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Original Article

Comparison of disease free survival in breast cancer molecular subtypes

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Abstract

Background: Breast cancer management depends on molecular subtypes. The aim was to compare disease-free survival (DFS) among the different subgroups. Overall survival (OS) is a secondary endpoint.

Methods: This cross-sectional study was done on breast cancer women that were treated in our center, from 2009 to 2015. Breast cancer molecular subtypes were determined based on clinicopathological criteria recommended by St Gallen and include; luminal A, luminal B Her- 2-neu positive, luminal B Her-2-neu negative, Her-2 enriched and triple negative. Patients with metastasis at diagnosis or those without follow-up were excluded. Patients were followed-up from 12 to 132 months. Cox regression analysis was used for analogy of DFS and OS between the subgroups.

Results: Out of three hundred patients, 221 were enrolled with median age of 47 years old (26 to 83). Luminal B, Her-2 negative was the most common subgroup with 83 patients (35.5%). Five and 10 years PFS were 95% and 81% for luminal A, were 95.5% and 92% for luminal B Her-2 positive, were 92% and 91% for luminal B Her-2 negative, were both 84% for triple negative and were 76% and 74% for Her-2 enriched subgroups, respectively. With multivariate analysis, the stage of tumor (HR=5.9 CI=1.06-32.69) and triple negative subgroup (HR=5.2 CI=1.33-20.31) were independent factors for recurrence.

Conclusion: Based on the results of this study, the triple-negative breast cancer and possibly Her-2 enriched subgroup have a shorter DFS than luminal breast cancers. Also, the stage of tumor is an independent factor for recurrence.

Keywords: Molecular subtypes, Breast cancer, Disease free survival, Overall survival.

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Breast cancer is a common cancer in the world, is a common cause of death and common cancer in women (1). Based on national report of cancer published by the Ministry of Health and Medical Education of Iran, in 2015, 12802 women were diagnosed with breast cancer which was the most common cancer in Iran (2). Several prognostic factors have been proposed in breast cancer. The most important factors associated with lower survival rate include: higher stage of the disease, more involved lymph nodes, higher grade of the tumor, less favorable histology, negative progesterone (PR) and estrogen (ER) receptors, amplification of her-2-neu receptor, age of onset before menopause, low socio-economic status and obesity (3-5).

One of the important predictors of tumor behavior is molecular characteristics and genetic changes of tumor cells, gene expression profile in tumor cells was determined with DNA microarray, but this method is not generally available. Expression levels of progesterone receptors (PR), estrogen receptors (ER) and Her-2-neu on tumor cells, accepted as indicators of genetic changes and molecular characteristics in breast cancer (6, 7).

Based on this, breast cancer is divided in different molecular subtypes, which include: Luminal A: ER/PR expression level is strongly positive but HER-2-NEU expression is rare, in terms of grading, it is mild to moderate and p53 mutation rarely occurs, the percentage of ki-67 is equal or less than 14%. Luminal B: ER/PR expression is variable positive, but HER2 expression is rare, in terms of grading, it is moderate to high and p53 mutation occurs uncommonly, the percentage of ki-67 is more than 14%.HER2/NEU: ER/PR expression is positive or negative, but HER2 is overexpressed, in terms of grading, it is moderate to high and p53 mutation is common, the percentage of ki67 is also increased. Basal like: ER/PR expression is negative and HER2 expression is also negative. In terms of grading, it is high grade and p53 mutation is common, the percentage of ki67 also increased (8-10). Tumor cell biology is different according to the pattern of gene expression in these subgroups, so that the basal-like group (triple negative), the luminal B and HER2 enriched group, have a higher chance of early recurrence than luminal A cancer. Also, the survival rate is different in different subgroups. In some studies, the triple negative subgroup had the worst prognosis (3, 11, 12). The rate of complete pathological response to neoadjuvant chemotherapy is not the same in different subgroups. Luminal A and luminal B cancers respond less to this type of chemotherapy than non-luminal subgroups (triple negative and HER-2 enriched) (13, 14). Considering the significance of molecular subtypes in the management of breast cancer, and due to the lack of any study in Iran, this study was performed with the aim of determining disease-free survival (DFS) in women with breast cancer referred to the Omid Oncology Clinic and Ayatollah Rouhani Hospital, Babol in different subgroups.

Methods

This retrospective cross-sectional study was performed on women with breast cancer who referred to the oncology department of Rouhani Hospital and Omid Clinic of Babol University of Medical Sciences during 2009 to 2015.

Demographic characteristics of patients including age, marital status, height and weight, BMI, menopausal status (pre-menopause, menopause). Also, the pathology reports of the patients were extracted from their files for the tumor size and number of involved lymph nodes and the status of hormonal receptors, Ki-67 and HER-2-neu expression. For metastatic work up, CT scan of the chest, CT scan or ultrasound of the abdomen and in cases where the patient complained of bone pain or the serum level of alkaline phosphatase was high, whole body bone scan was performed. Patients who had metastases at the beginning of diagnosis, patients who did not follow up after chemotherapy, and patients with incomplete files were excluded from the study. Estrogen and progesterone receptor expression levels were determined with immunohistochemistry staining on paraffin embedded sample of tumor tissue. If more than 1% of tumor cells were stained or Remmele score ≥ 3, they were considered positive. The intensity of receptor positivity in the pathology report, was divided into weak, moderate or strong. HER2 expression status was first assessed by immunohistochemistry staining. Based on the intensity of staining, if HER-2 expression in IHC was negative or one positive, it was considered negative, and if it was three positive, it was considered positive. If it was two positive, positivity or negativity of HER-2 was determined by in situ hybridization methods (FISH or CISH). Molecular subtypes of breast cancer were determined by clinicopathological criteria recommended by St Gallen and divided into the following subgroups:

1- Luminal A: ER and/or PR expression were positive, Her-2 overexpression was negative and Ki-67 equal or less than 14%
2- Luminal B Her-2 positive: ER and/or PR expression were positive, Her-2 overexpression was positive and Ki-67 more than 14%
3- Luminal B Her-2 negative: ER and/or PR expression were positive, Her-2 overexpression was negative and Ki-67 more than 14%
4- Her-2 enriched: ER and PR expression were negative, Her-2 overexpression was positive
5- Triple negative: ER and PR expression were negative, Her-2 overexpression was negative (15, 16).

American joint committee of cancer was the reference for Tumor node metastasis (TNM) staging (17). Common treatments were performed based on the disease stage and molecular subgroup. After chemotherapy and radiation treatments, patients were followed-up every three to six months. In addition to history and examination, mammography, annual ultrasound, blood tests and, if necessary, tumor marker CA 15-3 were performed for patients. In suspected cases of recurrence or metastasis, other imaging tests including CT scan and in some cases PET scan were performed and recurrence was confirmed by biopsy. The patients followed-up from 12 to 132 months and up to March 2020. The last status of the patients in terms of aliveness, death, date of death and its cause was obtained through an extraction from files or phone calls. The obtained data were analyzed with SPSS V22 software and

with a significance level of less than 0.05. To compare tumor size and the number of involved lymph nodes, chi-square test or Fisher's exact test, and to compare DFS, overall survival, and the effect of age in different subtypes of breast cancer, Cox regression model was used. Survival curves were shown by the Kaplan-Meier method.

This article was based on two studies that were approved in the Research Ethics Committee of Babol University of Medical Sciences with codes MUBABOL.HRI.REC.1397.174 and MUBABOL.HRI.REC.1398. The information of the patients was confidential and was not given to any natural or legal person. This article was taken from the thesis entitled "Study of disease-free survival rate in different breast cancer subgroups" and the thesis entitled "Study of the frequency of molecular subgroups in patients with breast cancer at Ayatollah Rouhani Hospital from 2009 to 2016".

Results

During 2009 to 2016, 300 patients with breast cancer visited Rouhani Hospital and Omid Clinic. 27 women were excluded due to file defects. Out of 273 remaining patients, 39 (14.7%) had metastases at diagnosis and were excluded from the study. Two hundred and thirty-four women were examined; whose median age was 47 years, with an age range of 26 to 83 years. In terms of age distribution, 152 (65%) people were between 40 to 60 years old. One hundred twenty-three (45.5%) people of the studied subjects were overweight and only 3 (1.7%) of the patients were single. The demographic characteristics of the studied women are shown in table 1. Eighty-three patients were in the luminal B HER-2 negative subgroup (35.5%) and the lowest number (13 patients) were in HER2 positive (5.6%) and 56 (23.9%) patients were in the basal like group. In dividing the involved lymph nodes based on their size, most of them were T2, between 2 and 5 cm (67%). Most of the patients had no lymph involvement (table 1). Thirteen patients did not return to hospital for follow-up after treatment and were excluded from the study, and 221 patients were followed - up. Patients were followed-up from 12 months to 132 months. Twenty-three patients (9.8 percent) died, and 4 of them (20.8 percent) died due to reasons other than breast cancer. Including deaths and patients who did not return for further follow-up, 79 people remained in the study until the end of the sixth year after diagnosis. One patient had a local recurrence after two years and 25 patients had systemic recurrence. The most recurrence was in basal like group (34.6%) (table 2).

The mean survival of all patients was 123.32 months (CI95%: 115.38-131.26) and the mean disease-free survival in patients was 118.74 months (CI95%: 113.39-124.07).5-year and 10-year OS was 91.5% and 78%, respectively (figure 1A). The median 5-year survival of the patients was not obtained. Five-year and 10-year disease-free survival was 89% and 75.5%, respectively (figure1B). A p- value of overall survival in different subtypes of breast cancer was 0.35. The highest 5-year overall survival was in the luminal A group and the lowest in the basal-like group (table 3, figure 2A). The highest 5-year disease-free survival was found in the luminal B HER2 positive group and the lowest in the HER2 positive group (table 3, figure 2B). To designate the effect of different variables on the risk of recurrence, Cox regression analysis was performed. In univariate analysis, age at diagnosis, body mass index, tumor size, number of involved lymph nodes, tumor stage and molecular subtype of breast cancer did not significantly increase the risk of cancer recurrence (table 4). But in multivariate analysis, cancer stage with Hazard ratio (HR) = 5.9 (CI = 1.06-32.69) and triple negative subgroup with HR = 5.20 (CI = 1.33-20.31) were independent factors in increasing the risk of recurrence (table 5).

Table 1. Basic characteristic of the breast cancer patients

Variable	number	percentage
Age		
<40	40	17.1
40-60	152	65
>60	42	17.9
BMI (body mass index)		
Normal	46	19.7
Overweight	107	45.7
Obese	81	34.6

Variable	number	percentage
Marriage		
Married	230	98.3
Not-married	4	1.7
Menopause		
Pre-menopause	137	58.5
Post-menopause	97	41.5
Molecular subgroups		
Lum A	54	23.1
Lum B-HER2 pos	28	10.3
Lum B-HER2 neg	83	35.5
basal like	56	23.9
Her2 enriched	13	5.6
Tumor size		
<2cm	50	21.4
2-5cm	149	63.7
>5cm	35	15
Number of tumoral glands		
0	99	42.3
1-3	81	34.6
4-9	37	15.8
>9	17	7.3
Stage of disease		
Stage 1	26	11.1
Stage 2	148	63.2
Stage 3	60	25.6

Table 2. The data of 26 patients with breast cancer recurrence

Recurrence	number	percentage
Total cases		
Local recurrence	1	3.8
Systemic recurrence	25	96.2
Molecular subgroups		
Lum A	5	19.2
Lum B-HER2 pos	1	3.8
Lum B-HER2 neg	8	30.8
basal like	9	34.6
Her2 enriched	3	11.5
Stage of disease		
Stage 1	1	3.8
Stage 2	16	61.5
Stage 3	9	34.6

Table 3. Five and ten-year overall survival and disease-free survival in breast cancer subgroups

Molecular subgroups	5-year disease-free survival	10-year disease-free survival	5-year overall survival	10-year overall survival
Luminal A	95	81	98	80
Luminal B-HER2 pos	95.5	92	92	92
Luminal B-HER2 neg	92	91	92	91
basal like	84	84	84	84
Her2 enriched	76	74	87	74

Table 4. Cox regression model univariate analysis results for disease-free survival according to molecular subgroups, age, BMI tumor size, number of involved lymph nodes, tumor stage

Variables	HR $_{crude}$	95% CI	P-value
Age at diagnosis(years)			0.125
<40	1		
40-60	0.98	0.28-3.50	0.982
≥ 60	2.41	0.64-9.15	0.195
BMI			0.603
Normal	1		
Overweight	0.59	0.21-1.67	0.320
obese	0.78	0.271-2.25	0.649
Stage at diagnosis			0.016
Stage 1	1		
Stage 2	1.11	0.23-5.37	0.892
Stage 3	3.75	0.76-18.38	0.104
lynphnode			0.031
0	1		
1-3	2.39	0.80-7.13	0.119
4-9	3.13	0.89-10.92	0.074
≥ 10	7.33	1.94-27.68	0.003
Tumor size			0.207
≥ 2cm	1		
3-5 cm	0.55	0.21-1.42	0.215
≤ 5 cm	1.30	0.41-4.19	0.655
Sub type mol			0.332
Luminal A	1		
Luminal B. her2	1.47	0.15-14.42	0.738
Luminal B. her2-	1.58	0.39-6.42	0.523
Her2 enriched	3.26	0.53-19.90	0.201
Basal.like	3.36	0.90-12.50	0.071

Table 5. Cox regression model multivariate analysis results for disease-free survival according to molecular subgroups, age, BMI, tumor stage

Variables	HR adjusted	95% CI	P-value*
Age at diagnosis(years)			0.113
<40	1		
40-60	1.39	0.35-5.49	0.632
≥ 60	3.58	0.85-15.11	0.082
Stage at diagnosis			0.003
Stage 1	1		
Stage 2	1.11	0.20-6.11	0.906
Stage 3	5.90	1.06-32.69	0.042
BMI (body mass index)			0.474
normal	1		
overweight	0.474	0.14-1.57	0.222
obese	0.628	0.17-2.22	0.471
Sub type mol			0.093
Luminal A	1		
Luminal B. her2+	0.941	0.09-9.74	0.959
Luminal B. her2-	2.52	0.58-10.95	0.217
Her2enriched	5.76	0.87-38.10	0.069
Basal like	5.20	1.33-20.31	0.018

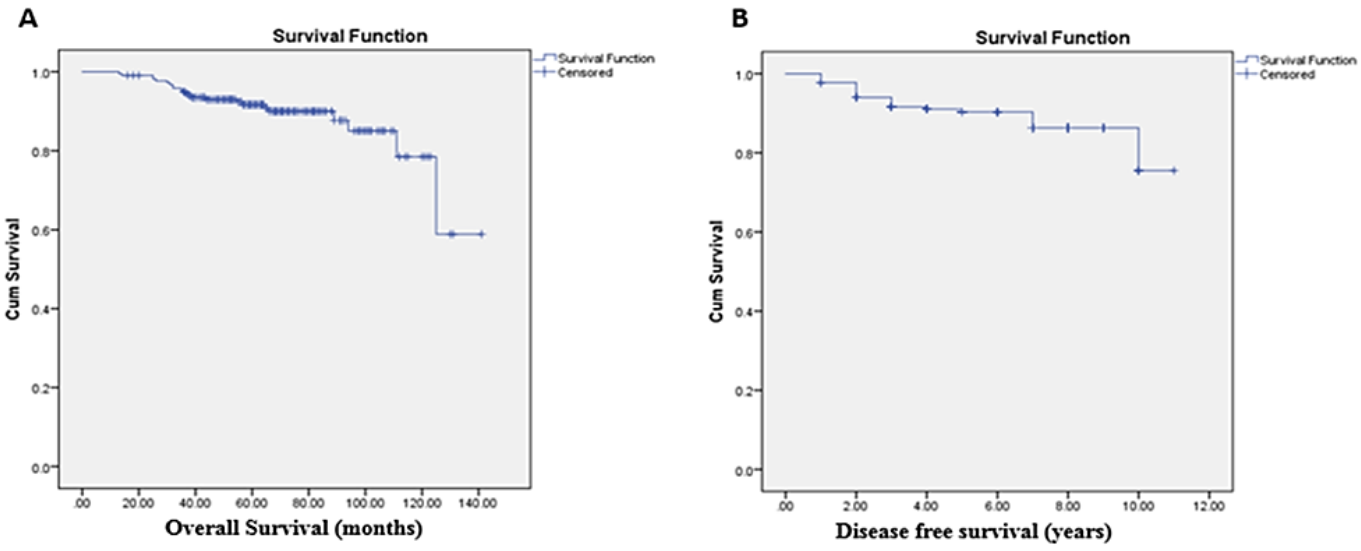

Figure 1. Survival curves in patients with breast cancer during 10 years, A) Overall survival B) Disease-free survival

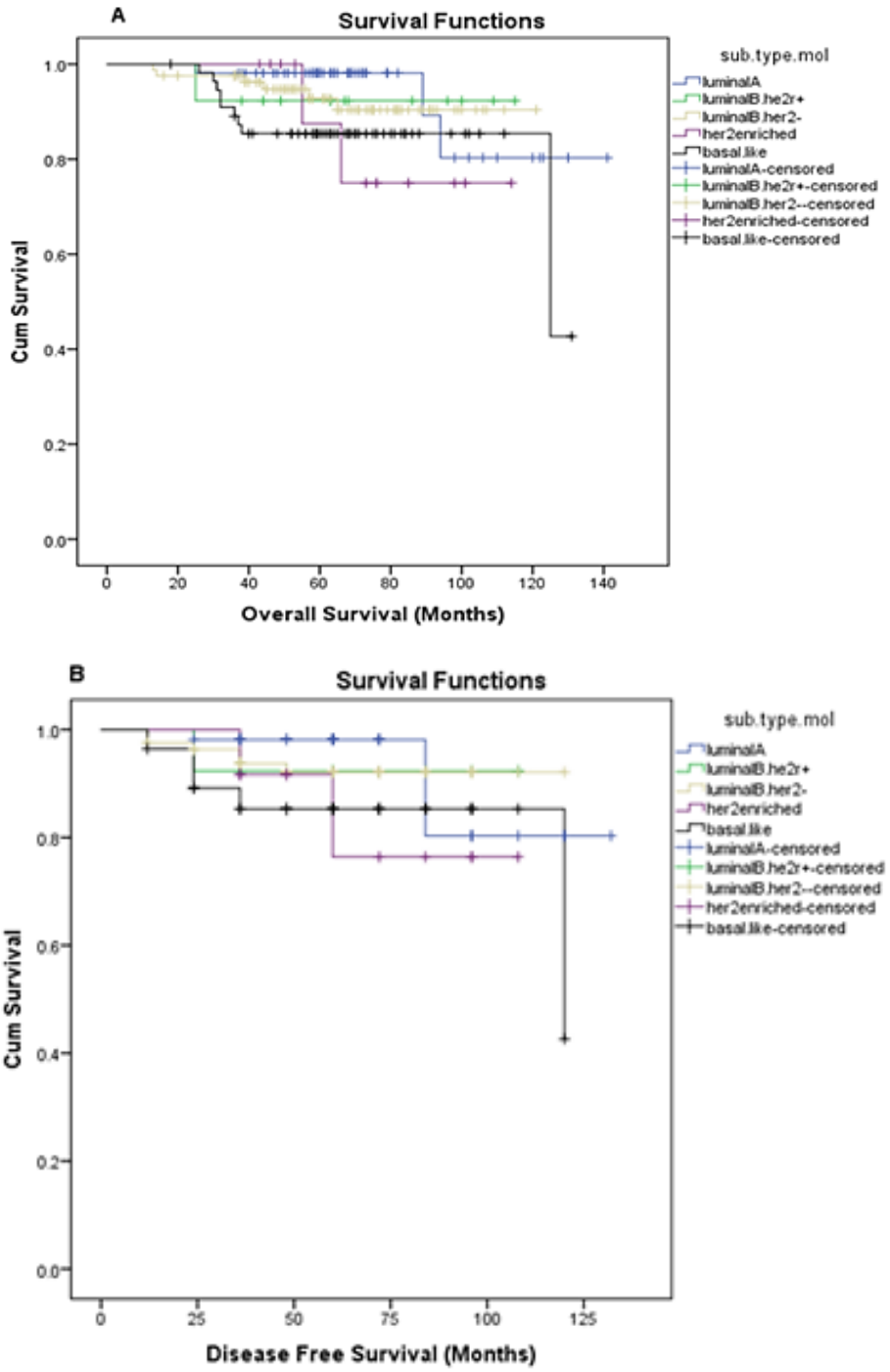

Figure 2. Survival curves in breast cancer patients according to molecular subtypes during 10 years, A) Overall survival, B) Disease free survival.

Discussion

This research is the first study to determine the prognosis of breast cancer based on its molecular subtypes in Iran, based on our knowledge. Treatment planning in breast cancer is based on the molecular characteristics of tumor cells. The status of estrogen or progesterone receptors and HER-2 receptor in the tumor cell membrane and Ki-67 level, which is an index indicating the degree of tumoral cell division and in relation to the S phase of the cell, are the main indicators of dividing breast cancer into different subtypes in St. Gallen consensus (7, 18). Treatment prognosis is different in different subgroups of breast cancer (11). The luminal A group seems to have the best prognosis and studies to exclude chemotherapy in this subgroup are ongoing (19). In Maisonneuve et al.'s study on patients who did not have metastases at the beginning of diagnosis,

patients of luminal A subgroup had higher distant-disease-free survival and less ten-year distant metastasis than luminal B subgroup (18). In our study, with multivariate analysis, we showed that the triple negative subtype and higher stage of breast cancer are independent factors associated with a higher risk of breast cancer recurrence, which is in accordance with the findings of other studies (11, 20, 21). In these studies, it was concluded that triple negative breast cancer is more common in premenopausal women, and is associated with lower survival and leads to 40% deaths in the first 5 years after diagnosis (20, 21).

The worse prognosis of the triple negative subgroup is attributed to the absence of an inhibitable target in the tumor cell. The presence of ER or PR, as well as increased expression of the HER-2 receptor, causes the effect of drugs that inhibit these receptors (which are prescribed for one to ten years in addition to chemotherapy drugs) in preventing the recurrence of the disease and increasing the survival of patients (11). In our study, the number of involved lymph nodes, tumor size, and age at diagnosis were not significantly associated with the risk of recurrence. Also, the risk of recurrence for the hre-2 enriched group was high compared to the luminal A group, although this difference was not statistically significant, probably due to the small number of patients in this subgroup. The luminal A subgroup showed a significant difference from other subgroups in terms of DFS, which means that the most recurrences occurred between 5 and 10 years, DFS in this subgroup dropped from 98% in the fifth year to 81% in the tenth year, which was the biggest drop among subgroups.

Therefore, triple negative and Her-2 positive patients who have not relapsed during 5 years after diagnosis, may be less likely to relapse or metastasize compared to the luminal A subgroup. In a meta-analysis, Chen et al. investigated the risk of breast cancer recurrence in different subgroups. In total, 15 studies with 21645 patients were analyzed. The result was that when the risk of recurrence was examined as a single receptor, patients with her-2 positive had a 1.97 times the risk of recurrence compared to her-2 negative patients (HR = 1.97, 95% CI: 1.41-2.75) But considering the status of all three receptors together, the triple negative group had the highest risk with a 3.19 times recurrence risk (22). In the present study, luminal B subtype, including HER-2 positive or negative, was the most common subtype (45.8%) and HER-2-enriched type with 5.6% had the lowest prevalence. Contrary to our results, in many studies (13, 23-26) , luminal A is the most common subtype with a frequency of more than 50%. In some other studies, luminal B (12, 24, 27, 28) was the most common subtype.

In our study, only 23% of patients were in the luminal A subgroup. Considering that most luminal B cases are negative in terms of HER-2 receptor expression (in our study, this group included 35.5% of all cases) and Ki-67 percentage is the basis of luminal A and B differentiation, and considering that the report of this index may be different by different pathologists (29), the reason for the difference in the prevalence of luminal A and B is justified to some extent. Also, the difference in the gene expression pattern of patients in different races may be involved in the type of their luminal manifestation.

In our study, the prevalence of the triple negative group was about 24%, which is alike to the prevalence reported in African Americans (24.6%) (30) and higher than Hispanics in Puerto Rico. (17.3%) (31) and her-2 enriched group constituted 5.6% of the cases. Because the fate of all patients who refused to continue the follow-up is unknown, the OS statistics are not exact. The highest 5-year overall survival was seen in the luminal A subgroup and the lowest in the triple negative subgroup. Five- and ten-year overall survival in our study was 91.5% and 78%, which are acceptable numbers in breast cancer. Five-year overall survival in the Vahdaninia's study in 2003 and Khodabakhshi's study in 2013 62% and 72% were reported respectively (32, 33).

Considering that in our study, patients with stage four did not participate, this difference is justified to some extent. Another factor is the time of the study, Vahdaninia's study is older and with the passage of time and more use of new treatments, the survival of patients has increased. Also, a 5-year overall survival of 71.2% was reported in Patrica's study in Puerto Rico. Hennig's study of 4102 breast cancer patients showed an overall survival of 95% for luminal A and 78.5% for triple negative subgroup during 55 months follow-up of patients (34).

About 80.3% of patients, in our study, were overweight or obese, and this indicates the importance of exercise and keeping body weight within normal limits in cancer prevention programs. Sixty-five percent of patients were in the age range of 20 to 60 years, which shows the importance of breast cancer screening programs in this age range. Based on the results of this study, the triple-negative subgroup has a lower DFS and a higher risk of recurrence than other breast cancer subgroups. Also the conclusion, with borderline significance statistically, may be correct for Her-2 enriched subgroup in comparison to luminal subtypes. Probably, recurrence risk, from 5 to 10 years after diagnosis in luminal subgroups, is more than triple negative and Her-2 enriched subgroups. It seems that overweight and obesity play a role in causing breast cancer.

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