ORIGINAL ARTICLE

Clinical and histopathological features of breast cancer in Jordan: Experience from a tertiary care hospital

Fatima Obeidat,[1] Mamoun Ahram,[2] Ali Al Khader,[3] Khairat Battah,[4] Mohammad Alchalabi,[5] Jamal Masad Melhem,[6] Ahmad Suleiman[7]

Abstract

Objective: To analyse breast cancer cases with respect to age, menopausal status, hormone receptors and human epidermal growth factor receptor 2 expression, in addition to nodal and distant metastases.

Methods: This retrospective study was conducted at Jordan University Hospital, Amman, Jordan, and comprised cases of breast carcinoma among females between 2006 and 2015. Clinicopathological data was collected from patient files and laboratory reports. Data was analysed using SPSS v 17.

Results: Of the 752 cases, 559(74.3%) were invasive ductal carcinomas of non-specific type, followed by 36(4.8%) cases of invasive lobular carcinoma. Upon investigating the clinicopathological data on the breast cancer cases, 466(61.97%) cases had sufficient information for further analysis. Of them, 414(61.97%) patients were aged above 40 years and 190(40.77%) were post-menopausal. Moreover, 221(47.42%) cases showed lymph node metastases, but only 32(6.87%) had distant metastases. The expression of oestrogen receptor, progesterone receptor, and human epidermal growth factor receptor 2 was found to be positive in 343(73.6%), 299(66.7%) and 97 (24.6%) cases, respectively. Besides, 42(9.01%) cases were triple negative, which were diagnosed only in females below 40 years age.

Conclusion: These results were in concordance with international reports, except for the association of triple negative breast cancer with age where it was mainly diagnosed among females younger than 40 years age.

Keywords: Prevalence, Cancer, Breast carcinoma, Triple negative breast cancer, Poor prognosis. (JPMA 67: 1206; 2017)

Introduction

Breast cancer accounts for 30% of all estimated new cancer cases worldwide among females and is the leading cause of death among women between the ages of 20 and 60 years.[1] The incidence of breast cancer is rising in the whole female population, particularly among younger women.[2] In Jordan, breast cancer accounts for 19.7% of all cancer cases among both genders and 37.4% of all cancer cases among females.[3] Approximately 37% of breast cancer cases in Jordan are diagnosed in advanced stages with a median age of incidence of 50 years, with only 17% of cases being diagnosed before the age of 40. Histologically, they are mainly diagnosed as ductal carcinoma (79.1%), followed by lobular carcinoma (6.1%).

The aetiology of this malignant tumour involves interplay of genetic, environmental and hormonal factors that influence the physiological status of the host.[4] Of the hormonal factors, sex steroid hormones are important in the development of tumours of the breast.[5] Endogenous oestrogens play a major role in the development of breast cancer. Oestrogen's effects are mediated through two types of receptors: oestrogen receptor alpha (ER-α) and beta (ER-β), which are ligand-dependent transcription factors that mediate the biological effects of oestrogens and anti-oestrogens.[6] In addition, the human epidermal growth factor receptor 2 (HER2) is overexpressed in 15-30% of invasive breast cancers, and has both prognostic and predictive implications. Breast cancers can have up to 25-50 copies of the HER2 gene, and up to 40- to 100-fold increase in HER2 protein-stimulating cell growth.[7] The dependence of breast cancer on these molecular factors has led to the development of targeted therapy that has proven successful in treating breast cancer. In fact, breast cancer is one of the few tumour types in which molecular classification has been successfully used for the design of individualised therapies leading to a significant improvements in disease-specific survival.[8]

Classification of breast cancer and, hence, treatment are determined by the immunohistochemical (IHC) profile of ER, progesterone receptor (PR), and HER2.[9] Such classification has been useful in guiding treatment of breast cancer.[10] The molecular classification of breast cancer introduced five main subtypes, including luminal

[1-6]The University of Jordan, [7]Yarmouk University, Jordan.
Correspondence: Fatima Obeidat. Email: fatimaobeidat@yahoo.com

A, luminal B, HER2-type, basal-like, and normal breast-like tumours.[11] The luminal subtypes make up the majority of the hormone receptor-positive tumours, while the basal-like and HER2+/ER- subtypes constitute the majority of hormone receptor-negative cancers. Luminal A tumours are ER+, conferring a more favourable prognosis that is partly due to the efficacy of anti-hormone therapies.[12] On the other hand, basal-like types have poor outcome and these subtypes tend to be triple negative breast cancer (TNBC), meaning that they lack the expression of ER, PR and HER2.[13] TNBC is considered a heterogeneous group of diseases that is diverse in biology, aetiology and treatment strategies. According to numerous studies, TNBC accounts for 10-24% of invasive breast carcinomas.[13] Patients with TNBC tend to have a higher recurrence rate after diagnosis, a short disease-free interval, reduced overall survival. Recurrences of TNBC usually develop between 1 and 3 years after the initial diagnosis and most deaths occur within five years.[13]

Due to the clinical significance of understanding the prevalence of the different types of breast cancer in regards to diagnosis and treatment, the current study was planned to assess breast cancer cases to reflect trends observed in Jordan. Such knowledge would assist in formulating better policies and targeted research activities. This is the first study of its kind performed in Jordan. Our aim was to statistically analyse the clinical and histopathological features of breast cancer among female patients and to compare these figures with regional and international ones.

Patients and Methods

This retrospective study was conducted at the Jordan University Hospital (JUH), Amman, and comprised cases of breast carcinoma among females from 2006 to 2015. JUH is a comprehensive and a major referral hospital in Amman, the capital city of Jordan, with 580 beds. Approximately half of the population of Jordan lives in Amman, while patients from other parts of the country are also seen by JUH specialists.

Approval for the study was granted by the institutional review board. Data and tissue blocks were retrieved from the archives of the pathology department. The collected clinicopathological data included the age at diagnosis, menopausal status, histological type, Nottingham grade, size of tumour, lymph node and distant metastasis status, as well as expression of ER, PR and HER2. In case HER2 staining was borderline (+2), fluorescence in situ hybridisation (FISH) analysis was performed. Some of the files contained incomplete data, resulting in discrepancy in the number of samples for each criterion.

Data was analysed using SPSS v 17. Descriptive statistics were used to report sample characteristics in addition to frequencies and percentages. Pearson's chi-squared test was used to find association of the different parameters with each other. $P<0.05$ was considered significant.

Results

Of the 752 cases of breast cancer tissue blocks,

Table-1: The histological types of breast cancer cases.

Type of carcinoma	Numbers	%
Invasive ductal carcinoma, NST	559	74.3
Invasive lobular carcinoma	36	4.8
Medullary carcinoma	15	2.0
Mucinous carcinoma	11	1.5
Tubular carcinoma	6	0.8
Cribriform carcinoma	5	0.7
Papillary carcinomas	3	0.4
Metaplastic carcinoma	2	0.3
Apocrine carcinoma	2	0.3
Micropapillary carcinoma	2	0.3
Encapsulated papillary	1	0.1
Secretory carcinoma	1	0.1
Others	23	3.0
Cannot be subtyped	86	11.4
Total	752	100

NST: Non-specific type.

Table-2: Patient characteristics.

Criteria	Numbers (%)
Age (years)	
< 40	52 (11.2)
40-55	217 (46.6)
> 55	197 (42.3)
Menopausal status	
Pre-	97 (33.8)
Post-	190 (66.2)
Cancer grade	
I	49 (13.1)
II	194 (51.9)
III	131 (35.0)
Tumour size	
< 2 cm	97 (27.2)
2-5 cm	190 (53.4)
> 5 cm	46 (12.9)
Inflammatory/dermal invasion	23 (6.5)
Lymph node status	
Positive	221 (62.4)
Negative	133 (37.6)
Distant metastasis	
Positive	32 (12.5)
Negative	225 (87.5)

Table-3: Frequency of receptor expression in breast cancer cases.

Criteria	ER Positive (%) 343 (73.6)	ER Negative (%) 123 (26.4)	p-value	PR Positive (%) 299 (66.7)	PR Negative (%) 149 (33.3)	p-value	HER2 Positive (%) 97 (24.6)	HER2 Negative (%) 297 (75.4)	p-value
Age (years)									
< 40	0 (0)	52 (42.3)		0 (0)	52 (34.9)		10 (10.4)	42 (14.2)	
40-55	146 (42.6)	71 (57.7)	0.001	116 (38.8)	97 (65.1)	0.001	49 (51.0)	138 (46.6)	0.582
> 55	197 (57.4)	0 (0)		183 (61.2)	0 (0)		37 (38.5)	116 (39.2)	
Menopausal status									
Pre-	18 (8.8)	79 (96.3)	0.001	14 (7.6)	80 (95.2)		32 (45.1)	59 (36.4)	
Post-	186 (91.2)	3 (3.7)		170 (92.4)	4 (4.8)	0.001	39 (54.9)	103 (63.6)	0.244
Cancer grade									
I	37 (13.6)	11 (11.1)		27 (11.7)	19 (14.8)		9 (10.8)	32 (14.0)	
II	140 (51.5)	53 (53.5)		119 (51.7)	66 (51.6)	0.665	44 (53.0)	110 (48.2)	0.674
III	95 (34.9)	35 (35.4	0.814	84 (36.5)	43 (33.6)		30 (36.1)	86 (37.7)	
Tumour size									
< 2 cm	74 (28.0)	21 (23.9)		64 (28.1)	28 (25.5)		26 (34.2)	56 (25.9)	
2-5 cm	140 (53.0)	48 (54.5)		120 (52.6)	60 (54.5)		37 (48.7)	120 (55.6)	
> 5 cm	32 (12.1)	14 (15.9)	0.727	28 (12.3)	16 (14.5)	0.847	9 (11.8)	27 (12.5)	0.584
Inflammatory/dermal invasion	18 (6.8)	5 (5.7)		16 (7.0)	6 (5.5%)		4 (5.3)	13 (6.0)	
Lymph node status									
Positive	162 (61.4)	59 (67.0)		139 (60.7)	72 (66.1)		50 (66.7)	133 (61.9)	
Negative	102 (38.6)	29 (33.0)	0.374	90 (39.3)	37 (33.9)	0.204	25 (33.3)	82 (38.1)	0.49
Distant metastasis									
Positive	22 (11.1)	10 (17.5)		23 (12.9)	9 (14.3)		5 (10.4)	22 (13.5)	
Negative	176 (88.9)	47 (82.5)	0.255	155 (87.1)	54 (85.7)	0.83	43 (89.6)	141 (86.5)	0.806
ER									
Positive				289 (96.7)	40 (26.8)		44 (45.8)	245 (82.8)	
Negative				10 (3.3)	109 (73.2)	0.001	52 (54.2)	51 (17.2)	0.001
PR									
Positive	289 (87.8)	10 (8.4)					35 (38.5)	224 (77.5)	
Negative	40 (12.2)	109 (91.6)	0.001				56 (61.5)	65 (22.5)	0.001
HER2									
Positive	44 (15.2)	52 (50.5)		35 (13.5)	56 (46.3)				
Negative	245 (84.8)	51 (49.5)	0.001	224 (86.5)	65 (53.7)	0.001			

ER: Oestrogen receptor
PR: Progesterone receptor
HER2: Human epidermal growth factor receptor 2.

559(74.3%) were classified as invasive ductal carcinomas, non-specific type (NST), followed by 36(4.8%) cases diagnosed as invasive lobular carcinoma. The rest of cases were distributed among medullary carcinomas 15(2%) cases, mucinous carcinomas 11(1.5%) cases, pure tubular carcinomas 6(0.8%) cases, cribriform carcinomas 5(0.7%) cases, and invasive papillary carcinomas 3(0.4%) cases. Moreover, 2(0.3%) cases of each of the following were reported: metaplastic carcinoma, apocrine-type carcinoma, and micropapillary carcinoma. Besides, 1(0.1%) case was reported as secretory carcinoma and another one was diagnosed as encapsulated papillary carcinoma. The remaining cases were mixed ductal lobular, mixed ductal mucinous, or cancers that could not be determined (Table-1).

Only 466(61.97%) cases had sufficient information for further analysis. Of them, 414(88.84%) cases were diagnosed in females aged 40 years or above, whereas and 190(40.77) cases were post-menopausal. In addition, 194(41.63%) cases were of grade II, 131(28.11%) were diagnosed as grade III, and 49(10.52%) as grade I. The size of tumour ranged from 0.5cm to 16cm. However, 190(40.77%) patients had tumours of 2-5 cm of size, whereas 97(20.82%) tumours had a size less than 2cm and 46(9.87%) of them were larger than 5cm. Moreover, 221(47.42%) cases were lymph node-positive, whereas 32(6.87%) had positive distant metastasis (Table-2).

The expression of the three receptors, i.e. ER, PR, and

Table-4: Association of breast cancer subtypes with clinicopathological criteria.

Criteria	Luminal A (%) 230 (63.9%)	Luminal B (%) 39 (10.8%)	HER2+ (%) 49 (13.6%)	TNBC (%) 42 (11.7%)	p-value
Age (years)					
< 40	0 (0)	0 (0)	10 (20.4)	42 (100)	
40-55	114 (49.6)	2 (5.1)	39 (79.6)	0 (0)	<0.001
> 55	116 (50.4)	37 (94.9)	0 (0)	0 (0)	
Menopausal status					
Pre-	14 (12.0)	0 (0)	29 (96.7)	42 (100)	<0.001
Post-	103 (88.0)	37 (100.0)	1 (3.3)	0 (0)	
Cancer grade					
I	25 (14.2)	2 (6.7)	6 (13.3)	3 (9.7)	
II	85 (48.3)	19 (63.3)	22 (48.9)	13 (41.9)	0.625
III	66 (37.5)	9 (30.0)	17 (37.8)	15 (48.4)	
Tumour size					
< 2 cm	44 (25.4)	13 (41.9)	9 (23.7)	7 (28.0)	
2-5 cm	98 (56.6)	15 (48.4)	19 (50.0)	11 (44.0)	0.429
> 5 cm	20 (11.6)	2 (6.5)	7 (18.4)	6 (24.0)	
Inflammatory/dermal invasion	11 (6.4)	1 (3.2)	3 (7.9)	1 (4.0)	
Lymph node status					
Positive	104 (60.1)	21 (72.4)	25 (62.5)	18 (72.0)	0.459
Negative	69 (39.9)	8 (27.6)	15 (37.5)	7 (28.0)	
Distant metastasis					
Positive	19 (14.0)	0 (0)	4 (18.2)	3 (16.7)	0.251
Negative	117 (86.0)	22 (100.0)	18 (81.8)	15 (83.3)	

ER: Oestrogen receptor
PR: Progesterone receptor
HER2: Human epidermal growth factor receptor 2
Luminal A: ER+ and/or PR+, HER2-
Luminal B: ER+ and/or PR+ and HER2+
HER+:ER-, PR-, and HER2+
TNBC: ER-, PR-, HER2-

HER2, is critical in diagnosing breast cancer and in determining the appropriate treatment as well. It is, therefore, important to elucidate the ratio of expression of the three biomarkers. ER was found to be expressed in 33(73.6%) of the cases. Similarly, PR was expressed in 299(64.16%) of the cases. On the other hand, HER2 was found to be highly expressed in 97(20.82%) cases. Whereas all females aged above 55 years were ER+ and PR+, all females younger than 40 years were negative for both biomarkers. In the 40-55 years' age group, 71(15.24%) females were negative for ER and 97(20.82%) for PR (p<0.001). Similarly, lack of expression of both ER and PR was found to significantly associated with breast cancer cases of pre-menopausal females where 79(16.95%) and 80(17.17%) of ER- and PR cases, respectively, were found in pre-menopausal patients (p<0.001). On the other hand, HER2 was not found to significantly associate with age or menopausal status. In addition, ER expression associated positively with the expression of PR with 289(62.02%) of ER-positive tumours always expressing PR and 109(23.39%) of ER-negative tumours always being PR-negative (p<0.001). On the other hand, the positive expression of both biomarkers was significantly associated with the absence of HER2 expression where 245(52.58%) and 224(48.07%) of HER2-negative tumours were ER+ and PR+, respectively (p<0.001). The expression of ER, PR or HER2 did not associate with the grade and size of tumour, lymph node status and distant metastasis status (Table-3).

Different breast cancer subtypes classified according to receptor status were then analysed in association with clinicopathological criteria. The cases were divided into four subtypes: luminal A (ER+ and/or PR+, HER2-), luminal B (ER+ and/or PR+ and HER2+), HER2+ (ER-, PR-, and HER2+), and TNBC (ER-, PR-, and HER2-). Whereas the luminal breast cancers were mainly diagnosed in older age groups and post-menopausal females, most of the HER2+ and TNBC types were diagnosed in younger age groups and pre-menopausal females. In

Table-5: The different morphologic subtypes of triple negative breast cancer.

Type of Triple negative breast cancer	Number of cases	Percentage
Invasive ductal carcinoma, NST	78	85 %
Medullary carcinoma	8	9%
Metaplastic carcinoma	3	3%
Invasive lobular carcinoma	1	1%
Encapsulated papillary carcinoma	1	1%
Mixed ductal lobular carcinoma	1	1%

NST: Non-specific type.

fact, all cases of TNBC were diagnosed in patients younger than 40. The different subtypes were not significantly associated with the grade and size of tumour, lymph node status, or distant metastasis status (Table-4).

Further analysis of the TNBC cases revealed that majority 78(16.74%) of the cases were diagnosed as invasive ductal carcinoma, NST. This was followed by medullary carcinoma 8(1.72%) and metaplastic carcinoma 3(0.64%). Individual single cases were diagnosed with invasive lobular carcinoma, encapsulated papillary carcinoma, and mixed ductal/lobular carcinoma (Table-5).

Discussion

Knowledge of the histopathological type of breast cancer and receptor status is important in predicting the prognosis and treatment options. Studies have shown that the expression of both ER and PR in breast cancer is a good prognostic factor where it is associated with lower mortality rates compared to tumours lacking expression of one of the receptors or both of them.[14] The clinical value of ER expression lies in decision-making regarding endocrine therapy. For this type of cancer, the best treatment option is targeting ER directly with inhibitors such as tamoxifen or indirectly via blocking the synthesis of oestrogen by aromatase inhibitors. Although ER positivity in breast cancer has better prediction of survival over HER2,[15] the over-expression of HER2 is a determinant of treatment options. Patients with over-expression of HER2 are treated with anti-HER2 monoclonal antibodies as a standard treatment.

Previous studies have illustrated that the majority of breast cancer cases are positive for ER expression.[16,17] These results are similar to ours whereby three-fourths of breast cancer cases were ER-positive. In general, the expression of ER increases with age. This trend has been observed in our study. The same observation is true with PR where cancer cases of older female patients are more positively stained that those of younger ones. In addition, the expression of ER and PR associate positively as reported in other studies as well as ours.[16,17] This is not surprising since the expression of PR is largely dependent on active ER pathway.[18] Hence, the lack of expression of PR in the presence of ER is an indication of faulty ER protein or signalling and, hence, a prediction of reduced efficacy of endocrine treatment. It has previously been shown that the expression of PR in conjunction with ER is an indication for better response to hormonal therapy.[17] In addition, the double expression of ER and PR is a good prognostic factor for both overall survival and disease-free survival.[16,17]

About three-quarters of breast cancer cases were negative for HER2, a rate that is compatible with previous reports.[19-22] Our results indicate that 13.6% of breast cancers were of the HER2 type. This rate is also compatible with numerous reports not only globally, but regionally as well.[20,22] An exception was reported in Oman where the rate of HER2+ breast cancer was reported to be 59%.[23] The expression of ER and PR negatively associated with HER2 expression. These results parallel other reports where significant inverse association between HER2 expression with ER and PR expression was found.[19-21] In contrary to ER and PR expression status, HER2 expression did not associate with age. The status of the three receptors, ER, PR and HER2 individually did not associate with any of the clinicopathological criteria, namely grade and size of tumour, lymph node status, and distant metastasis status.

The expression of ER, PR and HER2 has been widely used in the classification of breast cancer into primarily four classes: luminal A, luminal B, HER2-positive and triple-negative.[24] Whereas the expression of ER and/or PR is a good prognostic indicator, the expression of HER2 is the opposite where it is associated with lower survival rate.[16,17] In fact, it is the combination of the three expression patterns whereby breast cancers that are positive for ER and PR, but the lack the expression of HER2 appears to have the best prognosis that provides better prediction of the survival rate.[16] It gets worse with lack of expression of either hormone receptor with the positive expression of HER2. The worst outcome is registered for patients having positive expression of HER2, but lack the expression of both ER and PR.[6,16,17] Interestingly, the presence of HER2 appears to confer resistance to endocrine therapy.[25] It has been reported that a combination

treatment of ER+/HER2+ breast cancer with aromatase inhibitors and anti-HER2 drug, trastuzumab, is highly beneficial.[26]

Our study indicated that the prevalence of TNBC was 11.7%, which was in concordance with the results of previous international studies, which showed that TNBC accounts for 10-24%% of all breast cancer cases.[9] The majority of TNBC were invasive ductal carcinoma, NST accounting for 85% of cases, which parallels other reports.[9,27] On the other hand, other morphologic subtypes of TNBC, including medullary, metaplatic, lobular, encapsulated papillary and mixed ductal lobular collectively, accounted for 15%. Interestingly, all of TNBC patients in this study were below 40 years age, which was much younger than what has been reported in other studies.[9,27] but similar to rates reported in Turkey.[22] This has a very important implication since younger age is associated with lower survival as previously reported in Jordan[28] and others.[29,30] The type of breast cancer that affects young women, particularly TNBC, is characterised by less hormone sensitivity, higher HER-2/ estimated glomerular filtration rate (EGFR) expression, and breast cancer 1 (BRCA1) mutations.[11] Besides, the role of BRCA1, the contribution of unique genetic factors should be investigated and the initiation of advanced genomic studies such as whole exome sequencing can be of great value. In addition, awareness campaigns of breast cancer screening, which are actively taken place in Jordan, are hoped to reduce the rate of advanced disease.

Conclusion

The prevalence of the different types of breast cancer in Jordan was not different from what had been reported earlier, with the exception of the association of TNBC with younger age (<40 years).

This may aid in guiding treatment strategies of breast cancer in Jordan. However, further studies are necessary to investigate the prevalence of TNBC among young females. In addition, the validation of biomarkers in TNBC and the identification of novel biomarkers that can predict the susceptibility for breast cancer are warranted.

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