Research Article

Trends in clinico-pathological and risk factor profile of breast cancer; 10-year experience at a single center in Sri Lanka

Lakmini Mudduwa, Harshini Peiris, Thusharie Liyanage, Shania Gunasekera, Nadeeka Ranawaka

Department of Pathology, Faculty of Medicine, University of Ruhuna, Galle.

Abstract

Background
The incidence of breast cancer in Sri Lanka is increasing on par with the rest of Asia. Lifestyle changes increasing the prevalence of risk factors of breast cancer among Asian women are claimed to be one of the reasons for this trend.

Aim
To analyze the clinico-pathological and risk factor profile of a cohort of breast cancer patients to detect any change in the patterns, over time.

Method
All breast cancer patients whose hormone receptor and Her2 status were evaluated in our laboratory from 2006 to 2015 were included. Clinicopathological data was retrieved from the laboratory records. A pre-tested interviewer administered questionnaire was used to collect data on risk factors.

Results
A total of 1371 patients were included. There was a significant change in trend in the age (p=0.001) with an upturn in the breast cancer patients over 60 years of age.

A significant change in trend was also observed in TNM stage (p=0.002), tumour size, Nottingham grade and lympho-vascular invasion (p<0.001). Hormone receptor expression showed an upward trend towards the latter part of the decade (p<0.001). A parallel decline in the triple negative cancers was also noted (p<0.001). However, Her2 status, lymph node metastases and lymph node stage did not show a change in trend. The only risk factor with a significant change was family history of breast cancer which had a downward trend (p=0.002).

Conclusion
This study describes an upward shift in the hormone receptor expression which can be attributed to the upward trend in the percentage of patients of >60 years. No significant change in trend in the risk factor profile was observed except for the downward trend in family history of breast cancer.

Corresponding author; Prof. Lakmini Mudduwa
Senior Professor of Pathology
Department of Pathology
Faculty of Medicine, University of Ruhuna,
Galle (Postal code: 80000) Sri Lanka. Email:
lakminimudduwa@yahoo.com

Introduction:
Breast cancer is the commonest malignancy worldwide and in Sri Lanka [1,2] The current incidence is lower in the Asia-Pacific region compared to Australia and New Zealand [1]. However, the breast cancer incidence in Asia is on the rise highlighting an emerging healthcare problem [1]. It is often claimed that breast cancer in Asian countries is more common among the middle aged and are often high grade compared to the West [3].

Breast cancers detected at early stage can be treated very effectively and have good prognosis, whereas advanced stage cancers require aggressive treatment and carry poor prognosis. Compared to the developed countries, stage at presentation is expected to be higher in Sri Lanka since there is no mammographic cancer screening programme at national level.

Rapid change in global trends have resulted in Asian women including Sri Lankans embracing a more westernized lifestyle. This is considered a contributary fact to the increase in incidence of breast cancer in Asia [3]. The duration of breast feeding, and childbearing is decreasing reflecting those of the western world and such change of risk factors may have an effect on the biology and hence the clinico-pathological features of breast cancer. Therefore, we intend to analyse the clinico-pathological and risk factor profile of breast cancer patients to detect any change in the pattern, over time.

The immunohistochemistry (IHC) laboratory of our unit was the first IHC laboratory established in the Southern province of Sri Lanka for the assessment of hormone receptor and Her2 status of breast cancer. It remained the single unit in Southern Sri Lanka evaluating IHC prognostic markers of breast cancer from its inception in 2006 till 2015. Therefore, the patient data included in this study represent a considerable geographic area in the country and these patients have been treated at a single oncology unit.

Method:

All patients whose hormone receptor status was evaluated in our laboratory from 2006 to 2015 were included in the study. Clinico-pathological features of breast cancer patients were collected from records archived in the laboratory and the database created for a breast cancer research project.

Since the inception of the laboratory, estrogen receptor (ER) and progesterone receptor (PR) expression had been scored using the Allred score and Her2 expression has been assessed according to the UK recommendations [4]. A score of ≤2 for ER and PR and a score of 0 or +1 for Her2 were considered the criterion for categorizing as triple negative breast cancer (TNBC). ER and PR were considered positive when the Allred score for each was ≥3. Her2 was considered positive when the score was 3+. Patients with Her2 equivocal expression (2+) were excluded from the study when in situ hybridization results were not available.

A pre-tested interviewer administered questionnaire was used to collect data on risk factors, in diagnosed patients which included family history of breast cancer, age at menarche, age at menopause (whether <45 or >55 years), age at first full term pregnancy, parity and if children were breast fed or not. Patients were categorized as high risk or no risk considering each risk factor separately [5]

Chi square trend was used to assess any change in the pattern of clinico-pathological profile of breast cancer patients reported in our laboratory over the 10-year period. The total cohort was divided in to two groups to compare the prevalence of risk factors and Chi square test was used to find any significant change in the percentage of patients with risk factors over the years. A p value of <0.05 was considered significant.

This study was carried out following the approval from the Ethical Review Committee of the Faculty of Medicine, University of Ruhuna.

Results:

A total of 1371 patients were included in the study, 1370 were women and one was a man. The total numbers of patients included in each calendar year are tabulated in **Table 1**.

In the total cohort, 5.7% were <35 years of age. The majority (66.9%) were between 36 to 60 years while 27.4% were >60 years. The clinico-pathological profile of the total cohort is tabulated in **Table 2**. Data on risk factors of breast cancer was available for 1099 patients and tabulated in **Table 3.**

Table 1: Number and percentage of patients in the study cohort according to the calendar year

Year	Frequency	Percent
2006	79	5.8
2007	127	9.3
2008	123	9.0
2009	73	5.3
2010	125	9.1
2011	181	13.2
2012	147	10.7
2013	128	9.3
2014	229	16.7
2015	159	11.6
Total	**1371**	**100.0**

Information on risk factors was available for patients investigated from 2006 to 2014 only. Therefore, the total cohort was divided into two; 2006 to 2010 (n=573) and 2011 to 2014 (n=526) and compared for any change in the percentage of patients with the risk factor. The risk factor profile of the total cohort and subgroups is also listed in **Table 3.** The trends in clinico-pathological profile were assessed dividing the total group into ten subgroups according to the calendar year of presentation with breast cancer.

Table2: Clinico-pathological profile of the total cohort

Pathological feature		Percentage	Pathological feature		Percentage
Age at presentation		*n=1366*	TNM stage group		*n=1218*
	<35	5.7		I	16.2
	36-60			II	46.6
	>60	27.3		III	36.7
Tumour size		*n=1281*		IV	*0.6*
	T1	31.4			
	T2	58.9	Lympho-vascular invasion		*n=1314*
	T3	9.6	Present		42.0
Nottingham grade		*n=1265*			
	1	14.3	Estrogen receptor		*n=1342*
	2	47.9	Positive		47.6
	3	37.8			
Lymph node metastasis		*n=1232*	Progesterone receptor		*n=1333*
Present		57.3	Present		*47.3*
Lymph node stage		*n=1239*			
	N0	43.2	Triple negative		*n=1337*
	NI	27.1	Present		*28.3*
	N2	18.2			
	N3	11.5	Her2 status		*n=1336*
			Positive		21.2

Table 3: Risk factor profile of the two subgroups and the total cohort

Risk factor	Prevalence			p value
	2006-2010	2011-2014	Total cohort	
Family history of cancer *(n=988)*	171 (34.1%)	122(25.1%)	293(29.7%)	**0.002**
Nulliparity *(n=990)*	77(15.3%)	85(17.5%)	162(16.4%)	0.362
Early age at menarche. <12 years *(n=704)*	12(2.8%)	14(5.0%)	26(3.7%)	0.131
Late age at menopause. >55 years *(n=412)*	2(0.8%)	2(1.2%)	4(1.0%)	0.645
Late age at first full term pregnancy;>30 years *(n=662)*	113(27.0%)	72(29.6%)	185(27.9%)	0.462
Not breast fed ever. *(n=977)*	111(22.7%)	102(20.9%)	213(21.8%)	0.518

There was a significant trend in the age (p=0.001) and TNM stage (p=0.002) at presentation over the ten-year period **[Figure 1 and 2].** Tumour characteristics also had significant changes over this period (tumour size –p<0.001, Nottingham grade- p<0.001, lympho-vascular invasion-p<0.001) **[Figure 3, 4, 5].** Both ER and PR expressions had an upward trend towards the latter part of the decade (p<0.001) **[Figure 6].**

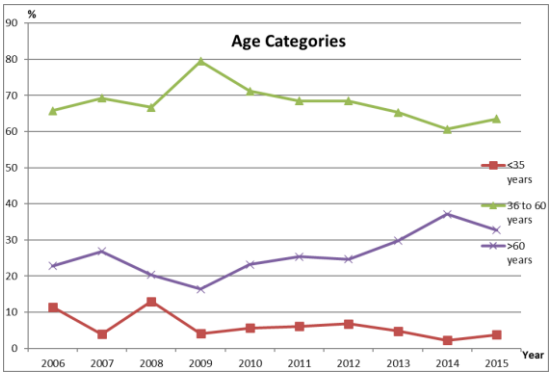

Figure 1: Trend in age at presentation from 2006 to 2015 (p=0.001)

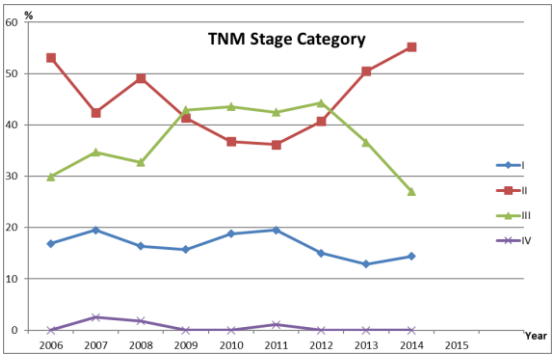

Figure 2: Trend in TNM stage category from 2006 to 2015 (p=0.002)

Parallel decline in the percentage of TNBC was also significant (p<0.001) **[Figure 6].** However, Her2 status did not show a change in trend

[Figure 6]. Presence of lymph node metastases (p=0.415) **[Figure 5]** and lymph node stage (p=0.306) at presentation also did not show a significant change in trend. The features with significant changes in trend are shown in Figures 1 to 6.

The age at presentation was categorized into three groups for the current analysis and a significant upward trend in the percentage of breast cancer patients presenting after 60 years of age was evident(p=0.001) **[Figure 1]**. The significant change in the Nottingham grade was mostly due to the upward shift in the percentage of grade 2 and a downward trend in grade 3 tumours (p<0.001) **[Figure 4]**. The size of the tumour did not show significant

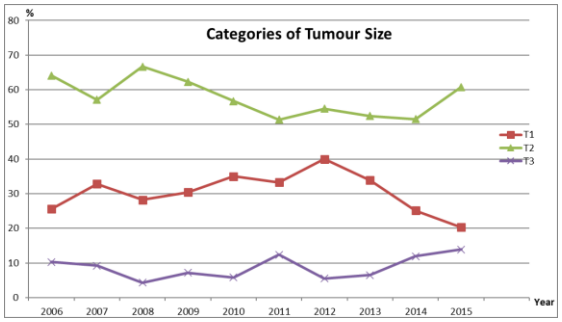

Figure 3: Trend in the tumour size from 2006 to 2015(p=0.001)

change across the three categories (T1, T2, T3). However, there was a decline in the percentage of T1 and upward trend in T2 tumours (p<0.001) **[Figure 3]**.

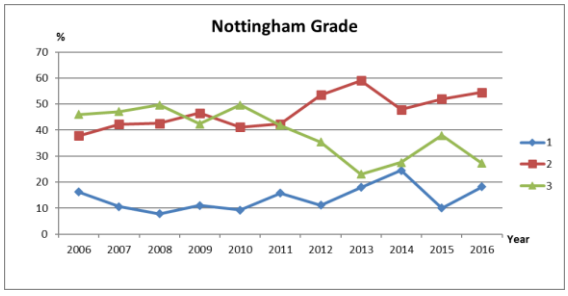

Figure 4: Trend in Nottingham grade from 2006 to 2015(p=0.001)

This had an effect on the overall TNM stage of the tumours even though lymph node status did not change over the decade (p=0.268). The percentage of TNM stage II breast cancers showed an upward trend while a parallel downward trend in stage III was observed **[Figure 2]**.

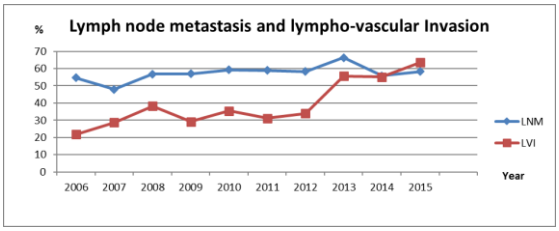

Figure 5: Trend in lymph node metastasis and lympho-vascular invasion from 2006 to 2015(p=0.001)

The detection of lympho-vascular invasion has increased (p<0.001) over the decade but did not show a parallel increase in the lymph node status **[Figure 5]**. The prevalence of ER and PgR expressing tumours show an upward trend (p<0.001). However, Her2 expression is static over the years. The net effect on the percentage of TNBC has been a downward trend [Figure 6].

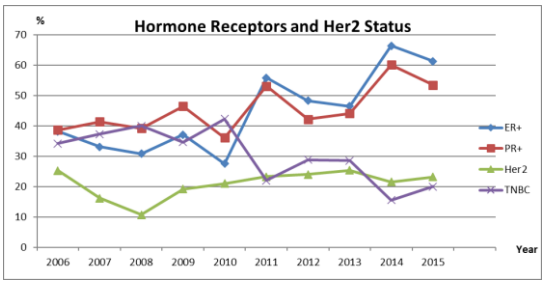

Figure 6: Trend in hormone receptor status and Her2 expression from 2006 to 2015(p=0.001)

Discussion

Breast cancer is the most commonly diagnosed cancer and the leading cause of cancer death in women worldwide. The highest incidence rates are found in Switzerland, white population in the U.S.A., Italy, and many other European countries, with low rates in Africa, Asia, and South America [6].

Comparison of descriptive epidemiology of breast cancer in Asia and the West reveals that the incidence is much lower in Asia although it is steadily rising [1]. Breast cancer incidence in Sri Lanka shows a steady increase since 1985 to 2015 where the age specific incidence has increased from 9.3 to 28.1 per 100,000 population [2].

The age distribution of breast cancer is also different in Asia with age group 45-50 years being the most affected, compared to a much older group of 55-60 years in the West [1]. According to the current study, the

commonest age group is 36-60 years (66.9%); consistent with other Asian studies. This has many important implications; a more economically productive age group is affected in our cohort similar to the rest of Asia.

Although effective targeted therapies are needed to safeguard the economic contribution of such women, most Asian countries may not be able to afford costly drugs due to Insufficient health budgets.

The high breast cancer incidence in women in the United States and European countries is attributed to the long-standing high prevalence of reproductive factors associated with increased risk of breast cancer; early menarche, late childbearing, low parity, use of menopausal hormone therapy, as well as increased detection [6]. Asian women are also adapting a more westernized lifestyle which can have a considerable impact on the susceptibility to develop breast cancer. However, our study does not reveal any significant change in the risk factor profile other than for the significant downward shift in patients with family history of cancer.

Well Women Clinics (WWC) distributed all over the country are designed to prevent non-communicable diseases among females in Sri Lanka. One of the important functions of the WWCs is to promote self-breast examination since a mammographic breast cancer screening programme is not available at national level. However, effectiveness of this method in reducing breast cancer morbidity needs to be further evaluated. The only study available in the pubmed related to this aspect is the study conducted by Vithana et al which reveals that breast cancer early detection service coverage in the Gampaha district of Sri Lanka remained low (2.2%) in 2007, 11 years after commencing WWCs.[7]

The cancer incidence data of Sri Lanka for 2015, the latest issue, reveals that majority of patients present at clinical stage II (40.0%). Only 13.0% patients have presented at stage I. [2] However, this data should be interpreted with care as, staging information was not available in 60% of breast cancer patients in the National Cancer Registry of Sri Lanka. Although the commonest stage at presentation is stage II, five-year breast cancer specific survival (grade 1 = 94%, grade 2 = 80%, and grade 3 = 72%) and five-year recurrence free survival (grade 1 = 86%, grade 2 =75% and grade 3 = 67%) are reported to be better compared to the neighboring countries [8].

The cancer control strategies require regularly evaluation to develop new strategies of prevention. Identifying trends in cancer biology and clinico-pathological profile are important in making policy on treatment and control strategies. Change in the pattern of diseases seen over long periods of time can be due to many reasons. Cancer burden is also expected to increase with increasing aging population. Changing lifestyle of females due to employment and urbanization affects the prevalence of reproductive risk factors for breast cancer. Asians including Sri Lankans are well known in the past to breast feed for longer periods and to have 2-3 children at a younger age which protected them from developing breast cancer. However, our study reveals that there is no significant change in the prevalence of these risk factors (early age at menarche, late age at menopause, late age at first full term pregnancy, no breast feeding and nulliparity) over the ten years. Instead, a statistically significant decline in the family history of cancer is evident. Therefore, the changes in the clinico-pathological profile that we reveal in this article cannot be explained in terms of known breast cancer risk factors.

It is unlikely that increase in hormone receptor positive tumours is purely due to technical improvements in laboratory procedures. The same protocol of manual immunostaining has been used throughout the 10 years in our laboratory. However, the increase in experience of the technical staff of the laboratory over the years may have contributed to the improvements in the quality of staining with minimal background staining, allowing better interpretation. Increased attention paid for better fixation of breast cancer resection specimens over the years may have contributed to the improve immunostaining and detection of hormone expression.

The increase in ER and PR expressing breast cancers over the years could be directly related to the change in the age at presentation. Percentage of females >60 years has significantly increased over the 10 years considered for this study. A publication based on data of the National Cancer Registry of Sri Lanka for the period 2001 to 2010 revealed that there is a true increase in the incidence of breast cancer in Sri Lanka which is mostly due to the increase in number of post-menopausal women with breast cancer [9]. Findings of our study cohort are on par with these national figures.

Sri Lanka has one of the fastest ageing populations [10] and this trend is likely to increase the number of breast cancers among older women exponentially [9]. Healthcare policy makers need to pay sufficient attention to these trends to effectively handle the increasing burden of breast cancer in the country [9].

In the current study, Nottingham grade of the breast cancer did not show a significant increase in grade 3 tumours. Instead, grade 2 tumours were on the rise. Upward trend in the hormone receptor positive breast cancers with the absence of parallel increase in the Her2 over-expression, also supports the age effect on the breast cancer pathological profile. Pathological features of breast cancer in aging women have been described in a few publications. The proportion of breast cancers with hormone receptor expression and favourable biological markers increase with age [11]. It may upturn expectations on better survival for breast cancer patients. However, the impact of other comorbid conditions in the elderly on survival might alter the true figures of survival. Sweeny et al demonstrated a lower risk ratio for some breast cancer risk factors for women aged ≥75 years. These included age at menarche, nulliparity, and age at first childbirth which represent hormonal exposures that occurred in the distant past [12]. This supports our argument on the effect of aging as the reason for increase in hormone expressing breast cancers in a background of an unchanged risk profile.

The incidence of breast cancer is increasing in the United States and Europe, along with an increase in the incidence of ER expressing tumours [13]. Pujol et al suggested several factors which may contribute to the rise in ER expressing tumours in the West: an improvement in methodology of detection of ER expression, a change in the characteristics of patients with breast cancer, or a change in tumor biology [13]. The question of whether the tumour biology of the current cohort of patients has changed over the 10 years cannot be established by this study; it needs further investigation with a different study design.

Mammographic screening is effective in reducing breast cancer mortality. At least part of the decline in mortality observed in UK, northern Europe and Australia can be attributed to screening. The increase in incidence of early stage and in situ breast cancers, followed by a decline in advanced cancer had resulted in subsequent decline in mortality [14].

Mammographic breast cancer screening is not done at national level in Sri Lanka although mammographic breast assessment is available in some tertiary care hospitals. This may be one of the reasons why there is no significant change in trend in the tumour stage at presentation. However, an increase in stage II and a downward shift in stage III was noted as shown in Figure 2. When routine mammographic screening is not available, only the effect of increase in awareness can be attributed to this favourable effect of decline in stage at presentation over the years. A study done in 2009 on patients who received hospital care for breast diseases in the southern part of Sri Lanka revealed a satisfactory knowledge on breast cancer [15].

In identifying time trends of diseases, cohort studies may not be as valued as population-based studies. Although this limitation is inherent to cohort studies, the important findings of this study will motivate researchers to initiate population-based assessment of time trends in breast cancer in Sri Lanka. This is the first study on trends in clinico-

pathological and risk factor profile of breast cancer reported from Sri Lanka.

Often, time trend analyses have been done using 5- or 10-year categories for age and period, which can blur short-term fluctuations, especially in cohort studies [16]. We analysed the trend of clinico-pathological features on a yearly basis which allowed the demonstration of downturn in stage III and triple negative cancers and upturn in hormone expressing breast cancers during the latter part of the study period. Since the data was collected retrospectively, data on some of the risk factors like body mass index could not be collected which is a limitation of this study.

Conclusions:

In this descriptive cross-sectional study on time trends in breast cancer, we have demonstrated an upward shift in the hormone expression which could most likely be attributed to the upward trend in the percentage of patients who are >60 years at presentation. However, the contribution by any change in tumour biology cannot be totally eliminated even though a trend in risk factor profile was not observed in the present cohort other than for the downward trend in family history of breast cancer.

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