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Impact of tumor biomarkers and patient's age on the "disease stage" in women with breast cancer in Erbil city

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Abstract

Background and objective: Female breast cancer is the most commonly diagnosed cancer worldwide, affecting more than one million women annually. The objectives of this study were, firstly, to evaluate the effects of breast cancer biomarkers such as human epidermal growth factor receptor-2and hormone receptor status on the stage of breast cancer at the time of presentation, and secondly, to assess the role of "women's age" on the level of biomarker expressions and on the advancement in breast cancer disease stage at the time of diagnosis in a sample of women diagnosed with breast cancer in Erbil City.

Methods: A retrospective analysis of medical records of women affected with breast cancer was performed from January 2013 to April 2014. Cancer staging was done based on the histopathological reports according to the American Joint Committee on Cancer TNM staging system. Patients were classified to either hormone receptor/human epidermal growth factor receptor-2 positive or negative based on immunohistochemistry or FISH analysis.

Results: The mean age (±SD) at diagnosis was 48.9 (±12.4) years. About a quarter of breast cancer cases were diagnosed in young women aged less than 40 years, who had a proportionally more hormone receptor negativity and human epidermal growth factor receptor-2 over-expression, and a significantly more advanced cancer stage at time of diagnosis compared to their older counterparts.

Conclusion: Breast cancer biomarkers have huge impacts on disease stage, and are greatly affected by age of women at time of diagnosis of breast cancer.

Keywords: Breast cancer, Disease stage, Tumor biomarkers, Erbil City.

Introduction

Female breast cancer is the most commonly diagnosed cancer worldwide, with a widely variable incidence between countries and regions. It also accounts for the second largest number of cancer-related deaths among women.[1] The overall worldwide burden of breast cancer has doubled between 1975 and 2010, and this is thought to be attributable to the increasing life expectancy and widespread adoption of westernized lifestyle with all its risk factors.[2] However, these trends are not seen in early onset breast cancer, as the rates have been more or less stable in most countries in the past 20 years.[3] The developed countries with a small proportion of the world population account for almost 50% of breast cancers diagnosed worldwide.[4] On the other hand, in the developing countries of Asia; the health care burden on account of breast cancer has been steadily mounting. Although it is expected that in the coming decades, these countries would account for majority of new breast cancer patients diagnosed globally. Several studies raised the notion that young breast cancer patients tend to present with more advanced stages than older women.[5-8] A retrospective cohort from Denmark of 10,356 women diagnosed before 50 years reported that patients aged ≤35 years at diagnosis were at higher risk of being node positive

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(51% vs. 46%; P=0.02) compared with patients between 35 and 50 years.[7] A study of 732 non-metastatic breast cancer patients from Mount Sinai Medical Center, New York showed that patients younger than 36 years had larger tumors (median 2.0 vs. 1.5 cm, P<0.001), more nodal involvement (50% vs. 37%, P=0.022), and were more likely to be diagnosed with stage II or III cancer (60% vs. 43%, P<0.001) than patients above 36 years.[8] Many studies have suggested that age is an independent prognostic factor; however, this issue is now considered controversial. Breast cancer in young women is more likely to be of a more aggressive subtype, hormone receptor negative or HER2 receptor positive, and is more likely to present at an advanced stage, either because of its biological aggressive subtype or because of a low index of suspicion and delayed diagnosis. This may translate into more loco-regional recurrences and distant metastases, which contributes to the poorer outcome of young women with breast cancer.[9,10] The aim of this study was to evaluate the potential effects of breast cancer biomarkers such as human epidermal growth factor receptor -2 (HER2)andhormone receptor status (estrogen and progesterone) on the stage of breast cancer at the time of presentation. The study also assessed the role of "women's age" at the time of diagnosis on the level of expression of hormone and HER2 receptor statuses and on the advancement in breast cancer disease stage in a sample of women diagnosed with breast cancer in Erbil City.

Methods

A retrospective analysis was performed on the medical records (review of cases) of women affected with breast cancer, who were visiting the Medical Oncology Department of Rizgary Teaching Hospital in Erbil for the purpose of management, from January 2013 through April 2014.The department manages around 300 new cases of female breast cancer annually. Inclusion criteria were women of any age group in whom the diagnosis of invasive breast carcinoma was confirmed histopathologically. Patients with defects in their medical records (for instance lacking adequate data in their case-notes), who were not histologically proven to have primary invasive carcinoma of breast, those with carcinoma in-situ, not properly staged for the cancer at the time of diagnosis, and those with unknown hormone receptor and/or HER2 receptor statuses were excluded from the study. Staging of the cancer was performed based on the histopathological reports, at the time of disease presentation, as to the measurement of the tumor size, the presence of axillary lymph node involvement and distant metastases according to the American Joint Committee on Cancer (AJCC) TNM staging system as follows:[11] Stage I (early stage): the primary breast tumor is no larger than two cm in greatest diameter, and has not spread to the regional lymph nodes. Stage II and III (early and late locally advanced): the primary breast tumor is more than two cm in size, and/or may have spread to the regional lymph nodes. Stage IV (metastatic): the primary breast tumor have spread to other distant organs and sites of the body such as lungs, bones, liver, brain…etc Based on the tumor biomarker status, patient cases were classified as hormone receptor-positive if either the estrogen receptor (ER) marker or the progesterone receptor (PR) was positive, and as hormone receptor-negative if both ER and PR were negative. Similarly, HER2 status was classified as positive (over-expressed) or negative based on immunohistochemistry and/or fluorescent in situ hybridization (FISH) analysis present in the patients' medical records. Patient's age at the time of diagnosis wasarranged into four age groups: (less than 40 years, 40-49 years, 50-59 years, and equal or more than 60 years of age). Those aged less than forty years old were considered as young, meanwhile those

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aged equal or more than 60 were classified as elderly. The study was retrospective based on the patients' medical records; therefore, ethical approval was not considered. Statistical analyses were conducted using statistical package for the social sciences (version 19). Associations between categorical variables as age group, disease stage, hormone receptor status and HER2 receptor status were tested using Pearson's Chi-squared test. Statistical significance required a two-tailed P value ≤0.05.

Results

The study involved a retrospective analysis of 245 case records of women with invasive breast carcinoma. Age, disease stage at the time of diagnosis, and tumor biomarkers of breast cancer as hormone receptor and HER2 status were plotted for each individual patient. The median age was 48 years, the mean age (± SD) at diagnosis was 48.9 (± 12.4) years, ranging from 23 to 92 years. About a quarter of breast cancer cases were diagnosed in young women aged less than 40 years. More than 50% of the patients with breast cancer were middle-aged groups (40-59 years old). Elderly women (those aged equal or more than 60) comprised about 20% of the studied breast cancer cases (Table 1). The stage distribution of breast cancer is presented in Table 2. Four stage categories were identified, stage I (localized), stage II (locally advanced), stage III (very locally advanced) and stage IV (distant metastasis). Of the studied patients, only 7% were diagnosed with stage I. More than two thirds of the patients were diagnosed withlocally advanced diseases (stages II and III). Patients who presented with metastatic disease formed about one fifth of the total number of women diagnosed with breast cancer.

Table 1: Distribution of sample by age

Age groups (years)	Number	(%)
<40	60	(24.5)
40-49	70	(28.6)
50-59	62	(25.3)
60+	53	(21.6)
Total	245	(100.0)

Table 2: Distribution of breast cancer patients by stage

TNM Stage	Number	(%)
I	17	(6.9)
II	86	(35.1)
III	87	(35.5)
IV	55	(22.4)
Total	245	(100.0)

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The study found that younger patients had a significantly more advanced cancer stage at the time of presentation compared to their older counterparts. Table 3 shows that only 3% of those who aged less than 40 years had a stage I disease compared to 8% and 13 percent in those aged 50-59 and more than 60 years respectively. Oppositely, around three quarters of the young patients under the age of 40 presented with some sort of very locally advanced or metastatic disease, mean-while only half of those aged 50-59 had advanced or metastatic disease. The associations between age at time of diagnosis of breast cancer and the disease stage were statistically significant at a P-value of 0.026. The hormone receptor status and HER2 receptor status were identified for each individual patient based on immunohistochemistry and or FISH testing. Table 4 reveals the number and percentage of the studied patients based on their hormone receptor and HER2 statuses. As it is illustrated, about 70% of the women had hormone positive disease; oppositely, HER2 receptor status was positive (over-expressed) in about one-third of the studied patients.

Table 3: Association between patient's age and disease stage at the time of diagnosis.

		TNM Stage				**Total**	**P**
		I	**II**	**III**	**IV**		
Age (years)	<40	2 (3.3%)	12 (20.0%)	25 (41.7%)	21 (35.0%)	60 (100%)	
	40-49	3 (4.3%)	25 (35.7%)	27 (38.6%)	15 (21.4%)	70 (100%)	
	50-59	5 (8.1%)	26 (41.9%)	21 (33.9%)	10 (16.1%)	62 (100%)	0.026
	60+	7 (13.2%)	23 (43.4%)	14 (26.4%)	9 (17.0%)	53 (100%)	
Total		**17 (6.9%)**	**86 (35.1%)**	**87 (35.5%)**	**55 (22.4%)**	**245 (100%)**	

Table 4: Distribution of hormone receptor and HER2 receptor status

		Number	**(%)**
Hormone receptor status	Negative	75	(30.6)
	Positive	170	(69.4)
	Total	**245**	**(100.0)**
HER2 receptor status	Negative	161	(65.7)
	Positive	84	(34.3)
	Total	**245**	**(100.0)**

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Regarding the tumor biomarkers, the study showed an increased proportion of hormone receptor negativity and HER2 over-expression in young women with breast cancer compared to their older counterparts. As it is demonstrated in Table 5, 40% of those aged younger than 50 years had a hormone receptor negative disease, compared to around 20% in those aged more than 50 years. Furthermore, about half of the patients under the age of 40 years had a positive HER2 status disease; this reduced to just more than 20% in those aged older than 50 years (Table 6). The differences were statistically significant. The study discovered that hormone receptor status positivity was associated with earlier disease stage. As illustrated, more than 90% of patients with stage I had a hormone receptor positive disease compared to only around 50% of patients with metastatic disease (Table 7).

Table 5: Rate of hormone receptor status positivity based on age of the patients.

		Hormone receptor status		Total	p
		Negative	Positive		
TNM Stage	I	1 (5.9%)	16 (94.1%)	17 (100%)	< 0.001
	II	15 (17.4%)	71 (82.6%)	86 (100%)	
	III	35 (40.2%)	52 (59.8%)	87 (100%)	
	IV	24 (43.6%)	31 (56.4%)	55 (100%)	
Total		**75 (30.6%)**	**170 (69.4%)**	**245 (100%)**	

Table 6: Rate of HER2 receptor status positivity based on age of the patients.

		HER2 receptor status		Total	p
		Negative	Positive		
Age (years)	<40	28 (46.7%)	32 (53.3%)	60 (100%)	0.001
	40-49	44 (62.9%)	26 (37.1%)	70 (100%)	
	50-59	48 (77.4%)	14 (22.6%)	62 (100%)	
	60+	41 (77.4%)	12 (22.6%)	53 (100%)	
Total		**161 (65.7%)**	**84 (34.3%)**	**245 (100%)**	

Table 7: Hormone receptor status according to disease stage.

		Hormone receptor status		Total	p
		Negative	Positive		
TNM Stage	I	1 (5.9%)	16 (94.1%)	17 (100%)	< 0.001
	II	15 (17.4%)	71 (82.6%)	86 (100%)	
	III	35 (40.2%)	52 (59.8%)	87 (100%)	
	IV	24 (43.6%)	31 (56.4%)	55 (100%)	
Total		**75 (30.6%)**	**170 (69.4%)**	**245 (100%)**	

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HER2 positivity (over-expression) was linked to a more advanced and metastatic disease status at the time of diagnosis. As demonstrated in Table 8, HER2 status positivity was found in just less than half of the patients with stage III or IV disease, meanwhile only around one fifth of patients with stage I or II disease had a HER2 positive breast cancer. The results were statistically significant (P < 0.001).

Discussion

The study showed the median age at time of diagnosis of breast cancer among the studied women was 48 years. Just less than a quarter of the patients at the time of diagnosis with breast cancer were young women aged less than 40 years. Compared to the developed countries, studies have shown that the median age of women at time of presentation with breast cancer is 61 years old, and only about seven percent of all breast cancer cases are diagnosed in women less than 40 of age, 2.4% in women less than 35, and 0.65% in women less than 30.[12,13] Additionally, genetic factors may play a role in affecting rates of early onset breast cancer in different areas, though their role cannot by itself account for international variation in risk. In the UK, approximately 3% of all breast cancers are attributable to mutations in BRCA1 or BRCA2, whereas this number increases in Ashkenazi Jews to up to 40%.[14]TP53 mutation, although very rare, is the causative agent of breast cancer in Li-Fraumeni syndrome, which tends to affect women between 20 and 40 years of age.[15] Some populations such as in Southern Brazil have relatively high mutation frequency of TP53 mutation, reaching one in 300 women.[16,17] Hormonal factors also vary in different populations, races, and ethnicities. In a study in Atlanta, USA, incidence rates of triple-negative tumors differed by race, with an incidence of 36.3 per 100,000 for black women, and 19.4 per 100,000 for white women.[18] Furthermore, various environmental hazards play roles in the causation of early breast cancer in various places in the world.[19,20] Though early onset breast cancer does not seem to be directly related to westernization or standard of living, where a weak correlation is found between country income level and early onset breast cancer.[21] Nevertheless, most of the variation in risk is believed to be due to differential environmental exposure to certain risk factors. Studies of migrants further emphasize this hypothesis; incidence of cancers tend to rise following migration from low to high incidence countries, especially if it occurs early in life.[22] Many risk factors for breast cancer have been well-established by case-control and cohort studies. However, there have been few efforts to quantify the magnitude of risk disparities between countries that might be explained by such factors. Further studies are needed in this field for the purpose of better clarification of this issue.

Table 8: HER2 receptor status according to disease stage.

		HER2 receptor status		Total	p
		Negative	Positive		
TNM Stage	I	13 (76.5%)	4 (23.5%)	17 (100%)	< 0.001
	II	70 (81.4%)	16 (18.6%)	86 (100%)	
	III	50 (57.5%)	37 (42.5%)	87 (100%)	
	IV	28 (50.9%)	27 (49.1%)	55 (100%)	
Total		**161 (65.7%)**	**84 (34.3%)**	**245 (100%)**	

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The current study demonstrated that only less than 7% of the women diagnosed with breast cancer had an early (stage I) disease. Oppositely, according to Surveillance, Epidemiology and End Results Program (SEER) which is an authoritative source of information on cancer incidence and survival in the United States, more than 60% of the patients presented with a localized disease that was confined to the primary site of the tumor. Furthermore, around a quarter of patients in our study revealed to have presented with a wide spread metastatic breast cancer, compared to only 5% according to the results published by SEER. At the same time, this low proportion rate of early breast cancer in the studied patients was compatible with the results of studies done in other developing countries such as India, where the proportion was at 1.4 to 7.8%. Also, 6–25% of Indian breast cancer patients had distant metastatic disease at presentation, with a higher incidence of skeletal metastases.[23,24] This difference in breast cancer stage at presentation between the developed countries and our locality could be widely attributed to the lack of an effective and well established national screening program for the purpose of earlier detection of breast cancer. There is a wide body of evidence that screening for breast cancer by mammography does have resulted in earlier detection and hence better prognosis and longer survival.[25-28] In addition, the study found that younger patients had a significantly more advanced cancer stage at the time of presentation compared to older patients. Several studies raised the notion that young breast cancer patients tend to present with more advanced stages than older women.[5-8] A retrospective cohort from Denmark of 10,356 women diagnosed before 50 years reported that patients aged ≤35 years at diagnosis were at higher risk of being node positive (51% vs. 46%; P=0.02) compared with patients between 35 and 50 years.[7] A study of 732 non-metastatic breast cancer patients from Mount Sinai Medical Center, New York showed that patients younger than 36 years had larger tumors (median 2.0 vs. 1.5 cm, P<0.001), more nodal involvement (50% vs. 37%, P=0.022), and were more likely to be diagnosed with stage II or III cancer (60% vs. 43%, P<0.001) than patients above 36 years.[8] The study also showed an increased proportion of hormone receptor negativity and HER2 over-expression (positivity) in young women with breast cancer compared to their older counterparts. This was compatible with the results of many studies which have confirmed the increased proportion of hormone receptor negativity, HER2 over-expression, and high grade in young women with breast cancer.[29,30] Based on various prospective and retrospective studies performed in the last two decades, it has been generally accepted that young age at diagnosis correlates with a worse clinical outcome compared to older ages.[31-35] This holds true irrespective of menopausal status, as age is still a risk factor among premenopausal women.[36] In addition, breast cancer survival rates are comparatively lower for women less than 40 years of age than for older women across all histological subtypes and stages.[12]However, the controversy lies in the question of whether age per se is an independent risk factor for worse prognosis. In this regard, the study results were compatible with other studies done around the world. For instance, a study of 399 breast cancer patients below 40 years by Collins et al.[10] revealed a lower proportion of hormone positive and HER2 negative disease and compared to numbers from population studies of breast cancer.[37-40] Fifty-five percent of patients had high grade tumors, and 31% of all tumors over-expressed HER2,[10] which is high compared to the 12.6% presented in a study of 1,842 breast cancer patients in Atlanta by Lund et al.[18] Hormone receptor negative and HER2 negative (triple negative) tumors have also been found to be over-represented in young

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women with breast cancer, with rates close to 26%.[41] Overall, many studies have refuted this hypothesis; they rather propose that the effect of young age on outcome is merely a reflection of over-representation of other known prognostic pathological factors, such as higher grade of differentiation, presence of lymphovascular invasion, higher mitotic rate, lower hormone receptor expression, and higher HER2 expression.[42-45] Yet other studies have attributed the inferior outcome of young age to the more advanced presentation at diagnosis, including higher rates of axillary lymph node positivity and larger tumor size.[5-8] Others have postulated that the effect of differential gene expression between different age groups might play a role.[46] In any case, knowing the true impact of age on prognosis may have an effect on our management. If it is indeed an independent factor, then young women might benefit from more aggressive treatment than their older counterparts with the same clinical and pathological scenario.

Conclusion

Overall, the study concluded that the median age at time of diagnosis of breast cancer among the studied women was 48 years. About a quarter of breast cancer cases were diagnosed in young women aged less than 40 years. More than two thirds of the studied patients presented with locally advanced breast cancer (disease stages II and III); and about one fifth of them had distant metastatic disease at the time of diagnosis. These figures suggested that, compared to developed countries, women in our country get breast cancer at an earlier age and with more advanced disease stage. Furthermore, comparable with many other studies, the present study found that younger patients with breast cancer had an increased proportion of hormone receptor negativity and HER2 over-expression (positivity) compared to their older counterparts. This may explain a more advanced disease stage and hence a worse outcome in the younger aged women with breast cancer.

Conflicts of interest

The authors report no conflicts of interest.

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