Original Article

Correlation between Biological Classification and Stromal Reaction in Breast Cancer

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Abstract

Background: Breast cancer is the most common cancer and a major cause of death from cancer in women. Understanding the factors, which can predict directly and indirectly the final fate of patients, can be useful in clinical decision-making and treatment choices.

Materials and Methods: In a retrospective descriptive-analytic study, 108 pathological samples of patients with primary breast cancer collected during 2011-2017 from the department of pathology in Imam Hossein Hospital (Tehran Iran). Classified regarding the association of stromal reactions in tumor tissue including necrosis rate, lymphocyte infiltrating rate, and tumor desmoplasia with different types of breast tumors including four groups of Basal like, *HER2/neu*, Luminal B, and Luminal A based on biological biomarkers.

Results: Mean age of the patients was 50.84±13.25 years. No significant relationship was found between age and type of groups. Majority of patients (60%) were in the pathological grade 2. A significant relationship was observed between three groups of Luminal B, and Basal-like with Grade 2 ($p<0.05$). Most patients suffered from intermediate desmoplasia which was significant only between three groups of Luminal B, *HER2/neu* and Basal-like ($p<0.05$). In terms of tumor necrosis, the majority of patients in the *HER2/neu* and Basal-like groups indicated non-extensive necrosis, which was significant ($p>0.05$). In both groups of Luminal A and Luminal B, most patients had no necrosis while the relationship between necrosis and pathological type of tumor was significant only in the Luminal B group ($p>0.05$). No significant relationship was found between the number of lymphocytes and the type of tumor.

Conclusion: This study indicated the relationship between pathological types of breast cancers based on biomarkers with pathological grade, necrosis ratio and tumor desmoplasia. Determination of the pathological type of tumor based on the status of biological markers (*HER-2/neu PR, ER, Ki67*) in patients with breast cancer is recommended for making decision about therapeutic plan.

Keywords: Stromal factors, Biologic classification, Breast cancer

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Introduction

Cancer as a major health problem of the century[1] is the second cause of death after cardiovascular diseases[2]. Breast cancer is the most common invasive cancer among women that afflicting one in eight[3] and the most significant cause of cancer deaths worldwide[4-6]. Despite the numerous advances in early diagnosis and treatment of this disease, breast cancer is still the main cause of death among women[7,8].

Breast cancer has been the most common malignancy among Iranian women in recent years[9]. Age of breast cancer in Iranian population is ten years younger than other countries[10,11]. Approximately, 70% of Iranian women are at advanced stages of the disease, which cannot be treated by medical teams at this stage[12]. In addition, this disease clinically passes a long latent stage, which is about eight to ten years to transform a cancer cell into a palpable tumor. Thus, the patient can be saved from death by identifying and recognizing these tumors in the early stages[13]. As indicated, the invasive breast carcinomas, like other cancers, have genetic changes causing molecular and biological fragmentation characterized by microarray methods. Researchers hope to find such new divisions clarify the tumor biology, predict tumor status and better therapeutic strategies. Each of these molecular variations caused the immunohistochemical properties, which can be traced and categorized by conventional pathological techniques such as IHC, which are regarded as a guide to the prognosis of cancer and its invasive feature, metastasis rates, and measure the effectiveness of treatment and the appropriate therapeutic method to recognize the cancer recurrence. Different types of tumors Immunohistochemical markers for breast cancer in terms of application significance are as follows: Estrogen receptor *(ER*), Progesterone receptor (*PR*), Human Epidermal growth factor (*HER2)*, *Ki67*. Based on the expression of the genetic profile, four subtypes were defined for breast cancer including luminal A, luminal B, *HER2*-overexpressing, and basal-like.

Tumor markers for breast cancer include estrogen receptor (*ER*) and progesterone receptor (*PR*) in order of application significance which are used for investigating the necessity of hormone therapy. Human epidermal growth factor 2 (*HER2*) is a 170 kDa glycogen protein, which is diagnosed by various methods such as IHC, FISH, Southern blot, and EIA, where the encoder is a tyrosine kinase receptor in the cell membrane. Based on these receptors, breast tumors are classified into luminal (*ER +*), *HER2*-overexpressing (*HER2*) (*ER-/HER2+*) and triple negative (TN) (*ER-, PR- and HER2-*). The luminal tumors are classified into two groups of luminal A (*HER2* and *Ki67* less than 14%) and luminal B (*HER2* - / + and *Ki67* more than 14%) according to *HER2* and *Ki67* in terms of positivity. TN and H2E tumors are invasive having a 5-year survival rate lower than the luminal type[14,15].

Since the practical predictive factors are not sufficiently categorized in breast cancer, further information is required for determining the prognosis and more specific treatments. The stroma surrounding cancer cells affects the tumor progression, tumor grade, and the tumor behavior in various organs. Various studies described the role of tumor stroma components in invasive breast cancer and the presence of tumor-derived atrophic stromal cells, fibroblasts, especially in fibrotic areas, is associated with metastatic tumor recurrence and death due to tumor. For this reason, this study attempted to examine the relationship between stroma components with tumor grade and tumor types. All of the above-mentioned factors are related to tumor prognosis in invasive breast cancers and new prognostic factors were proposed. Such factors are not only effective in the overall prognosis of the patient but also in the diagnostic and background criteria for new therapies. Based on the previous studies, stromal reactions including lymphocytic infiltrating, desmoplasic reaction, its type, as well as the presence and absence of necrosis. In another study by Gujam et al. (2014) on 361 patients with ductal carcinoma of the breast, it was found that high rates of tumor stroma were associated with a higher incidence and lower survival rate in tumor-suppressed tumors[16]. In addition, Matsumoto (2015) on 27 cases found that the level of Tumor Infiltrating Lymphocytes (TIL) in basal-like and her 2 patients is clearly higher than that of the luminal group resulting in better response to neoadjuvant therapy and an increase in pathological complete response (PCR)[17] .Despite extensive research on the molecular markers of breast cancer, the observed differences in the results and the effects of demographic factors on the status of these biomarkers highlighted the importance of further studies in different areas[13]. In recent years, few studies have been reported regarding the status of biomarkers in breast cancer and their relationship with *PR, ER, p53, HER2/neu* and other prognostic factors in breast cancer, most of which were limited to the relationship between prognostic biomarkers and clinical and

pathological characteristics of breast cancer[18]. The present study was conducted on the patients with breast cancer to determine the relationship between stromal factors and tumor biomarker classification in breast cancer and recognize the biomarkers as prognostic factors in breast cancer.

Methods

This study is a cross-sectional type in which 108 breast cancer pathology slides were studied for diagnosing breast cancer with grading pathology, stromal components, and immunophenotype components, during 2011-2017 from the department of pathology in Imam Hossein Hospital (Tehran Iran). The research findings were analyzed in terms of the relationship between stromal components and stromal component reactions including the presence of lymphocytic infiltrating, the presence or absence of a fibrous region in the tumor and its type, and the presence of necrosis and its rate. The other histologic findings such as tumor necrosis grafts, histological grade, tumor type, and invasive tumors were evaluated for histochemical markers such as *ER, PR, HER2* and *Ki67*.

Tumor infiltrating lymphocytes in breast cancer: Specific genes in triple tumors control a kind of host immune response to tumor tissue and its increase is unexpectedly associated with a worse prognosis in breast tumors. In this reaction, the lymphocyte population is heterogeneous. Heterogeneous means the mixture of lymphocytes with CD3 or CD4 markers. Several lymphocyte models can be infiltrated in the tumor tissue: Intra tumor infiltrating lymphocyte (TIL): It is observed inside the tumor nests and tumor cells and is not significant in terms of response to treatment and prognosis; Stromal TIL: It is observed around the tumor cell nests, which is important in determining the prognosis of response to treatment; The presence of lymphocytic follicles is usually found around the tumor tissue. Although it reflects the host's immune response, it is not valuable in determining the prognosis.

Significant criteria for TIL evaluation including: TIL is expressed as a percentage; TIL evaluation is important on the margins of the invasive tumor and within the stroma surrounding the tumor; Lymphocytes outside the margin of the tumor are not measured around the DCIS and the normal lobules; Lymphocytes in areas of artifact, necrosis, healenization, and position of previous biopsy are not included in the evaluation; All single-cell inflammatory cells (lymphocytes and plasma cells) are evaluated and neutrophils are excluded from this category; Examination of complete samples is preferable to needle samples. In addition, evaluating the samples is not conducted after the Neoadjuvant therapy; Average lymphocytes are reported by the pathologist; The percentages are reported as complete numbers, e.g. 15% instead of 13.5%.

In this study, the evaluation of TIL was expressed as a semi-quantitative parameter. For example, when TIL is 80%, it means that 80% of stromal regions indicate strong infiltrating of mononuclear cells[19-21].

The evaluation criteria of stromal fibrosis around the tumor: The desmoplacial or fibrotic reaction around the tumor is divided into three groups of mature, immature, and intermediate.

Mature: It happens when collagen fibers around the tumor are long and thin in several layers.

Intermediate: Thick fibers of collagen with bright Eosinophilic hyalinization similar to a colloid tissue are around the tumor.

Immature: Collagen fibers similar to Colloidal are randomly surrounded by a loose stroma[22].

In addition, Tumor necrosis was investigated in the presence or absence of necrosis and its rate was extensive (over 50% of tissue) and non-extensive (less than 50% of tissue). During this study, the experimental results of the *ER, PR, HER-2/neu* and *Ki67* markers in the patient's file were used. The variables were analyzed by SPSS software version 22, T-Test, and Chi-square (Determining the exact method of data analysis is possible after obtaining data and data features). Preserving the personal secrets and patient characteristics were considered during the study.

Based on a study the minimum required sample size was calculated to be 110 by using a sample size formula for comparative studies and considering 80% test power and 95% confidence[16].

Results

In this study, there were 108 patients with a mean and standard deviation of 50.84 ± 13.55 years (range of

Table 1: Frequency of the studied lams based on necrosis, pathological grade, and desmoplasia.

		Frequency	Percentage
Necrosis	Nonext	59	54.6
	Extent	6	5.6
	No	43	39.8
pathological grade	1	25	23.1
	2	64	59.3
	3	19	17.6
Desmoplasia	Immature	28	25.9
	Intermediate	64	59.3
	Mature	16	14.8

Table 2: Frequency of types of tumors with necrosis, grade, Desmoplasia.

Type		Necrosis			Grade			Desmoplasia			Total
		non.ext	Extent	No	1	2	3	immature	intermediate	mature	
	Basal	25	4	6	3	19	13	10	21	4	35
	HER2	13	1	8	3	17	2	5	14	3	22
	LuminalA	5	0	10	6	8	1	6	5	4	15
	LuminalB	16	1	19	13	20	3	7	24	5	36
Total		59	6	43	25	64	19	28	10	21	4

Table 3: Relationship between biological type of tumor and stromal factors.

LuminalA	LuminalB	HER2	Basal	
0.074	0.002	<0.001	0.004	**Pathological grade**
0.819	<0.001	0.009	0.002	**Desmoplasia**
0.692	0.003	0.886	0.078	**Lymphocytes rate**
0.197	<0.001	0.007	<0.001	**Tumor necrosis**

25-89 years). Luminal B group with 36 subjects (33.3%) had the maximum frequency followed by the basal like group with 35 subjects (32.4%), *HER-2/neu* with 22 subjects (22.4%) and luminal A group with 15 subjects (15.9%). In the present study, there was no significant relationship between age and type of groups ($p>0.05$). In terms of pathological grade among the three grades of disease, the majority of patients (60%) were in grade 2. Thereafter, there were grade 1 (23%), grade 3 (17.6%) and only a significant difference was observed between the three groups of luminal B, *HER2/neu*, Basal like and grade 2 ($p<0.05$).

The relationship between age and disease grade was not significant (p>0.05). In terms of desmoplasia, most patients in all four pathological groups had intermediate desmoplasia which was significant only between the three groups of luminal B, *HER2/neu*, Basal-like and intermediate desmoplasia (p<0.05). In terms of tumor necrosis rate, the majority of patients in the *HER2/neu* and Basal-like groups indicated non-extensive necrosis, which was significant (p>0.05). In both groups of luminal, A and luminal B, most patients did not have necrosis while the association between necrosis and pathological type of tumor was significant only in the luminal B group (p>0.05). In terms of the number of lymphocytes, the *HER2/neu* group with a mean of 35% lymphocyte in the tumor was ranked first followed by the luminal A group with a mean of 30% lymphocyte, the luminal B group with 28% and the basal like group with 24.9% lymphocyte. No significant relationship was obtained between the number of lymphocytes and the type of tumor. In this study, the patients were studied in terms of pathological grade that highest pathological grade among these patients was grade 2 and 59.3% (64 patients).

In this study, the lymphocyte rate of patients was quantitatively analyzed while 29.29±25.18 mean and standard deviation of lymphocyte rate among the subjects. The highest and lowest lymphocyte rates were 90 and 2, respectively. Based on the findings, the relationship between tumors was evaluated in this study in terms of tumor necrosis rate. In this study, Chi-square test was used to analyze the research data and the relationship between each variable and the type of tumors was investigated. In Table 3, the type of tumor represents p-value for each variable showed.

Based on the findings of this study, the relationship between age and pathological grade was evaluated and the difference in mean was reported between each group. In addition, no significant was reported the relationship between the within-groups and between-groups.

Discussion

The present study aimed at classifying the breast tumors in terms of *ER*, *PR*, *KI67* and *HER2/neu* markers expression (molecular and biological classification) and studying its relationship with stromal reactions as prognostic factors in invasive breast carcinoma.

In this study, the related data for 110 patients were extracted and two patients were excluded due to incomplete information. In the present study, the majority of patients (33%) were in the luminal B group and then in the basal group. Furthermore, the luminal A group had the lowest prevalence (13.8%) among the four groups.

In addition, regarding age and disease grade, no significant relationship was observed between age and three grades of disease and the patients with a higher or lower age indicated no higher grade (p>0.05). In terms of pathological grade among the three grades of disease, the majority of patients (60%) had grade 2. Finally, 23% and 17.6% had grade 1 and 3. A significant relationship was observed between the three groups of luminal B, *HER2/neu*, basal-like and grade 2 (p<0.05). In other words, most patients with these biomarkers who were in these three groups indicated grade 2 while this relationship was insignificant in the luminal A group (p>0.05).

In terms of desmoplasia in all four pathological groups, most patients had intermediate desmoplasia. A significant relationship was found between the three groups of luminal B, *HER2/neu*, basal-like and intermediate desmoplasia (p<0.05). The patients having these biomarkers in these three groups indicated intermediate desmoplasia. In the luminal A group, unlike most other groups, most patients indicated immature desmoplasia while this relationship was insignificant in the luminal A group (p>0.05).

In terms of tumor necrosis rate, the *HER2/neu* and basal-like groups mostly indicated the non-extensive necrosis patients, which was significant. In other words, the patients indicated non-extensive necrosis in the *HER2/neu* and basal-like groups (p>0.05).

In both groups of luminal A and B, most patients had no necrosis. However, the relationship between necrosis and pathological type of tumor was significant in the luminal B group (p>0.05) while this relationship was not significant in the luminal A group. In the present study, the *HER2/neu* group was in the first place with an average of 35% lymphocyte in the tumor.

Luminal A group with 30% lymphocyte, luminal B group with 28%, and basal-like group with 24.9% lymphocytes were in the next ranks. However, no significant relationship was reported between the number of lymphocytes and the type of tumor ($p>0.05$).

In another study by Kadivar et al. in Rasoul Akram and Atiyeh Hospitals in Tehran, 60 patients with breast tumors under 40 years of age and 57 patients with breast tumors over 60 years of age were included in the study. No significant difference was found between the size of the tumor, lymphatic involvement, histological grade, tumor stage, *PR*, *ER*, and *HER2/neu* in the group under 40 years of age and 60 years old. Results were consistent with the present study[23].

In another study by Keyhanian et al. 220 women with breast cancer were studied. Research findings indicated that 77.3% of patients were 55 years of age and 35% of patients were postmenopausal. Excessive expression of *HER2/neu* was found in 38.2% and P53 gene mutation was observed in 52.3% of patients. ER in 69.1% and PR in 63.6% of cases were positive. In the recent study, there was a significant relationship between *HER2/neu* biomarker with tumor size, between P53 biomarker status with tumor pathology, *ER* biomarker with stage of disease and tumor pathological grade, and *PR* biomarker with stage of disease and tumor pathological grade. In addition, no significant relationship was reported between the status of biomarkers and prognostic factors in this study ($p>0.05$)[24]. Since two biomarkers PR and ER are common in both groups of luminal A and B, other biomarkers including *Ki67* were used in this study for differentiation of these two biomarkers. Results of pathological grade were different from the above-mentioned study, due to use of other biomarkers in the present study and group classification.

In addition, Behrouz Najafi et al. (2006) considered the relationship between *HER-2* and other clinical diagnostic criteria in breast cancer patients and the relationship between HER2 membrane protein and other clinicopathological parameters such as tumor grade, presence of absence of lympho-vascular invasion and its association with the status of steroid receptors and *P53* in patients with breast cancer. This descriptive-analytical study was performed on 465 patients with breast cancer referring to two cancer centers of Guilan province (North of Iran) during 2000-2005. An immunohistochemical semi-quantitative method was used for *HER2* receptor P53 receptor protein and steroid receptors. As a result, 32% of patients had *HER2*-positive protein. The presence of *HER2* protein was significantly associated with *P53* ($p=0.000$). In addition, the presence of HER2 protein was related to the lack of steroid receptors with high grade pathological tumors (grade 3). Further, the absence of *HER2* protein was associated with the presence of steroidal receptors with a lower grade of tumor grade (grade 1). Furthermore, no significant relationship was observed between *HER2*, Lympho-vascular invasion, tumor size, and recurrence. Therefore, the presence of *HER2* protein in patients with breast cancer was significantly associated with tumor differentiation grade and the presence of *HER2* protein was related to other prognostic factors such as the lack of steroid receptor or presence of P53[25]. In another study by Matsumoto, studied on 27 cases, it was found that the level of tumor infiltrating lymphocytes (TIL) in basal-like and *HER2* patients was clearly higher than luminal group resulting in better response to neoadjuvant therapy and an increase in pathological complete response (PCR). The present study indicated a higher rate of TIL in *HER2* group[17].

Histopathological studies on 114 breast cancer patients indicated a strong correlation between immature desmoplastic reaction and axillary lymph node involvement. This study emphasized the role of desmoplastic reaction[23]. A comprehensive study in 2017 on 3771 patients with breast cancer indicated that the higher levels of TIL in the inner tissue of tumor in the basal-like and *HER2* patients were associated with better response to neoadjuvant therapy and immunotherapy. The effect of this stromal reaction on luminal types is not well-defined and requires further investigation[26].

Conclusion

Based on the research findings indicating the relationship between pathological types of breast tumors based on pathologic grade biomarkers, necrosis rate, tumor desmoplacial rate, TIL and determining the pathological type of tumor based on the status of

biological markers (HER2/neu PR, ER, Ki67) is recommended to decide on the treatment plan on patients with breast cancer.

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