Breast cancer in young vs old- A clinicopathological analysis

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Abstract

Background: Breast carcinoma in young women has been seen to show differences in clinicopathological characteristics than older women.

Aims: The aim of this study was to compare the clinicopathological characteristics of breast carcinoma in women below 40 years and women over 40 years, in our tertiary care hospital in Kashmir.

Settings and designs: This was a retro-prospective study in which 260 patients were compared, out of which 85 patients were 40 years. Patients were compared for various clinical and histopathological parameters and the study was conducted in the department of pathology, Sher- I -Kashmir institute of medical sciences, soura, Jammu and Kashmir, India.

Materials and methods: Cases of mastectomy and lumpectomy specimens of breast carcinoma were included in this study. The clinical and histopathological data of all cases were reviewed and correlated.

Results: Breast cancer was found to be more prevalent in older women (67.3%) than younger women (32.6%), with triple negative cases being more common in younger group (23.5%) than older group (8.6%). IDC was the most common type of carcinoma (80%) found in both the groups. Sarcomas though rare in breast, were seen mostly in younger women.

Conclusion: Breast carcinoma is more common in elderly populations, with demographic features and age playing a role in the pathogenesis of breast cancer. Triple negative breast cancer is seen more commonly in younger patients. Rare variants of breast carcinoma should always be considered a diagnostic possibility.

Keywords: Breast cancer, mastectomy, young, old, Triple negative, IDC.

Introduction

Breast cancer is the most commonly diagnosed cancer among women in the vast majority (140/184) of countries worldwide, representing a quarter of all cancers diagnosed in women. i In India, breast cancer (BC) has emerged as the second most common type of malignancy after cervical cancer with an increasing trend in its incidence.

The estimated number of incident breast cancer cases in India in 2016 was 118000 (98·1% of which were in females), and the prevalent cases were 526000iiBreast cancer is emerging as a major concern in female populations of the Kashmir Valley with its incidence showing an increasing trendiii The majority of cases have been reported from rural areas South Kashmir (46.02%), North Kashmir (31.86%) than from urban area Central Kashmir (22.12%).iv Women in Kashmir are generally diagnosed at a later, more advanced stage with poor prognosis. Although many factors contribute to an increased risk of breast cancer the epidemiological factor most consistently associated with breast cancer susceptibility and with most epithelial tumors is aging.

Cancer and aging are both multifactorial processes influenced by environment and endogenous factors. Among them some factors regulate intracellular functions such as proliferation, apoptosis and senescence. Other factors control extracellular components such as the stroma the, immune system and the endocrine system all of which contribute to controlling processes such as angiogenesis, tissue growth and tissue repair in normal tissues and also in tumors. v The general hypothesis for the age associated increase in many types of cancer incidence involves the accumulation of errors in somatic cells as a result of the accumulation of damage due to extrinsic factors such as reactive oxygen species or ionizing radiation, p53 mutation, c-erbB-2 over expression and tumor proliferation markers. 367 gene sets have been identified that may make a distinction between breast tumors in young women from those in older women, which may have an impact on prognosis VI The characteristics of tumors that arise in young women differ from those that arise in elderly women.

Women younger than 40 have a lower rate of ductal carcinoma in situ, higher histological grade, are mostly estrogen receptor (ER) and progesterone receptor negative vii are diagnosed at a more advanced stage, and have an inferior 5 year survival compared to their older premenopausal counterparts viii , ix It has been observed that the proportion of grade 3 .breast Cancer is more in the younger population as compared with older patients x The proliferation index (ki67) is higher in younger patients. Xi

Medullary and inflammatory breast cancers are more commonly observed in younger age group xii along with the increased frequency of both core basal and TN subtypes vi Elderly women with breast cancer have more DCIS component, lower histological grades, more estrogen receptor (ER) and Progesterone receptor (PR) positive, lower stage, and are associated with good prognosis and good clinical outcomes than their younger counterparts. vii, viii. They develop larger tumors (>5 cm) compared to younger counterparts, ix.

The proportion of grade 1 is substantially higher in the older group xi. Papillary, lobular and mucinous cancers are more commonly observed in the older age groups xiii, xiii the proliferation rate of tumors (ki67 immuno cytochemistry) has been observed to be lower in Older patients compared to younger ones xi along with a clear increase in luminal A tumors. Xiii

The aim of this study was to explore clinicopathological differences in younger and elderly patients in our tertiary care hospital, so as to gain valuable insights about the correlation between patient age at diagnosis, tumor histology, stage, biomarker status, and treatment response. So that a better understanding may enable the oncologist to tailor treatment more suited to the patient's age.

Materials and Methods

The study was an observational study, conducted over 5 years, out of which 3 ½ years study was retrospective and 1 ½ years study was prospective. It was conducted in the Department of Pathology, Sher-I-Kashmir Institute of Medical Sciences Soura, Srinagar which is the largest Tertiary Care Referral Centre in Kashmir. Patients were categorised into two groups on the basis of their age at presentation - a cohort of patients younger than 40 years and a cohort of patients greater than 40 years. These two groups were compared for clinicopathological features and biomarker expression according to proforma.

Inclusion criteria

All patients who were diagnosed as breast carcinoma and underwent mastectomy or lumpectomy.

Exclusion criteria

1. Male patients.

2. Patients who were diagnosed at stage iv and did not undergo mastectomy.

3. Patients whose paraffin blocks weren't available.

Ethical consideration

The study was conducted after taking permission from SKIMS Ethical Committee. Confidentiality and privacy of the subjects and the research data was maintained appropriately.

In the retrospective part of the study

The clinical and pathological data was obtained from the State cancer institute records and records of the pathology department, as per proforma. All the cases were reviewed. Paraffin embedded blocks were retrieved from histopathology archives.

In the prospective part of study

The data was collected as per proforma. The mastectomy/lumpectomy specimen received was fixed in 10% formalin and then studied for gross examination. It was then processed as per proforma and paraffin embedded blocks were made. In both prospective and retrospective 3-5 microsections were cut from each block and slides prepared were stained by H&E as per proforma Detailed microscopic examination was carried out as per proforma. Histopathological subtyping was done based on the 2019 World Health Organisation (WHO) histological criteria. Staging of breast cancer was performed according to American Joint Committee on Cancer (AJCC -8 th edition) TNM staging system.

Immunohistochemistry

Unstained slides containing paraffin embedded tissue sections from each specimen were subtyped based on ER, PR and HER 2 Neu status in each case. The scoring was done according to Allred scoring system and her 2 neu scoring system (Annexure VI) The cut off value to determine ER, PR positive was > or equal to 1% of tumour cells with nuclear staining. Tumours with HER2 score of 3+ were considered positive. Tumours were classified into 4 subtypes according to IHC markers

• luminal A (ER positive and/or PR positive, HG 1-2, HER2 negative),

• luminal B (ER positive and /or PR positive, HG3 and/or HER2 positive),

• Triple Negative (ER, PR AND HER2 negative),

• HER2 enriched (ER and PR negative, HER2 positive).

Statistical Analysis

Statistical package for social sciences (SPSS 21) was used for data compilation and analysis. Mean and standard deviation was calculated for quantitative variables. Frequency and percentage was calculated for qualitative variables. Fisher exact test was applied to determine association. P value ≤ 0.05 will be taken as significant.

Results

In this study, a total of 260 patients were included, with an age range of 21 to 80 years. The youngest patient diagnosed was 21 years old while the oldest patient was 80 years old. The median age for the diagnosis of younger population was 35 years and the median age for the diagnosis of older population was 52 years. The median age for diagnosis was 45 years for all patients. 32.6% were younger than 40 years and 67.3% were greater than 40 years, which implies that breast cancer was more seen in older women than their younger counter parts. (p value: 0.0001).

Among the younger patients 84.7% were married, 81.2% were parous and 72.9% had history of breast feeding. while in the older population 98.3% were married, 98.3% were parous and 92.6% were associated with breast feeding. (p values 0.00, 0.00, 0.00 respectively).

On ultrasonography, among the younger patients 10.6% were BIRADS VI (malignant) 30.9% were BIRADS VI (Malignant). Hence greater percentage of older patients were detected as malignant on ultrasonography than their younger counterparts which was statistically significant. (P value: 0.00) Among the young breast cancer patients 36.5% were treated with lumpectomy while in older only 20.0% were treated with lumpectomy. Therefore, the breast conservative surgery was mostly performed in the younger age group. The difference in choice of mastectomy and lumpectomy was statistically significant. (P value: 0.04)

On gross examination the tumor size of the specimen in the younger age group was between 2-5 cm in 63.5% of the patients and >5cm in 15.3% of the patients. While, among the older age group, between 2-5 cm in 58.3% of the patients and >5cm in 13.1% of the patients. The number of patients with large tumor size (>5cm) were slightly greater in younger patients. TABLE 1 Among both the groups, an equal percentage of patients had involved nodes- 50.6% and 50.3% in younger and older patients respectively and 72.9% had Lymphovascular invasion in younger group, and 76% in older group.

Although majority of the patients in both the groups did not have perineural invasion, the number was slightly greater in older (13.7%) patients compared to their younger (12.9) counterparts. Most of the patients in both the groups belonged to pT2 category with 57.6% in younger group and 52% in older group. With maximum cases in both age groups showing pN0 followed by pN1. TABLE 1.

Among the younger population 27.0% were stage IIA, and 9.4% were stage IV. While as in older 22.8% were stage IIA, and 6.2% in stage IV. TABLE 1. Though this difference wasn't statistically significant, however, the younger group showed a slightly more percentage of patients in stage IV than their older counterparts.

Among the younger 34.1% had grade III tumor, while as in older patients 26.2% had grade III tumor. Thus, the higher tumor grade was seen slightly more in younger population. The estrogen receptor staining in young patients was positive for 69.4% patients, while in older patients 86.3% were ER. Therefore, ER positivity was seen more in the older group then the younger group- a statistically significant difference. (P value: 0.03) The Progesterone receptor staining was positive for 69.4%, While as in older patients, 86.3% patients were positive. Thus, the older group showed more PR staining than the younger group. This difference was statistically significant. (p value:0.03)

Among the younger patients only 9.4% were positive for HER-2, while the majority of patients 87.1% were negative for the same. Whereas in older patients 19.4%

were positive for HER 2 and 80% were negative for the same. Therefore, more patients from the younger age group were negative for HER2 than their older counter parts. This difference was statistically significant (p value: 0.02)

Among the younger 23.5% were triple negative, while in the older group only 8.6% were triple negative. the majority of patients in both the groups were luminal. Moreover, the triple negative patients were more seen in younger patients than the older group. This difference was statistically significant. (p value: 0.01) Table 1

The majority of the tumor type in both the age groups was Infiltrating ductal carcinoma with 85.9% in younger age group and 86.9% in the older age group. Table 1

In the younger patient group 27.1% of patients were treated with neoadjuvant therapy While in older patients 14.9% were treated with neoadjuvant therapy This shows that neoadjuvant therapy was more of a treatment choice in younger patients compared to their older counterparts. This difference was statistically significant. (P value: 0.01)

Out of the total number of 260 patients that were included in this study, the majority of the patients were diagnosed as IDC- NOS with 80% belonging to the younger group and 83. 4% belonging to the older group. In addition three Non- epithelial tumors were also seen which were diagnosed as sarcomas on immuno histochemistry- Dermatofi brosarcoma protuberans which was documented in 1.2% with CD 34 and vimentin positivity and S-100 negativity on IHC, Ewing's sarcoma in 1.2% with CD99, vimentin and NKX2.2 positivity and angiosarcoma in 1.2% with positive CD31 and CD34 markers in younger group and one case of Non-Hodgkin lymphoma was also diagnosed as Diffuse Large B-cell Lymphoma with positivity for

CD 19, CD20, CD22 and negative for Tdt and Cytokeratins on Immunohistochemistry in older group. TABLE 2

Clinical features	<40 years (n = 85)		>40 years (n= 175)		P value
Menarche					0.6
10-12	56	65.9%	107	61.1%	
13-15	29	34.1%	67	38.3%	
16-18	0	0.0%	1	0.6%	
Marital status					0.00
Married	72	84.7%	172	98.3%	
unmarried	13	15.3%	3	1.7%	
Parity					0.00
parous	69	81.2%	171	98.3%	
nulliparous	6	18.8%	3	1.7%	
Breast feeding					0.00
Present	62	72.9%	162	92.6%	
Absent	23	27.1%	13	7.4%	
Ultrasonography					0.00
BIRADS IV (Suspicious)	23	27.1%	13	7.4%	
BIRADS V (Suggestive of Malignancy)	53	62.4%	108	61.7%	
BIRADS VI (Malignancy)	9	10.6%	54	30.9%	
Surgery					0.04
mastectomy	54	63.5%	140	80.0%	
lumpectomy	31	36.5%	35	20.0%	
pN					0.2
pN0	42	49.4%	84	48.0%	
pN1	21	24.7%	45	25.7%	
pN2	17	20.0%	26	14.9%	
pN3	5	5.9%	20	11.4%	
LVI					0.3
Present	62	72.9%	133	76.0%	
Absent	23	27.1%	42	24.0%	
PNI					0.5

Present	11	12.9%	24	13.7%	
Absent	74	87.1%	151	86.3%	
pT					0.3
pT0	5	5.8%	7	4.0%	
pT1	20	23.8%	53	30.2%	
pT2	49	57.6%	91	52%	
pT3	8	9.5%	13	7.4%	
pT4	3	3.5%	11	6.2%	
Stage					0.3
Complete response	3	3.5%	5	2.9%	
IA	14	16.4%	32	18.2%	
IB	1	1.2%	0	0.0%	
IIA	23	27.0%	40	22.8%	
IIB	141	16.4%	35	20%	
IIIA	16	18.8%	25	14.2%	
IIIB	11	1.2%	8	4.6%	
IIIC	4	4.7%	17	9.7%	
IV	8	9.4%	11	6.2%	
GRADE					0.1
GRADE I	7	8.2%	27	15.4%	
GRADE II	49	57.6%	102	58.3%	
GRADE III	29	34.1%	46	26.2%	
ER STAINING					0.03
POSITIVE	59	69.4%	151	86.3%	
NEGATIVE	23	27.1%	23	13.1%	
EQVIVOCAL	3	3.5%	1	0.6%	
PR STAINING					0.03
POSITIVE	59	69.4%	151	86.3%1	
NEGATIVE	23	27.1%	23	3.1%	
EQVIVOCAL	3	3.5%	1	0.6%	
HER STAINING					0.02
POSITIVE	8	9.4%	34	19.4%	
NEGATIVE	74	87.1%	140	80.0%	
EQVIVOCAL	3	3.5%	1	0.6%	
MOLECULAR TYPES					0.01
HER 2 ENRICHED	5	5.9%	7	4.0%	
LUMINAL A	55	64.7%	128	73.1%	
LUMINAL B	5	5.8%	25	14.3%	
TRIPLE NEGATIVE	20	23.5%	15	8.6%	
NEOADJUVANT					0.01
PRESENT	23	27.1%	26	14.9%	
ABSENT	62	72.9%	146	85.1%	

Table 1:

DIAGNOSIS					Younger age group		Older age group	
					No. (n)	%age	No. (n)	%age
Primary epithelial malignancy	Ductal carcinoma	DCIS	DCIS- solid		1	1.2%	1	0.6%
			DCIS- micropapillary		1	1.2%	0	0.0%
			DCIS-comedo		0	0.0%	1	0.6%
		IDC	IDC-NOS		68	80%	146	83.4%
			IDC-TIL rich		1	1.2%	4	2.4%
			IDC with DCIS		2	2.4%	1	0.6%
			IDC- Mucinous		1	1.2%	2	1.2%
			IDC- Neuroendocrine		2	2.4%	2	1.2%
			IDC+ILC		1	1.2%	0	0.0%
	Lobular carcinoma		Classic variant		1	1.2%	4	2.4%
			Histiocytoid variant		0		1	0.6%
			Solid variant		0		1	0.6%
	Invasive cribriform				0		1	0.6%
	Metaplastic		Adenosquamous		1	1.2%	0	0.0%
			Squamous		1	1.2%	2	1.2%
			Chondrosarcoma		0	0.0%	1	0.6%
			leiomyosarcoma		1	1.2%	1	0.6%

Vascular neoplasms	Angiosarcoma	1	1.2%	0	0.0%
Haematolymphoid neoplasms	NHL (DLBCL)	0	0.0%	1	0.6%
sarcomas	Ewing's	1	1.2%	0	0.0%
	DFSP	1	1.2%	0	0.0%

Discussion

In our study a total of 260 patients were included, out of which 85 (32.6%) were 40 years of age. The median age at diagnosis was 45 years. The mean age among young patients was 32.9 years and the mean age among older patients was 54.5 years. Therefore, there was less incidence of breast cancer in younger population (32.6%) compared to the older age group. Similar findings were observed in the studies done in Asian and African countries. However, there is significantly less incidence of breast cancer in younger population in the western and European countries. Anders CK et al vi in his study found that only 6.6% of patients

being diagnosed as breast cancer were <40 Year Darren R Brenner xi vet al in his study reported 7% of breast cancers to be diagnosed in younger age group. Similar findings were reported by Jennifer K Plichta et al xv in her study. The studies done in Asia and middle eastern countries follow a higher percentage of breast cancer in younger population. Study done by Abdul Kader M al basari, xvi

reported 24.4% of cases belonging to <40 0 years. Concordant findings were found by Nuzhat et al xvii and el kum et al xviii in Saudi Arabia.

There was a no significant difference between the age at menarche in young and older patients. Other demographic factors like marital status, parity, history of breast feeding was significantly different in the two age

groups with Greater percentage of patients being married in the older patients and associated with parity and history of breast feeding. Erica T warner et al xix examined the relationship between reproductive factors and risk of pre-menopausal breast cancer among women <40 and older pre-menopausal women. In their study associations with age at menarche and breast cancer were similar in both groups. Study done by ke wang et al xx found similar results with significant difference in age at menarche (p value 0.001), marital status (p value 0.001) and parity (p value 0.001) between the two groups.

In terms of clinical characteristics, there was a significant difference in the diagnosis of breast cancer in younger and older age group on mammography. only 22.4% of the younger women were diagnosed as malignant and 42.3% of elderly patients were diagnosed as malignant. A study done by Katherina zabicki et al xxi on-diagnosis disparity in young and older patients supported our finding. Zhang Q et al xxii in his study on retrospective clinicopathological comparison between young and elderly women also found that mammography was less sensitive in younger patients.

In terms of surgical characteristics, it was found that mastectomy was more of a surgical choice in older patients as compared to the younger patients. Francisco Acevedo et al, xxiii in their study conducted on 256 patients in Chile also found a similar result. A similar study by Anna Karin et al xxiv on 524 patients in Sweden reported that more breast conservative surgeries were performed on younger patients (36.2%) than their older (60.3%) counterparts.

In our study the tumor size at diagnosis did not differ significantly in the younger and older group. Katherina Z et al xxi compared 8892 breast cancer patients in a

Harvard based study in USA, as <40 years and between 50-60 years. They did not find any statistically significant difference between the mean and median tumor sizes in the younger and the older group. A study conducted by servet kocaoz et al xxv on 428 patients in Ankara turkey found that there was statistically significant difference (p value 0.047) in tumor size greater than 5cm in pre and post-menopausal patients.

In our study there was no statistically significant difference in tumor grade in young and older groups. Though a greater percentage of grade III patients (34.1%) belonged to younger age group. Maggard et al xxvi from USA found that young patients were more likely to present with more advanced tumor. Fabiana de lima Vazquez et al xxvii did a retrospective analysis and documented, that younger women presented with a higher proportion of tumors with grade III differentiation. Abdulkader M al basari xvi found in his comparative study that there were more patients with grade III breast carcinomas in younger age group compared to older age group.

Current study showed that the percentage of patients with lymph node involvement was equal in both groups. Considering Lymphovascular invasion (LVI) in younger and older groups, our study found that 72.9% in younger group and 76% in older group were positive for Lymphovascular invasion (p value 0.3). In our study we found that the two study groups did not show significant difference in perineural invasion (young 72.9%, older 76%, p 0.3). Francisco Acevedo et al, xxiii in their study found that the lymph node involvement in younger age group (62.10%) was significantly higher compared to older age group (42.70%). Julia C Radios et al xxviii In terms of Lymphovascular invasion, found that 33% of patients in younger age group and 29% of patients in older age group were reported positive for LVI (p value 0.28) . Abdulkader M al basari xvi in his study found that there was no statistically significant difference in lymph node involvement in patients of younger and older age groups (p 0.606). The results of this study in terms of lymph node involvement are in concordance with our study.

our study showed that percentage of patients in stage IV was comparatively higher in younger group (9.4%) than older group (6.2%). Yazmin San Miguel et al xxix conducted a study in USA. They found that incidence of stage II, III and IV, incidence was in younger age group compared to older age group. Lynn Chollet- Hinton et al xxx conducted a study in USA, university of North Carolina, on heterogeneity in breast cancer in premenopausal and post-menopausal groups. The study revealed that stage I and stage III incidence was higher in post- menopausal group and stage II and stage IV incidence was higher in pre-menopausal group.

On ER/PR staining we found that in younger age group, positive percentage for ER/PR was 69.4%,in older age group in terms of ER/PR staining positive percentage was 86.3%, the difference in positive percentage between the two groups was statistically significant (p value 0.03). Comparison of HER 2 staining was done in two groups and older age group was found to be positive in 19.4% of cases and younger age group was found positive in only 9.4% of cases (p value 0.02). Jennifer L Gnerlich et al xxxi found that 50.1% were positive for ER status in older age group compared to 39.1% in younger age group. in same study PR status was also evaluated and 42.5% in older age group, 36.2% in younger age group were found to be positive for PR status. The results of their study are in accordance to the findings of our study.

Erica T. warner et al xix conducted a study in New York USA and found that older age group had higher percentage of ER and PR (ER76%, PR-72%) positive cases compared to younger age group (ER63%, PR 60%). Yazmin San Miguel et xxix al found findings in accordance to results of our study.

In terms of molecular subtypes our study found, majority of cases to be luminal A type in both the groups, with older having higher percentage of luminal A compared to younger group (young 64.7%, old 73.1%). HER 2 enriched type was higher in younger group (5.9%) compared to older age group (4.0 %). 23.5 % triple negative cases were found in young group while as only 8.6% were found in older group.

Therefore, triple negative cases were more prevalent in younger patients as compared to older groups G. Can cello et al xxxii studied molecular subtypes and concluded that luminal B type was more prevalent in younger age group compared to older age group. However, luminal A type was more prevalent in older age group. Moreover, triple negative cases were also more prevalent in younger age group. The results of our study were in concordance to above mentioned study.

Abdulkader M alba sari xvi also concluded findings same as our study. Out of total number of 260 cases, we diagnosed 85.9% in younger age group and 86.9% in older age group as invasive ductal carcinoma (IDC). Second most common diagnosis in younger age group was metaplastic carcinoma (3.5%), followed by ILC (2.4%) and neuroendocrine (2.4%). A study was conducted in Egypt by Ayesha Nuzhat et al xvii which concluded that most prevalent histological subtype in both young and older groups was IDC which was followed by ILC. ILC was found to be significantly higher in older age group compared to younger counter parts Three rare primary sarcomas were identified under histological examination during our study in the younger age group. Single case of Dermatofibrosarcoma protuberns was diagnosed on the basis of immunohistochemistry findings with CD 34, Vimentin positivity and S-100 negativity. Another sarcoma was Ewing's sarcoma. It was documented with CD99, vimentin and NKX2.2 positivity. Angiosarcoma was also reported with positive CD31 and CD 34 markers.

In addition, one case of non-Hodgkin lymphoma was also diagnosed as diffuse Large B cell lymphoma with diffuse positivity for CD 19, CD 20, CD 22 and negativity for Tdt and Cytokeratins on IHC. In our study, 27.1 % of patients in younger age group and 14.9 % of patients in older group received neoadjuvant therapy showing that neoadjuvant therapy was preferably administered to younger patients and the difference between two groups was found to be statistically significant (0.01).

Ethics statement

The study was approved by Institutional Ethical clearance (IEC) board, Skims, soura.

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