

ORIGINAL ARTICLE

Long-term Survivorship of Breast Cancer Patients and Its Prognostic Factors: A Tertiary Oncological Center Experience in Penang

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ABSTRACT

Introduction: Breast cancer is the most common cause of cancer death among women. The purpose of this study is to determine the 5-years survival rate and prognostic factors among breast cancer patients in a tertiary oncological centre in Penang, Malaysia. **Methods:** A retrospective cohort study was conducted at the Advanced Medical and Dental Institute, Universiti Sains Malaysia. All 214 cases of breast cancer diagnosed from 1st January 2008 until 31st December 2012 were selected and retrospectively followed-up until 31st December 2017. The survival status for this study was referring to the record of the National Registration of Malaysia. Kaplan-Meier with Log-rank test and Cox regression were used for the univariable and multivariable analysis, respectively. **Results:** The mean (SD) age at diagnosis was 50.98 (\pm 10.75) years. The majority of the patients were Malay (55.7%) and married (96.5%). After controlling for the effect of underlying comorbidities, lymph nodes involvement, marital status, vascular involvement and adjuvant therapy; it was found that marital status (adj HR= 3.63, 95% CI 1.17-11.24) and lymph nodes involvement (adj HR=2.36, 95% CI 1.17-4.76) were the significant prognostic factors. **Conclusion:** This study re-emphasizes the role of marital status and lymph nodes involvement as independent predictors of the long-term survival of breast cancer patients. Further studies are needed to assess the promising benefit of personalized treatment and specific supportive care given to the patients with these risk factors for better cancer experience and survival.

Keywords: Breast cancer; 5-years survival; Marital status; Lymph nodes; Malaysia

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INTRODUCTION

Breast cancer has become one of the most common reasons for death among women these days. The World Cancer Report 2014 has reported that breast cancer has a higher incidence rate (43.3 per 100,000) than any other cancer. The second highest was colorectum (14.3 per 100,000), cervix (14.0), lung (13.6) corpus uteri (8.2) and stomach (7.5) (1). Surprisingly, there was a sharp rise in the previous five years, where more than 20% increase in breast cancer incidence with 14% mortality (1). Changes in lifestyle, environmental factors, and an

ageing population have led cancer as the leading cause of death for the past decades. For the past six years, the incidence rate of breast cancer has increased by 6.8% with the major risk factors detected; early menarche, late menopause, late full-term pregnancy (FTP), and low numbers of FTP (2).

In Malaysia, cancer was recorded as the second highest killer after cardiovascular diseases, with at least 8.8 million mortality in 2015 (3). Among all cancers identified in Malaysia, breast cancer patients were recorded to have 5-year relative survival less than 70%; Thyroid cancer (82.3%), Prostate (73.0%), Corpus uteri (70.6%), Colorectal (56.8%), Pancreatic cancer (14.0%), Hepatic (12.8%) and Lung cancer with 11% (3). Among all states in Malaysia, Penang has recorded the highest number with 50 cases per 100,000 women of breast

cancer cases and followed by the Federal Territory of Kuala Lumpur and Putrajaya with 42 cases per 100,000 women. Johor had the third-highest with 39 cases per 100,000 women (9).

Despite all the advanced treatments available, prognosis and survival rates of breast cancer patients greatly depending on their oncological characteristics, demographics and treatment history. Survival after the diagnosis of cancer is one of the important outcome measurements and a key criterion for assessing the quality of cancer control related to both preventive and therapeutic levels (4).

Although it has been established that risk factors for breast cancer in Asian populations are similar to those in Western populations, the prognostic factors may be different from those in Western countries due to the diversity in Asian culture, different socio-demographic background and lifestyles may contribute to a difference in the survivorship (5). In Taiwan, the researcher has reported that diabetic patients have a statistically higher risk of mortality from breast cancer contrasted to those non-diabetics patients (8). In a meta-analysis study done by Zhao and Ren (2016), the pre-existing diabetics were known to have more than 50% of all-cause of mortality as compared to those who without diabetes (6). Another study also It was also known that patients with diabetes were at higher risk of more than 20% as compared to those who were without diabetes (7).

Despite this fact, limited studies had been carried out to determine the survival of this group of patients. Hence, this study aims to determine the 5-years survival rate and its prognostic factors among breast cancer patients in Penang.

MATERIALS AND METHODS

Study Population and Methods

This was a retrospective cohort study that comprises a total of 214 breast cancer patients involving those diagnosed within 1st January 2008 to 31st December 2012 at Advanced Medical and Dental Institute, which located in Penang, North Peninsular of Malaysia. Advanced Medical and Dental Institute (AMDI) is an established governmental tertiary cancer treatment centre which caters to cancer patients in the Northern Region of Peninsular Malaysia coming from Penang, Kedah, Perlis, and Perak. Patients who were Malaysian, diagnosed with primary breast cancer between January 2008 to December 2012, age of more than 18 years, and diagnosed with TNM stage I-IV of breast cancer were eligible to be part of this study.

Meanwhile, those who were listed in the following groups (patients with prior history of any cancer, male breast cancer, and patients who have been transferred out to other tertiary hospitals) were excluded from this

study. Each of the patients was followed up for at least five years. The last date of followed up was 31st December 2017. Patients were identified through the AMDI internal cancer database, and convenience sampling was applied for sample recruitment for this study. Survival time and survival status of the patients were determined through the National Registration Department based on their unique individual identification card number. In this study, the survival time was defined as the time of breast cancer diagnosis to the time of the patient's death (in days). If the patients' data were lost from the follow-up record, they were included from their last visit. All survived patients were included in this study until the last follow-up date on 31st December 2017.

Instruments

Inpatient and outpatient medical records data on socio-demographic, lifestyle and clinical characteristics were obtained as independent variables to be analysed. Sociodemographic data assessed were age group, ethnicity, marital status, co-morbid and family history. Clinical factors assessed were TNM Staging, tumour grading, tumour receptor which comprises of estrogen receptor (ER), progesterone receptors (PR) and human epidermal growth factor receptor 2 (HER2), histological type of tumour, vascular involvement, lumpectomy, mastectomy, axillary surgery and hormonal therapy. A standard data collection proforma was used, and each case has its unique identification number to ensure patients confidentiality.

Statistical Analysis

Descriptive statistics were examined for their frequencies and percentage distributions for categorical variables, while continuous data were presented as means and standard deviation (SD). Data were analysed using IBM SPSS Statistics V24 (IBM Corporation, New York). Survival estimates were determined by the Kaplan Meier method and differences in survival were compared by the log-rank test. The predictors of survival among breast cancer patients were analysed by using the Cox proportional hazard model. The interaction was checked and adjusted for confounding factors. The principle of parsimony and Hosmer Lemeshow approach of using -2 log-likelihood ratios were used. Risk estimates by hazard ratios (HR) and 95% confidence intervals (CI). A p-value of < 0.05 is considered statistically significant.

Ethical consideration

No direct interview with human subjects was involved; this study only involved medical record review activity. Hence, the requirement for consent forms was waived by the ethics committee. However, permission to data access has been requested appropriately from the Head of Medical Record Unit and Director of Advanced Medical and Dental Institute before the study. Each of the data was handled with proper privacy and confidentiality. This study was approved by the Human Ethics Committee from Universiti Sains Malaysia (USM/

RESULTS

Demographic Data

A total of 214 breast cancer patients were identified within the period of this study with the mean age at diagnosis of 50.98 years \pm 10.75; the majority of the patients were aged at diagnosed between 41 to 59 years (65.4%) at diagnosis. From all patients involved, 55.1% of them are Malay, followed by 33.6% Chinese patients and 11.2% of Indian patients. Almost all of the patients (96.3%) were married. In term of history of comorbidities, 98.1% of the patients were non-diabetic, while 1.9% having diabetes. Less than 16% was recorded to have a family history of cancer. Majority of the breast cancer patients involved in this study presented at a later stage, with 43.9% of them presented at Stage 2 and 37.4% presented at Stage 3. Only 18.7% of the breast cancer patients were detected early at Stage 1 (Table I).

Table I: Sociodemographic characteristics of breast cancer patients (N=214)

	N (%)
Age at diagnosis (years) (Mean \pm SD)	50.98 \pm 10.75
Age Group at Diagnosis (years)	
\leq 40	29 (13.6)
41-59	140 (65.4)
\geq 60	45 (21.0)
Ethnicity	
Malay	118 (55.1)
Chinese	72 (33.6)
Indian	24 (11.2)
Marital Status	
Yes	212 (96.3)
No	8 (3.7)
Co-Morbid	
Diabetes	4 (1.9)
Non-Diabetes	210 (98.1)
Family History of Cancer	
No	181 (84.6)
Yes	33 (15.4)
Staging	
Stage 1	40 (18.7)
Stage 2	94 (43.9)
Stage 3	80 (37.4)

Survival rate and predictors of death among breast cancer patients

Survival rate at 1-year, 2-years and 5-years after diagnosis were 98.0%, 94.0% and 89%, respectively. Based on Kaplan-Meier plot, the mean survival was 11.7 years. The estimated time until death for married patients was 4313.52 days, whereas for unmarried patients was lower with only 2800.13 days. It was evidenced in a univariable analysis that unmarried patients had three times shorter time to death compared to those who were

married (crude HR=3.24, 95% CI 1.16-9.06) (Table II).

Table II: Predictors of death according to sociodemographic characteristics

Prognostic factor	n	Mean survival (days)	95% CI	Hazard ratio ^a	
				Crude (95% CI)	Ad-justed (95% CI)
Age Group at Diagnosis					
\leq 40	29	4451.66	3927.65 – 4975.67		
41-59	140	4145.40	3892.64 – 4398.17	1.48 (0.60-3.63)	
\geq 60	45	3953.80	3554.54 – 4352.04	1.61 (0.57-4.53)	
Ethnicity					
Malay	118	4261.81	3916.38 – 4607.23		
Chinese	72	4046.78	3776.90 – 4316.65	0.82 (0.42-1.58)	
Indian	24	4238.80	3722.57 – 4754.77	0.99 (0.43-2.29)	
Marital Status					
Yes	206	4313.52	4060.30 – 4566.75		
No	8	2800.13	1864.03 – 3736.22	3.24 (1.16-9.06) *	3.63 (1.17-11.24) *
Co-Morbid					
Non-Diabetes	210	4278.45	4025.00 – 4531.91		
Diabetes	4	2768.00	1965.93 – 3570.07	2.92 (0.70-12.08)	
Family History of Ca					
No	181	4263.70	3998.50 – 4528.89		
Yes	33	3706.47	3357.89 – 4055.06	0.99 (0.44-2.20)	

^a data was analysed by using Cox regression, * p-value <0.05

The lymph nodes involvement showed two times shorter time to death as compared to those with no lymph nodes involvement (crude HR=2.24, 95% CI 1.13-4.45) (Table III). Figure 1 shows the graphical effects of the marital status and lymph nodes involvement on the survival of the patients. This study found no significant contribution of treatment characteristics on the prognosis of breast cancer patients involved in the study (Table IV).

Next, variables that show significant contribution onto the survival of the patients in the univariable analysis (p<0.25) were selected to multivariable Cox Regression analysis to identify the independent prognostic factors of death among this group of breast cancer patients. After controlling for the effect of underlying comorbidities, lymph nodes involvement, marital status, vascular involvement, and adjuvant therapy; it was found that only marital status (adj HR= 3.63, 95% CI 1.17-11.24)

Table III: Predictors of death according to clinical characteristics

Prognostic factor	n	Mean survival (days)	95% CI	Hazard ratio	
				Crude (95% CI) ^a	Adjusted (95% CI) ^b
Type of Cancer					
Invasive ductal carcinoma	183	4189.32	3975.75 – 4402.88		
Invasive lobular carcinoma	27	4272.83	3679.38 – 4866.28	1.02 (0.44-2.32)	
DCIS	4	2611.25	1415.80 – 3806.71	3.05 (0.73-12.65)	
Position of breast cancer					
Right	109	4000.13	3763.38 – 4236.88		
Left	96	4244.99	3897.89 – 4592.08	0.95 (0.53-1.71)	
Both	9	3654.00	3258.74 – 4049.26	0.93 (0.22-3.94)	
Axilla node involvement					
Yes	18	4001.44	3574.58 – 4428.31		
No	64	4326.20	3931.52 – 4720.87	1.80 (0.41-7.92)	
Tumour size (cm)					
< 2	37	4451.07	4016.51 – 4885.63		
2-5	108	4364.75	4030.90 – 4698.59	1.44 (0.59-3.52)	
> 5	69	4127.11	3782.19 – 4472.02	1.77 (0.70-4.47)	
Tumour Grading					
Grade 1	40	4021.64	3657.89 – 4385.39		
Grade 2	94	4313.00	3965.37 – 4660.63	0.96 (0.43-2.12)	
Grade 3	80	3851.36	3600.72 – 4102.00	1.08 (0.49-2.40)	
Estrogen Receptor					
Positive	125	4377.81	4059.14 – 4696.49		
Negative	89	4227.01	3925.30 – 4528.72	0.94 (0.53-1.67)	
Progesterone Receptor					
Positive	118	4419.62	4098.43 – 4740.81		
Negative	96	4169.59	3871.53 – 4467.65	1.10 (0.63-1.93)	
HER2					
Positive	112	4359.52	4036.03 – 4683.02		
Negative	102	4285.47	4021.54 – 4549.40	0.77 (0.44-1.35)	
Molecular subtype					
Luminal A (ER+ and/or PR+, Her2-)	69	4042.96	3785.51 – 4300.42		
Luminal B (ER+ and/or PR+, Her2+)	67	4254.46	3833.93 – 4674.99	1.39 (0.68-2.84)	
Triple negative (ER-, PR-, Her2-)	34	4337.94	3879.48 – 4796.40	0.98 (0.40-2.43)	
Her2 overexpressing (ER-, PR-, Her2+)	44	3601.43	3295.16 – 3907.69	1.19 (0.51-2.79)	
Vascular involvement					
Yes	59	3849.11	3510.92 – 4187.30		
No	155	4364.24	4084.79 – 4643.68	0.65 (0.36-1.18)	
Lymph nodes involvement					
Yes	25	3561.65	2870.64 – 4252.66	2.24 (1.13-4.45)*	2.23 (1.11-4.51)*
No	189	4391.80	4097.14 – 4686.25		

^a data was analysed by using Simple Cox regression, ^b data was analysed by using Multivariable Cox regression, *p-value <0.05, HER2 Human Epidermal Growth Factor Receptor 2, ER Estrogen Receptor, PR Progesterone Receptor, DCIS Ductal Carcinoma In situ

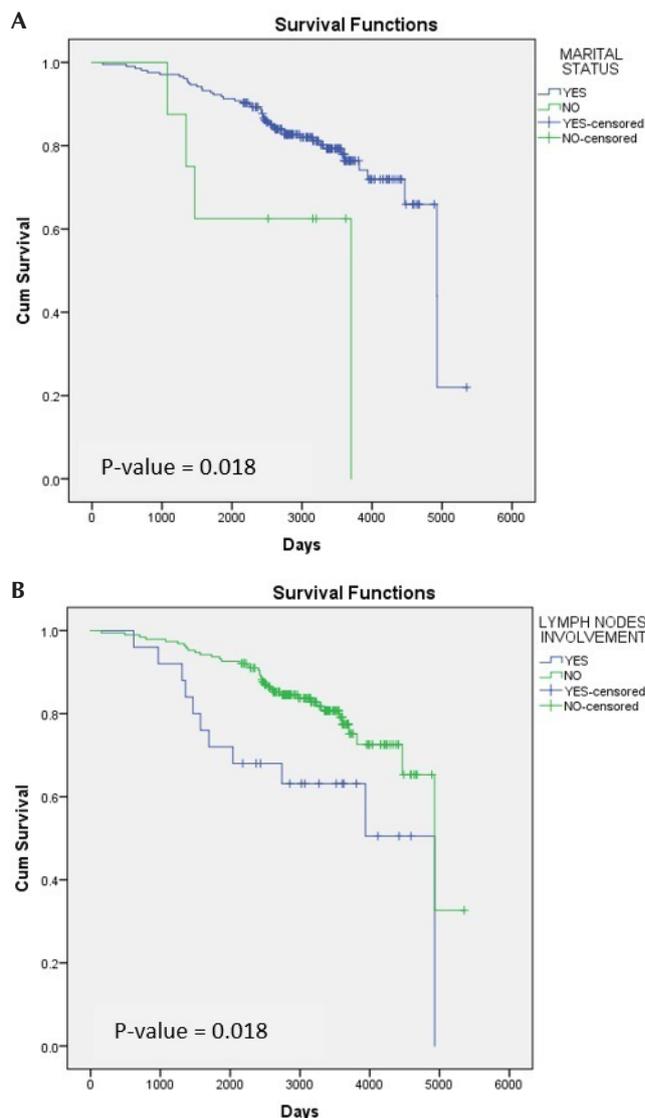


Figure 1: Log-rank test based on (A) Marital Status, (B) Lymph Nodes Involvement

Table IV: Predictors of death according to treatment characteristics

Prognostic factor	n	Mean survival (days)	95% CI	Hazard ratio	
				Crude (95% CI) ^a	Adjusted (95% CI) ^b
Adjuvant therapy					
Chemo + radio	185	4297.34	4033.33-4561.36	0.71 (0.33-1.51)	
Hormonal	100	4127.41	3755.73-4499.10	1.59 (0.90-2.80)	
Hormonal + radio	53	3878.95	3434.10-4323.79	1.75 (0.97-3.17)	
Chemo + radio + hormonal	45	3851.29	3359.97-4342.62	1.79 (0.97-3.29)	
Chemo + radio + targeted	-	-	-	-	-
Chemo + radio + targeted + hormonal	-	-	-	-	-

^a data was analysed by using Simple Cox regression, ^b data was analysed by using Multivariable Cox regression, *p-value <0.05, Chemo=Chemotherapy, Radio=Radiotherapy, Hormonal = Hormonal therapy

and lymph nodes involvement (adj HR=2.36, 95% CI 1.17-4.76) were the significant independent prognostic factors. We were unable to analyse detailed for adjuvant therapy due to a lack of data, especially for targeted therapy.

DISCUSSION

This recent study has demonstrated that the majority of breast cancer patients were diagnosed at age 41 to 59 years (65.4%). The youngest patient recorded in our study was aged 27 years while the oldest was 89 years. The age trend seen in this recent study is similar to the study done in 2008 by Mohd Taib et al. in another tertiary hospital in Klang Valley, Malaysia (10). Also, the study by Abdullah and Yip (2004), shows the trend of mean age at 50 years (11). However, the current study failed to prove any significant contribution of age on the survival of breast cancer patients. This is in line with the study by Rezaianzadeh et al. (2009) that obtained an insignificant result of age on survival of breast cancer (12). Aryandono et al. have also concluded that breast cancer among young women has more aggressive phenotype compared to older women, and this is due to different biological behaviour (13).

With regards to ethnicity distribution seen in this study, Malay ethnics comprises the majority of the patients (55.1%) followed by the Chinese and Indian; with 33.6% and 11.2% respectively. The proportion of the patients seen in this study is different to another study done by Mohd Taib et al. in University Malaya Medical Centre (UMMC) which indicates that the Chinese ethnics were the majority with 63%, followed by Malay and Indian, with 21% and 16% respectively (10). In term of survival, the Chinese patients have survived 63.5% in 5-years compared to Indian 57.4% and Malay with only 47.5% which recorded the lowest among all major ethnics in Malaysia (10). Also in a study by Nor Aini Abdullah et al., 2009 where the Malay patients showed relatively lowest on survival rate (14). Nevertheless, the Chinese breast cancer patients involved in this recent study showed the poorest 5-years survival, followed by the Indian and Malay.

The survival pattern seen in this current study is inverse with the latest national cancer report in Malaysia, whereby in 5-year relative survival, Chinese shows the 76.5% survival rate compared to Indian 70.5% and Malay ethnic indicate the lowest survival rate with 57.9% (3). This in line with a study by Bhoo-Paty et al., 2012 where the Chinese women were the highest in overall survival, followed by Indians and Malays. In addition, Chinese women had the highest overall survival among those patients with early breast cancer (Stage 1 and 2) as compared to the others (15). Comparing with Chinese, the Malay ethnicity was significantly associated with an increased risk of axillary lymph node metastasis (15). However, the present study did not indicate which

ethnicity has any significant association in term of axillary lymph node metastasis. Variation in the survival rate based on ethnicity could be explained due to different cohort of ethnicity and low experience of breast cancer. A study by Abdullah and Yip (2004) show Malay tend to perform at the advanced stage which led to poorer survival rate compared to Chinese and Indian patients and this differs with our study outcome (11). A study in UMMC also found that 40% of the Malay patients prefer to present at an advanced stage (Stage 3 and 4), whereas Chinese and Indian were recorded lower (10). A study in Singapore also found a similar pattern where the Malay ethnicity was associated with an advanced stage (16). Other factors of the delayed such as widowed, divorced and those who never performed were among the causes of the late presentation of the breast cancer (17).

Marital status had been shown to have a significant impact on the outcome of many types of cancer, including breast cancer (18). In this current study, the unmarried patients at diagnosis were detected to have a significantly four times higher risk of dying due to breast cancer as compared to married patients. The finding is in line with another study done by Martinez et al., 2017 where the outcomes showed the unmarried patients have a higher mortality rate as compared to married, which differentiated by the ethnicity, tumour subtype and socioeconomic status (19) which also confirmed that the marital status has influenced the overall survival of breast cancer patients as compared to the others. Another study by Osborne et al, 2005, mentioned in her study that unmarried patients had a significantly increased risk of death after controlling the risk factors such as stage at diagnosis and treatment (20).

This study found the demographics and pathological factors as a potential contributor in generating a significant relationship especially for stage, grading and surgery situations of the patients (21). Silliman et al., 1997 has found that the factors concerning about expenses related to treatment were among the contributor to a higher risk of receiving treatment for unmarried patients (22). However, no financial issue has been reported that leads to a higher mortality rate (19). In addition, the married patients were likely to have more support from their spouse in term of structural and functional support which includes informational support, instrumental support and emotional support which led to a better healthy lifestyle (20). Larger family members and friends in supporting breast cancer patients may help them to gain more confidence (23). Benefits of having good networking especially in social support and social networks may lead to improved a healthier lifestyle for breast cancer patients (20).

Patients presented with lymph nodes involvement shows to have a shorter time to death compared to those without in this study. Our finding is consistent with a study by Zhang et al. (2018) which was done among

breast cancer patients in China (24). Besides, a similar outcome was also obtained by El Saghir et al. (2006) which able to prove that breast cancer patients with lymph nodes involvement were two times more likely to die compared to those without this characteristic (25). Chakraborty, in his study, has mentioned that tumour histology has a significant association with a grade of nodal status. Moreover, it shows that lymph nodes metastasis is an important determinant factor for tumour size (26). In addition, Postaci et al. also has explained a similar outcome that tumour size and axillary lymph nodes have a close relationship (27).

The impact of diabetes on the prognosis of breast cancer patients remains controversial. In this recent study, we failed to prove the significant effect of Diabetes on breast cancer survival. This finding is coherent with Zhang et al. (2006) who showed no significant effects of comorbidities on the prognosis of breast cancer patients regardless of their age (24). However, our finding is contradicted to previous studies which showed that women with diabetes type 2 diagnosed before breast cancer diagnosis tended to have a higher risk of mortality compared to women without diabetes after adjustment for potential confounders (28). There are few speculations proposed in the literature as of the impact of diabetes to the survival of breast cancer patients; diabetic patients are less likely to receive adjuvant chemotherapy or radiotherapy to avoid complication (28,29) and the hyperglycaemic state and poor glycaemic control increased cancer mortality (28–30).

Patients of age less than 40 years who had adjuvant therapy were better 5-year overall from those who did not. Nevertheless, there was no statistical difference when comparing age (< 40 years and > 40 years) for those who underwent chemotherapy (31). Almost a similar outcome from the present study where the adjuvant therapy was not identified to be a significant prognosis factor.

This is a single tertiary-centre study. The nature of the retrospective study was based purely on the quality of secondary data. It prone to open-up for certain bias due to retrospective methods. Therefore, the findings of this study should be interpreted with care and cannot be generalised to all tertiary cancer centre in Malaysia. However, with the limitation identified, the present study able to re-emphasise on important prognostic factors to be aimed for better management of breast cancer patients. Future studies conducted on a bigger scale, looking into a different perspective, such as the impact of patients' psychosocial factors are recommended to identify other important factors affecting their survival.

CONCLUSION

In conclusion, this study highlighted the negative impact of unmarried and lymph nodes involvement on the

overall 5-years survival of breast cancer patients. Further studies are needed to assess the promising benefit of personalized treatment and specific supportive care given to the patients with these risk factors for better cancer experience and survival.

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REFERENCES

1. Bernard W. Stewart and Christopher P. Wild. WHO I World Cancer Report 2014. Who. 2015;
2. Bray F, Ferlay J, Soerjomataram I, Siegel RL, Torre LA, Jemal A. Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. *CA Cancer J Clin.* 2018;68(6):394–424.
3. Survival C. Malaysian Study On MySCan. Vol. 18. 2018.
4. Fisch T, Pury P, Probst N, Bordoni A, Bouchardy C, Frick H, et al. Variation in survival after diagnosis of breast cancer in Switzerland. *Ann Oncol.* 2005;16(12):1882–8.
5. Leong SPL, Shen ZZ, Liu TJ, Agarwal G, Tajima T, Paik NS, et al. Is Breast cancer the same disease in Asian and Western countries? *World J Surg.* 2010;34(10):2308–24.
6. Zhao X-B, Ren G-S. Diabetes mellitus and prognosis in women with breast cancer. *Medicine (Baltimore).* 2016;95(49):e5602.
7. Storey S, Cohee A, Gathirua-Mwangi WG, Vachon E, Monahan P, Otte J, et al. Impact of Diabetes on the Symptoms of Breast Cancer Survivors. *Oncol Nurs Forum.* 2019;46(4):473–84.
8. Tseng CH, Chong CK, Tai TY. Secular trend for mortality from breast cancer and the association between diabetes and breast cancer in Taiwan between 1995 and 2006. *Diabetologia.* 2009;52(2):240–6.
9. Sharma MS. Penang records highest number of breast cancer cases | New Straits Times | Malaysia General Business Sports and Lifestyle News [Internet]. 2019 [cited 2019 Nov 6]. Available from: <https://www.nst.com.my/news/nation/2019/05/492783/penang-records-highest-number-breast-cancer-cases>
10. Taib NAbt M, Yip CH, Mohamed I. Survival analysis of Malaysian women with breast cancer: Results from the University of Malaya Medical Centre. *Asian Pacific J Cancer Prev.* 2008;9(2):197–202.
11. Hisham AN, Yip CH. Overview of Breast Cancer in Malaysian Women: A Problem with Late

- Diagnosis. *Asian J Surg* [Internet]. 2004;27(2):130–3. Available from: [http://dx.doi.org/10.1016/S1015-9584\(09\)60326-2](http://dx.doi.org/10.1016/S1015-9584(09)60326-2)
12. Rezaianzadeh A, Peacock J, Reidpath D, Talei A, Hoseini SV, Mehrabani D. Survival analysis of 1148 women diagnosed with breast cancer in Southern Iran. *BMC Cancer*. 2009;9:1–11.
 13. Aryandono T, Harijadi, Soeripto. Breast cancer in young women: prognostic factors and clinicopathological features. *Asian Pac J Cancer Prev*. 2006;7(3):451–4.
 14. Abdullah NA, Mahiyuddin WRW, Muhammad NA, Mohamad Ali Z, Ibrahim L, Tamim NSI, et al. Survival rate of breast cancer patients in Malaysia: A population-based study. *Asian Pacific J Cancer Prev*. 2013;14(8):4591–4.
 15. Bhoo-Pathy N, Hartman M, Yip CH, Saxena N, Taib NA, Lim SE, et al. Ethnic differences in survival after breast cancer in South East Asia. *PLoS One*. 2012;7(2).
 16. Tan EY, Wong HB, Ang BK, Chan PMY. Locally advanced and metastatic breast cancer in a tertiary hospital. *Ann Acad Med Singapore*. 2005;34(10):595–601.
 17. Ghazali SM, Othman Z, Cheong KC, Hock LK, Mahiyuddin WRW, Kamaluddin MA, et al. Non-Practice of breast self examination and marital status are associated with delayed presentation with breast cancer. *Asian Pacific J Cancer Prev*. 2013;14(2):1141–5.
 18. Kravdal H, Syse A. Changes over time in the effect of marital status on cancer survival. *BMC Public Health*. 2011;11.
 19. Martnez ME, Unkart JT, Tao L, Kroenke CH, Schwab R, Komenaka I, et al. Prognostic significance of marital status in breast cancer survival: A population-based study. *PLoS One*. 2017;12(5):1–14.
 20. Osborne C, Ostir G V., Du X, Peek MK, Goodwin JS. The influence of marital status on the stage at diagnosis, treatment, and survival of older women with breast cancer. *Breast Cancer Res Treat*. 2005;93(1):41–7.
 21. Zhai Z, Zhang F, Zheng Y, Zhou L, Tian T, Lin S, et al. Effects of marital status on breast cancer survival by age, race, and hormone receptor status: A population-based Study. *Cancer Med*. 2019;8(10):4906–17.
 22. Silliman RA, Troyan SL, Guadagnoli E, Kaplan SH, Greenfield S. The impact of age, marital status, and physician-patient interactions on the care of older women with breast carcinoma. *Cancer*. 1997;80(7):1326–34.
 23. Cluze C, Rey D, Huiart L, BenDiane MK, Bouhnik AD, Berenger C, et al. Adjuvant endocrine therapy with tamoxifen in young women with breast cancer: Determinants of interruptions vary over time. *Ann Oncol*. 2012;23(4):882–90.
 24. Han W, Kim SW, Park IA, Kang D, Kim SW, Youn YK, et al. Young age: An independent risk factor for disease-free survival in women with operable breast cancer. *BMC Cancer*. 2004;4:1–8.
 25. Chen HL, Zhou MQ, Tian W, Meng KX, He HF. Effect of age on breast cancer patient prognoses: A population-based study using the SEER 18 database. *PLoS One*. 2016;11(10):1–11.
 26. Chakraborty A, Bose CK, Basak J, Sen AN, Mishra R, Mukhopadhyay A. Determinants of lymph node status in women with breast cancer: A hospital based study from eastern India. *Indian J Med Res Suppl*. 2016;143(October):45–51.
 27. Postaci H, Zengel B, Yararbaş Ü, Uslu A, Eliyatkin N, Akpınar G, et al. Sentinel lymph node biopsy in breast cancer: Predictors of axillary and non-sentinel lymph node involvement. *Balkan Med J*. 2013;30(4):415–21.
 28. Shao S, Gill AA, Zahm SH, Jatoi I, Shriver CD, McGlynn KA, et al. Diabetes and overall survival among breast cancer patients in the U.S. Military Health System. *Cancer Epidemiol Biomarkers Prev*. 2018;27(1):50–7.
 29. Luo J, Hendryx M, Virnig B, Wen S, Chlebowski R, Chen C, et al. Pre-existing diabetes and breast cancer prognosis among elderly women. *Br J Cancer* [Internet]. 2015;113(5):827–32. Available from: <http://dx.doi.org/10.1038/bjc.2015.249>
 30. Erickson JM, Beck SL, Christian BR, Dudley W, Hollen PJ, Albritton KA, et al. Fatigue, sleep-wake disturbances, and quality of life in adolescents receiving chemotherapy. *J Pediatr Hematol Oncol*. 2011;33(1).
 31. Foo CS, Su D, Chong CK, Chng HC, Tay KH, Low SC, et al. Breast cancer in young Asian women: Study on survival. *ANZ J Surg*. 2005;75(7):566–72.