Distribution of Breast Cancer Biomarkers by Age in Iran

Hassan Akbari[1,*], Farzad Taghizadeh Hesary[2] and Laya Rahnar Nikoukar[3]

[1]*Department of Pathology, Shahid Beheshti University of Medical Sciences, Mahdieh Hospital, Sharzad Street, Tehran, Iran And, Traditional Medicine School, Tehran University of medical Science, Enghelab Street, Tehran, Iran*

[2]*Department of Radiotherapy-Oncology, Shahid Beheshti University of Medical Sciences, Shohada Tajrish Hospital, Qods Square, Tehran, Iran*

[3]*Tehran University of Medical Sciences, Enghelab Street, Tehran, Iran*

Abstract: *Background and Objectives*: Breast cancer is the leading cause of cancer related death globally and presents as the most common female malignancy in Iran. Multiple factors are associated with an increased risk of developing breast cancer; for example first degree family history of breast cancer, BRCA1, 2 mutation and history of atypical hyperplasia on biopsy are the most important risk factors for developing breast cancer. Some prognostic factors are classically used that it would help us to either choosing recommended optimal treatment or recognizing the prognosis. In several studies it is shown that these factors have different patterns in age groups or histopathologic types. The aim of this study was to determine the age distribution of hormone receptors and biomarkers and determine their relation to the histopathologic types.

Methods: Data were gathered from the medical records of Baqiyatallah hospital, Tehran, Iran. Breast cancer patients whose disease was confirmed by pathologic studies and had immunohistochemical profile, were included. Estrogen receptor (ER), Progesterone receptors (PR), HER2/neu and p53 were selected as biomarkers of this study.

Results: Mean age of patients was 49.47±12.50 years (range 20 to 86). The most common histopathologic type was invasive ductal carcinoma. Distribution of ER and PR against age detected similar; ER positivity increased with age and it peaked in fifth decade of life, and PR positivity showed more regular pattern and it also peaked in fifth decade of life ($p < 0.05$) HER2/neu positivity also had trend to increase with age and it peaked in sixth decade of life, but P53 had trend to show unimodal distribution pattern that peaked in sixth decade of life, but this findings were not statistically significant ($p > 0.05$).

Conclusions: Our breast cancer patients were generally younger than patients round the world. The different distribution pattern of biomarkers in our studies in comparison with similar studies, may suggest different biologic behavior of breast cancer in our patients. Further studies will help illuminate this point.

Keywords: Age groups, Biological tumor markers, Breast Neoplasms, Pathology, Iran.

INTRODUCTION

In women, breast cancer is the most frequently diagnosed cancer and the second leading cause of cancer death in the United States [1], while being the leading cause globally [2]. It is the most common female malignancy in Iran, as well [3]. Multiple factors are associated with an increased risk of developing breast cancer; for example first degree family history of breast cancer, BRCA1, 2 mutation and history of atypical hyperplasia on biopsy are the most important risk factors for developing breast cancer. Other risk factors including age, duration of estrogen exposure (e.g. early menarche, nulliparity, late menopause), oral contraceptive, alcohol consumption (more than 2-5 drinks/day) [4]. Several risk and prognostic factors have been determined to help recommend optimal treatments. Lymph node status, tumor size, histopathologic features including tumor type and grade, and hormone receptor status are well-accepted as prognostic factors. Hormone receptor status is also used to predict the response to hormonal therapy [5]. Prognostic markers correlate with the survival independent of the systemic therapy. Classical prognostic factors are estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2/neu). ER-positive breast cancers are associated with a better prognosis. But ER/PR-negative tumors are often associated with aggressive disease.

ER status is, however, correlated with other established indicators of favorable prognosis, such as age, diminishing its role as an independent prognostic factor. The prevalence of ER positive tumors increases with age. It is observed that better prognosis related to positive ER status is less pronounced for women <40 years [6]. ER and PR are used as predictive markers for response to hormonal therapy and PR is also used as a prognostic factor in ER+ breast cancer. HER2, a proto-oncogene, is more common among the high

*Address correspondence to this author at the No 8-West Side-7th Floor, Moghaddam Lane, Ramin Street, Ferdos Avenue, Tehran, Postal Code 1481999461, Iran; Tel: 0098-21-26651517; Mob: 0098-912-6086713; Fax: 0098-21-26651517; E-mail: Farzadth89@Gmail.com

ISSN: 1927-7210 / E-ISSN: 1927-7229/17

grade tumors and is associated with poor prognosis [7]. Herceptin (trastuzumab) and Pertuzumab are the only FDA-approved therapeutic antibodies for HER2+ breast cancer [8]. ER status and HER2 are important factors in determining the suitable treatment for breast cancer, thus affecting survival. Aromatase inhibitors are favored over tamoxifen in PR negative and HER2 positive tumors, though ER/PR- HER2+ tumors are associated with lower responsiveness to any type of hormone therapy [9]. Studies have shown significant correlation with clinical outcomes.

There is a strong correlation between number of cells positive for Ki67 and nuclear grade, age and mitotic rate [7]. It is believed that breast cancer at younger age is more aggressive and is associated with poor outcome. Studies show that younger women present with higher grade and poorly differentiated tumors and ER negative and HER2 positive tumors are more common in this age group [10]. Earlier detection of breast cancer necessitates more effective and acceptable treatments and patient selection is crucial to obtain the best results. Some factors have prognostic values while predicting patient's response to therapy. Determining the pattern of distribution of these markers in breast cancer patients, may spot light on treatment options which should be used more widely in Iran. In this study we investigated the prevalence of breast cancer histopathologic subtypes and the biomarkers ER, PR and HER2; we also present the distribution of these factors in accordance with age.

MATERIAL AND METHODS

Inclusion and Exclusion Criteria

Studies were eligible if they met the following criteria: (1) the main exposure of interest was invasive breast cancer stratified by ER/PR, HER2/neu and P53 status (negative/positive or low/high expression); (2) male patients excluded from our study for unifying our study, because male patients with breast cancer have different pattern of biomarkers (3) over 240 patients were enrolled in the study, which did not present redundant data.

In this retrospective study, detailed clinico-pathological information of breast cancer patients from Baqiyatallah hospital was consecutively collected since March 2005 till March 2008. These patients were diagnosed with invasive breast cancer and were undergone surgical treatments. Major pathological parameters were obtained from the medical records of each patient and the final staging was performed based on the American Joint Committee on Cancer (AJCC) staging criteria version 7 and the situation of biomarkers delineated by immunohistochemical (IHC) procedure. Based on ASCO 2010 IHC criteria, ER and PR assays be considered positive if there are at least 1% positive tumor nuclei in the sample on testing in the presence of expected reactivity of internal (normal epithelial elements) and external controls [11]. Targeting a peptide on C-terminus of the 185 kDa HER2/neu protein, estrogen receptor antibody and progesterone receptor antibody in 1:50 dilution each. College of American Pathologists (CAP) and the American Society of Clinical Oncology (ASCO) recommended guidelines for grading HER2/neu status was used [12]. Some patient's profiles of hormone receptors and biomarkers were not complete. Due to small number of missing data, they were considered as negative.

All histological studies were performed by the same pathologist in the Baqiyatallah hospital and we used data, registered in patient's medical records.

The frequency and percentage of histopathologic types were calculated by age and receptor status. Finally, the distribution of breast cancer subtypes and receptor status was assessed across age. Qualitative variables were analyzed using Chi square test.

As a so important issue, we try our best to conduct this study in accordance with Declaration of Helsinki of 1996.

RESULTS

Age distribution: A total of 244 breast cancer patients were registered. 5 male patients were excluded due to exclusion criteria. The age distribution showed peak incidence in the age group 46-50 years, while the age group under 30 years had fewest patients. Mean age at diagnosis was 49.4 ± 12.39, ranging from 24 to 86 years. The frequency of breast cancer in each age group is shown in Table **1** and Figure **1**.

Histological types against age: The most common type of breast cancer in all age groups was invasive ductal carcinoma (80%). After that, invasive lobular carcinoma and medullary carcinoma were most frequent, each accounting for 5.2% of patients (Table **1**).

Biomarkers against histological type: The most common receptor in invasive ductal carcinoma was

Table 1: Frequency of Various Histopathologic Types by Age Groups

			HISTOPATHOLOGIC TYPES										
			IDC	*MC*	*MuC*	*PC*	*TC*	*ILC*	*IDC*	*LCIS*	*DCIS*	*PCIS*	*Total*
AGE GROUPS (years)	<31	Frequency	3	3	0	0	0	0	0	0	0	0	6
		% within age group	50	50	0	0	0	0	0	0	0	0	100
		% within pathology	1.6	25	0	0	0	0	0	0	0	0	2.6
		% of total	1.3	1.3	0	0	0	0	0	0	0	0	2.6
	31-40	Frequency	44	2	0	2	0	5	1	0	0	0	54
		% within age group	81.5	3.7	0	3.7	0	9.3	1.9	0	0	0	100
		% within pathology	23.8	16.7	0	50	0	41.7	50	0	0	0	23.6
		% of total	19.2	0.9	0	0.9	0	2.2	0.4	0	0	0	23.6
	41-50	Frequency	59	4	4	1	3	2	1	0	0	0	74
		% within age group	79.7	5.4	5.4	1.4	4.1	2.7	1.4	0	0	0	100
		% within pathology	31.9	33.3	66.7	25	60	16.7	50	0	0	0	32.3
		% of total	25.8	1.7	1.7	0.4	1.3	0.9	0.4	0	0	0	32.3
	51-60	Frequency	45	2	1	1	0	4	0	1	0	0	54
		% within age group	83.3	3.7	1.9	1.9	0	7.4	0	1.9	0	0	100
		% within pathology	24.3	16.7	16.7	25	0	33.3	0	100	0	0	23.6
		% of total	19.7	0.9	0.4	0.4	0	1.7	0	0.4	0	0	23.6
	61-70	Frequency	25	1	0	0	2	0	0	0	0	1	29
		% within age group	86.2	3.4	0	0	6.9	0	0	0	0	3.4	100
		% within pathology	13.5	8.3	0	0	40	0	0	0	0	100	12.7
		% of total	10.9	0.4	0	0	0.9	0	0	0	0	0.4	12.7
	>70	Frequency	9	0	1	0	0	1	0	0	1	0	12
		% within age group	75	0	8.3	0	0	8.3	0	0	8.3	0	100
		% within pathology	4.9	0	16.7	0	0	8.3	0	0	100	0	5.2
		% of total	3.9	0	0.4	0	0	0.4	0	0	0.4	0	5.2
Total		Frequency	185	12	6	4	5	12	2	1	1	1	229
		% within age group	80.8	5.2	2.6	1.7	2.2	5.2	0.9	0.4	0.4	0.4	100
		% within pathology	100	100	100	100	100	100	100	100	100	100	100
		% of total	80.8	5.2	2.6	1.7	2.2	5.2	0.9	0.4	0.4	0.4	100

IDC= Invasive ductal carcinoma; MC= Medullary carcinoma; MuC= Mucinous carcinoma; PC= Papillary carcinoma; TC= Tubular carcinoma; ILC= Invasive lobular carcinoma; IDC= Invasive ductal carcinoma; LCIS= Lobular carcinoma *in situ*; DCIS= Ductal carcinoma in situ; PCIS= Papillary carcinoma *in situ*.

HER2/neu. ER was the most common receptor in invasive lobular carcinoma and tubular carcinoma, and the second most common in invasive ductal carcinoma (Table **2**).

Biomarkers against age: Tumors with positive biomarkers were most frequent in patients under 50 years. ER and PR had heterogeneous age distribution (p=0.031, p=0.033, respectively) (Table **3**). These receptors were most frequently positive between 46-50 years of age. Other biomarkers were distributed normally and no age predominance was observed (p > 0.05). ER distribution had unimodal distribution that it increased in incidence to reach its peak in the range of 46-50 years old (17.5%); Thereafter its frequency decreased in accordance with age. However, regarding PR its distribution was more regular and it also peaked in fifth decade of life. (Figure **1**: Frequency of estrogen receptor by age, Hassan Akbari, Figure **2**: Frequency of breast cancer biomarkers by age in Iran, Hassan Akbari).

DISCUSSION

In Iran, as in many countries of Eastern Mediterranean Region, breast cancer is more

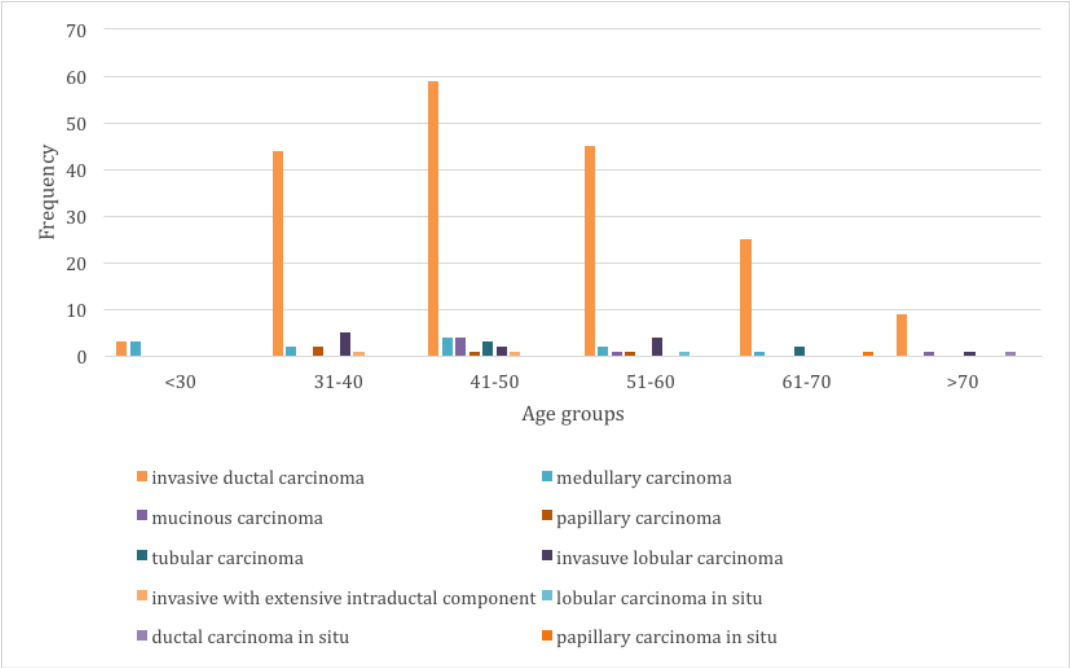

Figure 1: Frequency of various Histopathologic types by age.

Table 2: Frequency of Biomarkers by Histopathological Type

		BIOMARKERS			
HISTOPATHOLOGICAL TYPES		*P 53*	*Her2/neu*	*ER*	*PR*
Carcinoma in situ	Lobular carcinoma in situ (LCIS)	1 (1.2%)	1 (0.7%)	0	0
	Ductal carcinoma in situ (DCIS)	0	0	1 (0.7%)	1 (0.8%)
	Papillary carcinoma in situ	0	1 (0.7%)	1 (0.7%)	1 (0.8%)
Invasive carcinoma	Invasive ductal carcinoma	68 (78.2%)	129 (86.6%)	127 (82.5%)	102 (82.9%)
	Medullary carcinoma	5 (5.7%)	4 (2.7%)	0	0
	Mucinous carcinoma	4 (4.6%)	0	4 (2.7%)	4 (3.3%)
	Papillary carcinoma	2 (2.3%)	2 (1.3%)	3 (1.9%)	3 (2.4%)
	Tubular carcinoma	1 (1.1%)	3 (2%)	5 (3.2%)	4 (3.3%)
	Invasive lobular carcinoma	4 (4.6%)	7 (4.7%)	11 (7.1%)	6 (4.9%)
	Invasive with extensive intraductal carcinoma	2 (2.3%)	2 (1.3%)	2 (1.3%)	2 (1.6%)
P value		>0.05	>0.05	0.00	0.015

Table 3: Frequency of Biomarkers by Age Groups

	AGE GROUPS (years)										
BIOMARKERS	*<30*	*31-35*	*36-40*	*41-45*	*46-50*	*51-55*	*56-60*	*61-65*	*66-70*	*>70*	*P value*
P53	2 (2.4%)	8 (9.6%)	9 (10.8%)	12 (14.5%)	12 (14.5%)	14 (16.8%)	13 (15.7%)	5 (6%)	3 (3.6%)	5 (6%)	>0.05
HER2/neu	2 (1.5%)	14 (10.3%)	15 (11.2%)	21 (15.7%)	21 (15.7%)	18 (13.3%)	18 (13.3%)	10 (7.3%)	8 (6%)	8 (5.9%)	>0.05
Estrogen receptor	1 (0.7%)	14 (9.8%)	15 (10.5%)	21 (14.7%)	25 (17.5%)	20 (14%)	21 (14.7%)	9 (6.3%)	8 (5.6%)	9 (6.3%)	0.031
Progesterone receptor	1 (0.9%)	10 (8.6%)	10 (8.6%)	19 (16.3%)	20 (17.3%)	17 (14.6%)	17 (14.6%)	9 (7.7%)	5 (4.4%)	4 (3.6%)	0.033

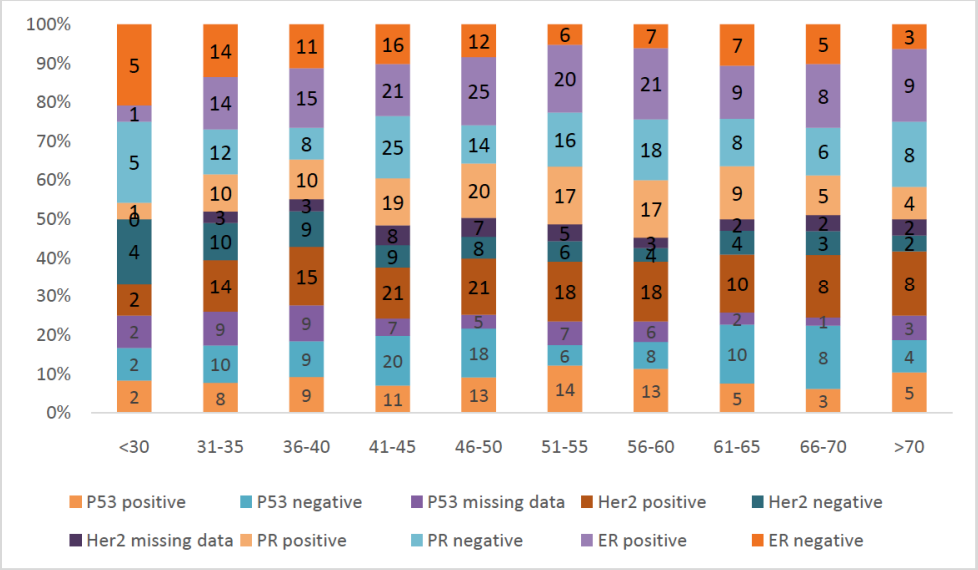

Figure 2: Frequency of breast cancer biomarkers by age in Iran.

commonly detected in women under the age of 50 [10]. Consistent with similar studies in Iran [14-18] the mean age of patients in this study was 49.5 years which is about one decade younger than patients in western countries [19]. It may suggest a difference in biologic behavior of tumors in our patients. More than half of patients in our study were younger than 50 years and this pattern was seen in all histological types, except for the invasive lobular carcinoma.

ER/PR receptors were most frequently positive between 46-50 years of age. In our study, frequency of estrogen receptor increased with age and peaked at fifth decade of life. Regarding progesterone receptor distribution, it showed more regular pattern and it also peaked in fifth decade of life. Regarding P53 and HER2/neu no age predominance detected (Figure **2**).

Invasive ductal carcinoma was detected as the most common type of breast cancer overall, followed by invasive lobular and medullary carcinoma. These figures are consistent with both Iranian and western studies [16, 19].

We compared our results with age distribution patterns for different histopathologic types of breast carcinoma, published by American Association for Cancer Research [18] (Table **4**). It shows a younger age at diagnosis in the Iranian patients.

The age-associated pattern of distribution of biomarkers that we observed was different from most studies reported from outside Iran. Many studies report a positive correlation between age and positive estrogen receptors [20-23], while progesterone receptor showed no significant age association [19, 20]. However, Pourzand *et al*. reported a direct correlation between positive progesterone receptor status and being younger than 40 years [24]. In our study, ER and PR showed heterogeneous patterns of

Table 4: Comparison of Age Distribution Patterns in USA and Iran

HISTOPATHOLOGICAL TYPES														
	Ductal NST		**Tubular**		**Lobular**		**Medullary**		**Inflammatory**		**Papillary**		**Mucinous**	
	USA	***Iran***	***USA***	***Iran***	***USA***	***Iran***	***USA***	***Iran***	***USA***	***Iran***	***USA***	***Iran***	***USA***	***Iran***
Total cases%	68.5	80.8	1.6	2.2	8.1	5.2	1.1	5.2	1.2	N/S	0.7	1.7	2.8	2.6
Median age	61	N/S	62	N/S	66	N/S	51	N/S	56		70	N/S	71	N/S
Peak age of incidence	<50	<50	50-69	<50	70-79	<50	<50	<50	<50		70-79	<50	70-79	<50
Positive Estrogen receptor%	62	68.6	73	100	75	91.7	17	0	36		59	75	75	66.7

Note: N/S: Not specified, NST: No special type.

Table 5: Comparison of Biomarkers in Young Patients between Taiwan and Iran

	Taiwan (<35)		Iran (<30)			Iran (31-40)		
	Positive	***Negative***	***Positive***	***Negative***	***missing***	***Positive***	***Negative***	***Missing***
Estrogen receptor	70%	30%	16.7%	83.3%	0	53.7%	46.3%	0
Progesterone receptor	58%	42%	16.7%	83.3%	0	63%	37%	0
P53	25%	75%	33.3%	33.3%	33.3%	31.5%	35.2%	33.3%
HER2/neu	25%	75%	33.3%	66.7%	0	53.7%	35.2%	11.1%

distribution in accordance to age and both were significantly more prevalent between age 40 and 50. Regarding the fact that most of our patients were in this age group, it may suggest a role for these receptors. Younger age of breast cancer patients in Iran may be attributed to early expression of markers. Besides, these receptors were the most common receptor types in all histological categories after HER2/neu.

A study in Taipei, China [25] reported comparison of prognostic molecular markers in women aged under 35 with older patients and it was found that women under 35 were, they found higher ER- and PR- positive than negative (Table **5**).

Consistent with other studies [10, 26], we observed that HER2 over-expression was more common in younger patients.

Among different histological types, HER2/neu over-expression was significantly high in invasive ductal carcinoma. Since this histological type is the most common one, this marker could be an important one in epidemiologic studies in Iran. This result was also reported by other researchers from Iran [27-29].

Since invasive ductal carcinoma is the most common histological type of breast cancer in Iran, and HER2/neu is the most common receptor in this tumor, Herceptin-therapy may be beneficial in Iranian breast cancer patients.

CONCLUSION

Our findings exhibit different results for age of onset and biomarkers of breast cancer, in comparison with other WHO regions. This issue may declare different behavior of breast cancer cells among Iranian women that would result in different response to therapies. Future studies needed to depict this important issue.

ACKNOWLEDGEMENT

We would like to thank Dr. Mohsen Reza Hyderi for his suggestions and comments to improve this paper.

DISCLOSURE

Financial Support

There was no grant for doing this study.

Conflict of Interest

None of the authors has any financial interest related to this study to disclose.

REFERENCES

[1] Siegel R, Ward E, Brawley O, Jemal A. The impact of eliminating socioeconomic and racial disparities on premature cancer deaths. CA cancer J Clin 2011; 61: 212-36. https://doi.org/10.3322/caac.20121

[2] Jemal A, Bray F, Center MM, Ferlay J, Ward E, Forman D. Global cancer statistics. CA Cancer J Clin 2011; 61: 69-90. https://doi.org/10.3322/caac.20107

[3] Harirchi I, Kolahdoozan S, Karbakhsh M, Chegini N, Mohseni SM, Montazeri A, *et al*. Twenty years of breast cancer in Iran: down staging without a formal screening program. Ann Oncol 2011; 22: 93-7. https://doi.org/10.1093/annonc/mdq303

[4] Clemons M, Goss P. Estrogen and the risk of breast cancer. N Engl J Med 2001; 344: 276. https://doi.org/10.1056/NEJM200101253440407

[5] Subramaniam DS, Isaacs C. Utilizing prognostic and predictive factors in breast cancer. Curr Treat Options Oncol 2005; 6: 147-59. https://doi.org/10.1007/s11864-005-0022-1

[6] Bentzon N, Düring M, Rasmussen BB, Mouridsen H, Kroman N. Prognostic effect of estrogen receptor status across age in primary breast cancer. Int J Cancer 2008; 122: 1089-94. https://doi.org/10.1002/ijc.22892

[7] Taneja P, Maglic D, Kai F, Zhu S, Kendig RD, Fry EA, *et al*. Classical and Novel Prognostic Markers for Breast Cancer and their Clinical Significance. Clin Med Insights Oncol 2010; 4: 15–34.

[8] Gemmete JJ, Mukherji SK. Trastuzumab (Herceptin). AJNR Am J Neuroradiol 2011; 32: 1373-4. https://doi.org/10.3174/ajnr.A2619

[9] Rastelli F, Crispino S. Factors predictive of response to hormone therapy in breast cancer. Tumor 2008; 94: 370-83.

[10] Kheirelseid E, Boggs J, Curran C, Glynn R, Dooley C, Sweeney K, *et al*. Younger age as a prognostic indicator in breast cancer: A cohort study. BMC Cancer 2011; 11: 383. https://doi.org/10.1186/1471-2407-11-383

[11] M. Elizabeth H, Hammond, Daniel F, Hayes, *et al*. American Society of Clinical Oncology/College of American Pathologists Guideline Recommendations for

Immunohistochemical Testing of Estrogen and Progesterone Receptors in Breast Cancer: ASCO guideline. J Clin Oncol 2010; 28: 16.

[12] Wolff AC, Hammond ME, Schwartz JN, *et al*. American Society of Clinical Oncology/College of American Pathologists guideline recommendations for human epidermal growth factor receptor 2 testing in breast cancer. Arch Pathol Lab Med 2007; 131: 18- 43.

[13] Khatib OMN, Modjtabai A. Guidelines for the early detection and screening of breast cancer. East Mediterr Health J 2006; 1020-0428.

[14] Harirchi I, Ebrahimi M, Zamani N, Jarvandi S, Montazeri A. Breast cancer in Iran: a review of 903 case records. Public Health 2000; 114: 143-5. https://doi.org/10.1016/s0033-3506(00)00324-3

[15] Hadi N, Sadeghi-Hassanabadi A, Talei AR, Arasteh MM, Kazerooni T. Assessment of a breast cancer screening program in Shiraz, Islamic Republic of Iran. East Mediterr Health J 2002; 8: 386-92.

[16] Kermani IA. Variation of tumor markers in 277 breast cancer cases. Asian Pac J Cancer Prev 2004; 5: 291-3.

[17] Vahdaninia M, Montazeri A. Breast cancer in Iran: a survival analysis. Asian Pac J Cancer Prev 2004; 5: 223-5.

[18] Mousavi SM, Montazeri A, Mohagheghi MA, Jarrahi AM, Harirchi I, Najafi M, *et al*. Breast cancer in Iran: an epidemiological review. Breast J 2007; 13: 383-91. https://doi.org/10.1111/j.1524-4741.2007.00446.x

[19] Anderson WF, Pfeiffer RM, Dores GM, Sherman ME. Comparison of age distribution patterns for different histopathologic types of breast carcinoma. Cancer Epidemiol Biomarkers Prev 2006; 15: 1899-905. https://doi.org/10.1158/1055-9965.EPI-06-0191

[20] Eppenberger-Castori S, Moore DH, Jr., Thor AD, Edgerton SM, Kueng W, Eppenberger U, *et al*. Age-associated biomarker profiles of human breast cancer. Int J Biochem Cell Biol 2002; 34: 1318-30. https://doi.org/10.1016/S1357-2725(02)00052-3

[21] Quong J, Eppenberger-Castori S, Moore D, 3rd, Scott GK, Birrer MJ, Kueng W, *et al*. Age-dependent changes in breast cancer hormone receptors and oxidant stress markers. Breast Cancer Res Treat 2002; 76: 221-36. https://doi.org/10.1023/A:1020886801674

[22] Alvarez Goyanes RI, Escobar Perez X, Camacho Rodriguez R, Orozco Lopez M, Franco Odio S, Llanes Fernandez L, *et al*. Hormone receptors and other prognostic factors in breast cancer in Cuba. MEDICC Rev 2010; 12: 36-40.

[23] Parise CA, Bauer KR, Caggiano V. Variation in breast cancer subtypes with age and race/ethnicity. Crit Rev Oncol Hematol 2010; 76: 44-52. https://doi.org/10.1016/j.critrevonc.2009.09.002

[24] Pourzand A, Fakhree MB, Hashemzadeh S, Halimi M, Daryani A. Hormone receptor status in breast cancer and its relation to age and other prognostic factors. Breast Cancer (Auckl) 2011; 5: 87-92.

[25] Lin C-H, Lu Y-S, Huang C-S, Kuo K-T, Wang C-C, You S-L, *et al*. Prognostic molecular markers in women aged 35 years or younger with breast cancer: is there a difference from the older patients? J Clin Pathol 2011; 64: 781-7. https://doi.org/10.1136/jclinpath-2011-200064

[26] Homaei-Shandiz F, Ghavam-Nassiri MR, Sharifi N, Homaei-Shandiz AH, Taghizadeh-Kermani A, Torshizi SA, *et al*. Evaluation of the relationship between human epidermal growth factor receptor-2/neu (c-erbB-2) amplification and pathologic grading in patients with breast cancer. Saudi Med J 2006; 27: 1810-4.

[27] Fakheri TN, B. Fadakar, Gh. The relationship between p53 and some clinical pathologic factors and steroid receptor in breast cancer. Journal of Guilan University of Medical Sciences 2006; 15: 1-6.

[28] Najafi BF, T. Fadakar, Gh. The relationship between HER2 and other pathologic diagnostic criteria in breast cancer. Journal of Guilan University of Medical Sciences 2005; 15: 21-7.

[29] Akbari M, Souri. 5-year survival in breast cancer patients referred to 2 hospitals in Tehran. Hakim 2006; 9: 39-44.

Received on 28-10-2016 Accepted on 22-11-2016 Published on 26-01-2017

https://doi.org/10.6000/1927-7229.2017.06.01.2