Triple-Negative Breast Cancer: Clinical Features and Patterns of Recurrence

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Abstract

Purpose: To compare the clinical features, natural history, and outcomes for women with "triple-negative" breast cancer with women with other types of breast cancer.

Experimental Design: We studied a cohort of 1,601 patients with breast cancer, diagnosed between January 1987 and December 1997 at Women's College Hospital in Toronto. Triple-negative breast cancers were defined as those that were estrogen receptor negative, progesterone receptor negative, and HER2neu negative. The prognostic significance of triple-negative breast cancer was explored.

Results: The median follow-up time of the 1,601 women was 8.1 years. One hundred and eighty of 1,601 patients (11.2%) had triple-negative breast cancer. Compared with other women with breast cancer, those with triple-negative breast cancer had an increased likelihood of distant recurrence (hazard ratio, 2.6; 95% confidence interval, 2.0-3.5; $P < 0.0001$) and death (hazard ratio, 3.2; 95% confidence interval, 2.3-4.5; $P < 0.001$) within 5 years of diagnosis but not thereafter. The pattern of recurrence was also qualitatively different; among the triple-negative group, the risk of distant recurrence peaked at ~3 years and declined rapidly thereafter. Among the "other" group, the recurrence risk seemed to be constant over the period of follow-up.

Conclusions: Triple-negative breast cancers have a more aggressive clinical course than other forms of breast cancer, but the adverse effect is transient.

The heterogeneous nature of breast cancer has implications for physicians and their patients. Increasingly, treatments are targeted toward molecular markers. The development of hormonal therapies validated the distinction between estrogen receptor (ER)-positive and ER-negative breast cancers. Tamoxifen was initially used as a treatment for all breast cancers, but it was later recognized that only patients with tumors that express hormone receptors benefit from tamoxifen. The introduction of trastuzumab therapy (Herceptin) highlighted the importance of identifying tumors with amplified or overexpressed HER2neu (HER2). Gene expression studies using DNA microarrays have identified subtypes of breast cancer that were not apparent using traditional histopathologic methods (1). Four common subtypes have been identified; two of these are derived from ER-negative tumors (basal-like and HER2 positive) and two are derived from ER-positive tumors (luminal A and B; refs. 2, 3). Basal-like breast cancers are overrepresented in African-American women (4) and in BRCA1 mutation carriers (5, 6).

Perou et al. (1) reported that women with basal-like breast cancers had shorter relapse-free survival times than women with other types of breast cancer. Basal-like breast cancers also have a tendency toward visceral (versus bone) metastasis (7, 8). In an analysis of 49 patients with basal-like breast cancer and 49 matched controls, Banerjee et al. (9) found that patients with basal-like breast cancer had significantly shorter disease-free and overall survival times than women with other tumors, but basal-like status was not a significant independent prognostic variable in the multivariable analysis.

To date, studies on patients with basal-like breast cancers have been limited by small sample sizes and short follow-up times. To some extent, this is because the basal-like phenotype is based on immunohistochemical staining of tumor slides using anti-keratin antibodies, and these are not yet in general clinical use. However, the "basal-like" category of tumors is composed almost entirely of "triple-negative" breast cancers [i.e., tumors that are negative for ERs, progesterone receptors (PR), and HER2]. It is therefore possible to classify with accuracy the majority of basal-like breast cancers (and non–basal-like breast cancers) using these three standard immunohistochemical markers. We present data on a large series of triple-negative breast cancers derived from a single institution with long-term follow-up.

Materials and Methods

Study patients. We studied a cohort of women with invasive breast cancer treated at the Henrietta Banting Breast Centre (HBBC). Details of

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Table 1. Characteristics of triple-negative versus other breast cancers

Variable	Other (*N* = 1,421), *n* (%)	Triple negative (*N* = 180), *n* (%)	*P**
Mean age at diagnosis (y)	57.7	53	<0.0001
Mean follow-up (y)	8.9	7.9	0.004
Lymph node status			
Positive	510 (45.6)	87 (54.4)	
Negative	609 (54.4)	70 (44.6)	0.02
Missing/not tested	97/205	7/16	
Mean tumor size (cm)	2.1	3.0	<0.0001
Tumor size (cm)			
T_1 (<2)	880 (62.7)	65 (36.5)	
T_2 (≥2 to ≤5)	461 (32.8)	99 (55.6)	
T_3 (>5)	64 (4.6)	14 (7.9)	<0.0001
Missing	16	2	
Tumor grade			
I	237 (19.9)	15 (9.8)	
II	616 (51.8)	37 (24.2)	
III	336 (28.3)	101 (66.0)	<0.0001
Missing			
Lymphovascular invasion			
Present	419 (32.3)	65 (39.6)	
Absent	878 (67.7)	99 (60.4)	0.06
Missing	124	0	
ER levels			
Positive	1167 (86.6)	0 (0)	NA
Negative	180 (13.4)	180 (100)	
Missing or borderline	74		
PR levels			
Positive	1,000 (75.2)	0 (0)	NA
Negative	350 (24.8)	180 (180)	
Missing or borderline	91		
HER2 status			
Positive	163 (16.4)	0 (0)	NA
Negative	831 (83.6)	180 (180)	
Not tested	427		
Chemotherapy treatment			
Yes	357 (25.5)	86 (48.6)	
No	1,040 (74.5)	91 (51.4)	<0.0001
Missing	20		
Tamoxifen treatment			
Yes	756 (54.2)	64 (36.2)	
No	640 (44.8)	113 (63.8)	<0.0001
Missing	25	3	

Abbreviation: NA, not applicable.
* *P* values were calculated with the use of the χ^2 test.

the database have been published elsewhere (10). The HBBC database is a hospital-based cohort of women diagnosed with primary breast cancer at Women's College Hospital. The HBBC database was established to systematically record data on clinical presentation, treatment, and outcome from women with breast cancer who received primary surgical treatment at Women's College Hospital. Patients were referred from family practitioners and other physicians from the surrounding medical community to one of five teaching surgeons practicing at HBBC. For the purpose of this study, women were included if they were diagnosed with invasive breast cancer at Women's College Hospital from January 1987 to December 1997 and were entered onto the HBBC database. Medical records and pathology reports were reviewed. Patient information was recorded at accrual and included details about the patient's age at diagnosis (in years), tumor grade, lymph node status, pathologic tumor size in centimeters, and treatment (surgery, chemotherapy, tamoxifen therapy, and radiation treatment). For this study, triple-negative breast cancers were defined as those that were ER negative, PR negative, and HER2 negative. "Other" breast cancers were defined as those that were positive for any of these markers.

Immunohistochemistry. For each patient in the database, a set of representative paraffin-embedded slides was requested for antibody staining in the reference laboratory of W.M. Hanna. Staining was done between 2000 and 2004. ER and PR status were determined using immunohistochemistry. For ER and PR, antibodies were from Novocastra, with cutoff levels for receptor positivity of >10%. For 25% of the patients, a paraffin-embedded slide was not available and the ER and PR status were determined by reviewing the patient pathology records. These historical assays were biochemical using a cutpoint of 10 fmol/mg protein. HER2 status was not routinely determined for patient treatment during the course of this study but was done solely in the research reference laboratory. The overexpression of the HER2 protein was evaluated using the CB11 monoclonal antibody (Novocastra) in representative paraffin sections of each tumor using the peroxidase-antiperoxidase technique for immunohistochemical assay. HER2 positivity was defined as strong complete membrane staining in at least 10% of tumor cells. One thousand six hundred one (80%) of 1,992 patients had sufficient details on hormone receptors and HER2 for classification and were eligible for the study.

Table 2. Tumor size by nodal status in the triple-negative and other groups

Tumor size	Lymph node status	
	Other (*N* = 1,421)	Triple negative (*N* = 180)
	Lymph node positive, *n* (%)	Lymph node positive, *n* (%)
<1 cm	38 (19.3)	5 (55.6)
≥1 cm to 2 cm	180 (39.3)	25 (55.6)
≥2 cm to 5 cm	238 (59.5)	43 (48.9)
>5 cm	53 (91.4)	12 (92.3)
	$P < 0.0001$	$P = 0.04$

NOTE: *P* values were calculated with the use of the χ^2 test for trend.

Follow-up. Follow-up has been maintained by the database coordinator by reviewing clinical charts and by contacting patients by telephone. Local-regional relapses and the subsequent surgery during the 90-day postsurgery period were considered to be part of the primary management: distant recurrence during this time disqualified the patient from study. Relapses after 90 days were considered events. Relapses were dated and reviewed by two of three medical oncologists (K.I.P., M.T., and C.A.S.); initial interobserver agreement was >95%. Eighty-six percent of the patients had been followed for a minimum of 4 years, and 75% of patients were under active follow-up (or were deceased). For deceased patients, dates and causes of death were obtained from the medical records.

Outcomes. Overall survival was defined as from the time of diagnosis to last follow-up or time of death. Breast-specific survival was determined from time of diagnosis until death from breast cancer (patients dying from another cause were censored at time of death). Relapse-free survival was defined as the time of diagnosis to development of first evidence of clinical or radiographic metastatic disease, and local recurrence survival was defined as the time of diagnosis to development of local recurrence. Survival was ascertained from the HBBC database, which is maintained regularly, with each patient followed up at least once yearly.

Analysis. Baseline demographic and tumor characteristics were compared between the triple-negative and other groups using a *t* test for means and χ^2 statistic for frequencies. To assess whether tumor size correlated with nodal positivity, we did χ^2 tests for trend in the triple-negative and other groups. We evaluated the differences in method of detection between the triple-negative and other group using the χ^2 statistic.

Kaplan-Meier survival analyses were carried out for overall survival, breast cancer–specific survival, distant recurrence-free survival, and local recurrence-free survival. The log-rank test was used to examine the statistical significance of the differences observed between the groups. A multivariate Cox regression model was also used. This was used to compute hazard ratios (HR) and 95% confidence intervals (95% CI), adjusting for known prognostic variables (age, grade, tumor size, nodal status, use of adjuvant tamoxifen therapy, and use of adjuvant chemotherapy). The model was also used to estimate the risk of distal recurrence following local recurrence. Estimates were considered statistically significant for two-tailed values of $P < 0.05$. All analyses were carried out with Statistical Analysis System 9.13 statistical program.

There was evidence from this and other studies to suggest that the risks of recurrence and death in these subgroups were not proportional over the entire follow-up period. Therefore, we compared hazard rates and HRs for different times with respect to diagnosis (i.e., at 0 to 5 years from diagnosis and from 5 years to the end of the follow-up period).

Results

Demographics and histopathology. In this sample, 180 of 1,601 patients (11.2%) were defined as having triple-negative breast cancers. The characteristics of the patients with triple-negative and other breast cancers are compared in Table 1. The mean age at diagnosis was significantly younger for the triple-negative group compared with other group (53.0 versus 57.7 years, respectively; $P < 0.0001$). Patients in the triple-negative group were more likely to have grade III tumors (66% versus 28%; $P < 0.0001$), and the mean tumor size was larger in the triple-negative group than in the other group (3.0 versus 2.1 cm, respectively; $P < 0.0001$). Only one third of the triple-negative tumors were <2.0 cm at presentation, whereas almost two thirds of the other cancers were <2 cm (36.5% versus 62.7%, respectively; $P < 0.0001$). The rate of node positivity was slightly higher in the triple-negative group compared with the other group (54.6% versus 45.6%, respectively; $P = 0.02$).

Nodal status. In the other group, there was a clear increase in node positivity as tumor size increased; 19% of women with tumors of <1 cm had positive lymph nodes compared with >90% of women of tumors >5 cm ($P < 0.0001$; Table 2). Among the triple-negative group, there was no correlation

Table 3. Method of breast cancer detection in the triple-negative and other groups

Method of detection of breast cancer	Other (*N* = 958), *n* (%)	Triple negative (*N* = 92), *n* (%)	*P**
Physician or patient clinically detected	509 (53.1)	65 (70.7)	0.0008
Radiographically detected	345 (36.0)	18 (19.6)	
Other	104 (10.9)	9 (9.8)	

NOTE: Patients diagnosed at age ≥50 y.
**P* values were calculated with the use of the χ^2 test.

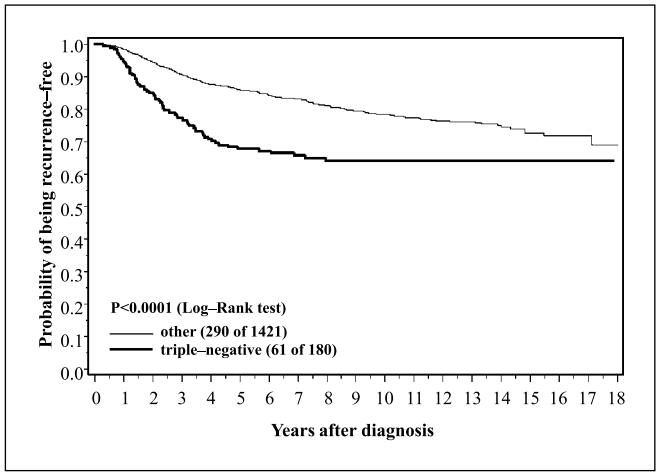

Fig. 1. Rates of distant recurrences in triple-negative and other breast cancers.

between tumor size and node status among women with tumors <5 cm. Even the small tumors in the triple-negative group had a high rate of node positivity; 55% of women with tumors of ≤1 cm had at least one positive lymph node.

Method of detection. We compared the proportions of breast cancers discovered initially by imaging (mammography or ultrasound) and by clinical detection (clinician or patient). Because screening mammography is routinely recommended to all women in Ontario after the age of 50, we restricted this analysis to women diagnosed at age ≥50. Patients with triple-negative breast cancers had a much lower proportion of breast cancers first detected by mammography or ultrasound than patients with other breast cancers (19.6% versus 36.0%; P = 0.0008; Table 3).

Outcomes. Patients with triple-negative breast cancers were more likely to have died than patients with other cancers (42.2% versus 28%, respectively; $P < 0.0001$). The median time to death was 4.2 years for patients with triple-negative breast cancers compared with 6 years for patients with other cancers ($P < 0.0001$). All deaths due to breast cancer in patients with triple-negative cancer occurred within 10 years of diagnosis. Deaths from breast cancer in patients with other cancer types continued to accrue up to 18 years after diagnosis.

A higher proportion of patients with triple-negative breast cancer experienced distant recurrence compared with patients with other breast cancers (33.9% versus 20.4%, respectively; $P < 0.0001$). The mean time to distant recurrence in patients with triple-negative cancer was less than that of the other group (2.6 versus 5.0 years, respectively; $P < 0.0001$). No distant recurrences occurred in the triple-negative group after 8 years of follow-up. In contrast, in the other group, distant recurrences continued to accrue for up to 17 years after diagnosis. Patients with triple-negative and other breast cancer had similar rates of local recurrence (13% versus 12%, respectively; $P = 0.77$); however, the mean time to local recurrence was shorter in patients with triple-negative cancers than other cancers (2.8 versus 4.2 years, respectively; $P = 0.02$).

Kaplan-Meier survival analyses were carried out to compare overall survival and distant recurrence-free survival rates (Figs. 1 and 2). To adjust for known prognostic variables, we used multivariate Cox proportional hazard models. In the unadjusted analysis, women with triple-negative breast cancer had an increased likelihood of death from breast cancer within 5 years of diagnosis (HR, 3.2; 95% CI, 2.3-4.5; $P < 0.0001$). After adjustment for age, grade, tumor size, nodal status, chemotherapy, and tamoxifen therapy, the risk of death from breast cancer remained higher for the triple-negative group up to 5 years from diagnosis (HR, 1.8; 95% CI, 1.3-2.6; $P = 0.0005$; Table 4). However, the increased mortality rate was not sustained for the period from 5 years after diagnosis to the end of follow-up (HR, 0.7; 95% CI, 0.4-1.1; $P = 0.1$). Thus, the excess deaths among the triple-negative group occurred in the first 5 years after diagnosis. Among the triple-negative patients, 70% of deaths occurred in the 5 years following diagnosis compared with only 44% of deaths in the other subgroup ($P < 0.0001$).

A similar effect was seen for distant recurrence. Compared with the other group, women with a triple-negative breast cancer had an increased likelihood of distant recurrence within 5 years of diagnosis (HR, 2.6; 95% CI, 2.0-3.5; $P < 0.0001$) but a significantly lower relative risk of recurrence thereafter (adjusted HR, 0.3; 95% CI, 0.1-0.8; $P = 0.02$; Table 4).

Few women with a triple-negative breast cancer experienced a local recurrence before a distal recurrence. Only 15 of 59 (25%) women with triple-negative cancer who were treated with breast-conserving surgery experienced a local recurrence before distal recurrence. Among women with other cancers, the proportion was 44% ($P = 0.02$ for difference). In the proportional hazards model, local recurrence was a risk factor for later distal recurrence among women with other cancers (HR, 1.5; 95% CI, 1.1-2.2; $P = 0.02$) but not among women with triple-negative tumors (HR, 0.6; 95% CI, 0.2-2.0; $P = 0.4$).

Time of recurrence. Traditionally, recurrence rates are represented by cumulative incidence curves. To evaluate more precisely the timing of recurrence for the two subgroups, we estimated the annual hazard rate of distant recurrence at 6-month intervals (Fig. 3). The pattern of distant recurrence was strikingly different between groups. In patients with triple-negative breast cancer, the risk of any recurrence rose sharply from date of diagnosis, peaked 1 to 3 years, and dropped quickly thereafter. Among patients with other cancers, there seemed to be a steady risk of recurrence throughout the entire follow-up period.

We were also interested in the time from recurrence to death. Of the 61 women with a triple-negative breast cancer who

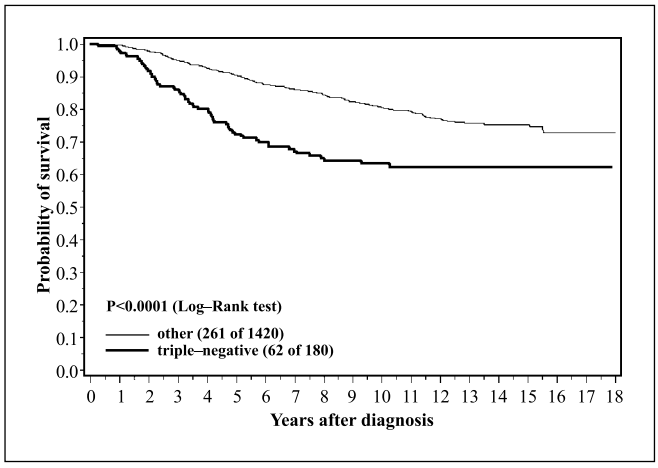

Fig. 2. Rates of breast-specific survival in triple-negative and other breast cancers.

Table 4. HRs in the triple-negative group compared with the other group

End point	Unadjusted		Adjusted	
	HR (95% CI)	*P*	HR (95% CI)	*P*
Risk of local recurrence				
Entire follow-up period	1.1 (0.7-1.7)	0.60	0.8 (0.5-1.3)	0.38
0 to 5 y follow-up	1.5 (1.0-2.5)	0.08	1.0 (0.6-1.7)	0.98
5 y to end of follow-up	0.4 (0.1-1.3)	0.1	0.3 (0.1-1.1)	0.08
Risk of distant recurrence				
Entire follow-up period	1.9 (1.4-2.5)	<0.0001	1.2 (0.9-1.5)	0.35
0 to 5 y follow-up	2.6 (2.0-3.5)	<0.0001	1.5 (1.1-2.0)	0.02
5 y to end of follow-up	0.5 (0.2-1.1)	0.09	0.3 (0.1-0.8)	0.02
Risk of death				
Entire follow-up period	1.7 (1.3-2.2)	<0.0001	1.3 (1.0-1.6)	0.09
0 to 5 y follow-up	2.6 (1.9-3.6)	<0.0001	1.7 (1.3-2.4)	0.0007
5 y to end of follow-up	1.0 (0.6-1.5)	<0.8	0.7 (0.5-1.2)	0.22
Death due to breast cancer				
Entire follow-up period	2.1 (1.6-2.8)	<0.0001	1.3 (1.0-1.7)	0.08
0 to 5 y follow-up	3.2 (2.3-4.5)	<0.0001	1.8 (1.3-2.6)	0.0005
5 y to end of follow-up	1.0 (0.6-1.7)	1.0	0.7 (0.4-1.1)	0.1

NOTE: A Cox model, including age at diagnosis, grade (1, 2, 3), nodal status (negative, positive), tumor size (T_1, T_2, T_3), chemotherapy (yes, no), and tamoxifen therapy (yes, no), was used to estimate the adjusted HRs. *P* values were determined by the log-rank test.

experienced a distant recurrence, 56 have died. The median survival time from recurrence to death was 9 months. This interval was significantly shorter than that for women with other types of tumors (median survival time, 20 months; $P = 0.02$ for difference). The HR for death following distant recurrence for women with triple-negative cancers was 1.6 compared with women with other tumor types (95% CI, 1.2-2.1; $P = 0.003$).

Discussion

This study addresses the short-term and long-term outcomes of patients with triple-negative breast cancers within the context of other known prognostic factors. Patients with triple-negative breast cancer have an increased likelihood of distant recurrence and of death compared with women with other types of cancer, and the difference persists after controlling for established prognostic factors. However, the patterns of recurrence in the two subgroups are qualitatively different. Patients with triple-negative breast cancers experienced high rates of recurrence only in the period from 1 to 4 years after diagnosis. The risk declined rapidly thereafter and no recurrences occurred after 8 years of follow-up. In the other group, the risk of recurrence and death was steady and continued for 17 years after diagnosis. Thus, despite having a high risk of early recurrence, it seems that women with triple-negative breast cancer who are disease-free for 8 years are unlikely to die of breast cancer. The salient characteristics of the triple-negative subgroup of patients are summarized in Table 5.

Patients in the triple-negative category had relatively large tumors (two thirds were >2 cm) and a high rate of node positivity (54%). Traditionally, as tumor size increases, the rate of node positivity increases, and this relationship was not seen among the triple-negative group. Foulkes et al. (11, 12) reported that this phenomenon is also present in BRCA-associated cancers and suggested that the mode of spread of these cancers is hematogenous.

The triple-negative breast cancers in this study were more likely to be detected through clinical exam than through imaging, such as mammography and ultrasound. This may reflect a more rapid growth rate or may be due to intrinsic differences in detectability. Collett et al. (13) evaluated interval cancers diagnosed in a screening program between 1996 and 2001 and found that triple-negative cancers were more likely than other breast cancers to present in the interval between regular mammograms. This may relate to differences in the density of the breast tissue in women with the triple-negative phenotype, rendering them more difficult to identify on traditional mammography. Another explanation is that triple-negative tumors may grow rapidly in relation to the screening interval.

We used triple-negative breast cancers as a surrogate to represent the basal-like category of breast cancers because the immunostaining data were available. Currently, there is no consensus about how best to define a basal-like breast cancer.

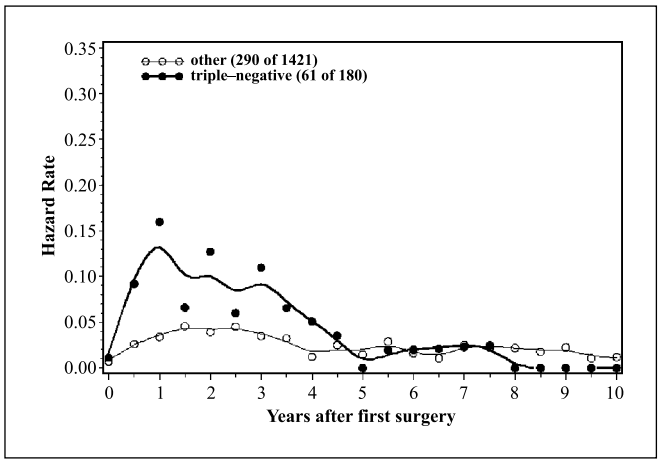

Fig. 3. Rates of distant recurrences following surgery in triple-negative and other breast cancers.

Table 5. Characteristic features of the triple-negative phenotype

Often present as interval cancers
Weak relationship between tumor size and node status
Rapid rise in risk of recurrence following diagnosis
Peak risk of recurrence at 1-3 y
Distal recurrence rarely preceded by local recurrence
Local recurrence not predictive of distal recurrence
Increased mortality rate first 5 y
Majority of deaths occur in first 5 y
Rapid progression from distant recurrence to death

Different immunohistochemical markers have been used by different investigators to identify basal-like differentiation, but there is no universally agreed-upon criteria or set of markers that is now in use to define this subtype of breast cancer. Nielsen et al. (14) developed a panel for identifying basal-like breast cancers based on a comparison of immunohistochemical profiles. Using their definition, basal-like carcinomas are negative for ER and HER2, in addition to being positive for either cytokeratin (CK) 5/6 or epidermal growth factor receptor (EGFR). Others have suggested that expression of high molecular weight CKs alone (including CK5, CK14, and CK17) could be used to identify these carcinomas (15, 16). It has been suggested that, until these criteria are developed, staining for ER, PR, and HER2 would correctly classify the majority of basal-like breast cancers.

We did not evaluate the main effects of treatment on survival in this cohort, but all HRs were adjusted for treatment received. None of the patients had been treated with trastuzamab. About one half of the patients had received chemotherapy and one half had received tamoxifen. Approximately one third of the patients with triple-negative disease had received tamoxifen; for most of these, the ER status was not known at the time of diagnosis (or treatment) but was obtained recently by the study team in the reference pathology laboratory. For a few patients, the original report was discordant with that of the reference laboratory (which used current technology).

Despite differences in taxonomy, there is a consistent trend across all studies confirming the relatively poor prognosis of the triple-negative or basal-like breast cancer subgroup (14–19). The majority of triple-negative breast cancer tumors overexpress the EGFR (12, 15) and may be candidates for anti-EGFR and/or anti–vascular endothelial growth factor therapies (20). Tumors in women with BRCA1 germ-line mutations have similarities to basal-like breast cancers (21, 22). *In vitro* chemosensitivity studies have found that human cells lacking BRCA1 may be sensitive to cisplatin and to other drugs that cause double-strand breaks in DNA (23). Thus, agents such as cisplatin or carboplatin may prove to be effective treatments for the basal-like group (clinical trials are now under way).

In conclusion, by using three standard pathologic markers, we are able to show that the triple-negative category of breast cancers exhibits a distinct pattern of recurrence. This pattern is characterized by a rapidly rising rate in the first 2 years following diagnosis, a peak at 2 to 3 years followed by a decline in recurrence risk over the next 5 years, and a very low risk of recurrence thereafter. Unlike women with other types of breast cancers, the great majority of women with triple-negative cancers who had no evidence of progression after 8 years did not recur thereafter. It is hoped that others will extend these results and conduct similar studies to determine to what extent distant-free survival at 8 years is predictive of "cure." The lack of association between tumor size and lymph node positivity, the high rates of distal recurrence, and the relative rarity of local recurrence all suggest that these patients have a tendency to develop visceral metastases early in the course of their disease. Novel therapeutic options are needed to target this aggressive type of breast cancer.

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