RESEARCH COMMUNICATION

Comparison of Breast Cancer in Indonesia and Malaysia – A Clinico-Pathological Study Between Dharmais Cancer Centre Jakarta and University Malaya Medical Centre, Kuala Lumpur

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Abstract

Introduction: The age standardised incidence rate (ASR) of breast cancer in Malaysia which is a high middle-income country is similar to Indonesia, a low middle-income country. (Globocan 2008) It is however unknown whether the presentation of breast cancer differs between these two countries. Objective: We compared the stage, age at presentation, and pathological characteristics of breast cancer between two tertiary hospitals in Indonesia and Malaysia; Dharmais Cancer Centre (DCC), which is the national cancer referral centre in Indonesia, and University Malaya Medical Centre (UMMC), which is an academic hospital with established breast oncology services in Kuala Lumpur. One thousand, one hundred and fourteen consecutive women (477 in UMMC: 637 in DCC) who were newly diagnosed with breast cancer between January and December, 2010 were included. Patient's age, TNM stage at presentation, and pathological characteristics were compared. Estrogen receptor (ER) and progesterone receptor (PR) were considered positive if 10% or greater of invasive cell nuclei were stained while HER2 was considered positive with an immunohistochemostry staining intensity of 3+. Logistic regression analyses were performed to identify differences. Results: Median age at diagnosis was 52 years in UMMC and 47 years in DCC, whereby patients in DCC were more likely to be very young at diagnosis (aged < 35 years) compared to their counterparts in UMMC (Odds ratio (OR): 2.09; 95%CI: 1.32-3.31). Approximately one third of patients in UMMC presented with TNM stage III or IV, compared to 63% in DCC. Patients in DCC were three times more likely to present with metastatic breast cancer compared to patients in UMMC (OR: 3.01; 95% CI: 2.02-4.48). The percentage of low grade tumours in DCC was higher than in UMMC (28% vs 11% respectively), and the difference persisted even after multivariate adjustment. Although the frequency of ER and PR positivity appeared to be higher in UMMC (65% and 55% respectively) compared to DCC (48% and 40% respectively), these differences were not statistically significant following adjustment for age, stage, HER2 status and grade. The frequency of HER2 positivity was 45% in DCC compared to 26% in UMMC, and remained significantly higher even after multivariate adjustment (multivarite OR:1.76; 95%CI:1.25-2.47, in DCC compared to UMMC). The proportion of triple negative breast cancer was however similar in the two centres (19% in UMMC vs 21% in DCC). Conclusion: Indonesian women with breast cancer seem to present at a younger age and at later stages compared to Malaysian women. Their tumors were more likely to be of low grade and HER2 positive, even after adjustment for other factors, while hormone receptor positivity proved similar in the two groups. The higher HER2 positivity rate in Indonesian patients warrants further study.

Keywords: Breast cancer - Malaysia - Indonesia - tumor characteristics - Asia

Asian Pacific J Cancer Prev, **12**, 2943-2946

Introduction

The breast cancer incidence in Asia is escalating more rapidly than in the west. For instance, in Singapore, the age-standardized incidence rate (ASR) of breast cancer had increased from 20.2 per 100,000/year between 1968 and1972 (Seow et al., 1996) to 54.9 per 100,000/year between 1998 and 2002 (Lim et al., 2007). It is therefore conceivable that in the relatively near future, the majority of breast cancer patients will be of Asian ethnicity.There are many possible explanations for this increasing trend in Asia including earlier age at menarche, later age at menopause, later age at first child-birth, increase in height and weight, decreasing fertility, as well as westernization of lifestyles (Porter, 2008).

Malaysia and Indonesia are neighbouring countries in South East Asia. While Indonesia is a low middle income country with a population of over 230 million and a GNI

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per capita of USD2580, Malaysia is a high middle income country with a population of 27 million and a GNI per capita of USD7900 . (http://data.worldbank.org/country/indonesia.) According to the International Agency on Research in Cancer, breast cancer is the commonest female malignancy in both Indonesia and Malaysia. The age standardised rates in both countries are similar ie 36.2 per 100,000 in Indonesia compared with 37 per 100,000 in Malaysia, whereas mortality is 18.6 per 100,000 in Indonesia compared with 14.7 per 100,000 in Malaysia. (http://globocan.iarc.fr/factsheets/cancers/breast.asp)) While the population of Malaysia and Indonesia to a certain extent share similar socio-cultural backgrounds, the differences in the degree of westernization of lifestyles and socioeconomic development between these countries may constitute distinct breast cancer presentation. Moreover, not much is known regarding the presentation of breast cancer of Asian women particularly in developing South East Asian nations. The objective of this study is therefore to compare the clinical and pathological characteristics of breast cancer patients between two tertiary public hospitals in Indonesia and Malaysia.

Materials and Methods

Patients from the University Malaya Medical Centre (UMMC) in Malaysia and Dharmais Cancer Center (DCC) in Indonesia were studied. UMMC is an academic tertiary hospital with established breast oncology services, situated in the city of Kuala Lumpur. Dharmais Cancer Centre (DCC) is situated in the city of Jakarta and is a national cancer referral centre in Indonesia.

One thousand, one hundred and fourteen consecutive women who were newly diagnosed with breast cancer between January and December 2010 in UMMC (477 patients) and DCC (637 patients) were included in this study. Data on patient characteristics included age at diagnosis, while variables on pathological tumour characteristics included tumour size (pT), tumour grade, stage at presentation, lymph node involvement (pN), estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor 2 (HER2) statuses. ER and PR were considered positive if 10% or greater of the nuclei of the invasive tumour was stained. HER2 status was determined by immunohistochemistry, using Dako polyclonal antisera, with a HER2 positive result defined as 3+ membrane staining in the invasive tumour. Grading of the cancer was according to the Bloom and Richardson grading system, (Bloom and Richardson 1957) The cancers were staged according to the 6th Edition of AJCC (American Joint Committee on Cancer). Logistic regression analyses were performed to compare clinical and pathological tumour characteristics between the two centres.

Results

Median age at diagnosis was 52 years in UMMC and 47 years in DCC. Seventy-six percent of women in UMMC and 81% of women in DCC were between 35-64 years old. However patients in DCC were twice more likely to be very young at diagnosis (aged < 35 years) compared to their counterparts in UMMC (Odds ratio (OR): 2.09; 95%CI: 1.32-3.31). Approximately one third of patients in UMMC presented with TNM stage III or IV, compared to 63% in DCC. Patients in DCC were highly likely to present with metastatic breast cancer compared to patients in UMMC (OR: 3.01; 95% CI: 2.02-4.48). The percentage of low grade tumours in DCC was higher than in UMMC (28% vs 11% respectively), and the difference persisted even after multivariate adjustment. (Table 4) Although the ER and PR positivity appeared to be higher in UMMC (65% and 55% respectively) compared to DCC (48% and 40% respectively), these differences were not significant following adjustment for age, stage, HER2 status and grade. HER2 positivity was 45% in DCC compared to

Table 1. Clinicopathological Differences Between DCC and UMMC

		UMMC	DCC	Total
Total		477(43)	637(57)	1114(100)
Median age (years)		52	47	49
Age	<35 years	27(6)	71(11)	98(9)
	35-64 years	365(76)	515(81)	880(79)
	>65 years	5(18)	51(8)	136(12)
Stage	0	28(6)	0(0)	28(3)
	1	126(27)	20(5)	146(16)
	2	161(34)	136(32)	297(33)
	3	120(25)	173(41)	293(33)
	4	40(8)	92(22)	131(15)
	Unknown	2	217	219
Grade	1	37(11)	137(28)	174(21)
	2	175(51)	180(36)	355(36)
	3	132(38)	179(36)	311(37)
	Unknown	133	141	274
ER	Positive	291(65)	255(48)	546(56)
	Negative	155(35)	277(52)	432(44)
PR	Positive	243(55)	211(55)	454(47)
	Negative	199(45)	199(45)	517(53)
HER2	Positive	116(26)	239(45)	355(37)
	Negative	324(74)	289(55)	613(63)
Triple negative breast cancer	Yes	86(19)	113(21)	199(20)
	No	357(81)	419(79)	776(80)

Table 2 Pathological Features - Multivariate Analysis

Grade	No (%)	Crude OR (95% CI)	Adjusted OR (95% CI)
Low grade (1)			
UMMC	37 (11)	1	1
DCC	137 (28)	3.17* (2.14-4.69)	4.42* (2.63-7.41)
ER positive			
UMMC	291 (65)	1.00	1.00
DCC	255 (48)	0.49 (0.38-0.64)	0.93**(0.58-1.48)
PR positive			
UMMC	243 (55)	1.00	1.00
DCC	211 (40)	0.54 (0.42-0.70)	0.72***(0.45-1.15)
HER2 positive			
UMMC	116 (26)	1.00	1.00
DCC	239 (45)	2.31 (1.76-3.03)	1.76****(1.25-2.47)

*Adjusted for age, TNM stage, ER status, PR status, Her2 status; **Adjusted for age, TNM stage, tumour grade, PR status, Her2 status; *** Adjusted for age, TNM stage, tumour grade, ER status, Her2 status; ****Adjusted for age, TNM stage, tumour grade, ER status, PR status

26% in UMMC, and remained significantly higher even after adjustment for these variables (multivariate OR:1.76; 95%CI:1.25-2.47, in DCC compared to UMMC). The proportions of triple negative breast cancer was however similar in the two centres (19% in UMMC vs 21% in DCC).

Discussion

In low and middle income countries, the burden of breast cancer is difficult to determine owing to lack of high quality data. (Harford et al., 2008) Indonesia does not have an effective population-based cancer registry, similar to Malaysia. Information on stage at diagnosis and mortality is scarce, except for some published hospital series. (Aryandono et al., 2006; Taib et al., 2008) It is such considerations that are currently widely recognized to constitute an important knowledge gap in breast cancer particularly in developing Asian countries, and this comparative study between the two tertiary hospitals in Malaysia and Indonesia is the first result of an initiative to close it. Based on estimates of breast cancer incidence between the two countries, the incidence in both countries are similar although Indonesia has a slightly higher mortality rate from the disease.

Breast cancer in Asia presents at a younger mean age compared to the West, as seen in the current study and previous studies (Yip, 2009; Pathy et al., 2011; Yip et al., 2011). This younger mean age at presentation is partly due to the population pyramid structure in developing countries, which have a broad base indicating a higher fertility rate, and hence the proportion of women in the older age groups are lower compared to Western countries. In breast cancer incidence, a cohort effect is seen, which means that the incidence of breast cancer increases with each age cohort, especially in the age cohorts after the Second World War. (Seow et al., 1996) Although both Indonesia and Malaysia have a similar median population age, ie 28.4 years in Indonesia compared with 26.2 years in Malaysia, (http://data.worldbank.org/country/indonesia.), women with breast cancer presenting to DCC are twice more likely to be very young (<35 years). DCC is situated in the capital city of Jakarta, and Indonesia has a higher rural population than Malaysia, and it may be that older women in Indonesia are more likely to reside in the rural areas and hence not present to DCC, which is in the urban setting.

Women in DCC are highly likely to present with metastatic breast cancer compared to women in UMMC, which again reflects the differences in socio-economic development of each country. While both countries do not have a population-based breast cancer screening programme, there seems to be a difference in breast health literacy between the two countries. The poverty level in Indonesia is higher than in Malaysia. Twenty-nine percent of Indonesians live below the poverty line (defined as an income of USD 1.25 per day) compared to 2% in Malaysia. (www.unicef.org/infobycountry/) The per capita total expenditure on health care in Malaysia is nearly 7 times higher than in Indonesia. Hence, breast cancer may be deemed as 'low priority' compared to infectious diseases by the health care system in Indonesia, leading them to be less responsive to breast cancer care in terms of early detection, breast health education and creating awareness. From the patients' perspective, the Indonesian women will not present early because of financial problems. Additionally, other recognized barriers to early detection of breast cancer in the Asian region include fatalism, belief in traditional medicine and lack of autonomy in decision making (Norsa'adah et al., 2011; Taib et al., 2011). These barriers may be more prevalent in poorer countries. (Parsa et al., 2006)

With the younger age of onset, women with breast cancer in Indonesia are more likely to present with higher grade tumours and hormone receptor-negative tumours, which are features of breast cancers in younger women. Previous reported studies from Indonesia have noted a low ER and PR positive rate. (Aryandono et al., 2006) In the current study, , there is no significant difference in the ER and PR statuses between DCC and UMMC following adjustment for age, stage, HER2 status and grade. The HER 2 positivity rate is 45% in DCC and this remained significantly higher even after accounting for other tumor characteristics. The higher rate of HER2 positivity in Indonesia has been previously reported and was as high as 64.2% (Aryandono et al., 2006). The triple negative breast cancer (where ER, PR and HER2 are all negative) rate in both countries are similar being 19% in UMMC versus 21% in DCC. This corroborates with other reported triple negative breast cancer rates in Asia. (Tan et al., 2009; Yin et al., 2009)

The percentage of low grade tumours in DCC is high (28%) compared to UMMC (11%). However, a previous Indonesian study showed that only 4.1% of breast cancers were low grade. (Aryandono et al., 2006) Therefore, it is uncertain whether the current study finding on tumour grade is due to laboratory errors, especially since the proportion of young women is high in our study and they are more likely to present with high grade tumors.

The differences in the pathological features could be real, or it could be due to variations in the protocols in each individual pathology laboratory. Such variation is an important limitation to this study. It is important to ensure availability of accurate diagnostic and prognostic / predictive information in order to deliver optimal treatment to women with breast cancer. Specialised training in breast pathology for pathologists and laboratory personnel is of utmost importance. (Yip et al., 2011). The assessment of HER2 status, ER and PR status should follow established guidelines, or be based on the findings of internal clinical validation of the scoring systems and cut-points used to define positive results. ER and PR positivity is partly dependent on tissue handling – and in particular the cold ischemic time prior to fixation i.e. if this is prolonged with degradation of the labile ER and PR antigens, this could result in erroneous false negative results. Although at the time of this study, 10% was taken as the cut-off point to define an ER and PR positive result, recent guidelines have advised that a cut point as low as 1% is predictive of response to hormonal therapy (Hammond et al., 2011). Changes in cut-offs can lead to ambiguities as to whether the ER is positive, or negative. A recent review of the

prevalence of HER2 overexpression in Asia showed that the reported prevalence of HER2-positive tumors in 22 studies on 14,398 patients varied widely between 6% and 65%, as did the assessment methods used and concluded that a standard, reliable assessment method for HER2 status across Asia is urgently required. (Tan, Han et al., 2010) Moreover, inter-observer variation in assessment of pathological parameters result in significant differences in tumour grade, ER and HER2 status, and subsequent adjuvant therapy decision making. (Bueno-de-Mesquita et al., 2011).

In conclusion, women with breast cancer in Indonesia present at later stages and at a younger age compared to their Malaysian counterparts. While the prevalence of hormone receptor positive tumors -are similar in both centres, the proportion of HER2 overexpressed tumors seems higher in Indonesian women. Our findings highlight the urgent need for breast health awareness programmes particularly in Indonesia to encourage their women to present at earlier stages. Furthermore, standardised laboratory protocols for pathological testing and assessment are warranted in developing countries to deliver optimal treatment to women with breast cancers.

Acknowledgements

This study was supported by a grant from GlaxoSmithKline and the High Impact Research grant (HIR) (A000006-50001) from the Ministry of Higher Education, Malaysia.

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