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Basal cell–like (triple-negative) breast cancer, a predictor of distant metastasis in African American women

Chukwuemeka U. Ihemelandu, M.D.[a,*], Tammey J. Naab, M.D.[b], Haile M. Mezghebe, M.D.[a], Kepher H. Makambi, Ph.D.[c], Suryanarayana M. Siram, M.D.[a], LaSalle D. Leffall Jr, M.D.[a], Robert L. DeWitty Jr, M.D.[a], Wayne A. Frederick, M.D.[a,c]

[a]*Howard University College of Medicine, Department of Surgery, 2041 Georgia Ave., Washington, DC 20060, USA*
[b]*Howard University College of Medicine, Department of Pathology, 2041 Georgia Ave., Washington, DC 20060, USA*
[c]*Howard University Cancer Center, 2041 Georgia Ave., Washington, DC 20060, USA*

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Abstract

Background: The aim of this study was to evaluate the prognostic significance of the basal cell–like molecular breast cancer subtype with respect to locoregional recurrence and distant metastasis in African American women treated for breast cancer.

Methods: A retrospective analysis was performed of the tumor registry database for all African American women diagnosed and treated for breast cancer from 1998 to 2005 who had assessable data for all 3 markers: estrogen, progesterone, and Her-2/neu.

Results: A total of 372 patients were included in our study sample. Of these, 22 (6.1%) had locoregional recurrence, 35 (9.8%) had distant metastasis, and 301 (84.1%) had no evidence of breast tumor recurrence. The median follow-up time was 36 months. Compared with the other molecular subtypes the basal cell–like subtype showed a statistically significant association to distant metastasis: 15 (42.9%) vs 13 (37.1%), 4 (11.4%), and 3 (8.6%) ($P < .001$), respectively, for luminal A, Her-2/neu, and luminal B subtypes. The basal cell–like subtype was an independent predictor of distant metastasis (odds ratio, 5.8; 95% confidence interval, 1.5–22.0, $P = .009$). The molecular subtypes showed no statistically significant difference with respect to locoregional treatment administered and tumor stage at time of diagnosis.

Conclusions: The basal cell–like molecular breast cancer subtype is an independent predictor of distant metastasis in African American women.

Keywords: Molecular breast cancer subtypes; Distant metastasis; African American women

The advent of DNA microarray analysis for gene expression profiling has led to the identification of 4 subtypes of breast tumors (luminal A, luminal B, basal cell–like, and Her-2/neu) characterized by distinct clinical and pathologic features and response to chemotherapy [1–4]. The basal cell–like tumors have been associated with aggressive clinical and pathologic features and a poor prognosis [5]; these tumors also have been shown in neoadjuvant studies to be responsive to chemotherapy. Despite this observed response to chemotherapy, these tumors still have a poor prognosis [6]. Locoregional recurrence and distant metastasis are 2 factors that significantly impact prognosis for breast cancer after surgical treatment (breast-conserving surgery plus radiation therapy or mastectomy); the use of adjuvant systemic therapy has been shown to be an important factor associated with a reduced risk of recurrence. A number of pathologic factors have been evaluated for their ability to predict an increased risk of recurrence in the surgically treated breast. Risk factors for locoregional recurrence reported in the literature include the following: young age [7,8], large tumors [9], positive tumor margins [7], and high nuclear grade [10]. Reported risk factors for distant metastasis include the following: mitotic index, nodal status, and tumor size [11]. Our goal in this study was to relate the molecular breast cancer subtypes to the risk of locoregional recurrence and distant metastasis in African American women.

Materials and Methods

A retrospective analysis was performed of the Howard University Cancer Center tumor registry database for all

* Corresponding author. Tel.: +1-202-865-6100; fax: +1-202-667-1686.
E-mail address: emeka_ihemelandu@hotmail.com

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African American women diagnosed and treated for breast cancer from 1998 to 2005 who had assessable immunohistochemical (IHC) data for estrogen receptor (ER), progesterone receptor (PR), and Her-2/neu receptor status (n = 372). Classification of the breast cancer cases into molecular subtypes was performed based on the IHC-based definitions [5,12]. IHC markers (ER, PR, and HER-2/neu) performed on formalin-fixed, paraffin-embedded samples were abstracted from the pathology registry. Based on IHC results these patients were classified into the various molecular subtypes: (a) luminal A: (ER + and/or PR+, HER2-), (b) luminal B: (ER+ and/or PR+, HER2+), (c) basal cell–like: (ER-, PR-, HER2-), (d) Her-2/neu: (ER-, PR-, and HER2+). The main outcome measure of interest was risk factors for locoregional and distant metastasis after surgical therapy as a function of the various molecular breast cancer subtypes and clinicopathologic variables of prognostic significance. Locoregional recurrence was defined as any clinical and/or histologic documented evidence of recurrent tumor developing in the ipsilateral (treated) breast or regional nodes. Distant metastasis was defined as clinical evidence of distant disease based on clinical and/or radiographic findings. Clinicopathologic variables included in our analysis were age at diagnosis, tumor size, nodal status, tumor stage, tumor grade, S-phase fraction, menopausal status, modality of locoregional surgical therapy (breast-conserving surgery and adjuvant radiation therapy, breast-conserving surgery alone, or mastectomy), and p53 and bcl-2 status. Breast cancer stage at diagnosis was defined by the American Joint Committee on Cancer Staging Manual 6th edition [13] and data obtained from the medical records. Histologic grade of the tumors based on the Nottingham combined histologic grade was used and the tumors were identified as grades I, II, and III, respectively. Institutional review board approval was obtained for this study.

Statistical analysis

The frequency distributions among the groups were assessed using descriptive statistics. Univariate analysis using chi-square statistics was used to compare categoric variables between groups. The analysis of variance F test was used to evaluate group means. Odds ratios using logistic regression were calculated to estimate the degree to which patient demographics and clinicopathologic tumor characteristics determined locoregional recurrence or distant metastasis. Statistical analyses were performed using SPSS 15 (SPSS Inc., Chicago, IL).

Results

Patient and treatment characteristics

On the basis of assessable IHC staining data for ER, PR, and Her-2/neu receptor status a total of 372 patients were included in our study sample, and using the IHC (molecular)-based classification, 206 (55.4%) patients were classified as luminal A, 79 (21.2%) were classified as basal cell–like (triple negative), 44 (11.8%) as luminal B, and 43 (11.6%) as Her-2/neu. The distribution of the molecular subtypes within the individual tumor stages showed no significant difference ($P = .26$): 75.3% of the basal cell–like (triple negative) tumors were staged as stage I/II compared with 84.1%, 87.5%, and 78.0%, respectively, for the luminal A, luminal B, and Her-2/neu subtypes. Of the basal cell–like (triple-negative) tumors, 24.7% were staged as stage III/IV compared with 15.9%, 12.5%, and 22.0%, respectively, for the luminal A, luminal B, and Her-2/neu subtypes. Patients with the basal cell–like (triple-negative) phenotype were significantly more likely to have a positive nodal status ($P = .02$), 45.8% vs 27.5%, 42.5%, and 40.0%, respectively, for luminal A, luminal B, and Her-2/neu subtypes. Of the 372 patients, 178 (47.8%) underwent mastectomy, 131 (35.2%) underwent breast-conserving surgery followed by radiotherapy, 48 (12.9%) underwent breast-conserving surgery alone, and 15 (4.0%) were patients with inoperable tumors and those who declined surgery. The mean age of the patients treated with breast-conserving surgery alone was 56.2 years, compared with 53.9 years for patients treated with breast-conserving surgery and radiation, and 58.4 years for those treated with mastectomy ($P = .03$). The mean tumor size for the patients treated with breast-conserving surgery alone was 2.5 cm, compared with 2.4 cm for patients treated with breast-conserving surgery and adjuvant radiation therapy, and 3.7 cm for those treated with mastectomy ($P < .000$). Based on molecular breast cancer subtypes our study sample showed no statistically significant difference in the type of local regional surgical therapy administered ($P = .64$) or surgical margin ($P = .45$). Patients classified as basal cell–like (triple negative) were significantly more likely to have received adjuvant chemotherapy (55.8% vs 27.5%, 50.0%, and 48.8% [$P < .001$], respectively) for luminal A, luminal B, and Her-2/neu subtypes. Twenty-two (6.1%) of the patients were found to have locoregional recurrence, 35 (9.8%) had distant metastasis, and 301 (84.1%) had no evidence of breast tumor recurrence at last follow-up evaluation. Eleven (50.0%) of the patients with locoregional recurrence, 18 (51.4%) of the patients with distant metastasis, and 111 (36.9%) of those with no evidence of recurrent disease were treated with adjuvant chemotherapy ($P = .13$). The median follow-up time was 36 months. Table 1 shows the demographic and treatment characteristics of our study sample with regards to locoregional recurrence, distant metastasis, and no evidence of recurrent disease. Patients with distant metastasis were significantly younger, had tumors that were significantly larger, and were significantly associated with the premenopausal status.

Molecular and histopathologic characteristics

Tumor molecular and histopathologic characteristics are presented in Table 2. We observed that a higher proportion of the patients with documented clinical and/or radiographic evidence of distant metastasis had tumors associated with the basal cell–like (triple-negative) phenotype, a high tumor stage (stage III/IV), a high proliferative index (S-phase fraction > 6%), and a positive axillary nodal status. No significant differences in tumor grade were found with regard to recurrence. Pathologic margin status did not differ significantly among the 3 groups. Eighty-eight percent of patients with no recurrence had known negative margins, compared with 85% of patients with locoregional recurrence and 80.6% of patients with distant metastasis. The incidence of p53 mutation and Bcl-2 overexpression was similar among the 3 groups.