

# Histopathological Feature of Early-Onset Breast Cancer: A Comparative Analysis

Iraj Feizi<sup>1</sup>,  
Khatereh Isazadehfar<sup>2\*</sup>,  
Farshid Sadegzadeh<sup>3</sup>,  
Paniz Farshadi<sup>3</sup>

## ABSTRACT

**Background:** Breast cancer is one of the most common malignancies among women. In some reports, it has been specified that the diagnosis of breast cancer at an earlier ages worsens the prognosis; this can be attributed to a combination of factors such as advanced stage of disease and late demonstration. Considering different results in last studies, this study's aim was investigation of breast cancer histopathology in two age groups of women under and above 40 years old.

**Material and Methods:** A cross-sectional study was performed on 64 patients with breast cancer referring to hospitals during 2014 and 2015 years. All histopathologic information is collected from patient's cases. Data were compared in two age groups with equal T. Also, the levels of axillary lymph nodes involvement were evaluated in the equal T for both groups.

**Results:** We evaluated 64 patients, 71.9% of them were over 40 years old and 28.1% were under 40 years of age. The most common type of tumor was invasive ductal carcinoma. Involvement of the axillary lymph nodes in the equal T was significantly higher in patients less than 40 years of age ( $p=0.005$ ) than patients over 40 years old ( $T=1$  and  $T=2$ ) ( $p=0.032$  and  $p=0.05$ ).

**Conclusion:** Our study signified that in equal T rates the level of axillary lymph nodes involvement in patients younger than 40 years old is higher than those older than 40 years of age. Therefore, breast cancer at early ages is associated with a worse prognosis.

**Keywords:** Breast cancer, Histology, Pathology, Axillary lymph node, Age group.

<sup>1</sup>Department of Surgery, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran

<sup>2</sup>Determinants of Health Research Center, Department of Community Medicine, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran

<sup>3</sup>General Physician, Ardabil University of Medical Sciences, Ardabil, Iran

**\*Send correspondence to**

Khatereh Isazadehfar

Determinants of Health Research Center, Department of Community Medicine, School of Medicine, Ardabil University of Medical Sciences, Ardabil, Iran,

E-mail: isazadehfar@yahoo.com

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## INTRODUCTION

Breast cancer is one of the most common malignancies among women. The peak age of breast cancer incidence in Iranian women is in the 4th and 5th decades of life, which is one decade below the age of the average global conflict<sup>1</sup>. The risk of developing breast cancer in women's lifetime is 12.5% (one in eight cases) and the mortality risk of breast cancer is 3.6% (one in twenty-eight cases). About 10 percent of women in the United States experience breast cancer in their lives and this cancer are the second leading cause of death from malignancies after lung cancers. About 5 percent of the breast cancers are hereditary and 80 to 90 percent occur sporadic. All breast cancers, although occur over the age of 50 but it may happen at any ages<sup>2,3</sup>. According to research results, almost 7% of breast cancer occurs in people under 40 years of age in the world<sup>4</sup>. Breast cancer accounts for about 23% of all female malignancies and its prevalence is increasing<sup>2,3,5</sup>.

Breast cancer rarely occurs in young women, and only about 2% of patients are under the age of 35 (Less than 17 cases per 100,000 women or less than 6% of the total number of women with breast cancer). The American National Cancer Society predicts that among women under the age of 40 in this country, of every 225 people one person, among women under the age of 60, out of every 22 people, 1 person, and among women under the age of 80, one in 10 people will be affected<sup>3</sup>. In some reports, it has been specified that the diagnosis of breast cancer at an earlier ages worsens the prognosis; this can be attributed to a combination of factors such as advanced stage of disease and malignancy of the tumor<sup>6,3</sup>.

Some studies indicate that the medullary carcinoma of the breast is more common in women under the age of 35 and lobular type in the elderly persons. The result of some studies suggests no difference in tumor size, lymph node involvement, and degree of tissue involvement among older and younger women with breast cancer<sup>7,8</sup>.

Discussions about more tumor invasion and worsening the prognosis of breast cancer in young women continue<sup>9, 10, 11, 12</sup>, but further studies are needed on the criteria of breast cancer, the rate of invasion, tissue involvement, and the type of tumor because with the proving of this probably a question can be raised that what is the cause of more invasion and tissue involvement of breast cancer in younger women? And this will be a trigger for further researches about this subject.

Considering the different results of the studies in this regard this study evaluates histopathological factors of breast cancer among women under the age of 40 and women over 40 years of age and compares them with each other to make a more complete analysis of the histological and pathological differences in these two groups.

## MATERIAL AND METHODS

A descriptive-analytic cross-sectional study was performed on 64 patients with breast cancer who were candidates for surgery and referred to all surgical centers and hospitals during 2014 and 2015 years. This study was approved by the Ethics Committee of University of Medical Sciences (IR.ARUMS.REC.1394.75).

Sixty-four patients with breast cancer after taking informed consent entered the study. Inclusion criteria consist of: primary breast cancers, non-specific invasive breast cancer which confirmed by pathology, unilateral disease, recurrence and metastasis of disease diagnosed by Computed Tomography (CT) or B-Mode ultrasound or Magnetic Resonance Imaging (MRI), having complete follow up and clinical information, candidates of radical or Moderate Mastectomy (MRM). Patients with carcinoma-in-situ, FNA diagnosed cancer cases which did not followed up for treatment, male's breast cancer and history of pre-operative chemotherapy were considered as exclusion criteria.

Clinical and pathological information collected included: age at diagnosis, number of involved lymph nodes, lymph nodes involvement level, tumor type, grade and size, vascular and lymphatic invasion, nipple and deep margin invasion, the location of the lesion. Patients were divided into two age groups: under and over 40 years of age, and all data were compared in both groups based on tumor size (in equal T).

For statistical analysis, SPSS version 22 was used. The difference between the two age groups was analyzed using independent T tests and Mann-Whitney U tests. For quantitative variables, the Chi-Square test and Fisher's exact test for the classified variables were analyzed as needed. All statistical tests were two tailed and the test results less than and equal to 0.05 were considered statistically significant.

## RESULTS

Out of 64 patients evaluated, 46 (71.9%) had over 40 years old and 18 cases (28.1%) under 40 years of age. The age range of patient's was between 30-86 years old with an average age of  $49.9 \pm 11.92$  years. In the group under 40 years old the mean age was  $36.8 \pm 2.9$  and in the age group over 40, the mean age was  $54.8 \pm 10.1$  years. The pathological characteristics of all patients are presented in Table 1.

In the case study, 87.5% of patients had lymphatic invasion, with the highest level of L1 involvement (21.9%). Most cases had a mass on the right side (54.7%), and the upper outer quadrant of the breast (73.4%) was the most common site of breast cancer in patients Table 1. The pathological and histological characteristics of the patients in the two age groups below and above 40 years are presented in Table 2. The highest number of involved lymph nodes in the age group under 40 years old was 4-9 lymph nodes (55.6% of cases) but in over 40 yrs. group

**Table 1: Pathological Characteristics of the Patients.**

Variable	Category	N=64
Lymph node Level (n (%))	L1	14 (21.9)
	L2	2 (3.1)
	L3	3 (4.7)
	ND	45 (70.3)
Lymphatic invasion (n (%))	Yes	56 (87.5)
	No	8 (12.5)
T Stage (n (%))	T1	19 (29.7)
	T2	34 (53.1)
	T3	10 (15.6)
	T4	1 (1.6)
Tumor Grade (n (%))	Grade I	25 (39.1)
	Grade II	30 (46.8)
	Grade III	9 (14.1)
Nipple involvement (n (%))	Yes	6 (9.4)
	No	58 (90.6)
Histology Type (n (%))	invasive ductal carcinoma	60 (93.6)
	invasive medullary carcinoma	1 (1.6)
	invasive lobular carcinoma	1 (1.6)
	mucinous carcinoma	2 (3.2)
Tumor Side (n (%))	Right	35 (54.7)
	Left	29 (45.3)
Site of origin (n (%))	upper outer	47(73.4)
	upper inner	9(14.1)
	lower outer	2(3.1)
	lower inner	6(9.4)

**Table 2: Histopathological characteristics of the breast cancer compared in the two age groups.**

Variable	<40 yrs. (N=18)	≥40 yrs. (N=46)	Pvalue
Lymph node (n (%))			0.005
negative	2 (11.1)	18 (39.1)	
01-Mar	2 (11.1)	14 (30.4)	
04-Sep	10 (55.6)	12 (26.1)	
≥10	4 (22.2)	2 (3.4)	
Lymph node Level (n (%))			0.061
L1	2(33.3)	12(92.3)	
L2	2(33.3)	0(0)	
L3	2(33.3)	1(7.7)	
Tumor Stage (n (%))			0.27
T1	5 (27.8)	14 (30.4)	
T2	12 (66.7)	22 (47.8)	
T3	1 (5.6)	9 (19.6)	
T4	0 (0)	1 (2.17)	
Tumor Grade (n (%))			0.93
I	7 (38.9)	18 (39.1)	
II	8 (44.4)	22 (47.9)	
III	3 (16.7)	6 (13)	
Histology Type (n (%))			0.323
invasive ductal carcinoma	16(88.9)	44(95.7)	
invasive medullary carcinoma	0(0)	1(2.2)	
invasive lobular carcinoma	1(5.6)	0(0)	
mucinous carcinoma	1(5.6)	1(2.2)	
Tumor Size $\mu \pm \delta$	3.38±1.61	3.69±1.95	0.56

N=number of patients in each age category.

**Table 3:** Pathological characteristics of the two groups in different T.

variable		<40 yrs. (N=18)	≥40 yrs. (N=46)	Pvalue
L1	Lymph node Level	1(33.3)	3(100)	0.08
L2		0(0)	0(0)	
L3		2(66.7)	0(0)	
Yes	Lymphatic invasion	5(100)	11(78.6)	0.34
No		0(0)	3(21.4)	
I	Tumor Grade	2(40)	7(50)	0.59
II		3(60)	5(35.7)	
III		0(0)	2(14.3)	
Yes	Nipple involvement	0(0)	0(0)	1
No		5(100)	14(100)	
L1	Lymph node Level	1(33.3)	7(87.5)	0.03*
L2		2(66.7)	0(0)	
L3		0(0)	1(12.5)	
Yes	Lymphatic invasion	11(91.7)	20(90.9)	0.721
No		1(8.3)	2(9.1)	
I	Tumor Grade	5(41.7)	8(36.4)	0.57
II		4(33.3)	11(50)	
III		3(25)	3(13.6)	
Yes	Nipple involvement	1(8.3)	2(9.1)	0.72
No		11(91.7)	20(90.9)	
L1	Lymph node Level	0(0)	2	-
L2		0(0)	0(0)	
L3		0(0)	0(0)	
Yes	Lymphatic invasion	1(100)	7(77.8)	1
No		0(0)	2(22.2)	
I	Tumor Grade	0(0)	3(33.3)	0.69
II		1(100)	5(55.6)	
III		0(0)	1(11.1)	
Yes	Nipple involvement	0(0)	3(33.3)	0.51
No		1(100)	6(66.7)	

most of patients (39.1%) hadn't any involved lymph node and this difference was statistically significant ( $P = 0.005$ ). Ductal carcinoma was the most abundant tumor in both age groups and the majority of patients in both groups had T2 stage of tumor.

There was not any deep margin involvement in any cases. Both groups did not have a significant difference in tumor size ( $P=0.56$ ). There was no significant difference in the lesion side (in right or left breast) ( $p=0.426$ ) and location of the tumor in the breast, in studied age groups ( $p=0.804$ ). The majority of patients in both the study groups (44.4% in the young age group and 47.9% in the old age group) were found to be exhibiting pathological grade II, followed by grade I (38.9% in young women vs. 39.1% in old women). Grade III was found to be the least common. ( $p=0.93$ ).

The evaluation of tumor grade, lymph node involvement, lymphatic invasion and nipple involvement in the both age groups, in different T are presented in Table 3.

At T1, the highest level of lymph node involvement in the younger age patients was related to the L3 level (66.7%) and in the next stage it is related to the L1 (33.3%) while in the older patients this level is only related to L1 (100%). At the stage of T2, L2 with 66.7% then L1 with 33.3% were

the highest level of lymph node involvement in younger patients, but in the older age group, L1 (87.5%) was still the most frequency) ( $p=0.03$ ).

## DISCUSSION

Among the various types of cancer, breast cancer accounts for 23% of the cancers in the females. This cancer is the most common cancer among the women and causes the highest mortality rate in females Also breast cancer is one of the important concern in the health of women in the world<sup>13</sup>. The prevalence of breast cancer in the United States and Europe is twice as high as in Asia, and in all countries the prevalence is increasing<sup>14, 15</sup>. In worldwide statistics from 1980 to 2010, the incidence of breast cancer has shown an annual 3.1% increase, and mortality from breast cancer has increased at an annual rate of 1-8%<sup>16</sup>.

According to the statistics from the Iranian Cancer Registry Report in 2009 in Iran, about 8616 new cases of breast cancer were diagnosed in this country and with an ASR of 28.1 per 100,000 females<sup>17</sup>. According to data from the Cancer Registry Department of the ministry of health and medical education in 2018 in Iran, the age- standardized rate for breast cancer was 33.21 per 100,000 and the age-standardized mortality rate was 14.2 per 100,000<sup>18</sup>.

In this study similar to the most common type of cancer in both groups was invasive ductal carcinoma. (93.75%). This is similar to a studies taken up by Obeidat, Kocic and Koshariya studies<sup>19, 20, 21</sup>. But in the study of Rosen et al., Medullary carcinoma was the most common type of tumor in the studied patients<sup>22</sup>. Differences between various histologic types of breast cancer by age have been noted in some studies. According to the results of most studies, the frequency of ductal carcinoma is constant by age, and the frequencies of papillary and mucinous carcinoma increases with age. The frequencies of medullary and inflammatory carcinoma either decrease with age or increase up to the age of 50 and then stops<sup>23, 24</sup>.

The present study showed that in each T and in equal T's (T = 1, T = 2 and T = 3) in two age groups studied, the ratio of the number of patients with lymph node involvement to the total number of patients in the group under 40 years is higher than this ratio in patients over the age of 40. This is the sign of more lymph node involvement, in patients with breast cancer under the age of 40 years. In agreement with our findings, many previous studies failed to demonstrate any significant association of histological grade with age<sup>25</sup>. In the study of Kocic et al, in young women compared to older women, the level of T3 and T4 involvement was higher, also grade 3 tumor was higher and most of the patients had 4 to 9 and more than 10 involved lymph nodes<sup>20</sup>. In most studies, the proportions of patients with high grade disease decrease with age, and younger patients are more likely to be diagnosed with a higher grade and a more advanced stage of disease<sup>9, 26</sup>. This discrepancy may be due to different strategies for disease screening at different ages.

In the present study, during the operation of removing the axillary lymph nodes, the level of involved lymph nodes was evaluated, and then in equal T, they were compared in two age groups. Performed analysis revealed that in T = 1 level, patients under the age of 40 had significantly higher involved lymph nodes than those in the age group above 40 years. Also in T = 2, the involvement level of axillary lymph nodes in younger patients was higher than in older. Limited information is available on the association between histological subtype of breast cancer and age.

Investigating the number of involved lymph nodes according to the age of patients showed that the number of involved lymph nodes in the age group under 40 years was significantly more than the patients over the age of 40. Also, tumor grade, vascular and lymphatic invasion were more common in patients under the age of 40 than in patients older than 40 years old, but this difference was not statistically significant.

The results were similar to studies conducted by Ghartimagar, Thangjam, Bonnier, Thapa and Kadivar<sup>3, 27, 28, 29, 30</sup>. In the Ghartimagar study, the most common stage in both age groups was stage 2. Stage 3 in patients of higher age group and stage 1 in the lower age group was more common. It was also shown that in than 35 years old, while at a younger ages, grade 3 was more common<sup>28</sup>. In

Bonnier's study, the number of undifferentiated tumors, microscopic involvement in lymph nodes and negative hormone receptors was higher in patients under the age of 35 years<sup>29</sup>. In Thangjam et al study, in women under 40 years of age, stage 3 was the most common stage while in women over 40 years stage 2 was more common<sup>3</sup>. In the study of Thapa et al, in young women, vascular and lymphatic invasions were more common. Tumor size, grade, and lymph node involvement was higher in younger patients than of the elderly ones<sup>27</sup>. The study of Kadivar et al. Was conducted in 2010 with the aim of investigating histopathology and biomarkers of breast cancer in two group women before menopause (under 40 years of age) and postmenopausal (over 60 years of age). It was found that there was no significant difference between the size of the tumor, lymphatic invasion, histologic grade and stage of the tumors between the group under 40 years old and the group over 60 years old<sup>30</sup>.

In the present study, nipple involvement, tumor grade, lymphatic and vascular invasion were also compared in two groups with the same T-score. The degree of tumor, vascular and lymphatic invasion, was higher in patients under the age of 40 than in patients older than 40 years, but this difference was not statically significant. In a study by Farouk et al, in 2016 that was analyzing, reporting clinical-pathological features and treatment methods of breast cancer in women of Egypt. It has been found that young patient's breast cancer has more aggressive biological behavior and advance stages of clinical manifestations. Therefore, this patients require special attention and appropriate treatment strategies with accurate methods<sup>31</sup>.

The most common place of breast cancer in the present study was the upper outer quadrant of the breast. Our study in this regard was similar to that of Kocic et al. Their study, with the aim of examining the biological and clinical-pathological characteristics of young patient's breast cancer, revealed that in both groups of patients under 40 and over 40, the left breast and upper quadrant was the most commonly involved location<sup>20</sup>.

In our study, the size of the tumor, the place and the side of the conflict in the two age groups were not significantly different. Our study of this view differed from study of Thangjam and Bonnier. In their studies, the size of the tumor was higher in patients under the age of 40 than in patients over 40 years of age<sup>3, 29</sup>. This difference could be due to the screening programs for breast cancer because palpable breast mass and cancer are larger and more advanced than breast cancer detected by screening. The large size of the breast mass or the advanced stage of the disease at the time of diagnosis can only be one of the reasons for the difference in the outcome of the disease in different age groups. Other factors are also influential in disease prognosis, including unfavorable biological parameters such as estrogen and progesterone receptors, gene expression, etc<sup>32</sup>.

This study attempted to cover many clinical and histopathological aspects of breast carcinoma in

association with age groups, but some limitations were incurred. First, for some patients clinical and pathological data were missing because not originally included in the medical records, and that may have to some extent influenced the associations evaluated. Moreover, the retrospective nature of the study and all associated inherent sampling biases must be acknowledged. We could not access sociodemographic characteristics such as marital status, socioeconomic status, and history of reproduction. Finally, the sample size was small and could not accurately represent the whole population. In spite of these limitations, this is a new clinicopathological point of view to breast cancer prognosis transition which may be beneficial for better understanding the tumour biology. The multicenter nature of the study was another strength of this study.

## CONCLUSION

The most common type of tumor in both groups was invasive ductal carcinoma. Our study revealed that in equal T, the rate and level of axillary lymph node involvement in patients under the age of 40 is higher than those older than 40 years of age. As a result, age should be considered as an important factor in the prognosis of patients with breast cancer and plans for educating women about this issue, the importance of breast self-examination, the utilization of healthcare facilities, and screening of breast cancer at an earlier age should be taken into account.

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## CONFLICT OF INTERESTS

None to declare.

## FINANCIAL DISCLOSURE

We declare that the authors have no financial interests related to the material in the manuscript.

## ETHICAL STATEMENTS

This study was approved by the Ethics Committee of University of Medical Sciences (Ethics Code IR.ARUMS.REC.1394.75). The study participants were informed about of the study's purpose. Prior to the study, written consent was obtained from all participants.

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