Different Breast Cancer Subtypes in Women More Than 65-Year-Old

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Abstract-Breast cancer is the most common malignancy of females. Breast cancer is a heterogenic disease; it consists of several subtypes based on the expression of different genes. Risk factors associated with each subtype is not completely understood, yet. Moreover, recognizing the cancer subtypes may alter the treatment plan. The aim of this study was to evaluate different breast cancer subtypes in women more than 65-year-old. This was a cross-sectional study done on patients with breast cancer aged 65 years and older presenting to clinics of Emam Reza and Omid Hospitals, Mashhad, Iran between 2005 and 2015. Statistical analysis was carried out using SPSS ver. 16. $P<0.05$ was considered statistically significant.A total of 225 breast cancer patients age 65 and older were included in our study. When we categorized our patients by breast cancer subtypes, 69.8% had the Luminal A, B subtype, 23.1% had Triple-Negative subtype, and the remaining 7.1% had HER-2 enriched subtype.Different breast cancer subtypes in patients aged 65-year-old and higher were Luminal A, B, HER-2 enriched and Triple-negative, respectively. We also showed that patients with Luminal A, B subtypes had significantly higher BMI and BSA compared to other subtypes.

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Introduction

Breast cancer is the most common malignancy of females accounting for more than 18% of all female cancers and incidence of more than 1 million cases annually. It is more common in developed countries such as USA, Australia, and northern and western Europe compared to developing countries due to the several factors associated with industrialization related social transformation including obesity, fatty diet, increased age of menarche, decreased rate of breastfeeding, and altering of pregnancy patterns (1). In the USA, more than 25,0000 people are diagnosed with breast cancer, and more than 4,0000 patients die due to breast cancer annually. However, the incidence rate of breast cancer has decreased by 1.8% per year during 1999-2007 (2). In Iran, breast cancer is the most common malignancy among women accounting for 21.4% of all female malignancies. Moreover, the mean age of patients is 10 years younger compared to developed countries. Mean age at diagnosis is 48.4 years old in Iran with the most common age ranging from 40 to 49 (3). Nevertheless, elderly patients are also notably diagnosed with breast cancer with the prevalence of around 220 per 10,0000 people aged 65-year-old and higher (4).

Breast cancer is a heterogenic disease; it consists of several subtypes based on the expression of different genes (5). Subtypes include Luminal A, Luminal B, HER-2 enriched and triple-negative. Each subtype has its own risk factors, treatment plan, and prognosis. The most common subtype is the Luminal subtype, which expresses the PR and ER genes, and it is further divided into Luminal A and Luminal B based on proliferative potential. HER-2 enriched subtype compromised around 10-15% of breast cancers, expressing high amounts of Human Epidermal Growth Factor-2 gene. Triple-negative tumors do not express any of ER, PR, and HER-2 genes; they are also known as the Basal-like subtype. Triple-negative tumors have the worst

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prognosis (6). Each subtype has its unique profile of risk factors, for example, number of parity and oral contraceptive use is a risk factor for Triple Negative cancers but no other subtypes (7). However, risk factors associated with each subtype is not completely understood yet. Moreover, recognizing the cancer subtype may alter the treatment plan as subtypes with positive ER respond well to hormone therapy, whereas triple-negative subtype does not respond to hormone therapy (8). Risk of recurrence and metastasis also differs among different subtypes with Luminal A having the lowest risk and HER-2 enriched having the highest risk (8).

Considering the previously noted importance of subtype recognition in breast cancer and the high incidence of breast cancer in Iran, we sought out to evaluate the prevalence of different breast cancer subtypes in patients older than 65 years old. To the best of our knowledge, this is the first study assessing the prevalence of different breast cancer subtypes in Iran.

Materials and Methods

Sample size and study design

This was a cross-sectional study done on breast cancer patients aged 65 years and older presenting to clinics of Emam Reza and Omid Hospitals, Mashhad, Iran between 2005 and 2015. A total of 225 patients were included in our study,andthe required information was collected from patients' medical records.

Acquired data

Collected data included age, Body Mass Index (BMI), Surface area (SA), pathology, grading, stage, location and immunohistochemistry of tumor, received treatment and operation type, metastasis location, family history, and past medical history. All relevant information was recorded in a premade checklist.

Statistical analysis

All quantitative data are reported as the mean±Standard deviation. Qualitative data were reported as the percentage of each category. Data normality was tested using Kolmogorov–Smirnov test. If normally distributed one way ANOVA was used otherwise Kruskal–Wallis test was used for assessment of correlation. Qualitative data were evaluated using parametric and non-parametric tests whenever appropriate. Statistical analysis was carried out using SPSS ver. 16. $P<0.05$ was considered statistically significant.

Results

Study population and characteristics

A total of 225 breast cancer patients aged 65 years and older were included in our study, the mean age of our patients was 70.83 years old. Only two of our patients had bilateral breast involvement. One hundred and twenty-six people had no past medical history, however among those with a positive past medical history hypertension was the most common co-morbidity. Forty-five patients reported a positive family history of cancer, from which 34 patients had cancer in the first degree,and11had cancer in second-degree family members. Majority of our patients had Grade 2 and Stage 2A disease. Nearly 90percent of our subjects had a pathologic diagnosis of Invasive ductal carcinoma. Only 23 patients had metastasis with bone being the most common metastasis site. When we categorized our patients by breast cancer subtypes 69.8% had the Luminal A, B subtype, 23.1% had Triple-Negative subtype,and the remaining 7.1% had HER-2 enriched subtype (Table 1).

The relationship between breast cancer subtypes and patients' characteristics

In order to assess the relationship between breast cancer subtypes and our quantitative data, initially, we tested the normality of distribution of age, BMI and BSA using Kolmogorov–Smirnov test. Age was not normally distributed; therefore, Kruskal–Wallis test was used, whereas BMI and BSA were assessed using one way ANOVA. Subtypes were significantly different in the case of BMI and BSA but not age (Table 2**Error! Reference source not found.**).

To further assess the relationship between BMI and BSA, we carried out LSD test that revealed that BMI is significantly higher in Luminal A, B compared to HER-2 enriched and Triple-Negative groups (P value 0.019 and 0.21, respectively). No significant difference was noted in the BMI between HER-2 enriched and Triple-Negative groups ($P=0.4$). Moreover, we found out that the BSA followed the same pattern and was significantly higher in Luminal A, B group compared to HER-2 enriched and Triple-Negative groups (P 0.02 and 0.036, respectively), but no significant difference was observed between HER-2 enriched and Triple-Negative groups ($P=0.35$).

We assessed the relationship between breast cancer subtypes and our other qualitative data using chi-square or exact test whenever appropriate. Our results suggested no significant association of breast cancer

subtypes with tumor location, grade, stage, metastasis, pathological diagnosis, past medical history and family history of cancer (Table 2).

Table 1. Patients' characteristics

		N	%
Mean age (Year)		70.83±4.78	
Mean BMI (Kg/m^2)		27.54±5.18	
Mean SA (m^2)		1.62±0.17	
Past medical	**No PMHx**	126	61.2
	HTN	51	24.7
	DM	19	9.7
	IHD	17	8.2
	Other	34	16.4
The family history of cancer	**None**	180	80
	Breast	22	9.6
	Gastrointestinal	10	4.6
	Genitourinary	8	3.4
	Other	5	2.4
Treatments received	**Palliative**	41	18.24
	MRM	164	72.88
	BCS	20	8.88
Mean number of removed lymph nodes		8.47±4.6	
Mean number of metastasized lymph nodes		2.8±3.58	
Tumor stage	**1A**	30	13.4
	2A	56	24.9
	3A	39	17.5
	2B	43	18.9
	3B	22	9.7
	3C	11	5.1
	4	24	10.6
Tumor Grade	**I**	32	14.2
	II	133	59.2
	III	60	26.6
Tumor location	**Right**	91	40.4
	Left	132	58.7
	Bilateral	2	0.9
Pathology	**Invasive ductal carcinoma**	202	89.77
	Lobular carcinoma	23	10.22
Metastasis	**None**	202	89.77
	Bone	13	5.77
	Lung	5	2.22
	Liver	6	2.66
	Brain	1	0.44
Cancer subtypes	**Luminal A,B**	157	69.8
	HER-2 enriched	16	7.1
	Triple-Negative	52	23.1

Table 1. The relationship between patients' characteristics and subtypes of breast cancer

		Luminal A,B	HER-2 enriched	Triple-Negative	*P*
Mean age (Year)		71.11±5.05	70.69±4.40	70.02±3.98	0.54
Mean BMI (Kg/m^2)		28.20±5.07	24.95±5.27	26.21±5.10	0.009*
Mean SA (m^2)		1.64±0.17	1.53±0.16	1.58±0.17	0.014*
Past medical	**Positive**	56 (40%)	6 (37.5%)	18 (36%)	0.87
	Negative	84 (60%)	10 (62.5%)	32 (64%)	
Family history of cancer	**Positive**	29 (18.5%)	5 (31.2%)	11 (21.2%)	0.46
	Negative	128 (81.5%)	11 (68.8%)	41 (78.8%)	
Tumor stage	**1A**	20 (13.2%)	2 (13.3%)	7 (14%)	0.38
	2A	43 (28.3%)	1 (6.7%)	10 (20%)	
	3A	23 (15.1%)	2 (13.3%)	13 (26%)	
	2B	28 (18.4%)	4 (26.7%)	9 (18%)	
	3B	16 (10.5%)	1 (6.7%)	4 (8%)	
	3C	5 (3.3%)	1 (6.7%)	5 (10%)	
	4	17 (11.2%)	4 (26.7%)	2 (4%)	
Tumor grade	**I**	23 (15.1%)	2 (13.3%)	6 (11.8%)	0.72
	II	89 (58.6%)	11 (73.3%)	29 (56.9%)	
	III	40 (26.3%)	2 (13.3%)	16 (31.4%)	
Tumor location	**Right**	68 (43.3%)	4 (25%)	19 (36.5%)	0.46
	Left	87 (55.4%)	12 (75%)	33 (63.5%)	
	Bilateral	2 (1.3%)	0 (0%)	0 (0%)	
Pathology	**Invasive ductal carcinoma**	136 (87.2%)	15 (93.8%)	51 (98.1%)	0.065
	Lobular carcinoma	20 (12.8%)	1 (6.2%)	1 (1.9%)	
Metastasis	**Positive**	17 (10.9%)	4 (25%)	2 (3.8%)	0.18
	Negative	138 (89.1%)	12 (75%)	50 (96.2%)	

Discussion

Our retrospective study included 225 patients with breast cancer. The age range was 65-90 and mean age was 70.83±4.78 years. Our results demonstrated that the most common subtype in our patients was Luminal A, B (69.8%) and the least common was HER-2 enriched (7.1%). Moreover, patients with Luminal A, B subtypes had significantly higher BMI and BSA compared to other subtypes.

Our review of the literature did not find a study that specifically assessed the prevalence of different breast cancer subtypes in elderly patients. Still, we found studies that assessed the prevalence of breast cancer subtypes in various age groups. Chukwuemeka*et al*.,the study suggested a 21% prevalence of HER-2 enriched subtype in patients aged 65 years and older compared to 7.1% in our study (9). Moreover, they found that age is

significantly associated with molecular subtype and patients with triple-negative or luminal B subtypes had a lower mean age than luminal a subtype. Overall, Luminal A was the most common subtype however in patients younger than 35-year-old triple-negative subtypes was the most common subtype. Kwan and colleagues demonstrated that luminal A subtype patients have a significantly higher mean age than other subtypes, furthermore they showed that alcohol consumption is significantly more prevalent in luminal A compared to Luminal B (10). Both of these studies showed that Luminal A is the most common breast cancer subtype, which is in line with our findings. Carey *et al*. compared the prevalence of different subtypes between African-Americans and non-African-Americans before and after menopause (11). They reported that luminal A is the most common subtype in post-menopausal women. This is also in agreement with our study although many post-menopausal patients are younger than 65-year-old.

We also compared the tumor grade between different subtypes and most of our patients had grade II tumors. In contrast to our findings Chukwuemeka*et al*., Carey *et al*., and Kurebayashi*et al*., studies reported the grade III to be most prevalent in HER-2 enriched and Triple-negative subtypes(6,9,11). In Kurebayashi*et al*., and Chukwuemeka*et al*., studies, most patients with luminal subtype had grade II tumors (6,9); however, in Carey study, luminal subtype had an equal distribution of different grades (11). In Chukwuemeka*et al*., study HER-2 enriched and Triple-negative subtypes had significantly higher grades than luminal subtype (9).

In all of the aforementioned studies, stage II disease was the most prevalent in all subtypes except in Kurebayashi*et al*.,a study in which stage I disease was a little more prevalent than Stage II in Luminal A subtype (6). In our study, patients with luminal and HER-2 enriched subtypes were most commonly in stage II. However, stage III was more prevalent in the triple-negative subtype. Similar to our studies, all of the previously noted studies reported the ductal carcinoma to be the most prevalent pathology in all breast cancer subtypes (6,9,11).

We carried out our study on patients aged 65-year-old and higher, whereas other studies included a variable range of age groups. Therefore we should keep this difference in mind when comparing our results with other studies.

Our study had several limitations including the inability to measure Ki-67 biomarker in samples before 2015. Therefore we could not differentiate between Luminal A and Luminal B subtypes. Moreover, several medical records of patients contained insufficient data forcing us to evaluate fewer variables than we originally intended to. We only included patients from two centers; a further multi-centered study may be more informative. We also were not able to carry out a suitable comparison between different subtypes' risk factors due to our cross-sectional study design and the lack of a control group. We suggest further studies for assessing the prevalence of different breast cancer subtypes in other age groups and bigger sample population. Additionally, further studies comparing the risk factors, prognosis and suitable treatment of different subtypes is feasible.

Our study demonstrated the prevalence of different breast cancer subtypes in patients aged 65-year-old and higher to be as followed: Luminal A, B 69.8%, HER-2 enriched 7.1% and Triple-negative 23.1%. We also showed that patients with Luminal A, B subtypes had significantly higher BMI and BSA compared to other subtypes.

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