RESEARCH COMMUNICATION

Who are the Breast Cancer Survivors in Malaysia?

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Abstract

Introduction: Worldwide, breast cancer is the commonest cause of cancer death in women. However, the survival rate varies across regions at averages of 73%and 57% in the developed and developing countries, respectively. Objective: This study aimed to determine the survival rate of breast cancer among the women of Malaysia and characteristics of the survivors. Method: A retrospective cohort study was conducted on secondary data obtained from the Breast Cancer Registry and medical records of breast cancer patients admitted to Hospital Kuala Lumpur from 2005 to 2009. Survival data were validated with National Birth and Death Registry. Statistical analysis applied logistic regression, the Cox proportional hazard model, the Kaplan-Meier method and log rank test. Results: A total of 868 women were diagnosed with breast cancer between January 2005 and December 2009, comprising 58%, 25% and 17% Malays, Chinese and Indians, respectively. The overall survival rate was 43.5% (CI 0.573-0.597), with Chinese, Indians and Malays having 5 year survival rates of 48.2% (CI 0.444-0.520), 47.2% (CI 0.432-0.512) and 39.7% (CI 0.373-0.421), respectively (p<0.05). The survival rate was lower as the stages increased, with the late stages were mostly seen among the Malays (46%), followed by Chinese (36%) and Indians (34%). Size of tumor>3.0cm; lymph node involvement, ERPR, and HER 2 status, delayed presentation and involvement of both breasts were among other factors that were associated with poor survival. Conclusions: The overall survival rate of Malaysian women with breast cancer was lower than the western figures with Malays having the lowest because they presented at late stage, after a long duration of symptoms, had larger tumor size, and had more lymph nodes affected. There is an urgent need to conduct studies on why there is delay in diagnosis and treatment of breast cancer women in Malaysia.

Keywords: Breast cancer - survival - ethnic group - delayed diagnosis - treatment -Malaysia

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Introduction

Breast cancer is well known as the most common cancer among women worldwide and ranked as the fifth cause of death from all cancers with 458 000 of deaths reported in the world (Jemal, 2011). The world breast cancer age standardized mortality rate in 2008 was 14.1 per 100 000 population (Jemal et al., 2011). It is still the most frequent cause of cancer death in women in both developed and developing regions. In more developed regions like all regions of Europe, Northern America, Australia/New Zealand and Japan breast cancer appeared to be the commonest cancer among women with incidence of 692 634 cases (26.7%), ASR was 66.4 per 100 000 population and mortality rate was 15.5% (189 455 cases) (Jemal et al., 2011).

The most frequent cancer in Malaysia was breast cancer (18%) followed by large bowel cancer (11.9%) and lung cancer (7.4%) (Lim, 2008). The incidence of breast cancer has been on increasing trend in most of the Asian countries as well as in Malaysia. The 3rd National Cancer Registry (NCR) in Peninsular Malaysia 2003-2005 showed that there were 11952 new breast cancer cases reported. This accounted for 31.3% compared to 31.0% as in the 2nd National Cancer Registry (Lim, 2004).

Locally, there are not many published report on the mortality rate of breast cancer but two studies had been conducted for this purpose at the same tertiary hospital on breast cancer patients of two cohorts. The earlier study was on breast cancer patients admitted from 1993-1997; showed a five year survival rate of 59.1%, with the survival of older age group was poorer compared to the 41-59 age group and racial discrepancy was seen among the three major ethnic groups, with Malay women surviving only 46%, while Indian and Chinese women having a 57% 63% and 5-year survival rate, respectively (Mohd, 2008). The second study was on breast cancer patients admitted from 1998 to 2002 whereby the same authors had reported improvement in the 5 years survival rate to 75.7%, which was seen in all stages and in all ethnicities; Malays, Indians and Chinese had 58.3%, 80.4% and 81.4%, respectively. Early detection and prompt treatment

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could had contributed to the improved of breast cancer.

Age, stage at diagnosis, nodal status, ER status, and tumor size were among the factors that have been attributed to survival differences. Other factors including socioeconomic status, access to health care, insurance status, co morbidities and treatment prescribed have also been suggested to influence survival (Ragland, 1991; Gordon, 1992; Potosky, 1997). Some researchers speculate that younger women have lower survival rates because their tumors may be more aggressive and less responsive to therapies (Golledge, 2000). Prognostic factors are important and useful to both clinician and policy maker but its data is still limited in Malaysia.

The study aimed to determine the survival rates among breast cancer women of Malaysia and factors associated with the survival.

Materials and Methods

A retrospective cohort on secondary data of breast cancer patients admitted to Hospital Kuala Lumpur from 2005 to 2009 was conducted. The list of patients was obtained from the Breast Cancer Registry of the hospital while the detail information of each patient was collected from their medical record. The variables collected were the demographic and tumor characteristics of patients. Demographic variables included the age at diagnosis, ethnicity, nationality, marital status, family history of breast cancer, parity and occupational status.

Variables on pathological tumor characteristics reviewed were tumor size, laterality of tumor (right, left, bilateral), and lymph node involvement (clinical staging: N0-N3), tumor histology, tumor grade (based on Scarff-Richardson and Bloom classification: grade 1-well differentiated, grade 2- moderately differentiated and grade 3-poorly differentiated), estrogen receptor (ER) status, and progesterone (PR) receptor status and HER2/neu status. Breast cancers were staged according to the 6th edition of TNM classification by American Joint Committee on Cancer (AJCC).Treatment data consisted of type of treatment (surgery only, surgery/chemotherapy/radiotherapy, neoadjuvant chemotherapy/surgery/radiotherapy, refused surgery/incomplete treatment).

Data analysis: All statistical analyses were performed using SPSS using Windows version 16.0 (SPSS Inc., Chicago, Illinois, USA). All categorical variables were described by proportions and compared using the Chi-Square test. Continuous variables were compared and expressed in median using Kruskal Wallis test. Two tailed p-value < 0.05 was considered statistically significant. Kaplan Meier analysis were conducted to estimate overall survival and compared by log rank test. Cox regression was used to identify independent prognostic factors.

Results

Demographic Characteristics of Breast Cancer Patients

A total of 868 records of breast cancer patients admitted to Hospital Kuala Lumpur from January 2005 to December 2009 were studied. Table 1 shows the demographic characteristics of breast cancer patients

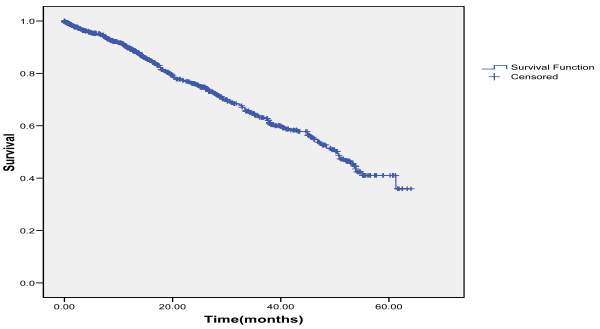

Figure 1. Survival Plot of Breast Cancer Patients in Hospital Kuala Lumpur, 2005-2009

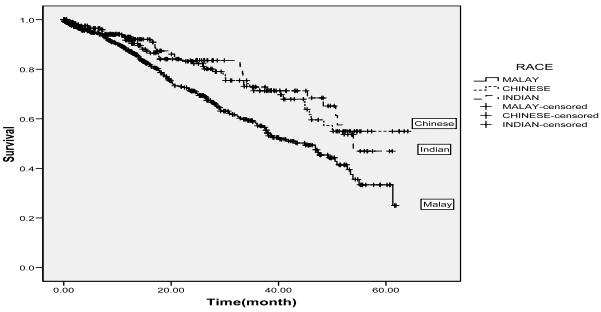

Figure 2. Survival Plot of Breast Cancer Patients According to Ethnic Group

reviewed in the study. It was observed that the prevalence of breast cancer was highest in the Malays (58%), followed by the Chinese (25%) and Indians (17%). The prevalence was also highest (62%) at age group 40 to 59 years old, among those unemployed (62%), married (87%), and had less than three children (68%).

5 Years Survival Rate

The overall 5 years survival rate of patient with breast cancer in this study was 43.5% (CI 0.573-0.597) with the median survival plot was 54 months. The mean follow up was 40.8 months with SD±17.6. Figure 1 shows the survival plot of breast cancer patients in this study.

According to ethnic group, Chinese and Indian women were found to have the highest survival rate, 48.2% (CI 0.444-0.520) and 47.2% (CI 0.432-512) respectively while Malays women was at 39.7% (CI 0.373-0.421). When the survival rates were tested by the log-rank test, the differences of survival functions among the ethnic groups were statistically significant (p-value < 0.001). Figure 2 shows the survival plot of breast cancer patients according to ethnic groups.

According to age, the highest survival rate by age was in the age group 40-59 years (58.7%, CI 0.573-0.602) and the poorest in the age group 39 years and below (57.4%, CI 0.542-0.606). The survival rate for age group 60 years and above was 58.3% (CI 0.555-0.610). However, the observed differences of survival based on age were not significant.

The survival rates of breast cancer at stages I and II were 58% (CI 0.542-0.618) and 52.7% (CI 0.502-0.551), respectively while stages III and IV were 39% (CI 0.358-0.426) and 19.8% (CI 0.170-0.227), respectively; (p-value 0.001). Grade 1 tumour had survival rate of 54.6% (CI 0.509-0.583) while grade 2 and 3 had survival rate of

Table 1. Distribution of Female Breast Cancer Patient in Hospital Kuala Lumpur from 2005-2009, N=868

Characteristic		No of cases (%)
Ethnicity:	Malay	501 (57.7)
	Chinese	218 (25.1)
	Indian	149 (17.2)
Age at diagnosis, years:	≤39	118 (13.6)
	40-59	538 (62.0)
	≥60	212 (24.4)
	Means±SD	51.6±11.54
Occupational status:	Employed	333 (38.4)
	Unemployed	535 (61.6)
Marital status:	Married	751 (86.5)
	Single	110 (12.7)
	Widow/Divorced	7 (00.8)
Parity:	Nulliparous	183 (21.1)
	1-3	409 (47.1)
	≥4	276 (31.8)
Family History:	Yes	99 (11.4)
	No	768 (88.5)
Year of Diagnosis:	2005	190 (21.9)
	2006	186 (21.4)
	2007	150 (17.3)
	2008	171 (19.7)
	2009	171 (19.7)
Duration of symptoms before diagnosis (months):		
	≤1	240 (27.6)
	2-4	298 (34.3)
	5-12	248 (28.6)
	>12	82 (09.4)
	Mean±SD	7±13
Histopathology:		
Infiltrating Ductal Carcinoma		779 (89.7)
Infiltrating Lobular Carcinoma		26 (03.0)
Mucinous carcinoma		21 (02.4)
Others		42 (04.8)
Diagnosis delay (months):	<1	790 (091)
	1-3	64 (07.4)
	>3	14 (01.7)
	Mean±SD	11±29
Treatment:		
Surgery only		88 (10.1)
Surgery-Chemotherapy-Radiotherapy		496 (57.1)
Neoadjuvant chemo-Surgery-Radiotherapy		85 (09.8)
Defaulted/Inoperable/Refused treatment		199 (22.9)
Stage:	1	127 (14.6)
	2	380 (43.8)
	3	222 (25.6)
	4	139 (16.0)
Tumour size, cm:	≤2.9	150 (17.3)
	3.0-5.9	429 (49.4)
	≥6.0	289 (33.3)
	Mean±SD	5.00±0.70
LN status:	0	315 (36.3)
	1-3	179 (20.6)
	4-9	100 (11.5)
	≥10	77 (08.9)
	Unknown	197 (22.7)
Grade:	1	141 (16.2)
	2	309 (35.6)
	3	216 (24.9)
	Unknown	202 (23.3)
ER/PR status:	+/+	306 (35.6)
	-/-	273 (31.5)
	+/- or -/+	171 (19.7)
	Unknown	118 (13.6)

Table 2. Cox Regression Analysis of Survival among Breast Cancer Patients at Hospital Kuala Lumpur, 2005-2009

Characteristics	Wald	ExpB	p-value	95% CI
ERPR				
+/+	Ref	-	-	-
+/-	03.438	1.460	0.064	0.979-2.179
-/-	09.329	1.796	0.002	1.233-2.614
Not Available	12.203	2.390	0	1.466-3.897
Stage				
1	Ref	-	-	-
2	02.368	1.822	0.124	0.849-3.911
3	14.597	4.280	0	2.030-9.027
4	32.733	8.830	0	4.187-18.62
Lymph Node status				
0	Ref	-	-	-
1-3	3.684	1.590	0.055	0.990-2.556
4-9	9.836	2.160	0.002	1.336-3.512
10	5.747	1.860	0.017	1.121-3.109
Not Available	1.068	1.300	0.301	0.789-2.147
Grade				
1	Ref	-	-	-
2	4.452	1.810	0.035	1.043-3.145
3	0.122	1.100	0.727	0.625-1.961
Not Available	7.607	2.450	0.006	1.297-4.658
Race/Ethnic				
Indian	Ref	-	-	-
Malay	6.80	1.700	0.009	1.142-2.557
Chinese	0.67	1.210	0.411	0.760-1.950

45.8% (CI 0.426-0.489) and 43.2% (CI 0.397-0.466) respectively.

Patients with no lymph node involvement were observed to have better survival rate of 54.3% (CI 0.515-0.572). Lymph node status of one to three had a survival rate of 47.9% (CI 0.439-0.518). Meanwhile, lymph node status of four to nine had survival rates of 38% (CI 0.330-0.431) and more than ten of 37.9% (CI 0.200-0.268). The observed differences were significant, p<0.001.

Patients with smaller tumour size (less than 3.0 cm) had survival rate of 53.4% (CI 0.500-0.569). Tumour size of 3.0 cm to 5.9 cm and above 6.0 cm had survival rate of 49.5% (CI 0.468-0.521) and 31.2% (CI 0.283-0.342) respectively, p<0.001.

Patients with ER+PR+ tumours had higher survival rate of 51.8% (CI 0.489-0.546). Patients with ER or PR negative (including ER+PR- and ER-PR+) tumours had survival rate of 42% (CI 0.380-0.459) and patients with ER-PR- tumours had survival rate of 40.4% (CI 0.158-0.253), p<0.001. Positive human epidermal receptor 2 (HER2) had survival rate of 44.7% (CI 0.404-490) while patients with negative HER2 of 44.9% (CI 0.427-0.471) survival rate, p<0.001.

Patients who came to seek treatment with duration of symptoms less than a month had higher survival rate of 49.6% (CI 0.464-0.528). Survival rates were observed to be in decreasing trend with increasing duration of symptoms. Patients with duration of symptoms for two to four months, five to twelve months and more than thirteen months had survival rates of 43.9% (CI 0.407-0.470), 37.8% (CI 0.341-0.414) and 37.6% (CI 0.317-0.436) respectively, p<0.05.

The Cox proportional hazard regression analysis was performed to assess the independent different prognostic factors after controlling for the effect of potential confounders of which the hazard ratio and the associated 95% confidence interval were obtained. At first stage, all variables were entered into the model; ethnic, age, stage, stage, grade, lymph node, ERPR status, and HER2 status, laterality and tumour size. Only ERPR, stages, grade and lymph node were kept in the final model as showed in Table 2.

The Cox regression analysis showed that ethnic, stage, lymph node status, ERPR status and grade of tumour were significant prognostic factors for breast cancer survival($p<0.05$). Being Malay would have the mortality risk of 1.70 (1.142-2.557) more than the Indians, $p<0.05$. The risk of mortality in patient at late stage (stages III and IV) was four to eight times more than those in early stage(stages I and II) of breast cancer. Also patients with involvement of four or more lymph nodes were at risk of mortality two times more than patients with negative node, $p<0.05$. Grade 2 patients had a hazard ratio of 1.8 compared to grade 1 breast cancer tumour, $p<0.05$. Also the hazard ratio of patients without ERPR receptor (negative ERPR) to those with ERPR (positive ERPR) was 1.8 ($p<0.05$).

Discussion

The number of breast cancer patients seen at Hospital Kuala Lumpur in the years 2005 to 2009 was between 150 cases to 191 cases per year. The number of new cases of breast cancer at the same hospital was similar to those reported for the years 1993 to 2003 (Hisham &Yip, 2004). The distribution of breast cancer according to ethnic groups and the trends in the distribution of breast cancer stages in this study also showed similar characteristics as those reported by Hisham & Yip, (2004) at the same hospital, and Taib et al. (2011) at another tertiary hospital. The proportion of cases at Hospital Kuala Lumpur according to stage of cancer in the earlier study and in this study showed a reduction for late stage; 50% to 60% in the years prior to 2001 to 45% in this study. However, in this study, the overall survival rate of breast cancer patients was 48.5% which was lower than the survival rate of the 2 cohorts that were reported by the same local tertiary hospital from 1993-1997 and 1998 to 2002; 58.4% and 75.7%, respectively (Hisham & Yip, 2004; Mohd, 2011).

In terms of ethnicity, as in the other two local studies, the Malays had always had the poorest survival rate at both hospital settings either in this study, in the early nineties (Hisham & Yip, 2004) or in the late nineties and early twenties (Mohd, 2011). This was expected as the prevalence of late stage breast cancer was highest among the Malays, followed by Chinese and Indians. Nevertheless, the survival rate of breast cancer patients for ethnic groups Chinese and Indian at HKL in general had improved from 48% and 47% in the nineties to 57% and 63% in the twenties, respectively.

The survival rate of breast cancer patients vary greatly worldwide, ranging from more than 80% in North America, Sweden and Japan to around 60% in middle-income countries and below 40% in low-income countries (Hebert, 2006). They also reported that the 5 year survival rate was 56% for late detection and reached to 85% for early detection of breast cancer women.

The incidence and mortality rates of breast cancer patients as reported by Ferlay et al. (2010) for countries at South East Asia which included Brunei, Cambodia, Indonesia, Lao People Democratic Republic, Malaysia, Singapore, Myanmar, Philippines, Thailand, Timor-Leste and Vietnam were 22.4% and 15.2%, respectively. Efforts had been made to compare the survival rates of breast cancer patients around the regions, among which Pathy et al. (2011) had reviewed the hospital-based breast cancer databases from the University Malaya Medical Centre, Malaysia and National University Hospital, Singapore. The two data bases were merged into a regional registry of breast cancer patients diagnosed between 1990 and 2007 of which the 5 year overall survival rate was reported at82.5% in patients with stage 0 to stage II cancer, and 30.2% in those with later stages.

The variations in the survival rate of breast cancer patients in the two hospitals of Malaysia could be explained by the factors as described by Hisham and Yip, (Hisham & Yip, 2004); women with breast cancer presenting to Hospital Kuala Lumpur were more likely to be Malay who present with a larger tumour and at a later stage compared to the women presenting to University Malaya Medical Centre. The differences between these two centres, both in Kuala Lumpur, show the different populations who utilise the two hospitals. Hospital Kuala Lumpur, which is a public hospital located in the main city centre that caters more to the lower socioeconomic group, mainly the Malay population. The University Malaya Medical Centre is located in a more affluent area, and sees a more middle-class group of women, with a good mix of the different racial groups.

Studies in other centers in Malaysia also confirm the late pattern of presentation in Malay women and other non-Chinese ethnic groups (Leong, 2007). Similar patterns of late presentation among Malay were also observed among Singapore breast cancer patients (Tan, 2005). Malays were postulated to be prone for traditional medicine hence the delay in breast cancer presentation. There is a local study reported that 40% user of traditional medicine was seen in Malay rural center (Taib, 2007). In United States, Caucasian American has high incidence of breast cancer, however African American has high death rate and was attributed factors including late stage diagnosis, socioeconomic factor, cultural belief and access to healthcare (May, 2000; Shavers, 2002; Jatoi, 2003).

Besides ethnic group Indian, other predictors of breast cancer survivors in this study were as in most studies, those at early stages (stage I and II), without involvement of lymph node, smaller tumour size (less than 3.0 cm), ERPR and HER 2 positive had better survival rate.

Stage at diagnosis is one of the recognized prognostic factors for breast cancer (Campbell, 2002). The findings in this study were as in other studies which reported survival rate in early (stage I and II) was higher than at late stage (stage III and IV) (Mohd, 2011; Pathy et al., 2011).

ERPR status is also a prominent role as prognostic indicators in breast cancer diagnosis. It started to be known as prognostic factors as early as 1977 and ERPR negative was reported to have poor outcome (Knight, 1977; Hawkins, 1996). In this study, and as in several other studies, there was a significant difference in the survival times among patients with ERPR status whereby patients with ERPR positive had better survival rate than those negative (Al-Naggar et al., 2009); (Ong, 2003). Another important prognostic factor of breast cancer survival is the involvement of lymph nodes and its extension. As in many other studies, the survival rate was worst as the number of lymph nodes increased (Gebauer, 2002; Banarjee, 2003; Rezaianzadeh et al., 2009).

Apart from stages of breast cancer, lymph node status is also an important significant prognostic factors (Carter, 1989; Saez, 1989). Lymph node status in our study found to be a significant prognostic factors both in univariate and multivariate analysis. While study in UMMC, Kuala Lumpur noted nodal status of more than four lymph node has hazard ratio of 1.34 times compared to negative nodes and was also an independent prognostic factors. In this study, poorer survival rate as the number of lymph node increases and the hazard ratio of nodal status more than four was 2.5 times compared to no lymph node involvement. A similar patterns was also reported in other studies (Gebauer, 2002; Banarjee, 2003; Rezaianzadeh et al., 2009).

In conclusion, the survivors of breast cancer among Malaysian women were mostly the Indians, those with earlier stage of cancer, without lymph node involvement, of lower grade tumour, size of tumour less than 3cm, ERPR positive, HER2 positive, and those with duration of symptoms less than a month. Therefore, it is important to promote breast cancer screening in all women for early diagnosis and treatment of breast cancer. Studies to look into factors that caused variations in the rate of survival of breast cancer between the different the ethnic groups should be conducted.

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