 doi:10.20944/preprints201906.0017.v1

Modelling Excess Mortality Among Breast Cancer Patients in the North East Region of Peninsular Malaysia, 2007-2011: A Population-Based Study

Tengku Muhammad Hanis[1], Najib Majdi Yaacob[1*], Suhaily Mohd Hairon[2], Sarimah Abdullah[1], Noorfariza Nordin[2], Noor Hashimah Abdullah[3], Mohd Faiz Md Ariffin[3]

[1] Unit of Biostatistics and Research Methodology, School of Medical Sciences, Health Campus, Universiti Sains Malaysia, Kelantan, Malaysia
[2] Department of Community Medicine, School of Medical Sciences, Universiti Sains Malaysia Health Campus, Kelantan, Malaysia
[3] Kelantan State Health Department, Ministry of Health Malaysia
* Correspondence: najibmy@usm.my; Tel.: (6)09 767 6558

Abstract: Measurement of breast cancer burden and identification of its influencing factors help in the development of public health policy and strategy against the disease. This study aimed to examine the variability of the excess mortality of female breast cancer patients in the North East Region of Peninsular Malaysia. This retrospective cohort study was conducted using breast cancer data from the Kelantan Cancer Registry between 2007 and 2011, and Kelantan general population mortality data. The breast cancer cases were followed up for five years until 2016. Out of 598 cases, 549 cases met the study criteria and were included in the analysis. Modelling of excess mortality was conducted using Poisson regression. Excess mortality of breast cancer varied according to age group (50 years old and below vs above 50 years old, Adj. EHR: 1.47; 95% CI: 1.31, 4.09; P=0.004), ethnicity (Malay vs non-Malay, Adj. EHR: 2.31; 95% CI: 1.11, 1.96; P=0.008), and stage (stage III and IV vs. stage I and II, Adj. EHR: 5.75; 95% CI: 4.24, 7.81; P<0.001). In conclusion, public health policy and strategy aim to improve cancer survival should focus more on patients presented at age below 50 years old, Malay ethnicity, and at a later stage.

Keywords: breast cancer, relative survival, excess hazard, excess mortality

1. Introduction

Breast cancer is the leading cause of mortality and morbidity among women globally [1]. In the Asia Pacific region about 24% of breast cancer cases were accounted for in 2012 [2]. According to the Malaysian National Cancer Registry report, breast cancer is the commonest cancer among Malaysian between 2007 and 2011, by which 99% of cases were female [3].

A study in 2014 reported that breast cancer accounted for 25% of cancer-related death in Malaysia, and this number was higher than neighbouring countries such as Indonesia (22%), Singapore (20%) and Brunei (17%) [2]. The study further reported that in term of mortality to incidence rate ratio Malaysia was at 0.49 which was higher than other South-Eastern Asian countries such as Indonesia (0.41), Brunei (0.23), Singapore (0.24), and Thailand (0.38). The only three South-Eastern Asian countries included in the study that had a higher or equal ratio than Malaysia were Myanmar (0.51), Timor-Leste (0.50), and Laos (0.49).

The use of relative survival approach in a population-based cancer study has been considered as a standard practice [4]. The main challenges of conducting the population-based study are the availability and the quality of the data. The cause of death in most of the cancer registry is not reliable and sometimes is not available at all. Thus, a cause-specific survival approach is not appropriate in this condition, and the relative survival approach is justified since the information on the exact cause of death is not needed in this approach.

Over the last ten years, in Malaysia, most of the research conducted to study the burden of breast cancer, and its prognostic factors used the local hospital registry data dan the cause-specific survival

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 June 2019 doi:10.20944/preprints201906.0017.v1

approach [5–12] with only a few were population-based studies [10–12]. Given the scarcity of breast cancer studies among Malaysian residents at the population level, this study was conducted to measure the prognostic factors of excess mortality among female breast cancer patients in one of the regions in Malaysia using data from a population-based cancer registry.

2. Materials and Methods

2.2. Study Location, Data Sources and Data Collection

North-East Region of Peninsular Malaysia consists of three states; Kelantan, Terengganu, and Pahang. This study was conducted in Kelantan state where the majority of the residents were Malay (94.6%), followed by Chinese (3.3%), Indian (0.3%), and others (1.8%) [3]. In this study, two sources of data were used for relative survival approach namely 1) the expected population mortality which was derived from the general population mortality data, and 2) the observed population mortality which was derived from the breast cancer data.

2.2.1. General population mortality data

General population mortality data for Kelantan was obtained from the Department of Statistics, Malaysia (DOSM). To be able to conduct the relative survival analysis, the general population mortality data must be in the form of a complete life table that matched breast cancer data by age, sex, and mortality year. However, the only available data from DOSM was in the form of the abridged life table. Consequently, the data need to be expanded to a complete life table. The general population mortality data for Kelantan between 2007 and 2016 were downloaded from the DOSM website (https://newss.statistics.gov.my/newss-portalx/ep/epLogin.seam) in the Microsoft Excel spreadsheet.

2.2.2. Breast cancer data

Breast cancer data was obtained from the Kelantan Cancer Registry in Non-Communicable Disease (NCD) unit, Kelantan State Health Department. Kelantan Cancer Registry data includes all cancer cases notified by all hospitals in Kelantan, which consist of nine public hospitals, five private hospitals, and one university hospital. The relevant information such as age at diagnosis, sex, ethnicity, cancer morphology, cancer staging, surgery, chemotherapy, radiotherapy, date of diagnosis, status, and date of death was assessed. Proforma checklist was used to guide the data extraction. The extracted data only included breast cancer cases diagnosed between 1st January 2007 and 31st December 2011.

2.3. Study Design and Patient Selection

This was a retrospective cohort study of female breast cancer using Kelantan Cancer Registry. All breast cancer cases were diagnosed with International Classification of Diseases for Oncology (ICD-O) codes C50 series. The inclusion criteria were that the cases must be diagnosed between 1st January 2007 and 31st December 2011, and a Kelantan resident. Additionally, male patients and patients with incomplete data of any variables were excluded. All breast cancer cases had a follow-up record until 31st December 2016. Out of 598 cases, only 549 of breast cancer cases met the study criteria.

2.4. Sample size determination

The sample size was calculated for each variable in the study using G*Power version 3.1.9.2 [13]. The largest sample size was 449 cases, which were for variable radiotherapy. After adjustment for 20% of missing data of any variable in the study, the final sample size needed was 539 breast cancer cases. After data cleaning, there were 549 breast cancer cases in the Kelantan Cancer Registry with complete information for each variable in the study. Thus, no sampling method was applied in this study due to the small difference between the estimated sample size and the number of cases in the registry.

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 June 2019 doi:10.20944/preprints201906.0017.v1

2.4. Statistical Analysis and Software

This study used MORTPAK for Windows version 4.3 [14] for expansion of the abridged life tables. R version 3.6.0 [15] was used for data cleaning and manipulation, descriptive statistics, univariable Poisson regression, multivariable Poisson regression.

2.4.1. Expanding abridged life table

The abridged life tables of Kelantan population mortality were expanded into the complete life tables using the UNABR application in the MORTPAK software [14]. The UNABR application used the Heligman-Pollard model for this expansion. The variant of the model used in the UNABR was:

$$ {}_1q_x = A^{(x+B)^C} + De^{-E(\ln x - \ln F)^2} + \frac{GH^x}{1+GH^x} \quad (1) $$

where ${}_1q_x$ denotes the probability of dying at a yearly interval, and A, B, C, D, E, F, G, and H were the parameters to be estimated. Several studies had agreed that the Heligman-Pollard model fits the Malaysian population considerably well [16–18].

2.4.2. Descriptive statistics

The numerical variables were checked for normal distribution visually by histogram and quantile-quantile plot (Q-Q plot). An approximation of a bell-shaped curved histogram and a 45° line in Q-Q plot were considered as a normally distributed variable. The numerical variables were presented in mean and standard deviation (SD) for a normally distributed variable, and in median and interquartile range (IQR) for a non-normally distributed variable. The categorical variables were presented in frequency and percentage (%). The survival time was presented in range, minimum value, maximum value, median, and IQR.

2.4.3. Poisson regression

This analysis was conducted using a relsurv package [19] in R software. The analysis of excess hazard was carried out using Poisson regression as proposed by Dickman et al. [4]:

$$ ln(u_{jk} - d^*_{jk}) = ln(y_{jk}) + x\beta + \gamma_k \quad (2) $$

where;

u_{jk} = number of death for observation j in interval k,

y_{jk} = person-time at risk for observation j in interval k,

d^*_{jk} = number of death in the expected population comparable to observation j in interval k,

$x\beta$ = a vector of covariate x assumed to be in multiplicative function with coefficient β,

γ_k = coefficient in time interval k

In univariable Poisson regression, the survival times were split into several time intervals. Thus, the time intervals were set according to the recommendation of the United Kingdom and Ireland Association of Cancer Registries (UKIACR) which were monthly up to 6 months, 3-monthly up to 2 years, 6-monthly during 2 to 5 years, and yearly up to 10 years [20]. However, for variable radiotherapy and chemotherapy, different time intervals were used since the univariable models for both variables did not converge. The time intervals used were monthly up to 6 months, 3-monthly up to 2 years, 6-monthly during 2 to 5 years, yearly up to 7 years, and 3-yearly up to 10 years. All variables with a p-value below 0.25 were included in the multivariable Poisson regression.

In modelling the multivariable Poisson regression, the analysis was conducted using the time intervals recommended by the UKIACR. Variable with the highest p-value above 0.05 was removed one at a time. Once the variables for the Multivariable Poisson regression were confirmed, the time intervals were reduced to achieve a more parsimonious model. Models comparison were done using

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 June 2019 doi:10.20944/preprints201906.0017.v1

Deviance (-2Log-likelihood), Akaike Information Criterion (AIC), and the most significant p-value for each variable.

Finally, the final model was tested for all possible two-way interactions between the variables, non-proportional excess hazard, and overdispersion. A p-value below 0.05 indicates a significant two-way interaction term. For the non-proportional excess hazard model, the interaction term between variable and time interval would be included in the model to adjust for the significant non-proportionate variable. A p-value below 0.05 for any variable in the non-proportional excess hazard test indicates a significant non-proportional excess hazard and the variable was considered non-proportionate with the time of diagnosis. The non-proportional excess hazard test is available in the relsurv package. Overdispersion was tested using the deviance statistics against the degrees of freedom of chi-squared distribution and p-value below 0.05 indicates a significant overdispersion in the model.

2.5. Research Ethics

This study was carried out in accordance with the Declaration of Helsinki. Ethical approval was obtained from the Human Research Ethic Committee, Universiti Sains Malaysia (USM/JEPeM/18090420), Medical Research and Ethics Committee, Ministry of Health Malaysia (NMRR-18-2675-43980(IIR)) and written approval from the Kelantan State Health Department.

3. Result

Out of 598 breast cancer cases, 46 cases with missing information on cancer staging and three cases of male breast cancer were excluded. All the remaining 549 cases were included in the analysis. The descriptive statistics were presented in Table 1.

Table 1. Characteristics of breast cancer cases in Kelantan Cancer Registry (n=549)

Variables	Total n (%)	Died n (%)	Censored n (%)
Survival time (years)[a]	9.9 (0.0, 9.9)	-	-
Survival time (years)[b]	5.4 (6.2)	-	-
Age at diagnosis (years)[c]	50.4 (11.2)	-	-
Age at diagnosis			
> 50 years	248 (45.2)	107 (42.0)	141 (48.0)
≤ 50 years	301 (54.8)	150 (58.0)	151 (52.0)
Ethnicity:			
Malay	471 (85.8)	240 (93.0)	231 (79.0)
Chinese	65 (11.8)	15 (6.0)	50 (17.0)
Indian	5 (1.0)	1 (0.0)	4 (1.0)
Siam	6 (1.1)	0 (0.0)	6 (2.0)
Others	2 (0.4)	1 (0.0)	1 (0.0)
Stages:			
Stage I	163 (29.7)	53 (21.0)	110 (38.0)
Stage II	161 (29.3)	33 (13.0)	128 (44.0)
Stage III	90 (16.4)	53 (21.0)	37 (13.0)
Stage IV	135 (24.6)	118 (46.0)	17 (6.0)
Morphology:			
Carcinoma, NOS	2 (0.4)	2 (0.8)	0 (0.0)
Carcinoma undifferentiated, NOS	1 (0.2)	0 (0.0)	1 (0.3)
Papillary carcinoma, NOS	17 (3.1)	9 (3.5)	8 (2.7)
Squamous cell carcinoma, NOS	7 (1.3)	4 (1.6)	3 (1.0)
Adenocarcinoma, NOS	68 (12.4)	38 (14.8)	30 (10.3)

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 June 2019 doi:10.20944/preprints201906.0017.v1

Adenoid cystic carcinoma	1 (0.2)	0 (0.0)	1 (0.3)
Infiltrating ductal carcinoma, NOS	448 (81.6)	202 (78.6)	246 (84.3)
Medullary carcinoma, NOS	1 (0.2)	0 (0.0)	1 (0.3)
Lobular carcinoma, NOS	2 (0.4)	1 (0.4)	1 (0.3)
Infiltrating ductal and lobular carcinoma	1 (0.2)	1 (0.4)	0 (0.0)
Sarcoma, NOS	1 (0.2)	0 (0.0)	1 (0.3)
Surgery			
No	275 (50.0)	154 (60.0)	121 (41.0)
Yes	274 (49.9)	103 (40.0)	171 (59.0)
Radiotherapy			
No	444 (80.9)	211 (82.0)	233 (80.0)
Yes	105 (19.1)	46 (18.0)	59 (20.0)
Chemotherapy			
No	386 (70.3)	170 (66.0)	216 (74.0)
Yes	163 (29.7)	87 (34.0)	76 (26.0)

[a]range(minimum value, maximum value)

[b]median(IQR)

[c]mean(SD)

NOS=not otherwise specified

For univariable Poisson regression, variable age was subdivided at 50 years old, variable cancer morphology was categorised into two subgroups; infiltrating ductal carcinoma and other types of morphology, and variable ethnicity was categorised into Malay and non-Malay. The result of univariable Poisson regression was presented in Table 2.

Table 2. Univariable Poisson regression of breast cancer cases in Kelantan Cancer Registry (n=549)

Variables	β coefficient (SE)	Crude EHR (95% CI)	Z statistics	P value
Age at diagnosis[a]				
> 50	0.00	1.00		
≤ 50	0.37 (0.15)	1.44 (1.08, 1.93)	2.47	0.014
Ethnicity[a]				
Non-Malay	0.00	1.00		
Malay	1.28 (0.35)	3.58 (1.81, 7.07)	3.675	<0.001
Stages[a]				
Stage I	0.00	1.00		
Stage II	-0.65 (0.30)	0.52 (0.29, 0.94)	-2.15	0.031
Stage III	0.82 (0.23)	2.28 (1.46, 3.54)	3.65	<0.001
Stage IV	1.89 (0.20)	6.60 (4.50, 9.69)	9.65	<0.001
Morphology[a]				
Others	0.00	1.00		
Infiltrating ductal carcinoma, NOS	-0.38 (0.17)	0.69 (0.49, 0.96)	-2.20	0.028
Surgery[a]				
No	0.00	1.00		
Yes	-0.84 (-0.15)	0.43 (0.32, 0.58)	-5.61	<0.001
Radiotherapy[b]				
No	0.00	1.00		
Yes	-0.43 (-0.20)	0.65 (0.44, 0.96)	-2.15	0.031

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 June 2019 doi:10.20944/preprints201906.0017.v1

Chemotherapy[b]				
No	0.00	1.00		
Yes	0.20 (0.15)	1.23 (0.92, 1.64)	1.37	0.170

[a]Time interval used (in year): 0.00, 0.08, 0.17, 0.25, 0.33, 0.42, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 8.00, 9.00, 10.00

[b]Time interval used (in year): 0.00, 0.08, 0.17, 0.25, 0.33, 0.42, 0.50, 0.75, 1.00, 1.25, 1.50, 1.75, 2.00, 2.50, 3.00, 3.50, 4.00, 4.50, 5.00, 5.50, 6.00, 7.00, 10.00

For multivariable Poisson regression, the final model was presented in Table 3. In this model, variable cancer staging was further categorised into early stage (stage I and II) and late stage (stage III and IV). Also, the model included interaction terms between variable surgery and time interval, and variable morphology and time interval, since the excess hazard was not proportionate for both variables. There were no significant two-way interactions between the variables and there was no overdispersion in the model before the adjustment for the significant non-proportional excess hazard (Chi-square (df) = 201.94 (250), P value = 0.989).

Five prognostic factors were found significant in this study were the age at diagnosis, ethnicity, stages, morphology, and surgery. Breast cancer patients diagnosed at age 50 years old and younger had 47% higher excess hazard of death compared to those diagnosed at an older age. Also, Malay breast cancer patients had a 2.31 higher excess hazard of death compared to non-Malay patients. Additionally, late-stage breast cancer patients had a 5.75 higher excess hazard of death than early stage breast cancer patients.

Table 3. Multivariable Poisson regression of breast cancer cases in Kelantan Cancer Registry (n=549)

Variables	β coefficient (SE)	Adjusted EHR (95% CI)	Z statistic	P value
Age at diagnosis				
> 50	0.00	1.00		
≤ 50	0.39(0.15)	1.47(1.11, 1.96)	2.66	0.008
Ethnicity				
Non-Malay	0.00	1.00		
Malay	0.84(0.29)	2.31(1.31, 4.09)	2.87	0.004
Stages				
Early stage (stage I and II)	0.00	1.00		
Late stage (stage III and IV)	1.75(0.16)	5.75(4.24, 7.81)	11.25	<0.001
Morphology				
Others	0.00	1.00		
Inf duct CA, NOS	-0.84(0.21)	0.43(0.29, 0.64)	-4.09	<0.001
Surgery				
No	0.00	1.00		
Yes	-1.67 (0.24)	0.19 (0.12, 0.30)	-7.05	<0.001
Morphology x Time				
Inf duct CA, NOS x Interval 2[b]	1.19(0.54)	3.30(1.15, 9.44)	2.23	0.026
Inf duct CA, NOS x Interval 3[c]	1.12(0.69)	3.06(0.79, 11.90)	1.62	0.106
Inf duct CA, NOS x Interval 4[d]	0.10(0.49)	1.11(0.43, 2.88)	0.21	0.831
Inf duct CA, NOS x Interval 5[e]	0.71(1.53)	2.02(0.10, 40.73)	0.46	0.645
Surgery x Time				
Yes x Interval 2[b]	1.23(0.38)	3.43(1.63, 7.22)	3.24	0.001
Yes x Interval 3[c]	1.16(0.48)	3.18(1.25, 8.07)	2.43	0.015
Yes x Interval 4[d]	2.13(0.49)	8.44(3.25, 21.91)	4.39	<0.001
Yes x Interval 5[e]	0.50(1.18)	1.64(0.16, 16.46)	0.42	0.672

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 June 2019 doi:10.20944/preprints201906.0017.v1

Time interval				
Interval 1[a]	-2.02(0.34)	0.13(0.07, 0.26)	-5.90	<0.001
Interval 2[b]	-4.01(0.58)	0.02(0.01, 0.06)	-6.95	<0.001
Interval 3[c]	-4.34(0.72)	0.01(0.00, 0.05)	-6.04	<0.001
Interval 4[d]	-4.68(0.55)	0.01(0.00, 0.03)	-8.51	<0.001
Interval 5[e]	-5.29(1.44)	0.01(0.00, 0.08)	-3.68	<0.001

AIC=419.38, Deviance=163.03

Interval 1[a]= 0-1 years

Interval 2[b]=1-2 years

Interval 3[c]=2-3 years

Interval 4[d]=3-6 years

Interval 5[e]=6-10 years

Inf duct CA, NOS=Infiltrating ductal carcinoma, not otherwise specified

The excess hazard for breast cancer morphology was not proportionate with the time of diagnosis. In Table 3, for example, breast cancer patients with infiltrating ductal carcinoma, not otherwise specified (NOS) in the second interval had a 3.3 higher excess hazard compared to breast cancer patients with infiltrating ductal carcinoma, NOS in the first interval, while those with infiltrating ductal carcinoma, NOS in the fourth interval had only 11% higher excess hazard compared to those with infiltrating ductal carcinoma, NOS in the first interval. The non-proportionate excess hazard effect of breast cancer morphology with the survival time was further categorised in Table 4. The excess hazard for breast cancer patients with infiltrating ductal carcinoma, NOS was lower than those with other types of breast cancer morphology for most of the survival time. However, the excess hazard was higher between one- and three-years following diagnosis. The same occurrence was observed for variable surgery. In Table 3, the breast cancer patients who received surgery in the fourth interval had a 8.44 higher excess hazard than breast cancer patients who received surgery in the first interval, while the ratio of the excess hazard of breast cancer patients who received surgery in the fifth interval compared to those in the first interval was only at 64%. The non-proportionate excess hazard effect of the surgery was further categorised in Table 5. Generally, breast cancer patients who received surgery had a lower excess hazard of death than those who did not receive surgery for most of the survival time. However, between period three- and six-years following diagnosis, the patients who received surgery had a higher excess hazard of death than those who did not receive surgery.

Table 4. Estimated excess hazard ratio (EHR) for variable morphology separated by time interval for breast cancer cases in Kelantan Cancer Registry

Morphology	Time interval				
	Interval 1 (0-1 year)	Interval 2 (1-2 year)	Interval 3 (2-3 year)	Interval 4 (3-6 year)	Interval 5 (6-10 year)
Others	1.00	1.00	1.00	1.00	1.00
Infiltrating ductal carcinoma, NOS	0.43	1.42	1.32	0.48	0.87

NOS=Not otherwise specified

Preprints (www.preprints.org) | NOT PEER-REVIEWED | Posted: 3 June 2019 doi:10.20944/preprints201906.0017.v1

Table 5. Estimated excess hazard ratio (EHR) for variable surgery separated by time interval for breast cancer cases in Kelantan Cancer Registry

Surgery	Time interval				
	Interval 1 (0-1 year)	Interval 2 (1-2 year)	Interval 3 (2-3 year)	Interval 4 (3-6 year)	Interval 5 (6-10 year)
No	1.00	1.00	1.00	1.00	1.00
Yes	0.19	0.65	0.60	1.59	0.31

4. Discussion

This study found that younger breast cancer patients had a higher excess hazard compared to older patients. Another study in Malaysia found an opposite result in which a higher excess hazard was observed in older breast cancer patients [11], while another study did not find age at diagnosis as a significant prognostic factor of breast cancer [10]. Both studies were population-based studies but use a cause-specific approach in the analysis which may explain the difference in finding. Our finding, however, is consistent with the other findings that concluded breast cancer patients diagnosed at younger age present with a more advanced and severe tumour thus has a higher risk of mortality [21–24].

Ethnicity is a significant prognostic factor of breast cancer in this current study which is in agreement with several other studies [9,10,25,26]. Malay breast cancer patients had been observed to present with a more aggressive and larger tumour compared to other ethnic groups [27,28]. Another study involving six public hospitals across Malaysia found that Malay breast cancer patients significantly associated with the use of complementary and alternative medicine which had been observed to significantly cause a delay in presentation and diagnosis of breast cancer [29]. Thus, these findings may explain the excess hazard of death observed among Malay breast cancer patients compared to other ethnic groups.

Several studies had reported that cancer staging is a significant prognostic factor of breast cancer [9,10,26]. Our initial finding did not find a significant difference of excess hazard between stage 1 and stage 2. Thus, the cancer staging was combined into early stage and late stage to better reflect the studied population. A presentation of breast cancer at an advanced stage is a significant contributing factor of breast cancer mortality especially in low-and-middle-income countries [30]. Additionally, a late-stage presentation of breast cancer in Malaysia may be explained by factors such social and cultural belief, the use of CAM, lack of awareness, and inaccessibility to health care services [31].

Additionally, breast cancer morphology was not proportionate with the time of diagnosis. This non-proportionality of the excess hazard of breast cancer morphology could be explained by other factors such as the occurrence of metastases and lymph node involvement. For example, a study had reported that infiltrating ductal carcinoma (IDC) and infiltrating lobular carcinoma (ILC) each has a distinct pattern of lymph node involvement and IDC has a less tendency for metastasis [32]. Unfortunately, this additional information is not available in this study.

Our study found that surgery was a significant prognostic factor of breast cancer although there was a non-proportionality of excess hazard between surgery and survival time. This finding is consistent with another population-based study in Kelantan despite the difference in the survival analysis approach [10]. Breast cancer patients who received surgery in the early period following diagnosis most probably those with a more advanced tumour, while in the latter period following diagnosis, those who received a surgery most probably patients who diagnosed with a less advanced tumour. Thus, the difference in the characteristic of breast cancer patients between each time interval may explain the different effect of surgery on breast cancer patients.

Radiotherapy and chemotherapy were not a significant prognostic factor in this study. Majority of breast cancer patients in this study did not receive these two treatments. However, a more focus study should be conducted to determine the association between a combination of different type of

 doi:10.20944/preprints201906.0017.v1

treatment and breast cancer mortality. So, the benefit of each treatment and in a combination of other treatments could be well observed.

This study used secondary data from a cancer registry to better reflect the studied population. The information available in this study is, however, limited to the information available in the cancer registry. Important information such as tumour size, degree of metastases, and lymph node involvement was not available. A complete life table of general population mortality was not available for Kelantan population, and therefore, complete life table was expanded from an abridged life table of general population mortality in this study. Other researchers may use a different method of expansion, leading to a lack of standardisation in the relative survival analysis among studies.

5. Conclusion

The relative survival approach has been considered as a standard practice among population-based studies, especially in cancer research. This approach provides a better alternative when the cause of death is not reliable or unavailable. A population-based study gives a perspective beneficial for public health planning and policy making. This population-based study had found three poor prognostic factors significantly associated with breast cancer mortality, which were age below 50 years old, Malay ethnicity, and late stage.

Acknowledgements

No external funding was received in support of the research work. The funding for the article processing charges will be supported by the School of Medical Sciences, Universiti Sains Malaysia.

Author Contributions

All authors contributed to the conceptual design of this study. NHA, MFMA, NN and TMH contributed to the acquisition of the data; TMH performed the statistical analysis. TMH, NMY, SMH, SA contributed to the drafting of this manuscript. TMH, NMY, SMH and SA finalized the manuscript. All authors read and approved the final manuscript.

Conflict of Interest

The authors declare no conflict of interest.

References:

1. Becker, S. A historic and scientific review of breast cancer: The next global healthcare challenge. *Int. J. Gynecol. Obstet.* **2015**, *131*, S36–S39.
2. Youlden, D.R.; Cramb, S.M.; Yip, C.H.; Baade, P.D. Incidence and Mortality of Female Breast Cancer in the Asia-Pacific Region. *Cancer Biol. Med.* **2014**, *11*, 101–15.
3. Azizah, A.M.; Nor Saleha, I.T.; Noor Hashimah, A.; Asmah, Z.A.; Mastulu, W. *Malaysian National Cancer Registry Report 2007-2011*; Putrajaya, 2015;
4. Dickman, P.W.; Sloggett, A.; Hills, M.; Hakulinen, T. Regression models for relative survival. *Stat. Med.* **2004**, *23*, 51–64.
5. Bhoo-Pathy, N.; Verkooijen, H.M.; Taib, N.A.; Hartman, M.; Yip, C.H. Impact of breast surgery on survival in women presenting with metastatic breast cancer. *Br. J. Surg.* **2011**, *98*, 1566–1572.
6. Subramaniam, S.; Bhoo-Pathy, N.; Taib, N.A.; Tan, G.H.; See, M.H.; Jamaris, S.; Ho, G.F.; Looi, L.M.; Yip, C.H. Breast Cancer Outcomes as Defined by the Estrogen Receptor, Progesterone Receptor, and Human Growth Factor Receptor-2 in a Multi-ethnic Asian Country. *World J. Surg.* **2015**, *39*, 2450–2458.
7. Balasundram, S.; Salekan, K.; Ahmad Shariffuddin, F.N.; Taib, N.A.; Adnan, T.H. Overall Survival and Local Recurrence Among Breast Cancer Patients in Hospital Sultanah Nora Ismail Batu Pahat, 2007-2013. *Asian Pacific J. Cancer Prev.* **2018**, *19*, 2409–2415.
8. Abdullah, M.M.; Mohamed, A.K.; Foo, Y.C.; Ling Lee, C.M.; Chua, C.T.; Wu, C.H.; Hoo, L.P.; Lim, T.O.; Yen, S.W. Breast cancer survival at a leading cancer centre in Malaysia. *Asian Pacific J. Cancer Prev.* **2016**, *16*, 8513–8517.

9. Taib, N.A.; Akmal, M.; Mohamed, I.; Yip, C.-H. Improvement in survival of breast cancer patients - trends over two time periods in a single institution in an Asia Pacific country, Malaysia. *Asian Pac. J. Cancer Prev.* **2011**, *12*, 345–349.
10. Nordin, N.; Yaacob, N.M.; Abdullah, N.H.; Hairon, S.M. Survival Time and Prognostic Factors for Breast Cancer among Women in North-East Peninsular Malaysia. **2018**, *19*, 497–502.
11. Abdullah, N.A.; Wan Mahiyuddin, W.R.; Muhammad, N.A.; Ali, Z.M.; Ibrahim, L.; Ibrahim Tamim, N.S.; Mustafa, A.N.; Kamaluddin, M.A. Survival rate of breast cancer patients in Malaysia: a population-based study. *Asian Pac. J. Cancer Prev.* **2013**, *14*, 4591–4.
12. National Cancer Registry; National Cancer Institute; Ministry of Health Malaysia *Malaysian Study On CANCER SURVIVAL*; Putrajaya, 2018;
13. Erdfelder, E.; FAul, F.; Buchner, A.; Lang, A.G. Statistical power analyses using G*Power 3.1: Tests for correlation and regression analyses. *Behav. Res. Methods* **2009**, *41*, 1149–1160.
14. United Nations MORTPAK for Windows (Handbook) [POP/SW/MORTPAK/2003]. **2013**.
15. R Foundation for Statistical Computing R: A Language and Environment for Statistical Computing 2019.
16. Ibrahim, R.I.; Ngataman, N.; Abrisam, W.N.A.W.M. Forecasting the mortality rates using Lee-Carter model and Heligman-Pollard model. *J. Phys. Conf. Ser.* **2017**, *890*.
17. Ibrahim, R.I. Expanding an Abridged Life Table Using the Heligman-Pollard Model. *Matematika* **2008**, *24*, 1–10.
18. Siran, M.S.; Yusuf, M.M.; Yusoff, Y.S.; Basah, M.Y.A. Expanding Abridge Life Table by Using Heligman Pollard Method: Malaysian Experience 2010-2013. *Int. J. Bus. Soc. Sci.* **2015**, *6*, 133–138.
19. Perme, M.P. relsurv: Relative survival. *R Packag. version* 2013.
20. Poole, J.; Bannon, F.; McPhail, S.; Barclay, M.; Coleman, M.; Emmett, M.; Evans, T.; Greenburg, D.; Nur, U.; Ormiston-Smith, N.; et al. Standard Operating Procedure: Guidelines on Population Based Cancer Survival Analysis This. **2016**.
21. Kheirelseid, E.A.H.; Boggs, J.M.E.; Curran, C.; Glynn, R.W.; Dooley, C.; Sweeney, K.J.; Kerin, M.J. Younger age as a prognostic indicator in breast cancer: A cohort study. *BMC Cancer* **2011**, *11*, 383.
22. McGuire, A.; Brown, J.A.L.; Malone, C.; McLaughlin, R.; Kerin, M.J. Effects of age on the detection and management of breast cancer. *Cancers (Basel).* **2015**, *7*, 908–929.
23. Tao, Z.Q.; Shi, A.; Lu, C.; Song, T.; Zhang, Z.; Zhao, J. Breast Cancer: Epidemiology and Etiology. *Cell Biochem. Biophys.* **2015**, *72*, 333–338.
24. Assi, H.A.; Khoury, K.E.; Dbouk, H.; Khalil, L.E.; Mouhieddine, T.H.; El Saghir, N.S. Epidemiology and prognosis of breast cancer in young women. *J. Thorac. Dis.* **2013**, *5*, S2–S8.
25. Sung, H.; Devi, C.R.B.; Guida, J.; Tang, T.S.; Anderson, W.F.; Yang, X.R. Abstract 3414: Ethnic disparities in breast cancer survival in Sarawak, Malaysia. *Cancer Res.* **2016**, *76*, 3414 LP – 3414.
26. Ibrahim, N.I.; Dahlui, M.; Aina, E.; Al-Sadat, N. Who are the Breast Cancer Survivors in Malaysia? *Asian Pacific J. Cancer Prev.* **2012**, *13*, 2213–2218.
27. Yip, C.H.; Teo, S..; Bhoo-Pathy, N. A review of breast cancer research in Malaysia. *Med. J. Malaysia* **2014**, *69*, 59–67.
28. Bhoo-Pathy, N.; Hartman, M.; Yip, C.-H.; Saxena, N.; Taib, N.A.; Lim, S.-E.; Iau, P.; Adami, H.-O.; Bulgiba, A.M.; Lee, S.-C.; et al. Ethnic Differences in Survival after Breast Cancer in South East Asia. *PLoS One* **2012**, *7*, e30995.
29. Mujar, N.M.M.; Dahlui, M.; Emran, N.A.; Hadi, I.A.; Wai, Y.Y.; Arulanantham, S.; Hooi, C.C.; Taib, N.A.M. Complementary and alternative medicine (CAM) use and delays in presentation and diagnosis of breast cancer patients in public hospitals in Malaysia. *PLoS One* **2017**, *12*, 1–12.
30. Unger-Saldaña, K. Challenges to the early diagnosis and treatment of breast cancer in developing countries. *World J. Clin. Oncol.* **2014**, *5*, 465–477.
31. Cheng, M.L.; Ling, D.Y.; Nanu, P.K.P.; Nording, H.; Lim, C.H. Factors influencing late stage of breast cancer at presentation in a district Hospital - Segamat Hospital, Johor. *Med. J. Malaysia* **2015**, *70*, 148–152.
32. Fernández, B.; Paish, E.C.; Green, A.R.; Lee, A.H.S.; Macmillan, R.D.; Ellis, I.O.; Rakha, E.A. Lymph-node metastases in invasive lobular carcinoma are different from those in ductal carcinoma of the breast. *J. Clin. Pathol.* **2011**, *64*, 995–1000.