

Locally Advanced and Metastatic Breast Cancer in a Tertiary Hospital

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Abstract

Introduction: The breast cancer incidence among Singapore women has risen through the years and is now the highest in Asia. Despite efforts to promote a greater awareness of breast cancer among the public, a significant number of patients still present with locally advanced or metastatic breast cancer. Our study aims to evaluate the clinical and pathological characteristics between patients presenting with locally advanced (LABC) and metastatic breast cancer (MBC) and those presenting with early breast cancer (EBC), to identify factors that predict for advanced disease. **Materials and Methods:** We reviewed 622 patients who were newly diagnosed with invasive breast cancer in our department over a 4-year period from January 2000 to December 2003. Patient and tumour characteristics including age, parity, family history, tumour size and histology, grade and hormonal receptor status were analysed. Comparisons were made between those with EBC and those with LABC and MBC, as well as between Malay women and women of other ethnic groups. **Results:** One hundred and thirty-four patients (21.5%) presented with either LABC or MBC. Adjusted analysis found that these patients were older and more likely to be nulliparous than those with EBC. Older patients tend to have larger tumours, but otherwise, age and parity did not correlate with tumour histology, grade or hormonal status. It was noted that Malay women, who were more likely to present with LABC or MBC, were more likely to have oestrogen receptor- and progesterone receptor-negative tumours. **Conclusions:** Older women and those who were nulliparous were found more likely to present with LABC and MBC. However, age and parity did not appear to be related to tumour histology, grade and hormonal status. Given that tumour size and stage have the greatest impact on overall survival, efforts to raise public awareness of the benefits of early detection and treatment should be continued, and possibly directed towards these groups of women who appear to be at an increased risk of presenting late.

Ann Acad Med Singapore 2005;34:595-601

Key words: Ethnic groups, Ethnicity, Malay, Nulliparity

Introduction

Breast cancer is the most common cancer among women in Singapore and accounts for 22.8% of all female cancers.¹ The incidence of breast cancer in Singapore has doubled between 1968 to 1972 and 1993 to 1997² and is now the highest in Asia, with an age-adjusted incidence of 53.1 per 100,000 women from 1998 to 1999.³ This is expected to rise further in the coming years to approach that of the Western populations.

In recent years, much effort has been made to promote a greater awareness of breast cancer among the public. October has been designated the Breast Cancer Awareness

Month. The various hospitals, together with the Breast Cancer Foundation, organise talks and seminars on breast cancer detection and treatment. In January 2002, the BreastScreen Singapore, a population-based nationwide mammography breast screening programme targeting women between 50 and 69 years of age, was launched⁴ with the aim of reducing breast cancer mortality by 10% by 2010.¹ In spite of these efforts, it is still not uncommon for healthcare professionals to encounter women who present with locally advanced or metastatic disease.

Singapore is a multi-racial society, with Chinese making up 76.2% of the population, Malays 13.8%, and Indians

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8.3%. The ethnic variation of breast cancer incidence has been well documented in the United States, where the age-adjusted incidence is much higher among white, Hawaiian and black women.⁵ This variation was found to be related to socioeconomic status, particularly among the Hispanic and Asian populations in California.⁶ Epidemiological studies examining these variations are valuable in identifying patterns and aetiological factors particular to the various ethnic groups. The Malay population in Singapore is known to have a lower cancer incidence compared to the other ethnic groups in Singapore.³ The incidence of breast cancer in Malay and Indian women is 20% lower than that of Chinese women.⁷ A similar trend was also observed amongst the Malay women in Malaysia although more Malay women seem to present late with locally advanced breast cancer (LABC) or metastatic breast cancer (MBC).^{8,9}

We are interested to determine if there are any differences in the clinical and pathological characteristics of women who present with LABC and MBC and those who present with early breast cancer (EBC). We also hope to determine if there is any ethnic variation in the clinical and pathological features among women presenting with LABC and MBC in the local population. This data would be valuable in the planning of breast cancer awareness programme and may highlight the need to target women of a particular ethnic group. It is important to address this problem of late presentation as breast cancer is potentially curable if detected and treated in the early stages. To meet these objectives, we set out to analyse the data of all women who presented with invasive breast cancer to the Department of General Surgery at Tan Tock Seng Hospital. In order to identify factors that may predict for late presentation of breast cancer, we compared the clinicopathological characteristics of those who presented with EBC and those who presented with LABC and MBC.

Materials and Methods

Our department's breast cancer database over a 4-year period from January 2000 to December 2003 was reviewed. The medical records of all women diagnosed with invasive breast cancer were recalled and reviewed retrospectively. Data concerning patient characteristics, including age, menstrual status, parity, family history, symptom presentation, as well as tumour characteristics including tumour size, stage, histology, grade and hormone receptor status were collected. Comparisons were made between those who presented with EBC and those with LABC or MBC. LABC refer to tumours that are larger than 5 cm in size or that involve the overlying skin or chest wall, as well as tumours with greater than N2 (>4 nodes) nodal involvement. This will include all Stage III tumours, as well as T3N0 tumours which are a subset of Stage IIb tumours.¹⁰

MBC refer to tumours that are associated with metastatic disease. Comparisons were also made between the Chinese and the Malay women who presented with LABC and MBC, as these 2 groups made up 95.5% of those with LABC and MBC.

Statistical analysis was done using Statistical Package for the Social Sciences (SPSS version 11.5). Associations between categorical variables were assessed using χ^2 or Fisher exact tests. Normality test was carried out for the continuous variables. Two sample *t*-tests were performed if the normality and equality of variances assumptions were satisfied; otherwise the Mann-Whitney U test was used. Logistic regression analysis predicting LABC or MBC adjusting for relevant covariates was performed. Statistical significance was set at $P < 0.05$.

Results

During the 4-year period from January 2000 to December 2003, 622 women were diagnosed with invasive breast cancer in our department. Four hundred and eighty-eight patients (78.5%) presented with EBC, 85 patients (13.7%) presented with LABC and 49 patients (7.9%) presented with MBC. Table 1 shows that most of the cases (40%) were presented in 2002 and only 17% of them presented in 2000. There was no significant trend found between the proportion of LABC or MBC and EBC presenting to the department over the 4-year period ($P = 0.234$, χ^2 test for trend). Of the 622 patients, 84.2% were Chinese, 9.6% Malays, 4.0% Indians and 2.1% were of other ethnic groups. The incidence of LABC or MBC of Malays was slightly higher compared to the incidence of EBC (15% vs 8%). Overall, breast cancer appeared to affect a similar proportion of women in the various ethnic groups ($P = 0.082$, χ^2 test).

Table 1. Number of Patients with EBC, LABC and MBC over 4 Years from January 2000 to December 2003 Among the Various Ethnic Groups

	LABC or MBC n = 134 (%)	EBC n = 488 (%)	Total n = 622 (%)
Year			
2000	23 (17.2)	84 (17.2)	107 (17.2)
2001	24 (17.9)	117 (24.0)	141 (22.7)
2002	54 (40.3)	193 (39.5)	247 (39.7)
2003	33 (24.6)	94 (19.3)	127 (20.4)
Race			
Chinese	108 (80.6)	416 (85.2)	524 (84.2)
Malay	20 (14.9)	40 (8.2)	60 (9.6)
Indian	5 (3.7)	20 (4.1)	25 (4.0)
Others	1 (0.7)	12 (2.5)	13 (2.1)

EBC: early breast cancer; LABC: locally advanced breast cancer; MBC: metastatic breast cancer

Table 2. Comparisons of Characteristics for Women Presenting with Locally Advanced or Metastatic Breast Cancer and Those Presenting with Early Breast Cancer

Characteristic	LABC or MBC (n = 134)	EBC (n = 488)	P value
Age (y)			
Mean (SD)	59.1 (14.5)	53.8 (12.2)	<0.001
Median (range)	58.0 (30.0 to 94.0)	52.0 (24.0 to 90.0)	
Post-menopausal status	97 (72.4%)	275 (56.4%)	0.001
Positive family history	10 (7.6%)	40 (8.2%)	0.824
Nulliparity	32 (26.7%)	99 (21.4%)	0.216
Symptom presentation			
Breast lump	128 (95.5%)	400 (82.0%)	<0.001
Non-breast lump	6 (4.5%)	88 (18.0%)	
Screen detected	1 (0.7%)	64 (13.1%)	
Breast pain	1 (0.7%)	11 (2.3%)	
Nipple changes	1 (0.7%)	11 (2.3%)	
Others	3 (2.2%)	2 (0.4%)	
Laterality of tumour			
Right	80 (59.7%)	237 (48.6%)	
Left	52 (38.8%)	239 (49.0%)	0.070
Bilateral	2 (1.5%)	12 (2.5%)	
Tumour histology			
Invasive ductal carcinoma	111 (86.0%)	427 (87.5%)	0.660
Non-invasive ductal carcinoma	18 (14.0%)	61 (12.5%)	
Invasive lobular carcinoma	8 (6.2%)	14 (2.9%)	
Mucinous carcinoma	5 (3.9%)	19 (3.9%)	
Medullary carcinoma	0 (0%)	5 (1.0%)	
Papillary carcinoma	3 (2.3%)	9 (1.8%)	
Others	2 (1.6%)	14 (2.9%)	
Tumour grade			
1	10 (11.0%)	84 (17.3%)	0.280
2	57 (62.6%)	270 (55.7%)	
3	24 (26.4%)	131 (27.0%)	
Tumour size (mm)			
Number	81	486	<0.001
Median (range)	60.0 (10.0 to 150.0)	20.0 (1.0 to 47.0)	
Number with involved nodes			
Number	47	468	
Median (range)	4.0 (0.0 to 36.0)	0.0 (0.0 to 36.0)	<0.001
Hormonal receptor status			
ER-positive	54 (58.7%)	291 (69.0%)	0.058
PR-positive	38 (41.8%)	246 (58.4%)	0.004

EBC: early breast cancer; ER: oestrogen receptor; LABC: locally advanced breast cancer; MBC: metastatic breast cancer; PR: progesterone receptor; SD: standard deviation

The mean age of all patients was 55.0 (standard deviation, 12.9) years and more than half (59.8%) were post-menopausal. A positive family history of breast cancer among first-degree relatives was found in only 8.1%. Most had at least 1 child while 131 patients (22.5%) were nulliparous. The majority of patients presented with a breast lump (84.9%), unilateral (97.8%) and invasive ductal carcinoma (87.2%). About 67.1% and 55.5% of these tumours were oestrogen receptor (ER)- and progesterone receptor (PR)-positive, respectively.

Table 2 presents the characteristics of women presenting with LABC or MBC in contrast to those presenting with EBC. Of those presenting with LABC or MBC, all but 6 patients presented with a breast lump. One patient presented with breast pain, 1 with nipple discharge, 3 with symptoms of metastatic disease (2 with dyspnoea from malignant pleural effusion and lung metastases, 1 with bone pain from bone metastases) and 1 patient was diagnosed incidentally when she presented with an unrelated complaint. Forty of these patients underwent a total mastectomy and axillary

Table 3. Comparison of Clinical and Pathological Features Between Malay and Non-Malay Women

Characteristic	Malays (n = 60)	Non-Malays (n = 562)	P value
Age [median (range)] (y)	49.0 (31.0 to 82.0)	53.0 (24.0 to 94.0)	0.005
Post-menopausal status	29 (48.3%)	343 (61.0%)	0.057
Positive family history	6 (10.2%)	44 (7.9%)	0.462
Nulliparity	6 (10.7%)	125 (23.7%)	0.027
Tumour size [median (range)] (mm)	25.0 (1.0 to 120.0)	20.0 (1.0 to 150.0)	0.144
Tumour histology			
Invasive ductal carcinoma	51 (85.0%)	487 (87.4%)	0.592
Others	9 (15.0%)	70 (12.6%)	
Tumour grade			
1	5 (9.4%)	89 (17.0%)	0.316
2	31 (58.5%)	296 (56.6%)	
3	17 (32.1%)	138 (26.4%)	
Number of involved nodes [median (range)]	1.0 (0.0 to 36.0)	0 (0.0 to 36.0)	0.008
Hormonal receptor status			
ER-positive	20 (40.8%)	325 (69.9%)	<0.001
PR-positive	18 (36.7%)	266 (57.5%)	0.006

ER: oestrogen receptor; PR: progesterone receptor

clearance; 4 of these patients also required an immediate latissimus dorsi flap reconstruction to cover the chest wall defect following mastectomy. Seven patients underwent a simple mastectomy (without axillary clearance), 4 patients underwent a wide excision and axillary clearance, and 1 patient underwent a wide local excision to remove a fungating tumour. Eleven patients with LABC underwent neoadjuvant chemotherapy. More than half of the 134 patients with LABC and MBC (61%) did not have any surgery.

Patients with LABC or MBC were significantly older ($P < 0.001$) and were more likely to be post-menopausal [odds ratio (OR) 2.0; 95% CI, 1.3 to 3.1; $P = 0.001$]. They were more likely to present with a breast lump, rather than other symptoms (OR 4.7; 95% CI, 2.0 to 11.0; $P < 0.001$). There was no significant difference in parity or a positive family history of breast cancer. Likewise, tumour characteristics like tumour histology, grade and ER status were similar between the 2 groups on univariate analysis, although a negative PR status was more commonly encountered in LABC or MBC (OR 2.0; 95% CI, 1.2 to 3.1; $P = 0.004$). Malay women were found to be 2 times more likely to present with LABC or MBC as compared to women of other ethnic groups. (OR 1.96; 95% CI, 1.1 to 3.5; $P = 0.019$). These Malay women presenting with LABC or MBC were younger (50 years vs 55 years; $P = 0.005$) and were less likely to be nulliparous ($P = 0.027$). The frequency of a positive family history of breast cancer was nevertheless similar to the rest of the women. Tumour histology and grade were also similar among the women of various ethnic groups. However, it was noted that Malay women were 4 times more likely to

have ER-negative tumours (OR 3.6; 95% CI, 1.1 to 11.7; $P = 0.026$) and twice more likely to have PR-negative tumours (OR 2.3; 95% CI, 1.3 to 4.3; $P = 0.006$). Malay women also appeared to have more extensive nodal involvement ($P = 0.008$) (Table 3). After having adjusted for age, ethnicity (Malays vs Chinese vs Indians/Others), menopausal status, positive family history, parity, symptom presentation, tumour histology, grade and hormonal responsiveness, only age and nulliparity remained as significant risk factors for LABC or MBC (Table 4). Older women had larger tumours (regression coefficient 0.25; 95% CI, 0.1 to 0.4; $P \leq 0.001$). Otherwise, no relation was found between age and parity and tumour characteristics such as tumour histology, grade and hormonal status (Tables 5 & 6).

Discussion

Breast cancer has remained the most common cancer among women in Singapore over the past 35 years.⁷ The recent years have seen a rise in the incidence of breast cancer among Singapore women. A review of data from the Singapore Cancer Registry over a 25-year period from 1968 to 1992 showed an average annual increase in breast cancer incidence of 3.6%.¹¹ The incidence rate from 1998 to 2002 was 53.1 per 100,000 women years. This is 2.7 times that from 1968 to 1972 and 25.6% higher than that from 1993 to 1997.⁷ Although this is still half the incidence rates among women in the United States and Europe, it is now the highest in Asia.⁷ This increase in incidence has been noted among all the various ethnic groups, but the rate of increase (4.4%) is steepest among the Malays.¹¹ This is rather interesting as Malays have been known to have a

Table 4. Logistic Regression Analysis Predicting Locally Advanced Breast Cancer or Metastatic Breast Cancer

Characteristic	P value	Odds ratio (95% confidence interval)
Age	0.001	1.05 (1.02 to 1.08)
Race		
Chinese	0.158	
Indian/Others	0.071	0.46 (0.20 to 1.07)
Malay*	0.137	0.32 (0.07 to 1.43)
Post-menopausal status	0.201	1.71 (0.75 to 3.87)
Pre-menopausal status*		
Positive family history	0.485	1.40 (0.54 to 3.64)
Nulliparity	0.047	1.85 (1.01 to 3.41)
Invasive ductal carcinoma	0.048	0.47 (0.22 to 0.99)
Non-invasive ductal carcinoma*		
Tumour grade		
1	0.270	
2	0.621	0.77 (0.28 to 2.14)
3*	0.300	1.43 (0.73 to 2.80)
Hormonal receptor status		
ER-positive	0.533	1.28 (0.59 to 2.79)
PR-positive	0.033	0.45 (0.21 to 0.94)

ER: oestrogen receptor; PR: progesterone receptor

* Reference groups

lower overall cancer incidence as compared to the Chinese.¹²

The finding that older women were at an increased risk of developing LABC or MBC is in contrast to several reports in the literature which reported that younger women were more likely to present with more advanced and aggressive disease.¹³ Women younger than 35 years were often found to have larger tumours and more extensive nodal involvement. In addition, the tumours were more

Table 5. Effect of Age on Tumour Characteristics

Characteristic	Age (y) [median (range)]	P value
Tumour histology		0.604
IDC	52.0 (27.0 to 94.0)	
Non-IDC	48.0 (24.0 to 88.0)	
Tumour grade		0.727
1	52.0 (24.0 to 90.0)	
2	52.0 (30.0 to 90.0)	
3	52.0 (27.0 to 90.0)	
ER status		0.250
ER-positive	51.0 (24.0 to 90.0)	
ER-negative	52.0 (27.0 to 90.0)	
PR status		0.912
PR-positive	51.0 (31.0 to 0.0)	
PR-negative	53.0 (24.0 to 90.0)	

ER: oestrogen receptor; IDC: infiltrating ductal carcinoma;

PR: progesterone receptor

likely to be of a higher grade and ER-negative.^{14,15} In our study, although tumour size was significantly larger in older patients, there appeared to be no relation between age and tumour histology, grade and hormonal status. A possible explanation may be that the older women in our society are less aware of breast cancer and are less willing to come forward to seek medical attention.

Nulliparity is a well-known risk factor for breast cancer. The protective effect conferred by increased parity has been reported in several population-based studies, with risk reduction in breast cancer of between 6% and 13% with each additional birth.¹⁶⁻¹⁸ Recently, it has been postulated that despite the similarity in the lobular composition of the breasts of menopausal women, the epithelial cells in those women who were nulliparous were

Table 6. Effect of Parity on Tumour Characteristics

Characteristic	Nulliparous women (n = 131)	Parous women (n = 491)	P value
Tumour size (mm)/[median (range)]	21.0 (1.0 to 150.0)	20.0 (1.0 to 120.0)	0.138
Tumour histology			0.071
IDC	106 (81.5%)	393 (87.7%)	
Non-IDC	24 (18.5%)	55 (12.3%)	
Tumour grade			0.148
1	28 (22.4%)	63 (15.0%)	
2	66 (52.8%)	237 (56.6%)	
3	31 (24.8%)	119 (28.4%)	
ER status			0.579
ER-positive	78 (69.0%)	247 (66.2%)	
ER-negative	35 (31.0%)	126 (33.8%)	
PR status			0.300
PR-positive	66 (59.5%)	201 (53.9%)	
PR-negative	45 (40.5%)	172 (46.1%)	

ER: oestrogen receptor; IDC: infiltrating ductal carcinoma; PR: progesterone receptor

more susceptible to carcinogenesis. Pregnancy was thought to alter the composition of mammary epithelial cells such that parous women, especially those who gave birth at a young age, had a higher population of epithelial cells that were refractory to malignant transformation.¹⁹ At present, nulliparity has not been linked to more advanced or aggressive disease. Although our study did not show nulliparity to be associated with more aggressive tumour features, larger population-based studies to evaluate the effect of parity on the incidence and clinical presentation of breast cancer in our local population may contribute towards further understanding of how hormonal changes in a woman's lifetime may influence the development and biological behaviour of breast tumours.

Although ethnicity did not appear to be significant on multivariate analysis, the finding that Malay women were twice more likely to present with advanced disease still deserves mention. Hisham and Yip,⁹ who reviewed 1526 women newly diagnosed with breast cancer at 2 major hospitals in Kuala Lumpur during a 4-year period from 1998 to 2001, found a similar trend among their patients. Malays were found to present with more advanced disease and larger tumours compared to the Chinese and Indians.^{9,20} It is interesting to note that despite an older age and nulliparity being associated with advanced disease, Malay women tend to be younger and multiparous. A possible explanation for the higher proportion of LABC and MBC noted among them could be related to the finding that tumours in Malay women tend more likely to be hormone unresponsive. ER-negative tumours have been reported to be more aggressive and to have a poorer prognosis compared to ER-positive tumours.²¹ It is postulated that the loss of ER status is associated with a progression towards less differentiated tumours with a greater propensity for metastasis.²² ER-negative MDA-MB-231 breast cancer cells that re-express functional ER have been shown to have decreased in vitro invasive and in vivo metastatic potential in the presence of oestradiol.²² While this may account for the greater extent of axillary nodal involvement seen among Malay women, our study did not otherwise suggest that ER-negative tumours belong to a more aggressive subgroup, given that the mean tumour size and grade and the incidence of distant metastasis is similar between Malay women and those of other ethnic groups. Although this study is limited by its small numbers and a referral bias, further studies to evaluate the variation of hormone responsiveness and clinical outcome among the various ethnic groups may provide further insight into the biological behaviour of breast tumours.

The biological behaviour of breast tumours has no doubt an important influence on the stage of the disease at presentation. However, as breast cancer is often slow-

growing and its associated symptoms, even in its late stages, are often more bothersome than life-threatening, public perception of breast cancer is likewise just as important in influencing when a patient decides to seek medical advice for a breast complaint. Epidemiological reports have linked the incidence of advanced disease with the level of awareness of breast cancer among the general public. Although the proportion of women in Singapore who present with LABC and MBC is lower than that of women in Malaysia, where there are no nationwide programmes to promote public awareness of breast cancer,^{8,9,20} it is still significantly higher than that observed in the United States where data from the National Cancer Institute's Surveillance, Epidemiology and End Results (SEER) Program showed only 7% of patients to have Stage III disease at the time of diagnosis.²³ The incidence of LABC is even lower in populations where women are well aware of breast cancer and undergo regular screening mammography.²⁴

Thus, it would appear that raising public awareness of breast cancer may provide a key to stemming the rise in breast cancer incidence among local women. Current modalities in breast cancer therapy still fail to adequately control widespread disease, and tumour size and stage remain the most significant determinants of overall survival rates.¹ As such, early diagnosis and treatment remain the best chance of long-term survival. Greater awareness about the prevalence of breast cancer and the survival benefits of early detection and treatment can encourage women to pay more attention to breast complaints and to seek medical advice early. Despite nationwide efforts to promote breast cancer awareness, many misconceptions still persist in our society. Although no studies have detailed the psychological attitudes of patients towards breast cancer in our population, it is not uncommon to come across patients who disregard a painless but progressively enlarging breast lump, thinking that only pain and rapid growth are associated with a "serious condition". This may explain the observation that it is the older patients, rather than the younger ones as reported in the literature, who are more likely to present to our department with advanced disease. There are also several common misconceptions that contribute to a reluctance to seek early medical attention. Some fear that surgery will "open up the tumour" and cause it to grow and spread faster. Many are also misinformed that total mastectomy is the only surgical option available and are concerned about the loss of their femininity and "wholeness",²⁵ which may affect their relationship with their husbands. These fears drive many to turn to traditional forms of treatment. Unfortunately, these alternative treatments do little to stop or reverse disease progression and many eventually present with fungating tumours or with breathlessness and bone pain from metastasis.

Conclusion

Much focus has been given to breast cancer in recent years in view of its rising incidence among women in Singapore. In our study, we found that older women and those who were nulliparous were at an increased risk of presenting with advanced disease. Age and parity were, however, not correlated with tumour histology, grade and hormonal status. Another interesting observation was that Malay women, who were twice more likely to present with LABC or MBC, tend to have hormone-unresponsive tumours. How much this affects the biological behaviour of the tumour and influences clinical presentation remain to be evaluated. Early detection and prompt treatment of breast cancer has been shown to improve overall survival rates. Therefore, efforts to raise public awareness of breast cancer should be continued, and possibly directed towards the older age groups, nulliparous women, as well as Malay women, who appear to have a higher risk of presenting with advanced disease.

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