

Prognostic Markers in Triple-Negative Breast Cancer

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BACKGROUND. Triple-negative breast cancer (estrogen receptor-negative, progesterone receptor-negative, and HER2-negative) is a high risk breast cancer that lacks the benefit of specific therapy that targets these proteins.

METHODS. In this study, the authors examined a large and well characterized series of invasive breast carcinoma (n = 1944) with a long-term clinical follow-up (median, 56 months) by using tissue microarray. The series were also stained with concurrent immunohistochemical prognostic panels (estrogen receptor, progesterone receptor, HER-2, androgen receptor, epidermal growth factor receptor (EGFR), P-cadherin, E-cadherin, and basal (CK5/6, CK14), and p53), to characterize this specific subgroup of breast cancer and to identify prognostic markers that can identify tumors with more aggressive behavior.

RESULTS. Of informative cases, 16.3% were of the triple-negative phenotype. The majority of these tumors were grade 3, ductal/no-specific-type carcinomas. There were positive associations with larger size, pushing margins, poorer Nottingham Prognostic Index, development of recurrence and distant metastasis, and poorer outcome. In addition, associations were found with loss of expression of androgen receptor and E-cadherin, and positive expression of basal cytokeratins (basal phenotype), P-cadherin, p53, and EGFR. In all tumors, tumor size, lymph node stage, and androgen receptor were the most useful prognostic markers. In the lymph node-positive subgroup, both size and androgen receptor retained their prognostic significance. However, in the lymph node-negative tumors, basal phenotype was the sole prognostic marker identified in this subgroup. Other parameters including age, histological grade, tumor size, vascular invasion or other biomarkers included in the current study were not significant.

CONCLUSIONS. The authors concluded that assessment of androgen receptor and basal phenotype, in addition to the established pathologic variables, mainly lymph node status and tumor size, can be used to select high-risk and low-risk patients at the time of primary surgery and can provide valuable information on treatment options in these triple-negative tumors. *Cancer* 2007;109:25-32.

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KEYWORDS: breast carcinoma, triple-negative phenotype, prognosis.

Human breast carcinomas represent a heterogeneous group of tumors that are diverse in behavior, outcome, and response to therapy. Although its incidence is still high, the overall mortality due to breast cancer has decreased, attributed in part to early application of various treatments. To reduce mortality from breast cancer further, there is a desire to examine and characterize tumors of poor prognosis, to predict their biology, to ensure adequate therapy, and to improve patients' outcome. There is also a need to develop additional forms of systemic treatment effective in those tumors that fail to express known targets such as estrogen receptor, progesterone receptor, or C-erbB-2 (HER2).

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Emerging data demonstrate that stratification of tumors by gene-expression profiles and other techniques¹⁻⁵ divides breast cancer into a mixture of at least 2 main types with 5 subtypes, according to hormone receptor (HR) expression (negative or positive) and/or epithelial cellular origin (basal or luminal), that have clinical implication. The hormone receptor-negative group has 3 subtypes: 1 with HER2 overexpression, 1 normal-like, and 1 basal subtype with positive epidermal growth factor receptor (EGFR), absent HR (estrogen receptor and progesterone receptor), and absent HER2 expression (triple-negative subtype). Previous DNA microarray and immunohistochemical (IHC) analyses have shown that 80% to 90% of triple-negative tumors are basal-like and have a clinical behavior similar to basal-like behavior. In addition, mammary stem cell studies have reported that this triple-negative phenotype is a feature of mouse mammary stem cells, which also express EGFR and other stem cell markers.⁶

HR-negative tumors are more likely to be poorly differentiated, of higher histological grade, associated with a higher recurrence rate and a decreased overall survival, and unresponsive to antiestrogens.⁷⁻⁹ However, a significant proportion of a small subset of invasive cancers, eg, adenoid cystic carcinoma and secretory carcinoma, are HR-negative.^{10,11} These tumors have an excellent prognosis with minimal regional recurrence. In addition, not all poorly differentiated, HR-negative tumors behave poorly. Medullary-like cancers are reported in some series to have a relatively better prognosis than expected.¹² All these features point toward the heterogeneous nature of a HR-negative subgroup of invasive breast cancers and may indicate the presence of more aggressive subgroups within these tumor types that can be benefit from an aggressive therapy. HER2 is a major target for the development of new cancer therapies and is similar to the estrogen receptor, which guides hormone therapy. Its greatest value as a predictive marker lies in the prediction of response to therapies that target HER2, such as trastuzumab (Herceptin). Although HER2-negative disease has a more favorable prognosis than HER2-positive disease, it lacks the benefit of using these targeted therapies. Previous studies have reported that HER2 status usually shows an inverse association with HR expression.¹³⁻¹⁶

In this study, we investigated the high-risk group of breast cancer with the triple-negative phenotype (estrogen receptor-negative, progesterone receptor-negative, and HER2-negative) that lacks the benefit of specific therapy that targets these proteins to characterize and identify additional prognostic markers that can identify tumors with more aggressive behavior.

MATERIALS AND METHODS

This study investigated a consecutive series of 1944 cases of primary operable invasive breast carcinoma obtained from Nottingham Tenovus Primary Breast Carcinoma Series from patients presenting between 1986 and 1998. This is a well-characterized series of primary breast carcinoma with a long-term follow-up that has been treated in a uniform way and previously used to study a wide range of biomarkers.^{17,18} Patient's clinical history and tumor characteristics were assessed in a uniform fashion. Information on therapy, local, regional, and distant recurrence, and survival was maintained on a prospective basis. The Nottingham Prognostic Index (NPI) was calculated by using the following equation: $NPI = 0.2 \text{ tumor size (cm)} + \text{grade (1-3)} + \text{lymph node score (1-3)}$.¹⁹ This index predicts the survival of patients with invasive breast cancer, and it can define 3 subsets of patients with different chances of dying from breast cancer; good (≤ 3.4), moderate (3.41-5.4), and poor (> 5.4) prognostic groups.²⁰ The disease-free interval (DFI) was defined as the interval (in months) from the date of the primary surgery to the first locoregional recurrence or distant metastasis. The overall survival (OS) was the time, in months, from the date of the primary surgery to the time of breast cancer-related death. The median OS of the whole series was 73 months, and the median time of event-free survival was 66 months (range, 1 to 206 months). Recurrence occurred in 335 (18.8%) cases (184 cases, 16.4%, in the lymph node-negative and 150, 23%, in the lymph node-positive group), distant metastases in 203 (11.4%) cases, and 176 (9.9%) patients died from breast cancer during the period of follow-up (75 cases [6.7%] in the lymph node-negative and 100 [15.4%] in the lymph node-positive group). The Nottingham Prognostic Index ranged from 2-8.6 (mean, 4.2). Hormonal therapy was given to 536 (35.8%) patients and chemotherapy to 261 (17.4%) patients.

Breast cancer tissue microarrays were prepared and immunohistochemically stained for estrogen receptor, progesterone receptor, HER2, EGFR, androgen receptor, p53, P-cadherin, E-cadherin, and basal cytokeratins (CK5/6 and CK14) (Table 1) as previously described.^{3,17,21-23} Positive and negative controls for each marker were used according to the supplier's data sheet (Zymed Laboratories, Inc., San Francisco, CA; DakoCytomation Ltd., Cambridge, UK; Launch Diagnostics Ltd., Kent, UK; BD Biosciences, Oxford, UK; Novocastra Vision Biosystems (Europe) Ltd., Newcastle Upon Tyne, UK). Two cores were evaluated from each tumor and only staining of the invasive malignant cells was considered. Each core was scored individually, and the mean of the 2 readings was calculated. Immunohistochemical scoring was performed in a blind fashion.

TABLE 1
Source, Dilution, Pretreatment and Cutoff Values of Antibodies Used

Antibody, clone	Dilution	Source	Pretreatment	Cutoff values
ER [clone 1D5]	1:80	DakoCytomation	Microwave	0% (negative)
PR [clone PgR 636]	1:100	DakoCytomation		0% (negative)
HER-2 (cerbB-2)	1:250	DakoCytomation	None	<10% (negative)
EGFR[clone EGFR.113]	1:10	Novocastra	Microwave	<10% (negative)
AR [clone F39.4.1]	1:30	Biogenex	Microwave	0% (negative)
p53 [clone DO7]	1/50	Novocstra	Microwave	>5% (positive)
CK5/6[cloneD5/16134]	1:100	Boehringer Biochemica	Microwave	≥10% (positive)
CK 14 [clone LL002]	1:100			
EGFR [clone EGFR.113]	1:10	Novocastra	Microwave	≥10% (positive)
Anti E-cadherin [clone HECD-1]	1:100	Zymed Laboratories	Microwave	≥100 (H-score; median)
Anti P-cadherin [clone 56]	1/200	BD Biosciences		≥5% (positive)

Statistical Analysis

Statistical analysis was performed using SPSS 13.0 statistical software (SPSS Inc, Chicago, Ill). We examined the association between triple-negative phenotype and other clinicopathologic variables, and the significance of different prognostic markers using chi-squared test, and chi-squared test for trend as appropriate. The association with survival was analyzed initially by Kaplan-Meier plot and log-rank test and also with Cox regression analysis to adjust for other prognostic indicators. A *P*-value of <.05 was considered significant. Cutoff values for different biomarkers included in this study were chosen before statistical analysis. Standard cutoffs were used for established prognostic factors and were the same as for previously published patient series³ (Table 1). Negative expression of estrogen receptor, progesterone receptor, and androgen receptor was defined as complete absence of staining (0%), whereas negative HER2 and EGFR was defined as absence of membrane expression of the protein in <10% of tumor cells. Tumors that showed positive staining in ≥5% of the tumor cells (P-cadherin and p53) or the modified Histo-score (H-score) was >100 (E-cadherin) were considered positive.

This research was approved by the Nottingham Research Ethics Committee 2 under the title of "Development of a Molecular Genetic Classification of Breast Cancer."

RESULTS

In the current study, 1726 cases of invasive breast carcinomas were informative for the 3 markers (estrogen receptor, progesterone receptor, and HER2). Of these informative cases, 282 (16.3%) showed a triple-negative phenotype (estrogen receptor-negative, progesterone receptor-negative, and HER2-negative, regardless of the expression of EGFR or basal cytokeratins) and

formed the basis of this study. The patients had a median age of 49.9 years (range, 25–70 years). The majority (80.9%) of tumors were ductal carcinoma of no special type (duct/NST) (compared with 56% in the whole breast carcinoma series; 1944 cases) and 3.2% were of metaplastic and salivary gland-like carcinomas (compared with 0.7% in the whole breast carcinoma series). The Nottingham Prognostic Index in these cases ranged from 2.3–7.6 (mean, 4.8). Fifty-three (23%) cases received hormonal therapy and 106 (55%) received chemotherapy. The median overall survival was 54 months, and the median time of event-free survival was 49 months (range, 1 to 146 months).

Table 2 shows the main features of triple-negative tumors compared with nontriple-negative tumors concerning different clinicopathological variables and biomarkers used in the current study. Triple-negative phenotype was associated with larger size, grade 3 tumors, pushing margin ($\chi^2 = 6.7$, *P* = .009), development of recurrence and distant metastasis, and poorer Nottingham Prognostic Index ($\chi^2 = 112.6$, *P* < .001). It also showed a specific pattern of distant metastasis with high frequency of spinal cord and meninges, brain, liver, and lung metastases ($\chi^2 = 48.5$, *P* < .001). No association was found with lymph node status. Triple-negative phenotype was associated with poorer outcome in terms of overall survival and disease-free interval (log-rank = 25.4, *P* < .0001 and log-rank = 14.3, *P* = .0002 in case of overall survival and disease-free interval, respectively) (Figs. 1 and 2). Interestingly, in this series of triple-negative breast cancer, basal phenotype as defined by the expression of CK5/6 and/or CK14 in ≥10% of tumor cells was detected in 157 (55.7%) cases. We also found that basal phenotype, within the triple-negative tumor series, was associated with negative lymph node disease (67% compared with 58% in the nonbasal phenotype triple-negative tumors), development of distant metastasis, and recur-

TABLE 2
Comparison of Tumors With Triple Negative and Non-Triple Negative Phenotype

Variables	Total no. (%)	Triple negative no. (%)	Non-triple negative no. (%)	χ^2 (P value)
Grade				236 (<.0001)
Grade 1	307	5	302	
Grade 2	565	19	546	
Grade 3	851	256	595	
LN status				0.03 (0.88)
Negative	1082	178	904	
Positive	637	104	534	
Size				28 (<.001)
≤1.5cm	599	59	540	
>1.5cm	1124	222	902	
Definite VI	727 (41)	106 (37)	621 (44)	3.3 (0.07)
DM	203 (11)	47 (17)	156 (10)	10 (.001)
Recurrence	335 (19)	69 (25)	266 (17.7)	8.2 (.004)
No. of breast cancer deaths	176 (10)	47 (17)	129 (8.6)	18.7 (<.001)
Positive AR expression	1036 (63)	36 (13)	1000 (73)	344.3 (<.0001)
Positive EGFR expression	286 (19)	92 (37)	194 (15)	65.4 (<.0001)
Positive P53 expression	478 (28)	157 (56)	321 (22)	133.2 (<.0001)
Positive P-cadherin	760 (52)	228 (93)	532 (44)	200.8 (<.0001)
Absent/reduced E-cadherin	933 (54)	179 (65)	754 (52.5)	13.4 (.001)
BP	321 (18.7)	157 (56)	146 (11.5)	305.8 (<.0001)

LN indicates lymph node; VI, vascular invasion; DM, distant metastasis; AR, androgen receptor; BP, basal phenotype.

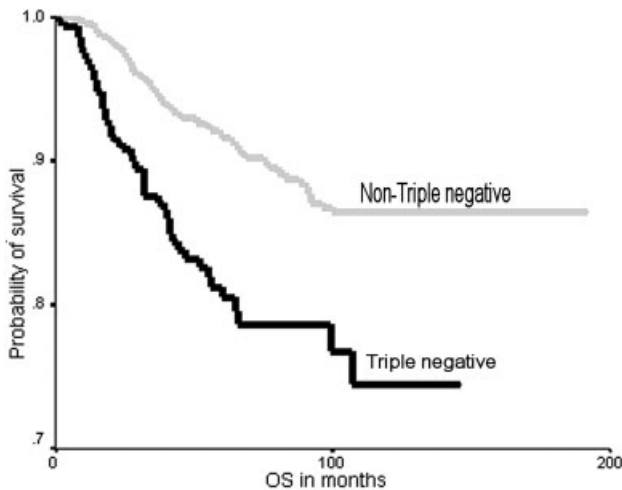


FIGURE 1. Correlation between triple-negative phenotype and overall survival (OS) in the whole breast cancer series.

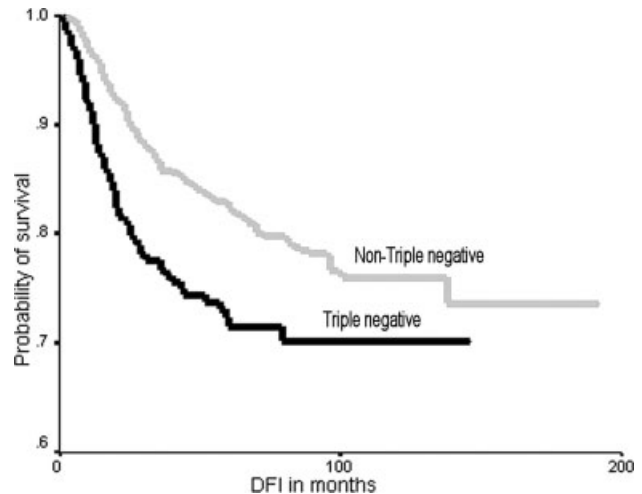


FIGURE 2. Correlation between triple-negative phenotype and disease-free interval (DFI) in the whole breast cancer series.

rence; however, this difference was not statistically significant.

To study the response of these tumors to adjuvant treatment, we stratified the informative breast carcinoma series into matching subgroups according to different grades, sizes, and the Nottingham Prognostic Index. We found that in the poor Nottingham Prognostic Index group (all were lymph node-positive, grade 3 tumors, and sized ≥ 1.5 cm; 227 cases after exclusion of 22 cases of grade 2 or size < 1.5 cm) triple-negative

tumors were associated with shorter overall survival and disease-free interval in the subgroup of patients who did not receive chemotherapy (log-rank = 6.9, $P = .008$ and log-rank = 5.99, $P = .014$ for overall survival and disease-free interval, respectively), whereas in the subgroup that received chemotherapy, this negative association of triple-negative phenotype with survival disappeared (log-rank = 0.17, $P = .68$, and log-rank = 0.06, $P = .799$ for overall survival and disease-free interval, respectively) indicating better response of

TABLE 3
Association Between Prognostic Variables and Outcome in Different Patients' Groups

	Overall survival		Disease-free interval	
	LR	P	LR	P
LN				
Whole series (282 cases)	20.5	<.0001	21.3	<.0001
Grade				
Whole series	1.24	.54	1.96	.375
LN negative (178 cases)	0.73	.69	1.4	.49
LN positive (104 cases)	2.1	.65	0.45	.5
Size				
Whole series	5.64	.017	2.8	.096
LN negative	2.01	.16	0.03	.87
LN positive	3.7	.05	5.33	.021
Vascular invasion				
Whole series	2.11	.15	2.5	.11
LN negative	1.8	.17	2.6	.11
LN positive	0.75	.38	0.06	.8
AR				
Whole series	3.9	.04	4.5	.033
LN negative	0.6	.45	1.1	.31
LN positive	3.7	.05	4.4	.035
BP				
Whole series	0.9	.42	1.8	.17
LN negative	5.6	.047	4.4	.03
LN positive	0.05	.82	0.06	.81
p53				
Whole series	0.6	.44	1.6	.21
LN negative	0.01	.99	0.14	.71
LN positive	1.4	.24	1.67	.19
p-cadherin				
Whole series	0.03	.86	0.57	.45
LN negative	0.11	.73	0.92	.34
LN positive	0.01	.911	0.01	.95
E-cadherin				
Whole series	0.03	.86	0.45	.5
LN negative	2.5	.12	0.11	.74
LN positive	2.2	.14	2.5	.11

BP indicates basal phenotype; LR, log-rank; LN, lymph node; AR, androgen.

these tumors to chemotherapy. However, no similar findings were found for hormonal therapy.

Prognostic Value of Different Markers in Triple-Negative Breast Cancer

In the overall series of triple-negative tumors, the absence of androgen receptor expression (234 cases, 87%) was associated with higher histological grade (χ^2 47.96, $P < .001$), development of recurrences (χ^2 4.3, $P = .038$) and distant metastasis (χ^2 3.9, $P = .049$). Higher grade was also associated with negative E-cadherin expression (χ^2 6.4, $P = .04$) and positive expression of P-cadherin (χ^2 18.3, $P < .001$) and p53 (χ^2 11.2, $P = .004$). However, no other associations between other biomarkers and any of the clinicopathologic pa-

TABLE 4
Multivariate Cox Regression Analysis of Factors Associated With Overall Survival and Disease-free Interval in the Triple Negative Tumors

Predictor	Overall survival		Disease-free interval	
	Hazards ratio (95% CI)	P	Hazards ratio (95% CI)	P
Whole series				
LN	2.11 (1.4-3.1)	$\leq .001$	1.6 (1.1-2.3)	.01
Size ≤ 1.5 cm	3.14 (1.15-3.9)	.03	1.7 (0.8-3.3)	.14
vs > 1.5 cm				
AR	0.36 (0.8-1.6)	.17	0.5 (0.2-1.3)	.14
BP	1.2 (0.7-2.1)	.6	1.34 (0.8-2.2)	.24
LN-negative group				
Size	2.6 (0.57-11.6)	.22	0.8 (0.4-1.8)	.67
AR	0.9 (0.2-4.7)	.96	0.89 (0.3-2.8)	.84
BP	2.7 (0.98-7.6)	.05	2.24 (1.1-4.5)	.02
LN positive group				
Size	4.2 (0.9-17.9)	.05	5.1 (1.2-21.3)	.03
AR	0.0 (0.0-5.9)	.97	0.0 (0.0-1.7)	.97
BP	0.8 (0.4-1.8)	.6	0.8 (0.38-1.6)	.51

LN indicates lymph node; AR, androgen receptor; BP, basal phenotype.

rameters were identified. Survival analyses showed that nodal status, tumor size, and negative androgen receptor expression were inversely associated with both disease-free interval and overall survival, but other markers were not. Multivariate analysis including age, tumor size, lymph node stage, androgen receptor, and basal phenotype showed that nodal status and size were the only variables of independent prognostic significance (Tables 3 and 4).

In the subgroup of node-positive patients (104 cases, 36.7%), larger tumor size was associated with the development of recurrence (χ^2 5.7, $P = .017$); negative androgen receptor expression was associated with higher grade (χ^2 17.3, $P < 0.001$), recurrence (χ^2 5.2, $P = .024$), and distant metastasis (χ^2 3.9, $P = .048$). In univariate analysis, both size and androgen receptor expression were associated with patients' survival, whereas other markers were not. Multivariate analysis showed that size, but not androgen receptor, was of independent prognostic significance for both disease-free interval and overall survival.

In the subgroup of node-negative patients (178 cases, 63.3%), basal phenotype was associated with development of recurrence (χ^2 3.5, $P = .063$) and increased mortality from breast cancer (χ^2 2.96, $P = .08$). Negative expression of E-cadherin was associated with higher grade (χ^2 6.5, $P = .04$) and development of distant metastasis (χ^2 3.8, $P = .05$), whereas positive expression of P-cadherin and p53 was associated with higher grade (χ^2 18.6, $P < .001$, χ^2 9.1, $P = .011$, respectively). Both univariate and multivariate analyses showed

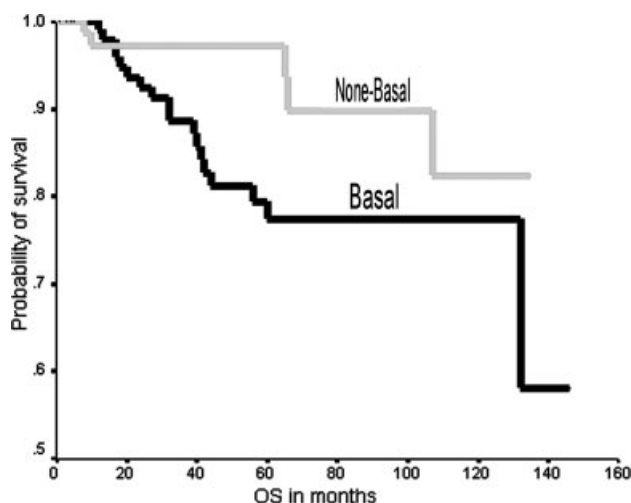


FIGURE 3. Correlation between basal phenotype and overall survival (OS) in the lymph node-negative subgroup of triple-negative tumors.

that basal phenotype was the only significant and independent prognostic marker in this subgroup (Tables 2 and 3, Figs. 3 and 4).

DISCUSSION

Currently, routine clinical management of breast cancer relies on traditional prognostic factors including nodal status, tumor histological grade, and primary tumor size, in addition to estrogen receptor, progesterone receptor, and HER2.^{24,25} Evaluation of these biomarkers is most valuable to predict response to therapy that targets these proteins. For example, it has been reported that 85% of tumors with positive estrogen receptor *and* progesterone receptor expression respond to hormonal manipulation, whereas only about 40% of those with only 1 type of receptor respond. Tumors with double-negative phenotype have less than 10% likelihood of responding.^{26,27} Hormone receptor-negative breast cancers are a heterogeneous group of breast cancers that are generally thought to be aggressive with poor prognosis and with fewer cancer prevention and treatment strategies compared with tumors expressing hormone receptor. In addition, HER2-negative tumors lack the benefit of specific therapy that targets this protein (eg, trastuzumab-based therapy). Therefore, treatment options for these triple-negative tumors are more limited.

The clinical course of a patient with breast carcinoma remains difficult to predict, as tumors of apparently homogenous morphological characteristics still vary in response to therapy and have divergent outcomes.²⁸ Therefore, additional markers are being sought to further refine classification, especially in patient subgroups whose outcome cannot be pre-

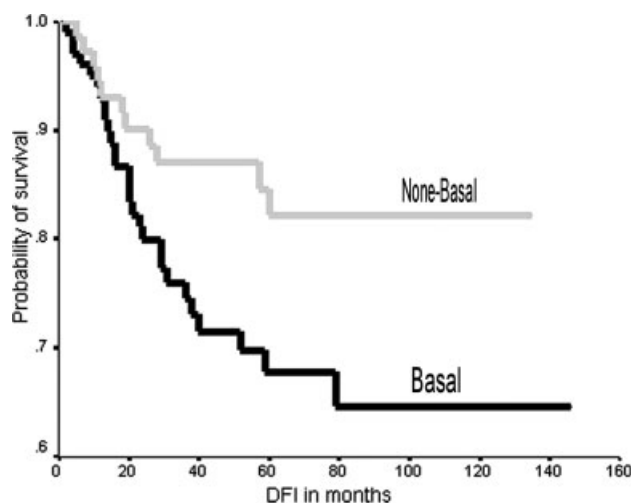


FIGURE 4. Correlation between basal phenotype and disease-free interval (DFI) in the lymph node-negative subgroup of triple-negative tumors.

dicted accurately by using conventional parameters. Previous studies have examined hormone receptor-negative tumors,^{7,29,30} HER2 positive or negative tumors,^{31,32} and triple-negative ductal carcinoma in situ.³³ In a previous study of 657 cases from the Carolina Breast Cancer Study, Carey et al.³⁴ found that 26% of cases were triple-negative. These triple-negative tumors were mainly of high histologic grade (grade 3), showed high mitotic index, and were found more frequently in premenopausal women. Umemura and colleagues³⁵ have reported that combined estrogen receptor-negative and HER2-negative tumors constitute 19% of cases (11 of 58 breast cancer cases). These tumors were associated with high expression of p53, vimentin, and EGFR, and these tumors showed the highest ki-67 Labeling Index and lowest expression of cyclinD1 when compared with other tumor groups. However, to our knowledge, comprehensive study and characterization of invasive breast cancer with triple-negative phenotype is lacking.

In the current study, we have investigated the main features and the prognostic value of different markers in a large series of triple-negative breast cancers. Triple-negative phenotype was found in 16.3% of the informative cases. The most common histological types were ductal carcinomas of no specific type, metaplastic and salivary gland-like carcinomas; the majority of these tumors were grade 3. There were positive associations with larger size, pushing margins, poorer Nottingham Prognostic Index, development of recurrence and distant metastasis, and poorer outcome in terms of overall survival and disease-free interval. In addition, associations were found with loss of expression of androgen receptor and E-cadherin, and positive expression of basal cyto-

keratins, P-cadherin, p53, and EGFR. We also found that there is a trend for tumors with triple-negative phenotype to have a more favorable outcome after use of chemotherapy, particularly in certain subgroups of breast cancer.

Our results showed that different markers played a diverse prognostic role in the diverse subgroups studied. In our whole triple-negative series, nodal status, tumor size, and androgen receptor expression are the most useful prognostic markers. When we stratified the cases into lymph node-positive and lymph node-negative subgroups, we found that in the lymph node-positive tumors, both size and androgen receptor expression retained their prognostic value. However, in the lymph node-negative group (63% of cases), basal phenotype was the sole marker that showed prognostic value whereas other markers, including patients' age, tumor size, and androgen receptor expression, were not significant. In these tumors, basal phenotype was associated with a poorer outcome and, thus, can define a group of patients that may benefit from a more aggressive therapeutic intervention. In our series, the majority (91%) of tumors were of high histological grade (grade 3 tumors³⁶), which could explain the lack of prognostic significance of grade in this group of breast cancers.

Our results are consistent with previous studies of breast cancer that have shown that time-dependent pathologic factors, like nodal status^{19,37} and size,^{38,39} are clinically useful prognostic factors, and that identification of alterations of a single protein of known biological relevance, such as p53,^{38,40} P-cadherin,⁴¹ or E-cadherin,⁴² have little or no clinical prognostic relevance. In addition, we have shown that androgen receptor and basal cytokeratin expression may add important prognostic information, particularly in the lymph node-positive and lymph node-negative tumors, respectively. These results are in agreement with previous studies, which have shown a prognostic value for basal cytokeratins in the lymph node-negative group of breast cancer (including both hormone receptor-positive and hormone receptor-negative tumors),^{43–45} and with the Malzahn et al. study⁴³ that demonstrated an association between basal cytokeratins and shorter survival in a subgroup of grade 3 tumors but not in other groups. The prognostic significance of androgen receptors has also been reported in breast cancer⁴⁶ as well as in the estrogen receptor-negative subgroup.⁴⁷ Moreover, in the lymph node-negative subgroup of breast cancer, some previous studies have demonstrated that p53 has no prognostic impact.⁴⁸

In conclusion, our study provides robust data supporting the assessment of basal cytokeratins and androgen receptors, in addition to the traditional pathologic parameters (tumor size and nodal status), in

order to provide prognostic information in the group of tumors with triple-negative phenotype. Assessment of p53, P-cadherin, and E-cadherin did not add significant prognostic information in this class of tumors. In the lymph node-negative subgroup, basal phenotype can provide powerful prognostic information independent of other well-established markers and can identify a specific subgroup of patients that may benefit from a more aggressive approach to adjuvant therapy. We, therefore, emphasize the importance of routine staining of triple-negative breast cancer with androgen receptors and basal cytokeratins. Further confirmatory study in a more appropriate or clinical trial setting is recommended.

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