. Univariate Logistic Regression for First Site(s) of Recurrence[a]

	Triple Negative vs HR+/HER2−		HER2+ vs HR+/HER2−	
Site[b]	OR (95% CI)	*P*	OR (95% CI)	*P*
Locoregional vs other	1.32 (1.01-1.74)	.045	1.12 (0.83-1.51)	.45
Lung vs other	2.17 (1.47-3.21)	<.001	1.73 (1.13-2.66)	.012
Brain vs other	3.50 (2.10-5.85)	<.001	3.97 (2.35-6.72)	<.001
Bone vs other	0.26 (0.19-0.36)	<.001	0.39 (0.29-0.54)	<.001
Liver vs other	1.09 (0.74-1.61)	.67	1.58 (1.07-2.33)	.02

Abbreviations: CI, confidence interval; HER2+, positive for human epidermal growth factor receptor 2; HER2−, negative for human epidermal growth factor receptor 2; HR+, hormone receptor positive (positive for estrogen receptor and/or progesterone receptor); OR, odds ratio; triple negative, negative for all 3 receptors (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2).

[a] The analyses were based on a cohort of 1389 patients with documented recurrence (triple negative, n = 480; HER2+, n = 373; HR+/HER2−, n = 536). The HR+/HER2− cohort was used as the referent group for all analyses.

[b] Other refers to any/all other distant/locoregional site(s).

cancers.[9] It is interesting to note that obesity may be associated with an increased breast cancer risk among breast cancer 1/2 (*BRCA1*/*BRCA2*) mutation carriers.[23] Other potential mediators include insulin, insulin-like growth factor-1, inflammatory cytokines, or a proangiogenic state.[24-26] Because these factors are not collected in the NCCN database, we were unable to assess their contribution to the observed association of BMI and triple-negative disease among premenopausal women in our cohort. Because we compared proportions among women with a breast cancer diagnosis rather than estimating population-based risk, it is also possible that the true effect of obesity is to reduce the risk of ER-positive breast cancer, leading to an apparent, but not real, increase in the risk of triple-negative breast cancer. Although our data do not point to a specific mechanism, they support the importance of assessing clinical and biochemical risk factors separately in younger women versus older women and by tumor subtype.

Our data clearly demonstrate that triple-negative tumors are less likely to be lymph node-positive than either HER2-positive or HR-positive/HER2-negative tumors, particularly in tumors >2 cm in greatest dimension. This has been an unresolved question in the literature with conflicting results from several smaller studies.[4,6] We also observed that the risk of recurrence was elevated relative to HR-positive/HER2-negative tumors, particularly in the first 2 years after diagnosis. Together, these data have direct implications for patient care. Published data indicate a median survival of only approximately 1 year among women with metastatic, triple-negative breast cancer.[16,27] Thus, even among older individuals, the benefits of adjuvant chemotherapy may outweigh the risks. Indeed, in a randomized trial evaluating capecitabine versus standard chemotherapy in women aged >65 years with early stage breast cancer, standard chemotherapy was identified as superior (3-year relapse-free survival, 68% vs 85%; overall survival, 86% vs 91%), and this effect was driven almost entirely by ER-negative tumors, approximately 90% of which were triple-negative.

Consistent with other studies, we observed an increased risk of CNS relapse among patients with triple-negative or HER2-positive tumors.[15,28-31] CNS metastases comprised a significant fraction of the documented recurrence events among women with these tumor subtypes. Unfortunately, the prognosis after CNS relapse in patients with triple-negative breast cancer is particularly poor.[32,33] Efforts to improve the outcomes of patients with HER2-positive or triple-negative cancer will likely require attention to the CNS, either by identifying patients at highest risk for prevention/prophylaxis trials and/or developing brain-permeable agents to effectively treat micrometastatic disease.

Our study had several limitations. First, we did not directly assess tumors for molecular subtype. Although most triple-negative breast cancers cluster with the basal subtype, concordance rate across studies varies from 70% to 100%.[2,34] We did not have information on the

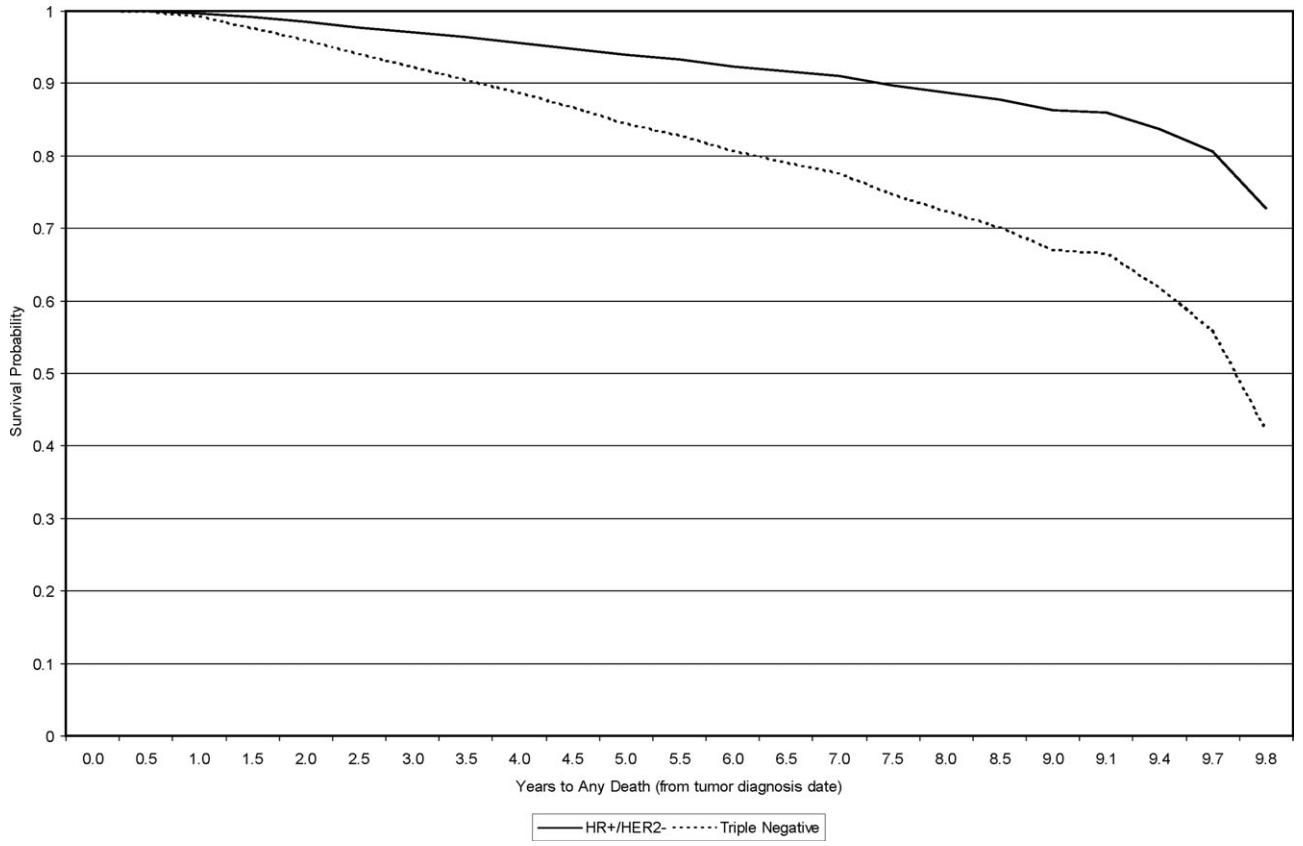

Figure 1. Overall survival is illustrated according to tumor subtype adjusting for patient age, disease state, race, receipt of chemotherapy, tumor size, histologic grade, and lymph node status. HR+ indicates positive for estrogen receptor and/or progesterone receptor; HER2−, negative for human epidermal growth factor receptor 2.

percentage of staining for ER or PR by IHC, nor did we have information on cytokeratin or epidermal growth factor receptor staining; these variables may influence the proportion of patients with a true basal subtype and separate triple-negative tumors into different prognostic groups.[35,36] Second, our analysis was limited to patients who presented to NCCN centers. The median age for our cohort was 55 years, or approximately 6 years younger than the median age of patients with breast cancer in the United States, suggesting a referral bias.[37] However, the distribution of subtypes in our database was similar to that in population-based registries.[4,7,38] In addition, there was no reason, a priori, to believe that the correlations between tumor characteristics and clinical phenotype that were the primary focus of our analysis would be systematically different in a population-based sample. Our definition of menopausal status also may have misclassified some women. However, because we were analyzing data from an existing registry that surveyed patients on cessation of menses in the 6 months before diagnosis, we were unable to assess alternate definitions of menopause.

Another limitation was the relatively short follow-up. Given the long natural history of HR-positive/HER2-negative breast cancer, it is likely that survival estimates will evolve over time in this subset.[39] In contrast, recurrences tend to occur early in patients with triple-negative tumors, and survival after a diagnosis of metastatic disease is only about 1 year.[6,16,28] Indeed, despite the short follow-up, 19% of patients with triple-negative breast cancer in our data set had a recorded recurrence event, and the greatest hazard of death occurred in the first 2 years after initial diagnosis.[6] Therefore, we believe that our description of the natural history of triple-negative breast cancer is likely to be a reasonably accurate reflection of outcomes.

In conclusion, the current report provides a comprehensive portrait of the presenting features and clinical outcomes of patients with triple-negative breast cancer relative to other breast cancer subtypes within the NCCN. Future analyses will hone in on the prognostic significance of tumor size and lymph node status in the triple-negative subset and on variations in patterns of care.

Table 7. Hazard Ratios for Triple-Negative Versus Hormone Receptor-Positive/HER2-Negative Tumors (n = 12,024)[a]

Endpoint	HR (95% CI)[b] Unadjusted	Adjusted[c]
Any death		
Entire follow-up period	3.28 (2.93-3.66)	2.72 (2.39-3.10)
0-2 y	7.75 (6.17-9.74)	6.10 (4.81-7.74)
2-6 y	2.74 (1.67-4.51)	2.30 (1.39-3.82)
From 6 y to the end of follow-up	1.15 (0.46-2.88)	0.96 (0.38-2.42)
BCA death		
Entire follow-up period	4.02 (3.56-4.55)	2.99 (2.59-3.45)
0-2 y	11.87 (8.99-15.66)	8.30 (6.23-11.05)
2-6 y	3.39 (1.87-6.17)	2.56 (1.39-4.69)
From 6 y to the end of follow-up	1.16 (0.41-3.27)	0.86 (0.30-2.46)

Abbreviations: BCA, breast cancer; CI, confidence interval; HR, hazard ratio.

[a] Triple-negative tumors are those that are negative for all 3 hormone receptors (estrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 [HER2]), and hormone receptor-positive tumors are positive for estrogen receptor and/or progesterone receptor.

[b] The sample excluded patients who had missing tumor size data (n = 562) and patients who did not have lymph nodes assessed (n = 16).

[c] The proportional hazards regression model was adjusted for age (ages <50 years or 50 years), disease stage (I, II, or III), race (Caucasian, African American, or other), chemotherapy (yes or no), tumor size (≤2 cm or >2 cm), histologic grade (low/intermediate, high, or unknown), and lymph node status (positive or negative).

It is our hope that these and other studies will aid in the planning and conduct of subtype-specific clinical trials for the prevention, detection, and treatment of this aggressive tumor subtype.

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