EDITORIAL

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Prognosis and Predictive Factors Related to Breast Cancer

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Dear Readers,

Breast cancer is the most common cancer type among women. The mortality rate has been significantly reduced in recent years because of its early diagnosis and the advanced methods of treatment; nevertheless, it is still the second leading cause of death from cancer in women in European and Western countries, preceded only by lung cancer [1,2]. Currently, breast cancer is the fifth leading cause of death from cancer in the Iran which affecting 1 in every 8 women and has an annual incidence rate of 31 per 100,000 women. Regarding to advantage screening methods, the age of breast cancer incidence has reduced in the last few years from the fourth decade of life to the second and third decades [2,3]. Various predictive and prognostic factors affect tumor progression [4-7]. Predictive factors are distinguished from prognostic factors in that the latter can be measured and are associated with the nature of the disease, whereas the former determine the response to treatments [5]. Prognostic factors include the type of tumor, number of involved lymph nodes at the time of diagnosis, size, tumor grade, Ki67 status (cellular marker for proliferation), and the patient's age [7, 8]. In addition, some factors are both prognostic and predictive, including estrogen receptor (ER) and progesterone receptor (PR) status, p53 mutation status, and human epidermal growth factor receptor-2 (HER-2/neu) overexpression [9, 10].

Numerous studies have been conducted on these prognostic and predictive factors and their relationships with one another. The current article is the short review of the some Prognosis and Predictive Factors Related to Breast Cancer.

Estrogen Receptor (ER)

ER is a prognostic and predicting factor of breast cancer. ER-positive patients have a better prognosis than ER-negative ones and better respond to anti-estrogen agents, which have become an important principle in the treatment of breast cancer [8,9]. Numerous studies have revealed that ER-positive tumors show lower response to hormone therapy than HER-2-negative and ER-positive tumors; this seems to be due to the intracellular functional interference of HER-2-negative with hormone receptors which result in resistance of some ER-positive tumors to tamoxifen [10].

Progesterone Receptor (PR)

PR is another predictive and prognostic factor that plays a key role in the treatment of patients with breast cancer [12, 13]. Some evidences revealed carcinoma in situ had the highest and

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medullary carcinoma the lowest frequency of PR expression, which might suggest that in situ carcinomas progress very slowly under hormone suppression therapy and it might even be possible to prevent them from becoming invasive over time [14]. In another survey conducted by Bae et al, however, the highest frequency of PR expression pertained to mucinous carcinoma [15].

P53 Mutation

TP53 is the best-known mutated gene in human cancers. Facing with stimuli such as ionizing radiation, chemotherapy, acidosis, deprivation from growth factors, and hypoxia, normal p53 which is the product of TP53 gene halts cell cycle through mediating certain pathways and leads cells toward apoptosis [14]. Mutated TP53 produces a half-life-increased protein lacking native conformation and unable to perform its normal activities [10]. Overexpression of p53, occurred in approximately one-third of breast cancers, can be well assessed through immunohistocytology; it is also correlated with high nuclear differentiation, aneuploidy, increased cell cycle, HER-2-positive, and ER-negative. Various studies demonstrated that p53 mutation in breast cancer predicts a weaker prognosis in these patients [14]. Kim et al study showed that with the increase in p53 mutation, tumors become more invasive and p53 mutation should be considered a negative predictor [16], yet there are still ambiguities in the routine evaluation of this factor in the different types of breast cancer.

Human Epidermal Growth Factor Receptor-2 (HER-2/neu)

HER-2 receptors are in breast cells and normally control their growth, division, and repair. In approximately 25% of breast cancers, the HER-2 gene amplified and the result is HER-2/neu overexpression that causes uncontrolled growth and division of breast cells [8]. Almost all of the high-grade in situ breast carcinomas have a HER-2/neu overexpression, but lobular carcinomas are less likely to demonstrate overexpression of HER-2/neu [17]. In the Taghipour Zahir et al. study, the patients had greater HER-2/neu overexpression compared with other studies as well as the highest frequency of HER-2/neu overexpression related to invasive ductal carcinomas and the lowest frequency related to mucinous carcinomas, suggesting the higher invasiveness and greater aggressiveness of ductal carcinoma compared with other types [3].

The Type of Tumor

The pathological type of tumor is also a prognostic factor in breast cancer. That is to say, the best prognosis is seen in tubular and the worse in ductal carcinoma of not specified type (NST) [14]. Previous studies demonstrated that 95.5% of HER-2-positive tumors were ductal carcinoma and only 0.8% was lobular. The researchers indicated that due to a weak possibility of positivity of HER-2 in lobular carcinoma, routine assessment of HER-2 is not necessary, while the highest HER-2-positive was seen in ductal carcinoma of NST. Therefore, there is a specific and significant relationship between HER-2-positive and ductal invasive carcinoma of breast [9,10,17].

Grade Differentiation

Differentiation grading is the most potent and best-known prognostic factor in breast cancer [18]. Tissue differentiation is considered as the morphological marker of tumor invasiveness. This factor acts somewhat independent of lymph nodes and is routinely found in tumor specimens [10]. There are several methods for determining differentiation, and Bloom and Richardson grading system are the best-known and the most used [10, 14]. The grading is performed based on three properties including tubules formation, mitosis counts, and nuclear polymorphism [19].

Tumor Grade

Another prognostic factor is tumor grade; higher tumor grades are associated with an increased degree of relapse, greater extent of involvement, and higher chance of distant metastasis. In one study, grade 2 tumors were more prevalent than the other tumor grades (1 and 3), and lobular carcinomas had the highest frequency of grade 2 tumors, followed by invasive ductal carcinomas [3, 9,10]. The comparison of the different types of carcinomas showed that medullary carcinomas

had the highest frequency of grade 3 tumors, and although high grade in appearance, this carcinoma acts as a low-grade tumor that does not progress rapidly and involves regional lymph nodes to a lesser degree [12].

Ki67

Ki67 was considered as a prognostic factor; in literature review high index labeled Ki67 is considered an unfavorable factor that influences tumor progression and is associated with poorer prognosis [20]. Previous studies showed that medullary carcinomas had the highest rate of Ki67 expression, followed by mucinous carcinomas, although both these carcinomas showed a lower degree of local relapse and lymph node involvement compared with the other carcinomas [10, 20].

Age

Age is also another predictive factor in the breast cancer. A survey in Iran (2013) on 2750 patients suffering from breast cancer showed that the number of patients with HER-2-positive in peri-menopausal age (46-55 years) was higher than older patients [14]. Consequently, the majority of cancer in this age range included HER-2-positive, ER-negative, p53 mutation, indicating poorer prognosis of them in comparison with older patients [14]. This outcome was also obtained in USA in 2003, revealing that the mean age of HER-2-positive patients was lower than HER-2-negative ones, i.e. HER-2-positive has frequently seen in younger ages. This can be attributed to the fundamental pathologic differences in breast cancer of younger patients and may indicate higher risk of relapse [21].

A similar study was carried out by Rodrigues et al to evaluate breast cancer biomarkers and their correlation with the age of sufferers [19]. It was concluded that breast cancers emerging at higher ages grow slowly and have higher possibility of ER-positive and lower possibility of HER-2-positive and positive p53 mutation [19].

In conclusion, based along evidences, the breast cancer patients with ER-positive, PR-negative and HER-2-negative as important prognosis factors, have a better prognosis. In addition, best prognoses were seen in the younger patients with low grade and well-differentiated tumors. However, breast cancer is the multifactorial disease and influenced by various inherited and environmental factors which needs future studies to determine both the therapeutic and diagnostic aspects of these factors.

Keywords: Breast Cancer; Prognosis; Estrogen Receptor; Progesterone Receptor; Human Epidermal Growth Factor Receptor-2

References

1. Mirmalek SA, Azizi MA, Jangholi E, Yadollah-Damavandi S, Javidi MA, Parsa Y et al. Cytotoxic and apoptogenic effect of hypericin, the bioactive component of Hypericum perforatum on the MCF-7 human breast cancer cell line. Cancer Cell Int. 2015; 16: 3.
2. Mirmalek S, Jangholi E, Jafari M, Yadollah-Damavandi S, Javidi M, Parsa Y et al. Comparison of in Vitro Cytotoxicity and Apoptogenic Activity of Magnesium Chloride and Cisplatin as Conventional Chemotherapeutic Agents in the MCF-7 Cell Line. Asian Pac J Cancer Prev. 2016;17 Spec No.:131-4.
3. Shokouh TZ, Ezatollah A, Barand P. Interrelationships Between Ki67, HER2/neu, p53, ER, and PR Status and Their Associations With Tumor Grade and Lymph Node Involvement in Breast Carcinoma Subtypes: Retrospective-Observational Analytical Study. Medicine. 2015;94(32):e1359.
4. Taghavi A, Fazeli Z, Vahedi M, Baghestani A, Pourhoseingholi A, Barzegar F et al. Increased trend of breast cancer mortality in Iran. Asian Pacific journal of cancer prevention: Asian Pac J Cancer Prev. 2012;13(1):367-70.
5. Moutafoff C, Coutant C, Bezu C, Antoine M, Werkoff G, Benbara A et al. Prognostic and predictive factors in multifocal breast carcinoma. Gynecol Obstet Fertil. 2011;39(7-8):425-32. [In French]

6. Ariga R, Zarif A, Korasick J, Reddy V, Siziopikou K, Gattuso P. Correlation of her-2/neu gene amplification with other prognostic and predictive factors in female breast carcinoma. Breast J. 2005;11(4):278-80.
7. Mahmood H, Faheem M, Mahmood S, Sadiq M, Irfan J. Impact of age, tumor size, lymph node metastasis, stage, receptor status and menopausal status on overall survival of breast cancer patients in Pakistan. Asian Pac J Cancer Prev. 2015;16(3):1019-24.
8. Mirmalek SA, Elhamkani F, Tabatabaee SAS, Mahmoodzadeh H, Parsa Y, Yadollah-Damavandi S, et al. Introduction of HER-2 and a Short Review on Its Role in Prognosis and Treatment of Breast Cancer. GMJ. 2014;3(3):132-44.
9. Mirmalek SA, Kani FE, Mehrabi A, Chavoshi-Nejad M, Salimi-Tabatabaee SA, Parsa Y et al. Breast Carcinoma; Human Epidermal Growth Factor Receptor-2 (HER-2) and Grading Correlation. IJTMGH. 2015;3(3):95-7.
10. Parsa Y, Mirmalek SA, Elham Kani F, Aidun A, Salimi-Tabatabaee SA, Yadollah-Damavandi S, et al. A Review of the Clinical Implications of Breast Cancer Biology. Electronic Physician. 2016; 8(5):2416-24.
11. Hahrel R, Woodings T, Vivian AB. Prognostic Value of estrogen receptors in primary breast Cancer. Cancer. 1979;44(2):671-5.
12. Akbar M, Akbar K, Naveed D. Frequency and correlation of molecular subtypes of breast cancer with clinicopathological features. J Ayub Med Coll Abbottabad. 2014;26: 290-3.
13. Salmen J, Neugebauer J, Fasching PA, Haeberle L, Huober J, Wockel A et al. Pooled analysis of the prognostic relevance of progesterone receptor status in five German cohort studies. Breast Cancer Res Treat. 2014;148(1):143-51.
14. Mirmalek SA, Hajilou M, Salimi Tabatabaee SA, Parsa Y, Yadollah-Damavandi S, Parsa T. Prevalence of HER-2 and Hormone Receptors and P53 Mutations in the Pathologic Specimens of Breast Cancer Patients. Int J Breast Cancer. 2014; 2014: 564308.
15. Bae SY, Choi MY, Cho DH, Lee JE, Nam SJ, Yang JH. Mucinous carcinoma of the breast in comparison with invasive ductal carcinoma: clinicopathologic characteristics and prognosis. J Breast Cancer. 2011;14(4):308-13.
16. Kim HW, Lee HM, Hwang SH, Ahn SG, Lee KA, Jeong J. Patterns and Biologic Features of p53 Mutation Types in Korean Breast Cancer Patients. J Breast Cancer. 2014;17(1):1-7.
17. Li CI, Uribe DJ, Daling JR. Clinical characteristics of different histologic types of breast cancer. Br J Cancer. 2005;93(9):1046-52.
18. De Potter C. The neu-oncogene: more than a prognostic indicator? Human pathology. 1994;25(12):1264-8.
19. Rodrigues NA, Dillon D, Carter D, Parisot N, Haffty BG. Differences in the pathologic and molecular features of in tra ductal breast carcinoma between younger and older women. Cancer. 2003;97(6):1393-403.
20. Wang B, Wang X, Wang J, Xuan L, Wang Z, Wang X et al. Expression of Ki67 and clinicopathological features in breast cancer. Zhonghua Zhong Liu Za Zhi. 2014;36(4):273-5. [In Chines]
21. Mai GF, Zheng H, Luo RC, Liao WJ, Zhang LS, He XB. Association of progesterone receptor and HER2 expressions with the survival time of patient with breast cancer. Di Yi Jun Yi Da Xue Xue Bao. 2003;23(4):372-4.