

RESEARCH ARTICLE

Editorial Process: Submission:09/18/2017 Acceptance:01/01/2018

Survival Time and Prognostic Factors for Breast Cancer among Women in North-East Peninsular Malaysia

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Abstract

Background: Breast cancer is the most common malignant disease and the leading cause of cancer death among women globally. This study aimed to determine the median survival time and prognostic factors for breast cancer patients in a North-East State of Malaysia. **Methods:** This retrospective cohort study was conducted from January till April 2017 using secondary data obtained from the state's cancer registry. All 549 cases of breast cancer diagnosed from 1st January 2007 until 31st December 2011 were selected and retrospectively followed-up until 31st December 2016. Sociodemographic and clinical information was collected to determine prognostic factors. **Results:** The average (SD) age at diagnosis was 50.4 (11.2) years, the majority of patients having Malay ethnicity (85.8%) and a histology of ductal carcinoma (81.5%). Median survival times for those presenting at stages III and IV were 50.8 (95% CI: 25.34, 76.19) and 6.9 (95% CI: 3.21, 10.61) months, respectively. Ethnicity (Adj. HR for Malay vs non-Malay ethnicity=2.52; 95% CI: 1.54, 4.13; p<0.001), stage at presentation (Adj. HR for Stage III vs Stage I=2.31; 95% CI: 1.57, 3.39; p<0.001 and Adj. HR for Stage IV vs Stage I=6.20; 95% CI: 4.45, 8.65; p<0.001), and history of surgical treatment (Adj. HR for patients with no surgical intervention=1.95; 95% CI: 1.52, 2.52; p<0.001) were observed to be the statistically significant prognostic factors associated with death caused by breast cancer. **Conclusion:** The median survival time among breast cancer patients in North-East State of Malaysia was short as compared to other studies. Primary and secondary prevention aimed at early diagnosis and surgical management of breast cancer, particularly among the Malay ethnic group, could improve treatment outcome.

Keywords: Breast cancer- Prognostic factor- Survival time- Malaysian Women

Asian Pac J Cancer Prev, **19** (2), 497-502

Introduction

Breast cancer in women is a major public health problem throughout the world. It is the most common malignant disease among women both in developed and developing countries (WHO, 2017). Malaysia has the highest mortality rate of breast cancer among the South-Eastern Asia countries which accounts for 18 per 100,000 compared to Singapore and Thailand which at 15 and 11 per 100,000 populations respectively (Globocan, 2012).

In Malaysia, a population based study among breast cancer patients reported an overall median survival time of 68.1 months (Abdullah et al., 2013). An institutional-based study by Ibrahim et al., (2012) revealed a shorter median survival time of 54 months. A collaborative study by Bhoo Pathy et al., (2011) using data from Singapore-Malaysia Breast Cancer Registry revealed median survival times of 164 months for Stage II, 53 months for Stage III and 17 months for Stage IV breast cancer.

Studies concerning survival time among breast cancer

patients had also been conducted globally and the findings were heterogeneous. Study in US by Khan et al. (2014) that used database from Surveillance, Epidemiology and End Results (SEER; 1973-2009) revealed overall median survival time of 82.5 months. While in Tehran, study done by Mousavi et al., (2008) using Tehran Cancer Registry found overall median survival time of 60 months. In Sweden, Sundquist et al., (2016) revealed median survival time which ranges between 13 and 33 months, depending on types of treatment received. In French, an improvement in survival time was reported in a study by Andre et al., (2004). In the period from 1987 to 1993 and 1994 to 2000, an increased in median survival time from 23 months to 29 months were reported among metastatic breast cancer patients that were treated in three French cancer centres. Another institutional-based study by Khanfir et al., (2013) in Tunisia, revealed the overall median survival time among metastatic breast cancer who received treatment was 18 months.

Prognosis of breast cancer is relatively favourable

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compared to other cancers, such as lung, colon, ovarian and pancreatic cancers. Hence, recognizing prognostic factors in patients with breast cancer plays an important role in treatment and care of patients as it may improve delivery of health care to at-risk groups. There are multiple factors that influenced the survival of breast cancer patients including age at diagnosis, ethnicity, cancer staging at diagnosis, lymph nodes status, treatment received, immunohistochemistry subtype, access to care and environmental factors (Bello et al., 2016; Cheng et al., 2016; De Camargo Cancela et al., 2016; Ibrahim et al., 2012; Karimi et al., 2014; Khan et al., 2014; Park et al., 2012; Taib et al., 2011)

There are limited population-based breast cancer survival time and its prognostic factors studies in Malaysia being published apart from study by Abdullah et al., (2013). Study by Abdullah et al., (2013) included the different cohort of breast cancer patients who were diagnosed between 2000 and 2005. Meanwhile our current study used the more recent cohort of breast cancer patients diagnosed between 2007 until 2011, which also taken from the population-based cancer registry's data.

Materials and Methods

Study location

North-east of Peninsular Malaysia consisted of three states; Kelantan, Terengganu and Pahang. Majority of the ethnic in Kelantan were Malay (94.4%), Chinese (3.4%), Indian (0.3%) and others (1.9%). The Age Standardize Rate (ASR) for breast cancer in Kelantan increased from 15.9 to 18.1 per 100,000 populations between 2007 and 2011.

Study design

This retrospective cohort study was conducted in Non-Communicable Disease Unit, Kelantan State Health Department from January to April 2017. Data were obtained from Kelantan Cancer Registry which is a population-based cancer registry that collects the notification of cancer cases from all government and private hospitals in Kelantan. All Kelantan resident diagnosed with International Classification of Diseases for Oncology (ICD-O) codes C50 series was selected and followed-up retrospectively until 31st December 2016.

Inclusion criteria for his study were; 1. Breast cancer cases (ICD-O classification C50.0 – C 50.9) diagnosed from 1st January 2007 until 31st December 2011, and 2. Kelantan resident. Males breast cancer patients and patients with incomplete data were excluded.

Sample size

The two median survival time's option in Power and Sample Size software (Dupont and Plummer, 1990) was used to determine the required sample size. With type I error of 5%, type II error of 20%, median survival time among younger age group of 50 months (Abdullah et al., 2013), estimated median survival time among older age group of 68 months, ratio between younger to older age groups of 1, accrual time and additional follow-up time of 60 months, the required sample size calculated was 617

after taking into consideration 20% drop-outs. Number of breast cancer cases registered in Kelantan Cancer Registry from 2007-2011 was 598 cases. No sampling method was applied due to smaller number of patients in the registry within the time period than calculated sample size. All available cases that fulfilled the study criteria were included in the study.

Data collection

Proforma checklist was used to guide data extraction and information needed which includes age, sex, ethnicity, cancer morphology, cancer staging, surgical treatment, chemotherapy, radiotherapy, date of diagnosis, status, date of death and cause of death. The required data was retrieved from Kelantan Cancer Registry. Proforma checklist used to extract only relevant data for this study. Data extraction has been done at Non-communicable Disease Unit, Kelantan State Health Department to ensure confidentiality.

Statistical analysis

Data from the registry was extracted to Microsoft Excel file and subsequently exported to SPSS software version 22 for data analysis. Exploratory data analysis was performed to check for missing values and distribution of numerical data. Numerical data was said to be normally distributed when the histogram with overlaid normal curve showed an approximately normal bell-shaped curve, absence of extreme outliers on boxplot, and a non-significant test of normality (Kolmogorov-smirnov and Shapiro-wilk test). Data were presented as; Mean and it's standard deviation (SD) for numerical variables, and, number (n) and percentage (%) for categorical variables.

Survival analysis (Kaplan Meier and Cox proportional hazard regression) was used to estimate the median survival time and prognostic factors of death. Event for this study was death due to breast cancer and patients who remain alive by 31st December 2016 or died due to other causes was considered as censored.

Kaplan Meier survival analysis was used to estimate the median survival time. It refers to the first observed time when 50% of breast cancer patients died due to breast cancer. In this study, analysis on the median survival time according to the stage at diagnosis was done because it was widely used in patient's management and counselling.

Survival analysis was performed using simple and multiple Cox's proportional hazard regression model to identify the important prognostic factor of death. At univariable analysis, variables with p-value of less than 0.25 were considered to be important, and included in multivariable analysis. At multivariable analysis, preliminary main effect model was obtained using Backward LR, Forward LR and Stepwise methods. All possible two-way interaction were checked using multiplicative method. Hazard Functions plot and Log-Minus-log plot was used to check the assumption of proportional hazard. The final model was presented as crude and adjusted Hazard Ratio (HR), 95% confidence interval (CI), Wald statistics and p-value. Two-tailed p-value of <0.05 was considered to be statistically significant.

Results

A total of 598 registered breast cancer cases were identified in the registry. However, 46 cases with missing cancer staging and 3 male cases were excluded. Number of death due to breast cancer was 257 (46.8%). Patient's profile was as shown in Table 1.

The median survival time could not be obtained for stage I and II because less than half of patients within these stages died (32.3% for stage I and 20.9% for stage II). Patients diagnosed in stage III had median survival time of 50.77 (95% CI: 25.34, 76.19) months and those diagnosed at stage IV had median survival time of 6.91 (95% CI: 3.21, 10.61) months.

Prognostic factors of death identified by Simple and Multiple Cox Proportional Hazard Regression Model were displayed in Table 2 and 3. The final model was obtained after employing backward selection procedure. Significant prognostic factor of death can be defined as

factor associated with death caused by breast cancer, which is statistically determined from the multivariable analysis (Cox Proportional Hazard Regression Model).

Ethnicity was found as significant prognostic factors by which Malay who diagnosed with breast cancer had 2.5 increase hazard of death as compared to non-Malay ($p < 0.001$). As compared to stage I, patients diagnosed at stage III and stage IV had 2.3 times and 6.2 times increased hazard to death. Among patients who did not receive any surgical treatment, the hazard of death will increase by 2 times as compared to patients who received surgical treatment ($p < 0.001$).

Discussion

In this study, cancer staging at diagnosis was the factor of interest in evaluating the median survival time because it is an important prognostic factor and widely used in other studies (Andre et al., 2004; Bhoo Pathy et al., 2011;

Table 1. Profile of Breast Cancer Patients Identified Through the Kelantan Cancer Registry, 2007-2011 (n=549)

Sociodemographic characteristics	n	(%)	Censored		Death	
			n	(%)	n	(%)
Age at diagnosis (years)*	50.4	(11.2)				
Age at diagnosis						
< 50	281	(51.2)	140	(49.8)	141	(50.2)
≥ 50	268	(48.8)	152	(56.7)	116	(43.3)
Ethnicity						
Malay	471	(85.8)	231	(49)	240	(51)
Chinese	65	(11.8)	50	(76.9)	15	(23.1)
Siamese	6	(1.1)	6	(100)		
Indian	5	(0.9)	4	(80)	1	(20)
Others	2	(0.4)	1	(50)	1	(50)
Stage at diagnosis						
Stage I	163	(29.7)	110	(67.5)	53	(32.5)
Stage II	161	(29.3)	128	(79.5)	33	(20.5)
Stage III	90	(16.4)	37	(41.1)	53	(58.9)
Stage IV	135	(24.6)	17	(12.6)	118	(87.4)
Morphology						
Ductal	448	(81.6)	246	(54.9)	202	(45.1)
Lobular	2	(0.4)	1	(50)	1	(50)
Adenocarcinoma	68	(12.4)	30	(44.1)	38	(55.9)
Squamous cell carcinoma	7	(1.3)	3	(42.9)	4	(57.1)
Others	24	(4.4)	12	(50)	12	(50)
Surgical treatment						
Yes	274	(49.9)	171	(62.4)	103	(37.6)
No	275	(50.1)	121	(44)	154	(56)
Radiotherapy						
Yes	105	(19.1)	59	(56.2)	46	(43.8)
No	444	(80.9)	233	(52.5)	211	(47.5)
Chemotherapy						
Yes	163	(29.7)	76	(46.6)	87	(53.4)
No	386	(70.3)	216	(56)	170	(44)

*Mean(SD)

Table 2. Prognostic Factors of Death Simple Cox Proportional Hazards Regression (n=549)

Variables	Crude <i>b</i>	Crude HR (95% CI)	Wald statistic	p-value
Age at diagnosis				
< 50	0	1		
≥ 50	0.19	1.21 (0.95, 1.55)	2.35	0.125
Ethnicity				
Non-Malay	0	1		
Malay	1.07	2.91 (1.78, 4.77)	18.13	<0.001
Cancer staging at diagnosis				
Stage I	0	1		
Stage II	-0.52	0.59 (0.38, 0.91)	5.59	0.018
Stage III	0.7	2.02 (1.38, 2.95)	13.02	<0.001
Stage IV	1.73	5.64 (4.06, 7.84)	106.47	<0.001
Surgical treatment				
Yes	0	1		
No	0.66	1.93 (1.50, 2.47)	26.46	<0.001
Radiotherapy				
Yes	0	1		
No	0.23	1.25 (0.91, 1.72)	1.91	0.167
Chemotherapy				
Yes	0	1		
No	-0.23	0.80 (0.62, 1.03)	2.94	0.086

b, Regression coefficient; HR, Hazard Ratio; CI, Confidence interval

Khan et al., 2014; Walters et al., 2013). Despite that, stage at diagnosis was very important for patient's management and counselling purposes. For stage III breast cancer, the median survival time was shorter than the median survival time from collaborative study by Bhoo Pathy et al., (2011), 53 months. The collaborative study enrolled 4058 breast cancer patients from year 1990-2007 that registered in Singapore-Malaysia Breast Cancer Registry. Majority of the patients in the study were Chinese (72%), followed by Malays (16%), Indians (8%), and other ethnics (4%) compared to our current study which majority were Malays (85.9%). This might be the contributing factor that leads to difference in survival between these two studies. The median survival time for stage IV breast cancer was also lower as compared to other studies. Based on study by Bhoo Pathy et al., (2011), the median survival time for stage IV breast cancer was 17 months. Meanwhile, study by Andre et al., (2004) found ranged of survival time between 23 to 29 months depending on the treatment received.

In Malaysia, there were differences in cultural, health belief and socioeconomic factors among its multi-ethnic groups that may affect their breast cancer survival. This study found that older age at diagnosis; Malay ethnic, late stage of cancer at diagnosis, no surgical and no radiotherapy treatment had increased the hazard of death among breast cancer patients in Kelantan. However, only ethnicity, cancer staging at diagnosis and surgical treatment were statistically significant as the prognosis factors of death.

Approximately 50% of women were diagnosed before the age of 50 years in Malaysia, compared to 20% in

Table 3. Prognostic Factors of Death by Multiple Cox Proportional Hazards Regression (n=549)

Variables	Adj. <i>b</i>	Adj. HR (95% CI)	Wald statistic	p-value
Ethnicity				
Non-Malay	0	1		
Malay	0.92	2.52 (1.54, 4.13)	13.43	<0.001
Cancer staging at diagnosis				
Stage I	0	1		
Stage II	-0.31	0.73 (0.47, 1.13)	2.01	0.157
Stage III	0.86	2.31 (1.57, 3.39)	18.14	<0.001
Stage IV	1.83	6.20 (4.45, 8.65)	115.95	<0.001
Surgical treatment				
Yes	0	1		
No	0.67	1.95 (1.52, 2.52)	26.64	<0.001

Adj. *b*, Adjusted regression coefficient; Adj. HR, Adjusted Hazard Ratio; CI, confidence interval; Interaction terms were not significant in all factors; Proportional hazard assumption by hazard function plot and log-minus-log plot were checked and assumptions were met.

Western countries (Yip et al., 2014). Similarly, this study also found that 51.1% of breast cancer cases in Kelantan were diagnosed during pre-menopausal period. Younger age at diagnosis was found as one of the poor prognostic factor for breast cancer survival (Cheng et al., 2016; De Camargo Cancela et al., 2016; El Saghir et al., 2006; Soerjomataram et al., 2008; Taib et al., 2011; Youlden et al., 2014). In this study, age was not found as significant prognostic factors of death among breast cancer patients in Kelantan and this finding was in concordance with study by Karimi et al., (2014).

Ethnicity has been recognized as important prognostic factors worldwide. For example, Caucasian has lower hazard to death as compared to African American (Ren et al., 2016). This study revealed Malay patients who diagnosed with breast cancer had increase hazard of death as compared to other ethnics and this findings is similar as reported by other studies (Ibrahim et al., 2012; Taib et al., 2011). Although Chinese has the higher incidence of breast cancer with ASR 44.2 per 100,000 population as compared to Malay's ASR 25.3 per 100,000 population, the prognosis was worst among the Malay ethnic (Abdullah et al., 2013). Different screening practices, poor health seeking behaviour and poor treatment compliance might be the cause of poor prognosis among Malay as compared to other ethnic group in Malaysia (Taib et al., 2007). According to other studies, Malay presented with more advanced disease compared to Chinese and Indians which might contribute to poor survivorship among Malay (Leong et al., 2007; Taib et al., 2011). Study done by Taib et al., (2007) which was conducted in two different settings namely Kota Bharu, Kelantan and Universiti Malaya Medical Centre (UMMC) Kuala Lumpur found that 45.3% patients in rural area used traditional medicine as compared to 15.5% in urban. It was the fact that UMMC managed more Chinese patients compared to Kota Bharu that managed more Malay patients. This study might explain that even though 59% of breast cancer cases in Kelantan were diagnosed in early stage, the prognosis of death is worse among Malay as they choose to seek for

traditional remedies first before modern medicine. Even though their cancer had been diagnosed in early stage, they might loss to follow-up and presented later on late stage which caused the treatment more difficult and complicated

A standardized staging system, TNM system, is used widely to facilitate management of the patients and able to make comparison between countries. Several studies shows that late stage upon diagnosis have increased hazard to death as compared to early stage (Karimi et al., 2014; Kongsiang et al., 2014; Taib et al., 2011). In this current study, the risk of death increased by two times when patient presented with stage III breast cancer. Meanwhile, the risk of death increased by six times higher when patient presented at stage IV. The significant of stage at diagnosis as a strong prognostic factor of death among breast cancer patients was similar with other studies (Karimi et al., 2014; Kongsiang et al., 2014; Taib et al., 2011).

There are several treatment options available for breast cancer which includes surgery, chemotherapy, radiotherapy, hormonal therapy, bisphosphonates, and targeted therapy. Our study found that surgery was a significant factor associated with death caused by breast cancer. The risk of death will increase by two times among patients who did not receive any surgical treatment. This finding was similar with other studies (Bello et al., 2016; Cortadellas et al., 2015; Pathy et al., 2011; Ruiterkamp et al., 2010). A study by Pathy et al., (2011) at UMMC found that the risk of death was lower among patients who undergone surgical treatment. Meanwhile, a meta-analysis by Ruiterkamp et al., (2010) also showed that surgical treatment were associated with lower mortality and improve survival.

In this study, radiotherapy was not found as significant prognostic factor and majority of the patients did not received radiotherapy treatment. Several studies showed that the risk of local recurrence post-breast conserving surgery can be reduced by radiotherapy (McGale et al., 2014; Wang et al., 2017).

There were studies reported that overall survival improved following chemotherapy (Azrif et al., 2011; Liu et al., 2012). However, chemotherapy was also not found as significant prognostic factor in this study and 70.5% of the cases did not receive chemotherapy.

Limitations and recommendations

In this study, data was retrieved from Kelantan Cancer Registry, which was considered as a valid and reliable tool for cancer surveillance system in Malaysia. However, there are many other possible significant prognostic factors that were not available in the registry such as lymph node status, tumour size and immunohistochemistry subtype. To achieve better understanding about the prognostic factors of death among breast cancer patients, future research should be proceed with focusing on a bigger diversity of other factors such as social, cultural, and economic contribution. Meanwhile, in order to achieve more complete understanding on how to improve the survival among breast cancer patients in Kelantan, a more focused study on factors associated with refusal of modern cancer treatment should be carried out to plan for targeted intervention.

In conclusion Identification of the significant prognostic factors might guidance for better treatment among breast cancer patients that can be performed not only during active treatment but also during the survivorship period. The requirements to improve specialties and modalities required could be supported by evidence from this study.

Ethical approval

Ethical clearance was obtained from Human Research Ethics Committee of the University Sains Malaysia USM/ JEPeM/16120585 and the Medical Review and Ethical Committee from National Institute of Health, Ministry of Health NMRR-16-2340-33520 (IIR).

Conflict of interest

No conflict of interest.

Acknowledgements

Thanks to Director General, Ministry of Health Malaysia for the approval to publish this research.

Funding statement

This study and manuscript was not funded.

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