DEMOGRAPHIC, CLINICAL AND MAMMOGRAPHIC CHARACTERISTICS OF INVASIVE DUCTAL CARCINOMA OF THE BREAST: A SRI LANKAN EXPERIENCE

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Abstract

Breast cancer (BC) ranks the highest among all cancers of women worldwide. Mammography is the most widely utilized imaging tool for evaluation of breast cancer with the final diagnosis being made on histopathology. This study aimed at describing the demographic, clinical and mammographic characteristics of histologically proven invasive ductal carcinoma (IDC) of breast in a group of Sri Lankan women. The study was carried out using a database on mammography maintained by the principal investigator. Study sample consisted of 177 subjects. The mean age of subjects was 52.2 years (SD ± 1.1). Majority (63.8%) were postmenopausalwomen. 93% of them presented with symptomatic breast disease, and the commonest symptom was a palpable mass (90.7%). Presentation for mammography after observing symptoms showed a median delay of 28 days. BC was found mostly in involuting type of breasts. Commonest mammography characteristic was a mass (86.4%). Size of the mass was between 2 cm to 5 cm in majority (84.3%) with T stage II disease. In conclusion, mean age of the subjects was comparable to other Asian countries but relatively lower than that of the west. Majority of patients presented with a palpable mass within four weeks from the onset of symptoms. The size of the mass did not show a significant correlation with the duration of symptoms and the age. This study did not find a significant association between mammographic breast density with IDC.

Keywords: Breast cancer,Invasive ductal carcinoma, Mammography

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Introduction

There is a significant increase in the incidence of breast cancer (BC) worldwide with 1 million new cases each year[1]. BC contributes to 18% of all cancers of women[1].The age standardised incidence rates (ASR) of BC vary from 19.3 in Eastern Africa to 89.9 in Western Europe[2]. In Sri Lanka too, breast cancer ranks highest among all the cancers in female and ASR of BC has risen substantially from 9.4 in 1985 to 23 in 2010[3]. Age is one of the most important risk factors of developing a BC. At the age of 30 a woman has 0.44% of risk of developing BC over a period of 10 years where as at the age of 60 years it increases to 3.46%[4]. According to the cancer registry 2010 in Sri Lanka, higher proportion of BC were in above 50 years age groups and it was highest in the age category of 60-64years[3]. It has been shown that there is a higher risk of breast cancer after menopause, but the data on incidence of BC during the pre and postmenopausal years of women has been controversial[5,6].

A palpable mass is the most common symptom and the initial complaint for about 50% of the breast cancer patients[7]. The overall sensitivity of symptoms in detecting BC is found to be 35.5%[8].

There are many imaging methods available to detect BC such as ultrasonography, MRI and scinti-mammography (Tc^{99m} Sestamibi) with variable degrees of sensitivity, but mammography remains the most widely used method up to date, with a sensitivity ranging from 75% to 90% and specificity from 90% to 95%[9].

Mammographic breast density is a known strong predictor of breast cancer[10,11]. Wolfe proposed a classification of breast densities on mammography and he defined four parenchymal patterns also known as Wolfe grades along with the risk of breast cancer related to each category in 1976. They are: N1 pattern of fatty radiolucent breast, P1 pattern with less than 25% prominent fibroglandular tissue (FG), P2 pattern with more than 25% prominent FG tissue and DY pattern with dense FG tissue[12].According to Wolfe's study, N1 pattern has a 0.1% incidence of breast cancer compared to P2 and DY patterns where there is 17 to 22-fold increase in the incidence of BC respectively[12].

It has been reported that certain histological types of BC have a tendency to show a specific mammographic appearance but there are results on the contrary[13,14,15].In high-grade ductal carcinoma in situ (DCIS), debris from tumour necrosis leads to characteristic pleomorphic microcalcification, which gives a branching pattern on mammography. Invasive ductal carcinoma (IDC) induces fibrous response when it infiltrates outside the duct and it contributes to mass formation along with the malignant cells[16]. This explains the variable appearances on mammography ranging from visible mass particularly with an irregular or spiculated margin, architectural distortion, asymmetric density and pleomorphic microcalcification. Further invasion of the IDC leads to skin thickening, nipple

retraction, spread to locoregional lymph nodes and distant metastases.
Moreover, breast cancer management strategyis another important fact considered in the interpretation of mammogram. The most widely used such guideline is the Breast Imaging Reporting and Data System (BIRADS) categories[17].

The aim of this study was to describe the clinical presentation, demographics and mammographic characteristics in a group of Sri Lankan female population, who were confirmed to have IDC on histopathology.

Materials and Methods

This was a descriptive study, carried out using a mammography database maintained by the principal investigator at a mammography facility between 2006 and 2016 in Kandy district, Sri Lanka. Inclusion criterion was the subjects with BC proven on histopathology as IDC. Among 209 BC cases in the database, 177 with IDC were selected as subjects.Mammograms were carried out by using a Bennett USA mammography unit by two experienced radiographers. Data on demographic and mammographic characteristics were recorded in a pre-coded questionnaire. Mammographic characteristics namely, size, density, margin and site of the mass, presence of microcalcification, architectural distortion, skin thickening, nipple retraction and asymmetric density on standard views (MLO and CC), reported by the principal investigator with more than 15 years experience on imaging BC were considered in this study.Double reading of each mammogram was performed by the same investigator. Histopathological reporting was done by an experienced senior histopathologist. Standard statistical methods such as chi-square test, Spearman correlation and frequency were used. Statistical Package for the Social Sciences statistical software (version 20.0; SPSS Inc., Chicago, IL, USA) was used in analysis. Ethical clearance was obtained from the ethics review committee of the Faculty of Medicine, University of Peradeniya.

Results

Out of 84.7% IDC subjects, 80.4% were in isolation whereas 4.3% had coexistent DCIS (Table 1). Age ranged from 30 to 83 years (mean age 52.2, SD ± 1.1). There were 32.2% (n=57) and 31.1 % (n=55) representing age groups 40-49 and 50-59 years. 10.7% (n=19), 26% (n=46) were below 40 years and above 60 years respectively. 63.8% (n=111) of them were postmenopausal where as 36.2% (n=63) were premenopausal and the mean age of menopause was 48.1 (SD ± 5.1) (Table 1).

Of the total study population, 93% (n=161) presented with symptomatic breast disease.The most common clinical presentation of the symptomatic women was a palpable mass (90.7%,n=157). 63% (n=109) of the masses were isolated and 27.7% (n=48) were associated with few other symptoms such as mastalgia (25.4%), nipple discharge (2.9%) or skin dimpling (2.3%). Second commonest cause of presentation for mammography was mastalgia, mostly with another symptom (25.4%) than in isolation (2.3%). Seven percent (n=12) women sought

mammography without any symptoms. With regard to the time taken for presentation for mammography from the point of symptoms, delay of one week was found in 15.4% (n=23) women and more than three months in 21.5%, but 63.1% (n=94) had presented within one to eleven weeks after observing symptoms with a median delay of 28 days (Table 1).

Among them, 70.5% (n=120) had involuting P1 Wolfe type of breast on mammography whereas 21.8% (n=37) had adipose breasts and only 2.9% (n=5), 4.7% (n=8) had dense and involuting P2 types respectively (Table 2). Among the premenopausal group 73.8% (n=45) and 68.8% (n=75) of the postmenopausal group had P1 type of involuting breasts. Pre and postmenopausal groups had 4.9% and 1.8% DY type and 11.5% and 0.9% P2 types respectively (Table 2).

When considering the mammographic features of IDC among subjects, 86.4% (n=153) had a mass on mammograms. 43.8% (n=67) were in isolation without microcalcification, nipple retraction, skin thickening or architectural distortion (Table 3). On analysis of the side and the site of the mass lesion on mammogram, 59% (n=66) were found in right breast and according to quadrant, right upper outer quadrant (RUOQ) had 43.8% (n=49), left upper outer quadrant (LUOQ), left upper inner quadrant (LUIQ), and right upper inner quadrant (RUIQ) had 23.2%, 9.8% and 8.0% respectively (Table 3). Unilateral disease was found in 98.6% (n=140) of the subjects. With regard to the focal distribution of the masses, 91.3% (n=126) were found to be unifocal. 5.8% (n=8) and 2.9% (n=4) of them had multifocal and multicentric disease respectively (Table 3). Further analysis of the characteristics of the mass on mammograms revealed that 67.4% (n=93) of the masses were of high-density while 26.8% (n=37) were isodense (Table 3**)**. There were 87% (n=127) masses with a spiculated margin and 84.3% (n=129) of the masses were between 2-5 cm in size (mean 3.1 ± SD1.5) of T stage II. Only 5.2% (n=8) had more than 5 cm masses (T stage III) and 10.5% (n= 16) had less than 2 cm masses (T stage I) on mammography (Table 3).

27.6% (n=49) of the subjects showed microcalcification on the mammogram. Among them, 46 subjects presented with a mass combined with other mammographic features, three subjects showed microcalcification with other features but without a mass (Table 3). 84.2% had architectural distortion either in isolation (6.2%) or with other mammographic signs. 78.4% (n=124) of the subjects were in the BIRADS 5 category whereas 5.1% (n=8) in each BIRADS 3 and BIRADS 6 categories. Analysis of the correlation between the duration of symptoms and the tumour size did not reveal any significant association (Table 4).Similarly age of the patient and tumour size also did not show any significant association (Table 5). Of the 177 BC patients who underwent mammographic examination, 51 had metastatic axillary lymph nodes (LN). However, mammography detected only 21 (41.2%) metastatic LN (sensitivity=41.2%) (Table6).

Discussion

Breast cancer is a complex disease of many histological and molecular subtypes with a wide spectrum of clinical presentations, risk factors and outcomes. In the current management of BC, mammography plays a crucial role in establishing the diagnosis.Randomized clinical trials have shown that mammography has contributed to the reduction of overall breast cancer mortality by 30% in women aged 50 to 59 years who were screened for BC on mammography[9]. Demographic, clinical and mammographic characteristics on various histological types of BC are well documented in the literature, based on western data, however, revisits in local literature is sparse. Invasive ductal carcinoma was exclusively selected in this study, as this is the commonest (84.7%) among all the histological types of this study population. This is comparable with global figures of 70%-90% IDC among all histological types[18,19].

It revealed that the majority of women with IDC in the age ranges between 40-49 (32.2%) and 50-59 (31.1%) years with a mean age of 52.2(SD ± 1.1) years. This age distribution is comparable with the figures given for Asia, but it is somewhat lower than that of western countries where the mean age is between 60-70 years[5,20,21]. However, age specific BC incidence showed a peak incidence at 60-64 years in all types of BC[3]. Incidence of BC among pre and postmenopausal years of women has been extensively investigated in various studies, but the results are inconclusive[5,6]. Studies done in Spain and Canada showed that IDC was more common in postmenopausal than premenopausal women[13,15]. However, there were results on the contrary in a study by Jiang *et al*. who found that 57.4% were premenopausal[5]. Moreover, Lancet oncology 2012, based on a meta-analysis reported that premenopausal woman have a greater risk of breast cancer than postmenopausal women of identical age[6]. In this study, the majority (63.8%) were postmenopausal and the mean age of menopause was 48.1 years.

Symptoms of BC vary from a painless breast lump to skin dimpling, blood stained nipple discharge and nipple retraction. Seltzer MH, Newark found that 50% of subjects present with a new lump or a mass as the most common symptom[7]. Commonest clinical presentation of the index study was a palpable mass, either in isolation (63%) or with some other associated symptoms (27.7%). There is no national mammographic breast-screening program in Sri Lanka and the current guideline is the clinical and self-breast examination according to National Cancer Control Program based on WHO recommendation. However 7% of study population sought mammography without any symptoms. Presentation for mammography from the time of onset of symptoms could be delayed due to patient factors such as time taken for consultation or other factors related to accessibility for mammography. Majority (63.1%) of our subjects had presented within eleven weeks with a median delay of 28 days. A German study showed that the median patient delay is 16 days and 18% of BC patients wait for more than three months prior to consultation[22].

There is strong evidence that dense breasts with a larger proportion of glandular tissue carry a higher risk of developing BC, which has also been proven by Wolfe[10,11,12]. Similar association was shown in 2007, in Mayo clinic where they found that overall mammographic density is a general marker of BC risk but it is not specific for side or the location of the cancer developed eventually[10]. This concept was not supported in our study as majority (70.5%) had involuting type P1 pattern. Dense breasts, P2 and DY types, were seen only in a minority being 4.7% and 2.9 % respectively. Moreover, both pre and postmenopausal groups had involuting P1 type in the majority. This was on par with the results of a study done in India, where there was no added risk fromincreased breast density in postmenopausal women[11]. However, they found that there was an increased risk of developing BC in younger women[11]. This study did not reveal a higher incidence of BC in dense breasts even in the premenopausal age group.

A high-density mass with a spiculated margin is considered the hallmark mammographic manifestation and a predictor of invasive carcinoma. In our study 86.4% had a mass lesion on mammograms. This was relatively higher in proportion compared to a Spanish study (74%) but it is comparable with that of the UK (82.5%)[13,14]. Of the masses, 43.8% were in isolation without microcalcification, nipple retraction, skin thickening or architectural distortion. 67.4% of the subjects of our study had high-density and it was comparable with a study done in USA in which 70.2% had high-density masses[23]. The UK study however did not favour this finding, as they could not find a difference of density between invasive lobular carcinoma (ILC) and IDC subjects[14]. Spiculated margin of a mass is more commonly described in IDC than ILC. In this study, margin of the masses werespiculated in majority (87%), but this was not supported in a Chinese study where they found 57.1% of masses to have non-spiculated margins[5]. The UK study found that both ILC and IDC have spiculated margins in equal number of subjects[14]. 27.6% of the subjects had microcalcification (MC) on the mammogram and among them 6.1% did not accompany a mass. Few studies done in Canada and in the UK found a relatively higher proportion of MC amounting to 40.9% and 46% respectively[14,15]. BC was commonly seen as unifocal disease. However, bilateral, multifocal and multicentric disease do exist either synchronous or metachronous. Similar to other studies most (91.3%) of our patients also presented with unifocal disease[14]. Upper outer quadrant predilection was observed, which contributed to 67% of BC among all sites. There was slight right breast predominance, but the bilateral disease was rare (1.4%) in our sample. Invasive lobular carcinomas are known to produce bilateral disease than IDC[24]. However, a few studies are on the contrary reporting invasive duct carcinoma as the most common histological type in bilateral BC[25,26]. Multifocal and multicentric disease was not a common finding in this study.

Size of the BC is most accurately measured at the time of histopathological diagnosis and it carries a high prognostic implication, thus used in the T staging. Among the

subjects of our study, T Stage I or less than 2 cm tumour was found only in 10.5% of the study population. 84.3% of the masses were between 2 cm to 5 cm and were of T stage II. Only a minority (5.2%) had T stage III disease with more than 5 cm mass size. A study conducted in Canada revealed that the mean tumour size was 2.5 cm[15]. An analysis of a BC series in USA showed that 61% presented with less than 2 cm tumour size [21]. Nevertheless, tumour size on mammography did not show any strong correlation with duration of symptoms in our study. Similarly, age of the patient and tumour size did not show significant correlation.

BIRADS 5 category carries more than 95% likelihood of a mammographic mass being malignant[17]. In our study, majority (78.4%) were in BIRADS category 5 and about 5.1% of our subjects were in BIRADS 3 category.

Axillary lymph node status is still considered an important prognostic factor for BC survival despite marked evolution of breast cancer assessment by means of molecular and genetic characterization. In a few studies done in USA, it has been shown that 33%-36% of invasive duct carcinoma of breast has axillary LN metastases[21,27]. Our study showed a substantial but slightly lower frequency (28.8%) oflocoregional LN metastases on mammography.

Conclusions: Mean age of presentationof patients with IDC was 52.2 years,which is comparable to other Asian countries but relatively lower than that of the west. Majority of the patients presented with a palpable mass, within four weeks of the onset of symptoms. Unifocal and unilateral high-density mass of T stage II was the commonest mammographic abnormality and size of the mass did not show a significant correlation with the duration of symptoms. Interestingly, poor correlation was found between higher mammographic breast density and IDC, among both pre and postmenopausal women, which is different from many other studies.

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Table 1. Demographic and clinical characteristics of the IDC subjects

Variables	Frequency (%)	Mean/Median
Histological type (n=209)		
IDC	168 (80.4)	
IDC+DCIS	9 (4.3)	
DCIS	22 (10.5)	
Other	10 (4.8)	
Age (n=177)		Mean age 52.2(SD ± 1.1)
30-39	19 (10.7)	
40-49	57 (32.2)	
50-59	55 (31.1)	
60-69	36 (20.4)	
>70	10 (5.6)	
Menopausal status (n=174)		Mean Age at menopause 48.1 (SD ± 5.1)
Pre	63 (36.2)	
Post	111 (63.8)	
Clinical Presentation (n=173)		
Mass(in isolation)	109 (63.0)	
Mastalgia	4(2.3)	
Mass+mastalgia	39 (22.5)	
Mass+mastalgia+nipple discharge	4(2.3)	
Mass+mastalgia+skin infiltration	1(0.6)	
Mass+nipple discharge	1 (0.6)	
Mass+skin infiltration	3 (1.7)	
Asymptomatic	12 (7.0)	
Duration of Symptoms (n=149)		
<1w	23 (15.4)	Median delay 28 days (4 weeks)
1-3w	46 (30.9)	
4-11w	48 (32.2)	
12-24w	19 (12.8)	
=>25w	13 (8.7)	

Table 2. Correlation between menopausal status with Wolfe breast density grades

		Wolfe Breast Density type (%)				
		N1	P1	P2	DY	Total
Menopause	Pre	6(9.8%)	45(73.8%)	7(11.5%)	3(4.9%)	61(100%)
	Post	31(28.5%)	75(68.8%)	1(0.9%)	2(1.8%)	109(100%)
Total		37(21.8%)	120(70.5%)	8(4.7%)	5(2.9%)	170(100%)

Missing information-7; Spearman correlation coefficient –0.07, P=0.001

Table 3.Mammographic Characteristics of IDC

Variables	**Frequency(%)**
Mass (n=153)	
Mass in isolation	67 (43.8)
Mass+ (Skin thickening [ST]+Architecture distortion [AD]+Microcalcification [MC])	86 (56.2)
Site of the mass (n=112)	
RUOQ	49 (43.8)
RUIQ	9 (8.0)
LUOQ	26 (23.2)
LUIQ	11 (9.8)
RLOQ	1 (0.9)
RLIQ	7 (6.3)
LLOQ	6 (5.3)
LLIQ	3 (2.7)
Position of the mass (n=142)	
Unilateral	140 (98.6)
Bilateral	2 (1.4)
Focus of the mass (n=138)	
Unifocal	126 (91.3)
Multifocal	8 (5.8)
Multicentric	4 (2.9)
Mass Density (n=138)	

High density	93	(67.4)
Isodense	37	(26.8)
Other	8	(5.8)
Margin of the mass (n=146)		
Spiculated	127	(87.0)
Non spiculated	19	(13.0)
Size of the mass and T stage (n=153)		
<2cm (T1)	16	(10.5)
2-5cm (T2)	129	(84.3)
>5cm (T3)	8	(5.2)
Architectural distortion (AD) (n=14)		
AD in isolation	11	(78.6)
AD+ ST	3	(21.4)
Microcalcification (MC) (n=49)		
MC+ Mass+ AD+ ST+ Nipple retraction	46	(93.9)
MC+ AD+ ST	3	(6.1)
BIRADS category (n=158)		
3	8	(5.1)
4	18	(11.4)
5	124	(78.4)
6	8	(5.1)

Table 4. Correlation between the duration of symptoms and size of the mass

		Size of the Mass (cm)			Total
		<2	**2-5**	**>5**	
Duration of presentation	**<1w**	3	10	2	15
	1-3w	4	40	2	46
	4-11w	6	37	3	46
	12-24w	2	17	0	19
	=>25w	0	10	1	11
Total		15	114	8	137

Missing information – 40; Spearman's correlation coefficient- 0.022, P=0.79

Table 5. Correlation between the age and size of the mass

		Age group					
		30-39	**40-49**	**50-59**	**60-69**	**>69**	**Total**
Mass Size	**<2cm**	1	3	8	4	0	16
	2-5cm	15	39	38	28	9	129
	>5cm	0	3	2	3	0	8
Total		16	45	48	35	9	153

Missing information – 24; Spearman correlation - 0.07; P- 0.57

Table 6. Axillary LN status on mammography and histopathology

	Histology +	**Histology -**	**Total**
Mammo +	21 (41.2%)	28 (22.2%)	49
Mammo -	30 (58.8%)	98 (77.8%)	128
Total	**51 (100.0%)**	**126 (100.0%)**	

Sensitivity of mammography = 41.2%

Specificity of mammography = 77.8%