OUTCOME AFTER BREAST CANCER IN SINGAPORE AND MALAYSIA

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NATIONAL UNIVERSITY OF SINGAPORE

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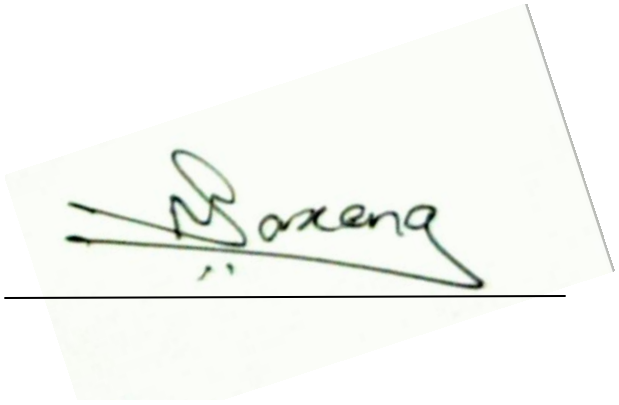
DECLARATION

I hereby declare that this thesis is my original work and it has been written by me in its entirety. I have duly acknowledged all the sources of information which have been used in the thesis.

This thesis has also not been submitted for any degree in any university previously.



NAKUL SAXENA

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TO MOM, DAD and DIPTI

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Summary

Breast cancer results in significant mortality and morbidity across the world. In Asia, the burden of breast cancer is increasing at a rapid rate due to increasing incidence rates. Survival rates on the other hand vary based on levels of economic development for Asian countries. This thesis focuses on the clinical outcome of breast cancer patients from Singapore and Malaysia. Data for the studies was obtained from the Singapore Malaysia Breast Cancer Working Group (SMBCWG) Hospital based Breast Cancer Registry [1].

In order to estimate the differences in presentation, treatment and outcome of breast cancer patients between a middle income and a high income country in SE Asia, we compared patients from Malaysia and Singapore, two SE Asian countries with varying levels of economic development. The results from this study indicate that differences in way of presentation and treatment of patients from Singapore and Malaysia with breast cancer were present, but small. Patients from Malaysia present slightly more often with advanced stage and unfavorable tumor characteristics, however, the overall survival of breast cancer patients from Malaysia was much lower (Adjusted Hazard Ratio 1.6, 95% CI 1.4 to 1.8) than that of Singaporean patients. Poorer compliance with treatment, unfavorable life style factors and competing risks could potentially explain the higher mortality risk of Malaysian breast cancer patients.

In order to quantify the excess mortality among Singaporean breast cancer patients, we conducted a comparison study with Surveillance Epidemiology and End Results (SEER - USA) breast cancer patients. Overall 5-year relative survival was higher for SEER patients than Singaporeans especially for late stage disease and all age groups. Had the SEER stage-specific relative survival rates been reached in Singapore, 410 instead of an

estimated 529 breast cancer deaths would have been observed (reduction of 22.4%). Much of the survival differences can be explained by differences in stage at diagnosis, which could be due to lower disease awareness and the low uptake of the mammography screening program in Singapore.

The prognostic value of a new indicator, namely, the Lymph Node Ratio (LNR – ratio of the number of positive to the total number of axillary nodes removed) was evaluated and compared to the current pN staging in both the neoadjuvant and adjuvant chemotherapy setting. Both LNR and pN staging were equally good in predicting all cause mortality for patients receiving neoadjuvant chemotherapy. In the adjuvant setting, LNR was superior to pN in categorizing mortality risks for women ≥ 60 years, those with Estrogen Receptor (ER) negative or grade 3 tumors. In combination with other factors (i.e. age, treatment, grade, tumor size and receptor status), substituting pN by LNR did not result in better discrimination of women at high versus low risk of death, neither for the entire cohort (c statistic 0.72 [0.70-0.75] and 0.73 [0.71-0.76] respectively for pN versus LNR), nor for the subgroups mentioned above.

With the increasing incidence of breast cancer in general, the shift towards the older age groups and the aging population of Singapore (the median age of the Singaporean population is currently in the late thirties, but by the year 2050, the majority Singapore women will be ≥65 years of age), it is crucial to have a good understanding of breast cancer in older Singaporean women. This study showed that older Singaporean women were more often diagnosed with advanced stages and estrogen receptor positive tumors. They were less likely to have undergone an axillary clearance, radiotherapy post breast conserving surgery and chemotherapy for lymph node positive disease. Older women had

poorer relative survival than younger women; however these differences largely disappeared after stage stratification.

In summary, breast cancer patients from Singapore and Malaysia have substantial differences in terms of overall survival which are not completely explained by tumor characteristics and treatment differences. Elderly Singaporean patients present with more advanced disease and are less likely to receive adequate treatment compared to younger Singaporean patients. Singaporean patients overall still have some way to go before they can achieve survival rates seen for the SEER patients which can partly be achieved by early detection / presentation. Lastly, based on the results from the LNR studies, it is clear that LNR does not add any prognostic value over the current pN staging system for patients from Singapore and Malaysia.

List of Tables

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List of Abbreviations

Full name	Abbreviation
Adjusted Hazard Ratio	HRadj
Adjusted Odds Ratio	ORadj
American Joint Committee of Cancer	AJCC
Body Mass Index	BMI
Breast Cancer Gene	BRCA
Breast Conserving Surgery	BCS
Clinical Breast Examination	CBE
Concordance statistic	C statistic
Confidence Interval	CI
Estrogen Receptor	ER
Fine Needle Aspiration Cytology	FNAC
Food and Drug Administration	FDA
Hazard Ratio	HR
Hormone replacement therapy	HRT
Human Epidermal growth factor Receptor 2	HER2/NEU
Lymph Node Ratio	LNR
Lymph Nodes	LN
Lymphovascular Invasion	LVI
Magnetic Resonance Imaging	MRI
National University Hospital	NUH
Nottingham Prognostic Index	NPI
Net Reclassification Index	NRI
Odds Ratio	OR
Overall Survival	OS
Pathological Nodal Staging	pN Staging
Progesterone Receptor	PR
Radiotherapy	RT
Relative Risk	RR
Relative Survival	RS
Relative Survival Rate	RSR
South East Asia	SEA
Singapore Malaysia Breast Cancer Working Group	SMBCWG
Single Nucleotide Polymorphism	SNP
Surveillance Epidemiology and End Results	SEER
Tumor, Nodes, Metastasis	TNM
Pathological nodal status for patients treated with neoadjuvant chemotherapy	ypN

List of Publications

1) **Saxena N**, Hartman M et al. Impact of older age on presentation, management and outcome of breast cancer in the multi-ethnic Asian population of Singapore. Journal of Geriatric Oncology 2011; 2 (2011) 50-57 (DOI: 10.1016/j.jgo.2010.08.002)
2) **Saxena N**, Hartman M et al. Prognostic value of axillary lymph node status after neoadjuvant chemotherapy. Results from a multicenter study. European Journal of Cancer 2011; 47 (2011) 1186-1192 (DOI: 10.1016/j.ejca.2010.12.009)
3) **Saxena N**, Hartman M et al. Does the axillary lymph node ratio have any added prognostic value over pN staging for South East Asian breast cancer patients? **Accepted** for publication in PLOS ONE (DOI: 10.1371/journal.pone.0045809).
4) **Saxena N**, Hartman M et al. Breast cancer in South East Asia: Comparison of presentation and outcome between a middle income and a high income country. **Accepted** for publication in the World Journal of Surgery (Epub ahead of print) (DOI: 10.1007/s00268-012-1746-2)
5) Bhoo Pathy N, Yip CH, Taib NA, Hartman M, Iau P, Bulgiba AM, **Saxena N**, et al. Breast cancer in a multi-ethnic Asian setting: results from the Singapore-Malaysia hospital-based breast cancer registry. Breast J, Volume 20, Supplement 2 , Pages S75-S80, April 2011 (DOI:10.1016/j.breast.2011.01.015)
6) Bhoo Pathy N, Verkooijen HM, Yip CH, Taib NA, **Saxena N**, et al. Ethnic differences in outcome after breast cancer in South East Asia. PLOS ONE (DOI: :10.1371/journal.pone.0030995).

7) Bhoo Pathy N, Yip CH, Hartman M, **Saxena N**, et al. Adjuvant! Online is overoptimistic in predicting survival of Asian breast cancer patients. European Journal of Cancer Volume 48, Issue 7 , Pages 982-989, May 2012 (DOI:10.1016/j.ejca.2012.01.034)

Conferences

1) Poster presentation at the San Antonio Breast Cancer Symposium; **Accepted** for December 2011- titled: Ethnic differences in the association between tumor size and lymph node status among breast cancer patients in South East Asia. **Saxena N,** Verkooijen HM et al

2) Poster presentation at the San Antonio Breast Cancer Symposium; **Accepted** for December 2011- titled: Validating the Lymph Node Ratio as a prognostic indicator among South East Asian breast cancer patients. **Saxena N,** Hartman M et al

3) Poster presentation at the San Antonio Breast Cancer Symposium; **Accepted** for December 2010- titled: Association between ethnicity and survival after breast cancer in a multi-ethnic Asian setting: results from the Singapore-Malaysia hospital-based breast cancer registry. Bhoo Pathy N, Verkooijen HM, Taib NA, Lee SC, **Saxena N**, Iau P, Yip CH, Hartman M.

4) Poster presentation at the San Antonio Breast Cancer Symposium; **Accepted** for December 2010- titled: Impact of Young Age on the Presentation, Management and Outcome of Breast Cancer in a Multi-Ethnic Asian Setting: Results from the Singapore-Malaysia Hospital-Based Breast Cancer Registry. BhooPathy N, Yip

CH, Taib NA, **Saxena N,** Iau P, Bulgiba AM, Lee SC, Hartman M, Verkooijen HM.

5) Oral presentation at the Asia Link Clinical Epidemiology and Evidence Based Medicine in Global Perspective; **Accepted** for November, 2010- titled: Lymph node status after neoadjuvant chemotherapy. Results from a multicenter study. **Saxena N**, Hartman M et al.

6) Poster presentation at the Roche Asian Oncology Summit; **Accepted** for September 2010- titled: Breast Cancer in Asian Women: Presentation, Treatment and Survival. Bhoo Pathy N, Yip CH, Taib NA, Hartman M, Iau P, **Saxena N**, Lee SC, Verkooijen HM.

7) Poster presentation at the San Antonio Breast Cancer Symposium; **Accepted** for December 2009- titled: Impact of older age on presentation, management and outcome of breast cancer in the multi ethnic Asian population of Singapore. Verkooijen HM, **Saxena N** et al.

Chapter 1 Introduction

With a million new cases of breast cancer each year, breast cancer is the most common type of cancer and the most common cause of cancer deaths among women worldwide [2, 3]. In contrast to Europe and the US, where breast cancer incidence rates have stabilized or even decreased, Asian breast cancer rates are increasing dramatically [4-7]. The rise in incidence observed in Asia is attributed in part to the trend for young Asian women to adopt western lifestyles [1]. Coupled with this, the sheer increase in the absolute number of women in countries like India and China, makes it reasonable to assume that in the relatively near future, the majority of breast cancer patients will be of Asian ethnicity. Despite this, there is a lack of good quality breast cancer data with long term follow up on Asian breast cancer patients and thus little is known about the presentation, management and outcome of breast cancer among multi-ethnic Asian women. Extending breast cancer research into Asia is very much needed as the Western based knowledge of breast cancer etiology [8], diagnosis [9], prognosis [10] and treatment [11] cannot be simply transferred to the Asian population. Asian women have different genetic make-up, ethnicity, lifestyle, cultures, diet and health beliefs compared to their Western counterparts and as such, each of these may play a distinct role in breast cancer incidence, prognosis and treatment. Healthcare systems are also different in Asia with limited resources thus requiring different approaches towards preventive strategies and treatment of breast cancer [12].

South East Asia (SEA) which sees a diversity of ethnic subgroups with distinct genetic, cultural and lifestyle profiles was recently highlighted as an emerging focus for global health [13]. Keeping this in mind, it is important to fill the knowledge gap pertaining to

breast cancer in SEA, especially Singapore and Malaysia, where data is more readily available and most of the work presented in this thesis is the first result of an initiative to fill this void.

Outline of the thesis

The Singapore Malaysia Breast Cancer Working Group (SMBCWG) was established in November 2009 with the aim of improving the understanding of breast cancer in the region of SEA. This was a joint effort on the part of epidemiologists, oncologists and breast surgeons from two tertiary teaching hospitals, namely, the National University Hospital (NUH), Singapore and University of Malaya Medical Center, Malaysia (UMMC) [1]. Under this international, multidisciplinary collaboration, the breast cancer registries of the above mentioned hospitals were merged to form an international hospital based breast cancer registry.

The first section of the thesis focuses on a detailed literature review (**Chapter 2)**. This chapter discusses what is known about breast cancer in South East Asia, particularly focusing on Singapore and Malaysia and provides a detailed write up on screening, clinical investigation and survival of breast cancer patients. Keeping in mind, the core research component of this thesis, a detailed description of the various prognostic indicators for breast cancer is also discussed.

Chapter 3 discusses the key epidemiological concepts that were taken into consideration while analyzing the data as well as the statistical methods used throughout the studies and their significance towards the analysis.

Globally, the burden of breast cancer is increasing with an estimated 1.7 million new cases of breast cancer by 2020, the majority of which will arise from Asian countries [14]. **Chapter 4** explores the differences in presentation, treatment and survival between breast cancer patients from a high income country (Singapore) and a middle income country (Malaysia). Additionally, the excess mortality among Singaporean breast cancer patients is quantified by comparing survival between Singaporean and SEER (USA) breast cancer patients.

Breast cancer is a disease of the elderly [15, 16] with a majority of Caucasian patients being over 65 years of age at diagnosis [17, 18]. **Chapter 5** investigates differences in tumor characteristics, treatment and survival among older (≥ 65 years) and younger (< 65 years) female breast cancer patients from Singapore.

Axillary lymph node status is one of the most important prognostic factors for breast cancer [19-21]. Existing evidence suggests that the Lymph Node Ratio (LNR) (the ratio of the number of positive nodes to the total number of nodes excised), could be a superior prognostic indicator compared to the absolute number of nodes involved [22-26]. **Chapter 6** studies the Lymph Node Ratio (LNR) as a potential prognostic indicator for Singaporean and Malaysian patients in both the neoadjuvant and adjuvant chemotherapy setting. The added prognostic value of LNR over pN stage in the adjuvant setting is also evaluated.

Chapter 2 Literature review

Accurately maintained population based and hospital based breast cancer registries provide an efficient and useful source of data for analysis. This review focuses on the clinical workup, treatment, survival as well as prognostic indicators for breast cancer with special attention being paid to breast cancer in Singapore and Malaysia.

Breast cancer in South East Asia

Developing countries have seen a rapid rise in breast cancer incidence over the past few decades in comparison to developed countries where breast cancer incidence has grown at a slower rate [16]. Mortality rates on the other hand have been fairly stable between 1960 to 1990 in most of Europe and Americas after which they showed an appreciable decline [16, 27, 28].

In Asia, breast cancer is the commonest cancer among women [29, 30]. Several differences between SE Asian and Western breast cancer patients exist. The incidence rates of breast cancer in SE Asia are lower than those seen in Western countries (Table 2.1a and 2.1b). Breast cancer onset in SE Asian women is at a much younger age (mid 40s) as compared to the West where a majority of the cases arise after 60 years of age [30, 31], and unlike the West, the age-specific incidence rates in Asia decrease after the age of 50 years [32]. However, due to the aging Asian population and a shift towards the older age groups, it is quite likely that the median age of onset for breast cancer in Asia will mimic that seen in the West in the years to come. Due to the lack of a population based screening program in most SE Asian countries [33, 34], the majority of patients

present with advanced disease [1, 30]. There is a higher proportion of hormone receptor-negative patients, and some evidence that the cancers in Asia are of a higher grade [35].

Table 2.1a Incidence rates of breast cancer by geographic region.

Location	Incidence	
	Numbers	**Age Standardized Rate (weighted)* per 100,000**
World	**1,151,300**	**37.4**
Northern America	229,600	99.4
Europe	360,700	62.3
Australia and New Zealand	13,500	84.6
Japan and Korea	37,800	30.0
All more developed	**641,600**	**67.8**
China	126,200	18.7
India	83,000	19.1
Latin America & Caribbean	96,600	40.3
Northern Africa & Western Asia	41,800	28.6
Sub-Saharan Africa	48,600	23.5
Other developing	113,500	23.6
All less developed	**509,700**	**23.8**

*weighted average of the age specific rates for each of the populations with respect to the world population.
Source: Breast Cancer Epidemiology, Chapter 1. Ferlay et al. (2009)

Table 2.1b Age Standardized Incidence and Mortality rates of breast cancer in South East Asia (for year 2008)

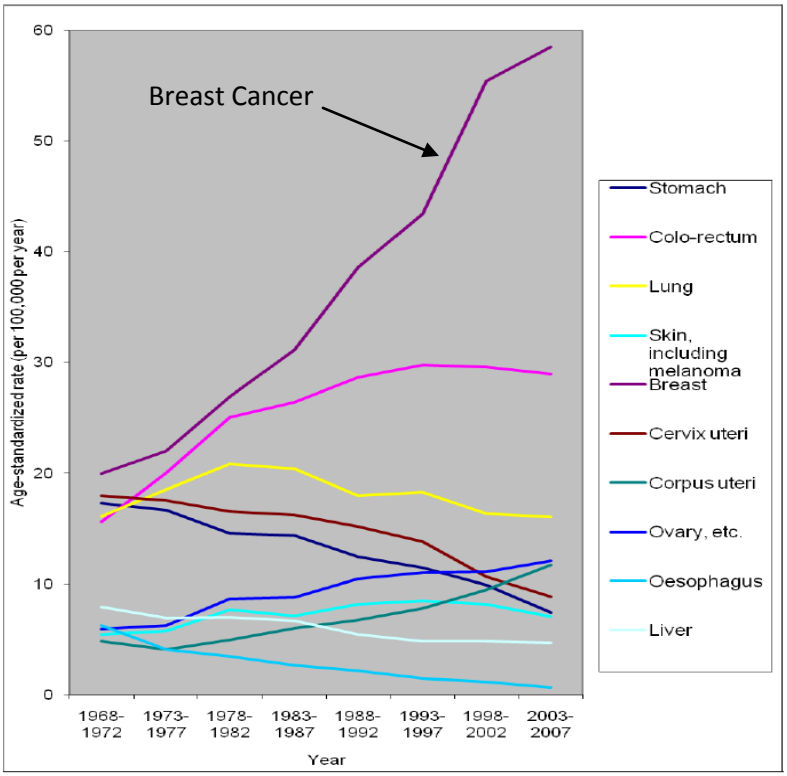
Country	Incidence Rate*	Mortality Rate*
Entire SE Asia	31.0	13.4
Brunei	21.5	17.8
Burma	32.5	12.2
Cambodia	20.7	8.0
East Timor	29.6	17.3
Indonesia	36.2	18.6
Malaysia	37.0	14.7
Philippines	31.9	11.9
Singapore	59.9	13.6
Thailand	30.7	10.8
Vietnam	15.6	5.7
* per 100,000 person years		

Source: GLOBOCAN 2008 website (globocan.iarc.fr)

Singapore has the highest incidence rates for breast cancer in SE Asia (Table 2.1b) [36]. Breast cancer is the most common form of cancer among Singaporean women and accounts for 29.7% of all female cancers in Singapore [37]. Incidence rates in Singapore showed an almost three fold increase from 1968 to 2007 (Figure 2.1). Incidence rates for breast cancer differed across the three major ethnic groups namely Chinese, Malay and Indian in Singapore [5]. In the 1970s, Indian women had the highest incidence rates but by the mid1980s, the highest rates were seen among the Chinese [5]. Today a Singaporean woman has a lifetime risk of 1 in 20 to develop breast cancer [38]. There has been a shift in the peak age of incidence from the mid forties to the late fifties (Figure 2.2) and this can partially be attributed to the cohort effect [39].

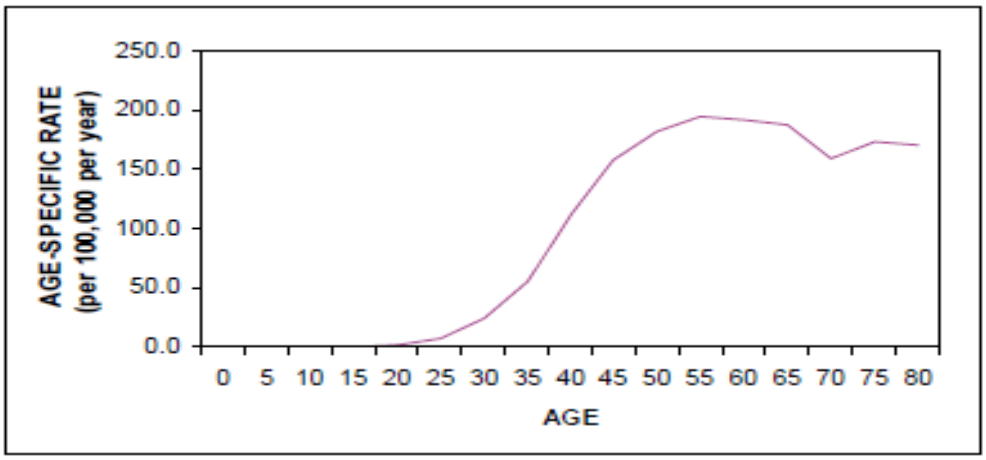
The age standardized incidence rates for all three ethnic groups of Singapore (Chinese, Malay and Indian) steadily increased from 1968 to 2002 [5, 40]. Possible reasons for this could be the transition of Singapore from an industrialized to a developed country, lifestyle changes among the Singaporean women, delayed child bearing and reduction in the family size as a consequence of the 2 child policy introduced in 1972 [41]. However, the post 65 year age category sees a drastic difference in incidence rates among the three ethnic groups (Figure 2.3b). The incidence rates for the Chinese remained constant after the age of 65 years, for the Indians, increased and for the Malays, decreased [5]. These differences can possibly be explained by the ethnic differences in the exposure to certain risk factors or the ethnic difference in the response to similar changes to risk factors or both [5]. Obesity, with possibly limited effect on fertility among postmenopausal Indian women (known risk factor for breast cancer) could have led to the increasing rates of breast cancer in the elderly [5].

Figure 2.1 Age standardized incidence rates for selected cancer sites in Singaporean females from 1968 to 2007



Source: Singapore Cancer Registry report no. 7
(http://www.nrdo.gov.sg/uploadedFiles/NRDO/Publications/inc_report_v8%281%29.pdf)

Figure 2.2 Age-specific incidence rates for breast cancer. Singapore 2003–2007.



Source: Singapore Cancer Registry Report number 7.

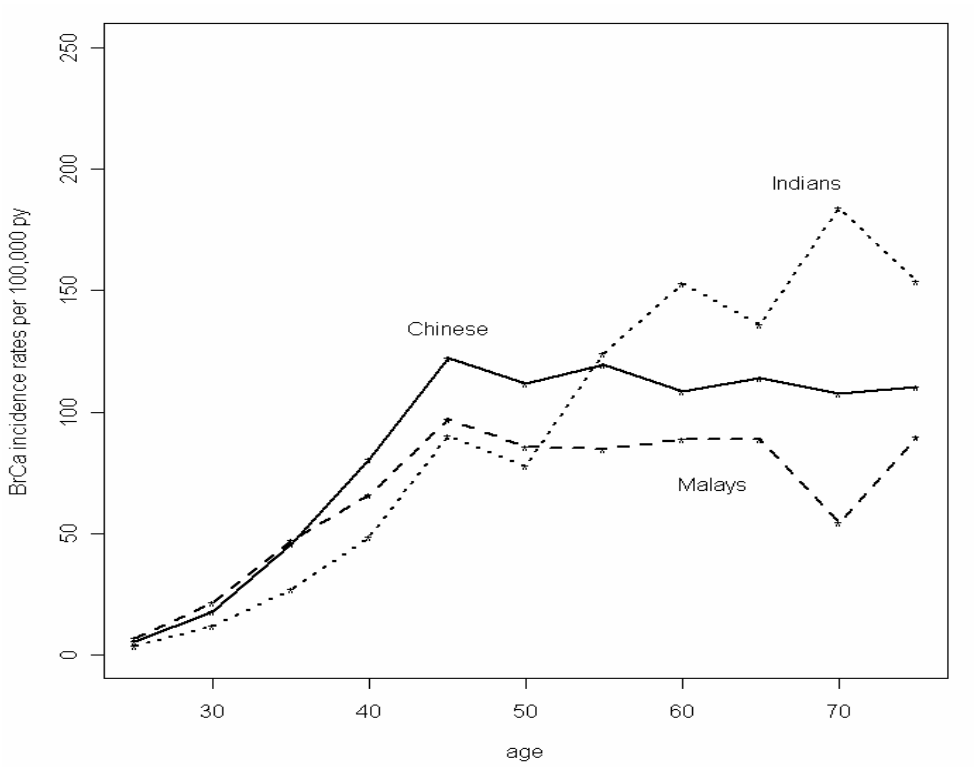
(http://www.nrdo.gov.sg/uploadedFiles/NRDO/Publications/Cancer%20Redistry%20lores%5B1%5D%20hcopy%20101210.pdf)

Incidence rates of breast cancer in Malaysia are lower than those seen in Singapore [35] and roughly one in every twenty women will develop the disease during their lifetime. The median age of disease onset in Malaysia is 50 years [1] and like Singapore, the median age of onset of the disease in Malaysia is lower than that seen in developed countries [35]. Figure 2.4 shows a comparison of age specific incidence rates for Malaysian, Singaporean and South Australian female breast cancer patients. Patients from Singapore and Malaysia follow a similar trend with an initial rise in breast cancer incidence rate up to the age of 45-50 years after which a dip is seen whereas patients from South Australia tend to follow the western pattern with increasing incidence rates with increasing age. Possible explanations for this trend could be the increased use of Hormone Replacement Therapy (HRT) among post menopausal women in developed countries which is a known risk factor for breast cancer. HRT use is not prevalent in Singapore and Malaysia. This could also be due to a "cohort effect" where succeeding generations of women are exposed to differing risk factors; the generation of women born after the Second World War has successively higher risk of developing breast cancer than previous generations.

The breast cancer IR and MR (per 100,000) for all SEA countries, in 2008, was 31.0 and 13.4 respectively (Table2.1b). Breast cancer IR in other SEA countries such as Brunei, Laos, Cambodia, Thailand and Indonesia are lower compared to Western countries (Table 2.1b)[42] but breast cancer is still the most common cancer among women in these countries [43, 44] . Among all SEA countries, the highest IRs were seen in Singapore while the lowest rates were seen in Vietnam (Figure 2.5). Mortality rates per 100,000 were the highest in Indonesia (18.6) (Table 2.1b). A study looking at time trends

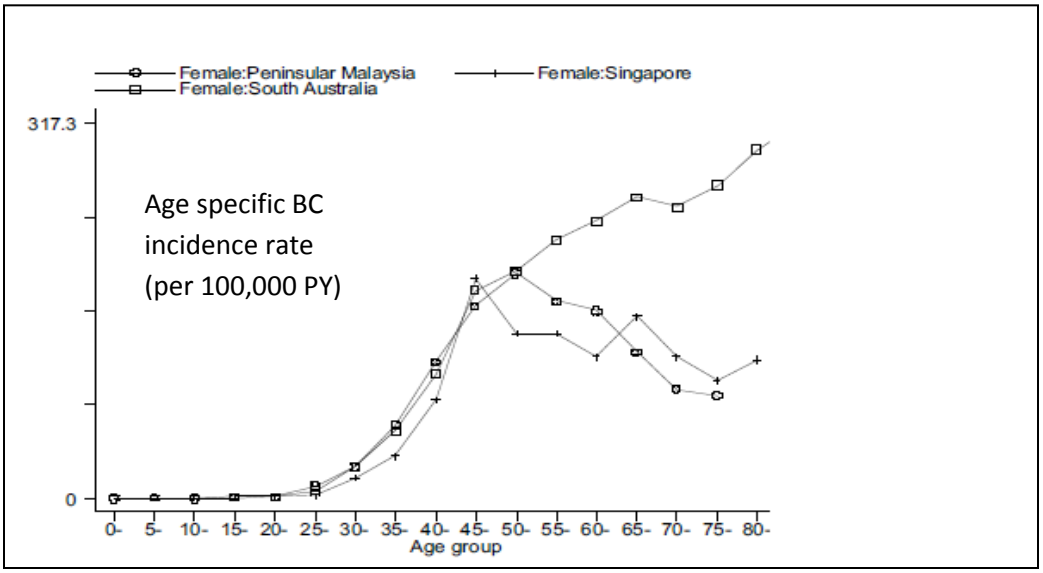
in breast cancer incidence rates showed an increase in truncated age standardized IR from the first 5 year period (1993 to 1997) to the next 5 year period (1998-2002) for SEA countries like Singapore, Thailand and Philippines (Figure 2.6) [45].

Figure 2.3 Overall age specific breast cancer rates in Singapore stratified by ethnicity from 1968-2002.



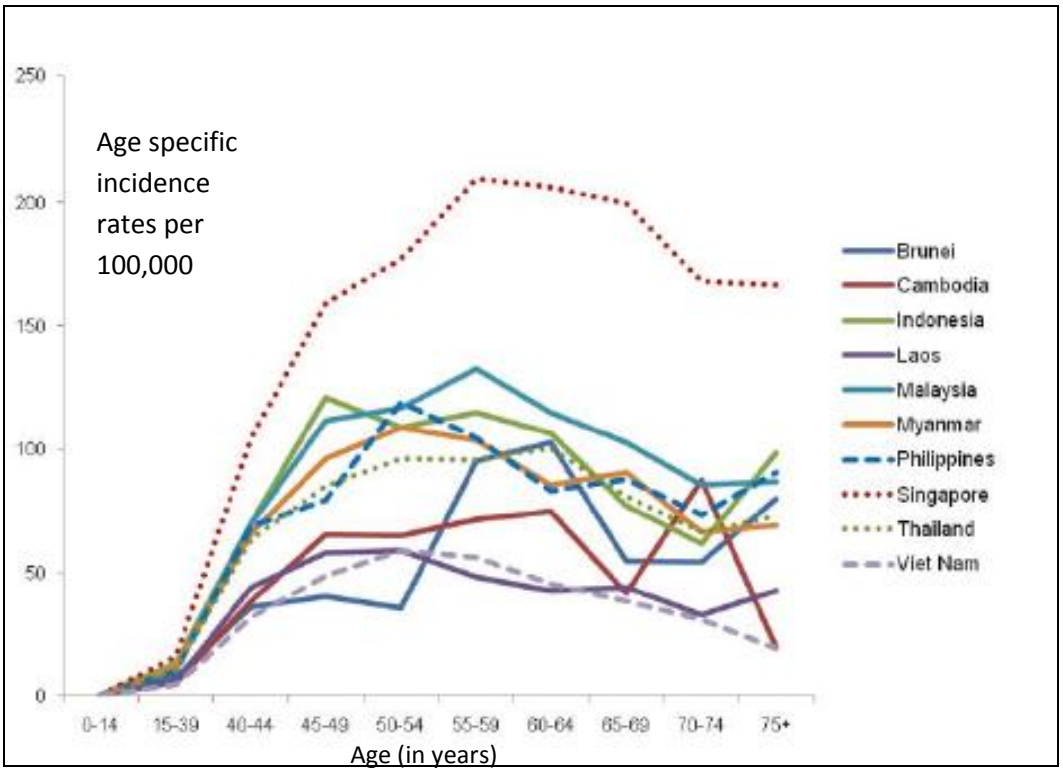
Source: Ethnic differences in the time trend of female breast cancer incidence: Singapore, 1968-2002. Sim X et al.(2006)

Figure 2.4 Age dependent incidence of breast cancer



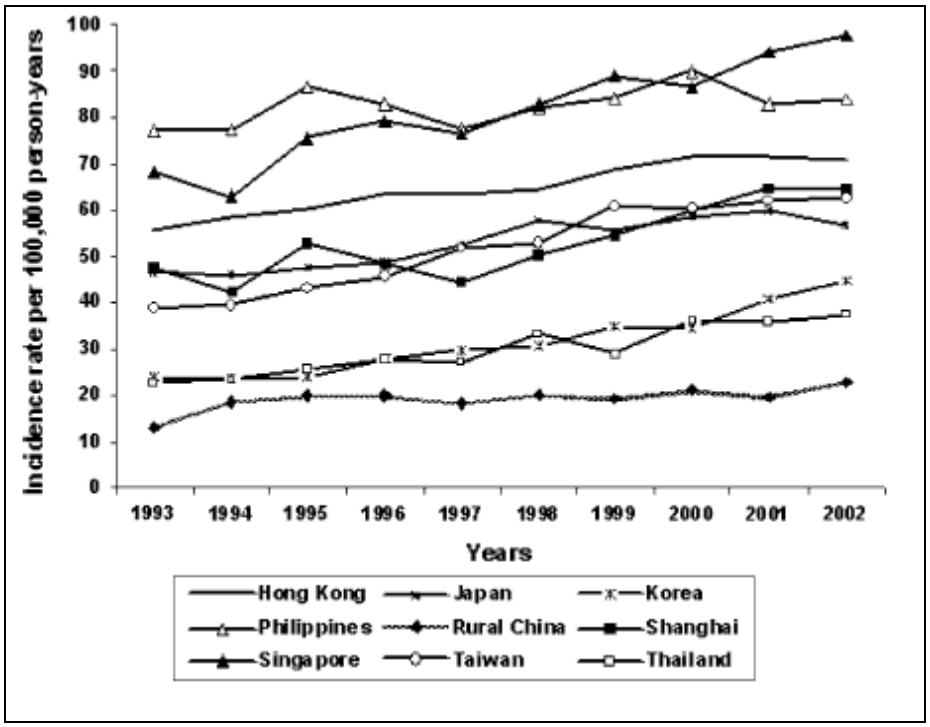
Source: Epidemiology of Breast Cancer in Malaysia. Yip et al (2006)

Figure 2.5 Estimated age specific incidence rates (per 100,000 female population) for breast cancer, by country for SEA in 2008



Source: The burden of cancer in member countries of the Association of South East Asian Nations (ASEAN). Kimman M et al. (2010)

Figure 2.6: Trends in invasive breast cancer incidence during 1993-2002 by country.



Source: Recent trends and patterns in breast cancer incidence among Eastern and Southeastern Asian women. Shin et al. (2010)

With rising incidence of breast cancer in SEA [5, 45], improving breast cancer healthcare in the region remains a priority. This may be addressed by increasing disease awareness, implementing rigid screening programs and increasing funding to improve the quality of life and prolong survival of the patients.

Screening for breast cancer

Screening is the identification of individuals within an asymptomatic population who have (or who are likely to develop) a specified disease, at a time when intervention may result in improvement of the prognosis of the disease. In the case of breast cancer, the intervention can be in the form of surgery, radiotherapy or chemotherapy. Screening can

be in the form of a self breast examination, a clinical breast examination or the use of imaging techniques such as mammography or ultrasound.

Screening allows for early detection, thus bringing forward the time of diagnosis and improving the prognosis of breast cancer.

Clinical examination

Clinical breast examination (CBE) aims at detecting breast abnormalities in order to find palpable breast cancers at an early stage of progression. Although CBE detects some cancers that are missed by mammography, the magnitude of its contribution to early detection is small [46]. For women who have not been recommended mammography as they are either under the age of 40 years or are not subjected to mammography as per guidelines, CBE may play an important role in early detection [47]. CBE encompasses the clinical history, visual inspection, palpation as well as reporting and interpretation of symptoms. Barton et. al. pooled data from 6 studies and obtained an overall estimate of 54.1% sensitivity and 94.0% specificity for CBE [48]. As regards survival, physicians can detect lumps as small as 3.0 mm which is well within the size range for which a survival advantage has been reported [49].

A few trials have evaluated the mortality reduction associated with CBE but none of these studies showed effective reduction in mortality associated with CBE [50, 51]. No trial comparing CBE with mammography has been conducted to date and the fact that mammography screening reduces breast cancer mortality makes it even less likely that such a trial will be conducted [52].

Imaging

Mammographic screening (an x-ray of the breast) has been introduced in many parts of the world, targeting women aged 50 years and above, and this has led to an increased detection of early breast cancers resulting in inflated incidence rates [53] including Singapore [54]. Screening is said to reduce mortality in Singapore by up to 25%. However, there is considerable debate as to whether screening truly decreases mortality, especially in developed countries and whether it is truly beneficial to women with breast cancer (Table 2.2).

Table 2.2 Estimated benefits and harms associated with 10 year course of screening mammography for 2500 women who are 50 years of age*.

Benefit	**Harm**
One woman will avoid dying from breast cancer.	Upto 1000 women will have at least one "false alarm" about half of who will undergo biopsy. Breast cancer will be over diagnosed in 5 to 15 women, who will be treated needlessly with surgery, radiation, chemotherapy or a combination.
* The assumed benefit of screening mammography is a reduction of 10% in the rate of death from breast cancer.	

Source: Screening Mammography- A Long Run for a Short Slide? Gilbert Welch. (2010)

The Singapore Breast Screening Project (1993-1996) led to an increase in the detection rate of ductal carcinomas in situ [36]. The Singapore Cancer Registry data showed that there had been a shift in the age of peak incidence of breast cancer from 45-49 years in 1993-1997 to 50-55 years in 1998-1999. This, coupled with the fact that Singapore is increasingly following the Western lifestyle pattern (later age at first birth, lesser number of children, shorter duration of breast feeding, increased alcohol and smoking consumption, decreased physical activity), led the Government of Singapore to introduce

the first population based screening program in Asia called BreastScreen Singapore in 2002 [36]. This program targeted women aged 50 to 69 years with the aim being to reduce the mortality by 10% by the year 2010 [55].

Results from eight randomized controlled trials across various geographic regions showed that mammography decreased mortality by 25-30% among breast cancer patients and though this was debated by many researchers, the general consensus is that the efficacy of mammography in reducing mortality holds true [56-58].

Mammography can detect tumors that are not detectable by clinical breast examination; such tumors generally have a good prognosis and can even be cured by appropriate treatment [56]. A major drawback of mammography is that a majority of the women presenting with abnormal mammograms do not have breast cancer leading to an increase in the number of false positives thereby inflating incidence rates [59, 60]. For many years there has been a debate regarding screening mammography of women in their 40s [61]. The effect of screening in younger women is slower to appear than women aged above 50 years. This is probably due to mammographically denser breasts in younger women resulting in reduced sensitivity of the mammography [62]. The 15 year mortality from breast cancer among women in their 40s decreased by about 20% as a result of screening [63, 64].

Elderly patients are not entered in clinical trials for mammography. A case control study conducted in The Netherlands showed that mammographic screening among women aged 65 to 74 led to a 55% decrease in mortality from breast cancer, however, the reduction in risk was boarderline significant [RR = 0.45 (95%CI, 0.20 to 1.02) [65]. This study does

however suggest that mammography could result in a mortality reduction among elderly women.

Ultrasound has an established role in the further evaluation of clinical and mammographic breast abnormalities at all ages and is the imaging method of first choice for the assessment of symptomatic breast lesions in younger women (< 35 yearsof age) [66]. It is reliable in distinguishing cystic from solid lesions and recent improvements in ultrasound resolution and advances in colour Doppler technology have meant that benign and malignant lesions can be identified with some degree of confidence, particularly when used in conjunction with clinical and mammographic assessment [66].

Ultrasound is used either separately to screen women with high familial risk [67] or in conjunction with mammography to detect cancer among women with highly dense breast tissue [68]. Up until the early 1990's ultrasound was mainly used to distinguish solid breast masses from cysts [68, 69] but more recently, its diagnostic potential has improved.

Magnetic Resonance Imaging (MRI) as a preoperative diagnostic tool has gained importance over the last decade due to its high sensitivity to detect occult breast cancer in both the affected as well as the contralateral breast [70].

MRI has been documented to be a superior diagnostic tool for those women with a high risk of breast cancer in several studies [71, 72]. From the mid to the late 1990's there were at least 6 prospective studies carried out in the The Netherlands, UK, Canada, Germany, US and Italy to compare the efficacy of MRI to mammography and to gauge the additional benefit MRI gave to women having undergone mammography. These

studies reported a greater sensitivity of MRI compared to mammography or any other imaging tool.

Table 2.3 shows the differences in specificity and sensitivity between the three major imaging tools namely mammography, ultrasound and MRI for the six major studies published to date. These studies looked at differences between diagnostic tools to detect breast cancer in high risk individuals.

Table 2.3 Published breast screening results

	The Netherlands	Canada	United Kingdom	Germany	United States	Italy
Centres (n)	6	1	22	1	13	9
Women (n)	1909	236	649	529	390	105
Age Range (yrs)	25-70	25-65	35-49	>= 30	>=25	>= 25
Cancers (n)	50	22	35	43	4	8
Sensitivity %						
MRI	80	77	77	91	100	100
Mammogram	33	36	40	33	25	16
Ultrasound	n/a	33	n/a	40	n/a	16
Specificity %						
MRI	90	95	81	97	95	99
Mammogram	95	>99	93	97	98	0
Ultrasound	n/a	96	n/a	91	n/a	0

Source: American Cancer Society Guidelines for Breast Screening with MRI as an Adjunct to Mammography. Saslow D et al (2007).

Clinical investigation of breast cancer

For all suspected breast cancer patients a general approach to diagnose or rule out breast cancer has been formalized and is called “triple assessment”. Triple assessment is the triad of clinical sign and symptoms (clinical examination), imaging (Mammography and Ultrasound) and histologic confirmation (needle biopsy). Triple assessment ensures that an accurate diagnosis of the suspected lump is arrived at so as to decrease the chance of missing out the cancer.

Clinical examination and Imaging were discussed in detail under the heading "Screening for breast cancer"

Breast Biopsy

Breast biopsy is performed once a suspicious breast finding is detected either clinically or by imaging. Though lumps are detected with the help of imaging tools, it is not possible to tell from these imaging tests whether the growth is benign or malignant. Hence a biopsy is performed. A common procedure is to conduct a core needle biopsy using stereotactic or ultrasonographic guidance or perform fine needle aspiration cytology (FNAC). However, for lesions that are later proven to be cancerous, the core biopsy has the advantage of providing a greater quantity of sample for histological diagnosis, receptor information and is thus used as an additional test before the patient is subject to surgery [73, 74].

Triple assessment aims at minimizing false positive as well as false negative findings thereby reducing morbidity. If a cancer is detected early, more effective treatment can be implemented resulting in improved quality of life as well as improved disease free survival.

Patient demographics and tumor characterization

Determining patient sociodemographic information helps in predicting whether the patient will have a recurrence and in predicting survival of the patient. Age, ethnicity, socioeconomic status, family history, education are important predictors of breast cancer incidence. Several studies in the West have shown that breast cancer survival is poorer in developing countries and among women with low socioeconomic status (SES) [3, 75-78].

Women with a higher educational level also had better survival as compared to those with a lower education background [79]. Some studies suggest that patients with a family history of breast cancer had a better survival probability as compared to those without any family history [80] which may be due to increased awareness about the disease and various treatment options.

Some patients have indolent disease which can be dealt with using only local therapy while some have a more aggressive and often fatal systemic disease. It is important to identify patients with indolent and low risk tumors to avoid medically unnecessary and potentially harmful interventions.

Tumors can be either malignant or benign. Breast lesions are believed to progress in a linear pattern from ductal hyperplasia without atypia to atypical ductal hyperplasia and then to ductal carcinoma insitu and invasive cancer [81]. A benign lesion progresses to a malignant one as the number of genetic mutations increases. Several studies have shown that during this transformation, the levels of estrogen receptor alpha and HER2/NEU receptor levels increase [82].

Tumors can be characterized by size, grade, and receptor status. For patients with invasive breast cancer, tumor size has been recognized as an important predictor of survival [83, 84]. Tumor size is also an important predictor of treatment and is a vital piece of information when it comes to staging of breast cancer patients.

Tumors are assigned grades based on microscopically detected abnormalities and depending on how quickly the tumor is likely to grow and spread. Tumor grade, also

called differentiation, refers to how much tumor cells resemble normal cells of the same tissue type.

The majority of tumor grading systems used for breast cancer combine scores for nuclear grade, tubule formation and mitotic rate. The grading of a cancer in the breast depends on the microscopic similarity of breast cancer cells to normal breast tissue, and classifies the cancer as well differentiated (low grade or grade 1), moderately differentiated (intermediate grade or grade 2), or poorly differentiated (high grade or grade 3), reflecting progressively less normal appearing cells that have a worsening prognosis.. The cumulative score for all three elements gives the "grade" for that tumor [85, 86]. The most popular grading system for breast cancer is the Elston-Ellis modification of the Scarff-Bloom-Richardson grading system [87, 88] and is called the Nottingham grading system.

Receptor implication in breast tumor cells is an important prognostic indicator and, more importantly a predictive marker for receipt of anti-hormonal therapy or targetted therapy [89]. There are two major steroid receptors implicated in breast cancer namely the estrogen receptor (ER), progesterone receptor (PR).The human epidermal growth factor receptor (HER2/NEU) is also implicated in certain breast cancer patients.

Estrogen receptor's implication in breast cancer was detected as early as 1896 by Beatson [90]. The alpha subtype of the ER as well as ER regulated PR are of special interest as their protein levels are elevated in premalignant and malignant breast lesions as opposed to normal tissue. Furthermore, both receptors are valuable predictive and prognostic indicators of breast cancer [91] and blockade of ER alpha has become one of

the major pathways for treating and controlling the disease [92]. Anti estrogens are now used successfully to inhibit ER mediated activation of gene transcription. HER2/NEU receptor is also a therapeutically and prognostically important factor for breast cancer [93] and unlike the hormone receptors, it is a tyrosine kinase receptor. Structurally it is closely related to the epidermal growth factor receptor and its overexpression acts as a predictive marker for tumor agressiveness and responsiveness to therapy [94]. HER2/NEU protein overexpression has been associated with a higher recurrence risk for both node positive and node negative breast cancers [95].

Treatment of breast cancer

The three major modes of treatments for breast cancer are surgery, chemotherapy including anti-hormonal therapy and radiotherapy. No one treatment fits every patient and usually a combination of two or more is required. Treatment heavily depends upon the age, stage, tumor characteristics, comorbidities and hormonal receptor status of the patient [96].

Limited data is available on the differences in the treatment modalities for native Asian patients and whether different modalities of treatment are practiced or available in SE Asian countries [1]. Clinical trials on newer chemotherapeutic agents are not extensively carried out in the Asia-Pacific region and thus clinical experience with existing treatment in the Asia–Pacific region is limited and variable [97]. Studies carried out in the West suggest that Asian American women were more likely to undergo mastectomy as compared to White American women [98] and that Chinese women were less likely to initiate adjuvant hormone therapy as compared to the Non Hispanic Whites [99].

Surgery

Surgery has always been the primary mode of treatment for breast cancer and is so today. Surgery is indicated for operable disease only. Surgery for breast cancer has drastically improved from deforming ablative procedures to procedures that not only preserve the breast but also the axillary anatomy of the patients [100, 101]. Mastectomy, i.e., the complete removal of the breast is required for women with extensive or multi-centric disease for whom breast conservation is inappropriate. Women undergoing mastectomy for early stage breast cancer as well as those undergoing risk reduction (prophylactic) mastectomy generally do not require adjuvant radiotherapy and are good candidates for immediate breast reconstruction [101]. Many women opt for bilateral mastectomy with immediate breast reconstruction as their preferred method for dealing with high lifetime risk of developing the disease with uptake rates for surgery of 43% and 32% respectively for BRCA1 and BRCA2 gene mutation carriers [102].

Tumorectomy or breast-conserving surgery involves the removal of the affected portion of the breast thereby conserving the breast. Breast conserving surgery has become the standard treatment for early stage breast cancer [103, 104]. The administration of radiotherapy following breast conserving surgery decreases both the risk of ipsilateral breast cancer [105, 106] as well as breast cancer specific mortality [107] . This combination is still preferred by most surgeons provided tumor size and grade are within limits for breast conserving surgery [108]. The outcome of patients who have undergone breast conserving surgery has been improving and the risk of local recurrence in such patients is now less than that reported in initial clinical studies [109].

As part of the surgical treatment, a sentinel lymph node (SLN) (first lymph node to drain lymph from the breast) biopsy may be performed either independent or in conjugation with an axillary clearance. The technique of SLN biopsy, introduced in the mid 1990s to detect lymph node metastases [110], was developed to provide surgeons with enough information to avoid axillary dissection provided the sentinel node is negative [111]. Some studies suggest that the need for axillary dissection following a positive sentinel node biopsy may be over rated and could lead to increased morbidity [112, 113]. There is however the possibility of false negative results for the sentinel node biopsy and thus the surgeon should also consider other indicators for distant metastases such as tumor receptor status, poor tumor cell differentiation and over expression of HER2/NEU receptors before omitting an axillary dissection [114]. Axillary dissection is the surgical procedure in which an incision is made in the armpit (axilla) region to identify, examine and/or remove lymph nodes. Adequate lymph node dissection requires the removal of at least 10 LN [115]. Proponents of the axillary lymph node dissection (ALND) note that about 50% of breast cancer patients will have a non-sentinel axillary lymph node metastasis [116, 117] suggesting that an (ALND) could provide additional prognostic information and could decrease axillary recurrence [110]. However, another study conducted by Giuliano et al suggested that among patients with limited SLN metastatic breast cancer treated with breast conservation and systemic therapy, the use of SLN dissection alone compared with ALN dissection did not result in inferior survival [118].

Chemotherapy and hormone therapy

Surgery alone is usually not sufficient to optimally manage breast cancer. Systemic treatment, that is the administration of chemotherapeutic agents, can be done after

(adjuvant therapy) or before (neoadjuvant therapy) surgery depending on the grade, tumor size, stage, and age of the patient. Adjuvant therapy has had a major effect in prolonging both disease free and overall survival [119]. Another form of adjuvant treatment is beneficial to selective patients based on tumor characteristics (targeted therapy) for example, the administration of adjuvant tamoxifen (an ER modulator) to ER positive breast cancer patients has shown to improve their 15 year survival rate by 31%, but it does not benefit women with estrogen receptor negative disease [120]. Trastuzumab, a monoclonal antibody used for targeted therapy, when administered as an adjuvant to surgery, showed an improvement of almost 50% in disease free survival in 15% to 20% of the patients over expressing the HER2/NEU receptor [121, 122]. In addition to these targeted approaches, adjuvant chemotherapy in the form of alkylating agents, antimetabolites, anthracyclines and taxanes in various combinations has contributed to the overall improvement of patients with operable breast cancer.

Neoadjuvant (also known as primary or induction) chemotherapy or Neoadjuvant endocrine therapy, that is the administration of chemotherapeutic agents prior to surgery. Neoadjuvant chemotherapy is administered to allow breast conservation or to downsize the locally advanced cancer or both. When administered for locally advanced disease, the main aim is to downsize the tumor so that it reaches an operable size. The National Surgical Adjuvant Breast and Bowel Project (NSABP) B-18 trial showed that the administration of neoadjuvant chemotherapy resulted in high rates of tumor response (downsizing), axillary nodal down staging and increased rate of breast preservation [123].

Radiotherapy

Radiotherapy is an equally important mode of treatment for breast cancer and is mandatory post breast conserving surgery [120, 124]. It is commonly administered in fractions 2 Grays/day with a total of 50 Gray [125].

Prognostic indicators of breast cancer

Prognosis is a medical term for predicting the likely outcome of an illness and a factor that predicts this outcome is a prognostic indicator. In an ideal world, once a malignant disease is detected, treatment is administered to effect a cure [126]. If a cure is not possible, an estimate regarding recurrence or more importantly death is made. These estimates are most often derived from information provided by pathology reports, conveniently translated into a numerical index and are termed prognostic estimates.Prognostic factors are important for forecasting outcomes in individual patients and can be used by the clinicians to alter or adjust treatment options. One of the most important parameters to define risk categories for breast cancer specific death in early breast cancer patients is the nodal status (positive or negative) [127]. By assigning a risk category to every patient, appropriate prognostic predictions can be made. Table 2.4 gives the three risk categories into which patients can be classified depending on their nodal status as well as tumor characteristics [128].

Many variables have been shown to correlate with the prognosis of patients with breast cancer. Among the most useful are the number of positive lymph nodes, tumor size and histological grade. The Nottingham Prognostic Index (NPI) combines these three prognostic factors to give a score/index for each patient. This index was developed in 1982 based on a retrospective analysis of 9 factors (of which only the above 3 mentioned

were significant) in 387 patients [129, 130]. The higher the index for a patient , the worse the prognosis.

Table 2.4 Categorization of patients with operable breast cancer into risk categories based on tumor characteristics.

Risk Category	**Disease/Patient Characteristic**
Low	Node negative plus *all* of the following: • Pathological tumor size ≤ 2 cm • Tumor grade 1 • No peritumoral vascular invasion • HER2/*neu*gene neither over expressed nor amplified • Patient age ≥35 years
Intermediate	Node negative plus *at least one* of the following • Pathologic tumor size > 2cm • Tumor grade 2-3 • Peritumoral vascular invasion • Confirmed HER2/*neu* gene over expression or amplification • Patient age <35 years
High	Node positive (1-3nodes) *plus* • Confirmed HER2/*neu* gene over expression or amplification Node positive (≥4 nodes)

Source: Meeting Highlights: International Expert Consensus on the Primary Therapy of Early Breast Cancer. Goldhirsch et al. (2005)

The NPI is calculated as follows:

Nottingham Prognostic Index (NPI) =0.2 (Size in cm) + LN involvement (lymph node, 1-3 bylevel) + Grade (1-3: good, moderate, poor) [each factor is weighted according to regression coefficients of a Cox Proportional Hazards analysis and calculated for each patient]

LN involvement: 0 =1, 1-3 = 2, >3 = 3

Grade: Grade I =1, Grade II =2, Grade III =3

The NPI has been validated by further studies in Nottingham and by studies from several other countries[131, 132]. When combined with predictive factors (estrogen and HER2/NEU receptor status), patients' personal preferences and menopausal status, the NPI is a useful tool which gives advice to clinicians regarding the choice of adjuvant systemic treatment to be administered [133]. One of the advantages of the NPI is its simplicity and though studies have shown that inclusion of other factors such as HER2/NEU status, vascular invasion and basal phenotype could improve the prognostic value of the NPI, validation for such inclusions will be needed [133].

Adjuvant! Online for Breast Cancer is a free web-based prognostication tool which was developed based on the Surveillance, Epidemiology and End Results (SEER) database and treatment efficacy data from meta-analyses [134]. It estimates individual ten year survival probabilities, and risks of relapse in patients with breast cancer, based on clinical characteristics and systemic treatment. In addition, Adjuvant! Online helps to predict the absolute benefit of adjuvant therapy in individual patients.

Since its introduction in early 2000s, Adjuvant! Online has gained worldwide recognition amongst clinicians as a tool to aid patient counselling and clinical decision making in the management of women with early breast cancer [135]. The program has been validated by several groups in Canada and Europe [135, 136]. Two studies have shown that the model accurately predicts survival probabilities across most patient groups [135, 137], whereas the study conducted in United Kingdom found that Adjuvant! Online systematically overestimated survival by about 5.5 percent [138].

In South East Asia, Adjuvant! Online predicted 10 year survival (70.3%) was significantly higher than the observed 10 years survival for Malaysian breast cancer

patients (63.6 %, difference of 6.7%; 95%CI: 3.0- 10.4%) [139]. The model was especially overoptimistic in women under 40 years and in women of Malay ethnicity, where survival was overestimated by approximately 20% (95%CI: 9.8-29.8%) and 15% (95%CI: 5.3-24.5%) respectively [139].

Lymph node ratio

The most accurate of prognostic indicators to date is the pathological nodal staging system. It categorises patients depending upon the number of axillary lymph nodes involved. The classification is as follows:

N0 : 0 lymph nodes affected

N1 : 1 to 3 lymph nodes affected

N2 : 4 to 9 lymph nodes affected

N3 : >= 10 lymph nodes affected

It has been noted that patients classified as N3 are at a survival disadvantage and should be given aggressive therapy [140]. A major limitation to this prognostic indicator is the fact that the number of positive nodes identified is dependent on the number of nodes excised. The process of axillary dissection that determines the number of positive nodes varies across institutions as well as across surgeons from the same institution. The pathological nodal staging system also depends heavily on the pathologists' experience which also varies across institutions. Hence Vinh-Hung et al, taking the above into account, proposed an alternative to the current pN staging system called the "lymph node ratio (LNR)" [22, 23, 141]. Although the LNR hasn't yet been accepted as an alternative

or supplement to the current pathological nodal staging system, preliminary studies show that it is as good (if not better) a prognostic indicator for breast cancer patients [24, 25, 142, 143].

The LNR is calculated as follows:

Lymph node ratio = number of positive axillary nodes / total number of nodes excised

Being a ratio, it did not take into account the number of lymph nodes excised alone, nor did it require the mode of treatment to predict survival [22]. The LNR could be viewed as a per patient standardization in which the number of involved nodes is standardized to the number of nodes removed [141]. Figure 2.7shows the survival curves for the 1829 patients from the Geneva Cancer Registry stratified by pN staging (N1, N2 and N3) as well as by LNR (0.01-0.2, 0.2-0.65, 0.65-1) each category corresponding to low, intermediate and high risk of breast cancer specific death [22]. The researchers noted that the breast cancer specific survival curves for the intermediate and high risk groups, stratified by pN stage, crossed after 15 years of follow up whereas no such crossing of survival curves was seen when the patients were categorized based on their lymph node status. This indicated that the LNR could possibly be a better prognostic indicator for breast cancer specific survival in this setting [22]. Their conclusions were further fortified by the results from the multivariate Cox Regression analysis (Table 2.5) which showed an overlapping confidence interval for the breast cancer specific hazard ratios for the N2 and N3 categorized patients. No such overlap was seen for the intermediate and high risk patients stratified by LNR.

A study from Korea showed no overall difference between LNR and pN staging in categorizing poor, intermediate and good survivors, except for certain subgroups, i.e.

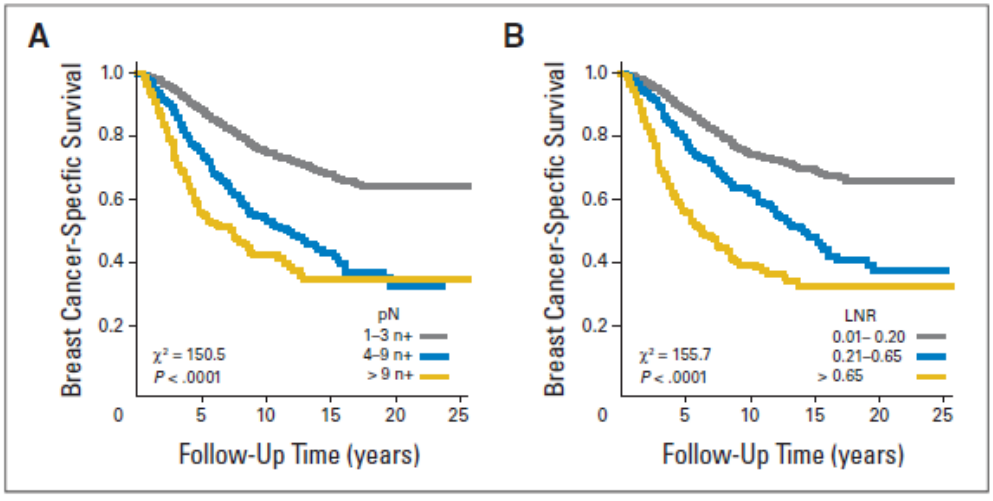
women aged <35 years, HER2 over expressing and triple negative tumors[26]. Other studies conducted in different populations also suggested that LNR was a significant and independent predictor of outcome for breast cancer patients [10, 23-25, 142]

Table 2.5 Effect of LNR and pN classification on breast cancer mortality among patients with lymph node-positive breast cancer.

Variable	Hazard Ratio*	95% CI	*P*
Lymph node ratio			<0.0001
Low, ≤ 0.20	1	Reference	
Medium, > o.20 and ≤ 0.65	1.78	1.46 to 2.18	
High, >0.65	3.21	2.54 to 4.06	
pN			<0.001
pN1	1	Reference	
pN2	2.07	1.69 to 2.53	
pN3	2.94	2.23 to 3.61	
* Cox proportional hazards model; only deaths from breast cancer are considered. Hazard ratios are adjusted for age, year of diagnosis, socioeconomic class, tumor location, histologic grade, tumor size, radiotherapy, chemotherapy and endocrine therapy.			

Source: Lymph Node Ratio as an alternative to pN staging in Node Positive Breast Cancer. Vinh-Hung et al. (2009)

Figure 2.7 Kaplan Meier survival curves according to risk groups. (A) risk groups defined by pN. (B) risk groups defined by lymph node ratio (LNR).



Source: Lymph Node Ratio as an alternative to pN staging in Node Positive Breast Cancer. Vinh-Hung et al. (2009)

Lymph node ratio is rapidly gaining importance as a prognostic indicator for breast cancer. Validation studies in different settings are still required before a firm conclusion about the informativeness of the LNR is made.

Survival of breast cancer patients

Breast cancer is the most prevalent cancer in the world today due toits high incidence and reatively good prognosis[144]. Improved treatment and early detection has increased breast cancer survival to such an extent that previously rising mortality rates have been on the decline for the past 15 years in most Westernized countries[27, 28]. Figure 2.8shows us the age standardized incidence and mortality rates for breast cancer stratified by geographic regions of the world.

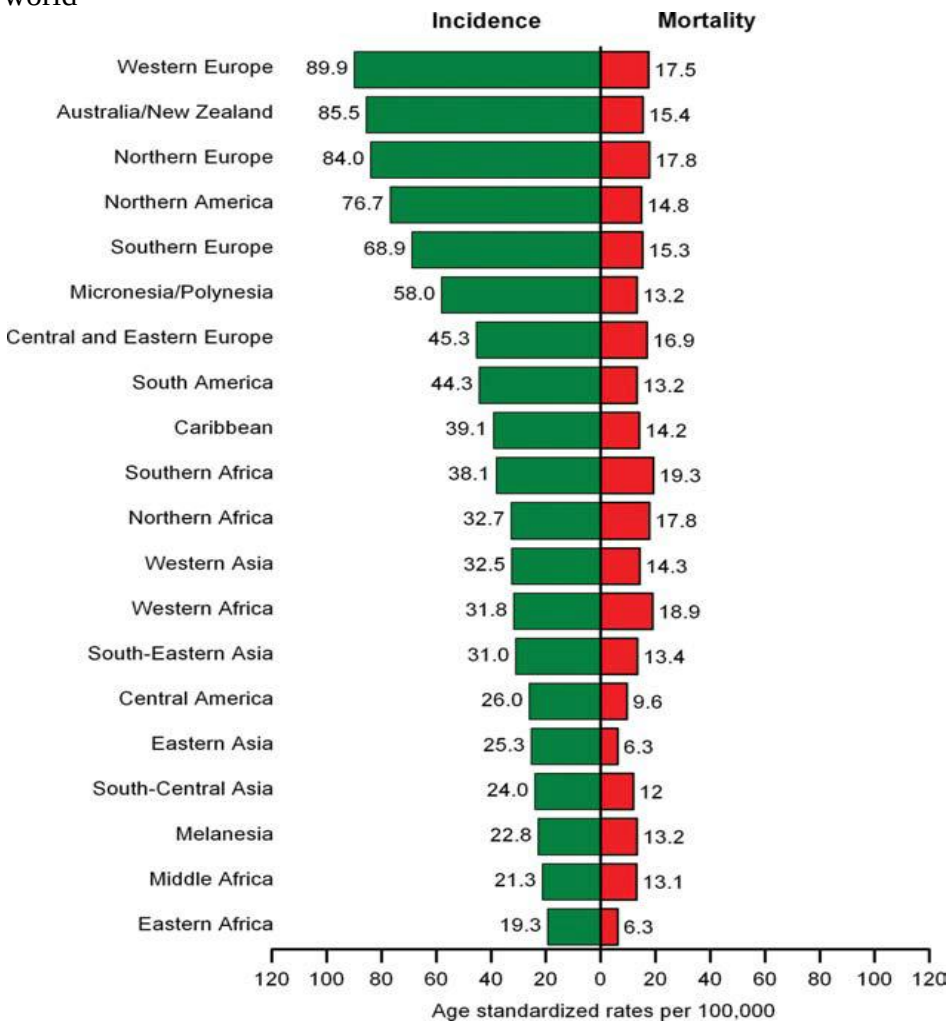
It is seen that mortality rates fluctuate to a lesser extent than incidence rates with lower mortality rates in developing countries as compared to the more affluent ones. The favourable survival of breast cancer cases in Western countries (89% in five years in cases registered in the SEER program from 1995-2000) can be attributed to screening [144].Today, more than half of incident cases occur in the developing world. Combined with still high case-fatality rates, this means that mortality from breast cancer is a leading cause of death among women in developing countries [145]. The high probability of dying from breast cancer—the case fatality rate, which is approximated by the ratio of mortality to income—across the developing world further reflects the inequities in early detection and access to treatment. The number of deaths as a percentage of incident cases in 2008 was 48% in low-income, 40% in low middle-income, and 38% in high-middle-

income countries, while it was 24% in high-income countries according to the most recent Globocan/IARC data [145].

Singaporean women diagnosed between 1980-1999 experienced an overall poorer survival than their European counterparts [39]. In our analysis we noted that there were differences in overall survival rates for women diagnosed in Singapore or Malaysia when stratified by the three major ethnic groups, Chinese, Malay and Indian with Malays having a lower overall 5 and 10 year survival than the other two ethnicities.

The overall 5-year survival from breast cancer in Malaysia correlatedwell with the average of 57% in developing countries [35]. Looking at survival according to stage at diagnosis, it was clear that early diagnosis is associated with a better survival. The survival of 81.7% in Stage 1 disease could be further improved by improved treatment, as it is now possible to obtain a survival of 90% or more[35]. If survival is mainly dependent on early diagnosis and treatment, these are clearly the areas that we need to workon to improve the outcome from breast cancer in South East Asia.

Figure 2.8 Age standardized incidence and mortality rates for breast cancer aroung the world



Source: Global Cancer Statistics,2008. Jemal A et al (2011)

Ethnicity amd survival of SE Asian breast cancer patients

Malaysia and Singapore are multiethnic South East Asian nations comprising 3 major ethnic groups i.e. Malays, Chinese and Indians [146, 147]. In these populations, age-standardized incidence rates (ASRs - world standardized) of breast cancer differ substantially, whereby the rate is highest among the Chinese (Malaysia: 59.7 per 10^5, Singapore: 57.0 per 105 person-years), followed by the Indians (Malaysia: 55.8 per 10^5,

Singapore: 45.8 per 105 person-years) and the Malays (Malaysia: 33.9 per 10^5, Singapore: 44.8 per 105 person-years) [146, 147]. Results from the SMBCWG rsearch showed that the five year overall survival was not significantly different between the Chinese (72.4%; 95%CI: 70.4%-74.4%) and Indian (65.3%; 95%CI: 59.4%-71.1%) patients, but was substantially lower in Malay patients (47.4%; 95%CI:42.7%-52.1%)[148]. Compared to the Chinese, Malay ethnicity was associated with 60% higher risk of all cause mortality (HR: 1.60; 95%CI: 1.44-1.77), independent of patient profile, TNM stage, tumor characteristics and treatment [148]. Indian ethnicity was also associated with a modest increase in mortality risk (HR: 1.16; 95%CI: 1.03-1.32)[148].

Treatment and survival of breast cancer

Effective treatment has been shown to improve overall survival of breast cancer patients. When treatment and its effect on survival is studied, there is an underlying assumption that improved overall response rates would translate into long term survival benefits [149].

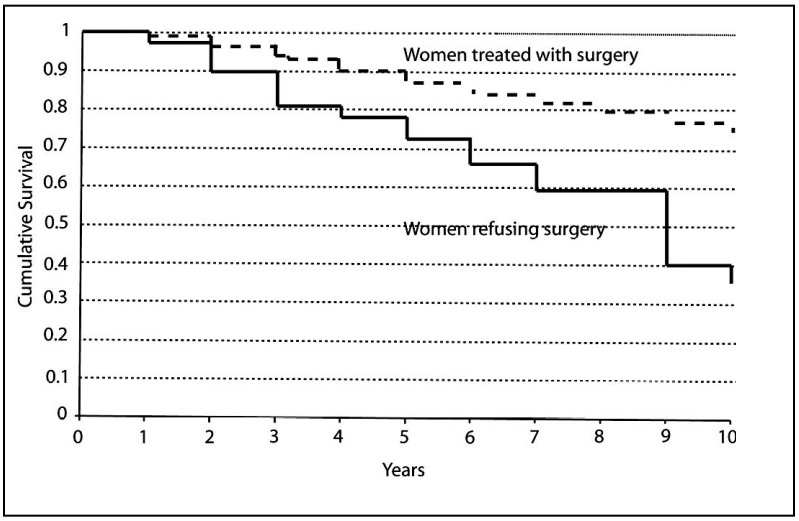
In a population based analysis of overall survival conducted in British Columbia, the introduction of new agents over the last ten years such as taxanes, aromatase inhibitors, and trastuzumab was associated significantly with improvement in overall survival time across the population [150].

In addition to this , a number of randomized clinical trials have been conducted and have reported a statistically significant survival imporvement in women with metastatic breast cancer [151-154].

Surgery is the main mode of treatment for breast cancer. In a population based study using patient data from the Geneva Cancer Registry, Verkooijen et al observed that women refusing surgery for various reasons had a poorer breast cancer specific survival than those patients who didn't refuse surgery (Figure 2.9).

This is reported to be the first study to look at the impact of lack of surgery on breast cancer specific survival with women refusing surgery being at a two fold increased risk of breast cancer specific death even after adjusting for stage, tumor characteristics and non surgical treatment [155].

Figure 2.9 Observed breast cancer specific survival of breast cancer patients in relation to receipt of primary surgery of the breast.



Source: Patients' Refusal of Surgery Strongly ImpairsBreast Cancer Survival. Verkooijen et al. (2005).

Relative survival

Relative survival is defined as the ratio of the proportion of observed survivors in cohort of cancer patients to the proportion of expected survivors in the background population with same age and period distribution[156].Relative survival is described in detail in chapter 3.

Table 2.6 gives the 5 year relative survival estimates of women diagnosed with breast cancer between 1990 to 1994 in various geographic locations in Europe.

Table 2.6 Age standardized relative survival (%) for breast cancer 5 years after diagnosis for women diagnosed between 1990-1994.

	Relative survival (%) female		Relative survival (%) female
Austria	75.4	**Norway**	77.2
CZ	64.0	**Poland**	63.1
Denmark	74.9	**Portugal**	71.9
Estonia	61.9	**Slovakia**	59.5
Finland	81.4	**Slovenia**	67.4
France	81.3	**Spain**	78.0
Germany	75.4	**Sweden**	82.6
Iceland	79.6	**Switzerland**	80.0
Italy	80.6	**UK - England**	73.6
Malta	74.8	**UK - Scotland**	72.3
Netherlands	78.2	**UK - Wales**	69.5

CZ: Czech Republic, UK: United Kingdom

Source:EUROCARE-3: survival of cancer patients diagnosed 1990–94—results and commentary. Sant et al. (2003).

Limited data is available on relative survival estimates for breast cancer patients from South East Asia. A study conducted by the International Agency for Research on Cancer (IARC) showed that the age standardized RSRs for breast cancer patients from Philippines and Thailand were significantly lower than those of the US white patients for the period of 1974 to 1991 [157].

Long term relative survival rates like 5 and 10 year estimates should be interpretted with some caution as patients from different periods of diagnosis could have been subject to different treatment and diagnostic procedures [158] and the predominance of one such group in the analysis could drastically influence the results.

Objective

This thesis focusses on the clinical outcomes of breast cancer among female breast cancer patients from Singapore and Malaysia and special attention is paid to the progosis of the patients. We alsoestimate the prognostic value of the axillary lymph node ratio among Singaporean and Malaysian breast cancer patients and study the impact of older age on presentation and management of breast cancer patients from Singapore. The data for these studies were obtained from the Singapore Malaysia Breast Cancer Working Group (SMBCWG) Breast Cancer Registry.

Chapter 3 Epidemiology concepts and statistical methods used for analysis

This chapter highlights the key epidemiology concepts that were taken into consideration while analysing the data as well as the statistical tests used during analysis throughout the thesis.

Confounding

A confounder is an extraneous variable that correlates with both the dependent and independent variable. A problem posed in many epidemiology studies is that we observe a true association and are tempted to derive a causal inference, when in fact, the relationship may not be causal. This is due to the effect of the coufounding variable. Ways to deal with confounding include:

1) Stratified analysis
2) Matching cases and controls for the potential confounding factor
3) Adjusting for the confounding factor during data analysis.
4) Exclusion of those data points with the confounding factor.

Example from this thesis: Stage is a strong confounder in the association between "place of diagnosis (Singapore or Malaysia)" and all cause mortality. One way to account for this is to adjust for stage in the multivariate Cox Regression analysis to determine the true association between place of diagnosis and all cause mortality.

Confounding by Indication

Evaluating treatment effects from observational data is problematic. Prognostic factors may influence treatment decisions, producing a type of bias referred to as "confounding by indication"[159]. Controlling for known prognostic factors may reduce this problem, but it is always possible that a forgotten or unknown factor was not included or that factors interact complexly. Confounding by indication has been described as the most important limitation of observational studies of treatment effects.

Example from the thesis: In our study comparing survival between elderly and young Singaporean patients, elderly patients presented with more severe disease characteristics, and as a result, could have received less appropriate treatment. However, this confounding by indication did not seem to affect the association between “age” and “all cause mortality”. This is because, even though large survival differences were observed between old and young patients overall, on stage stratification, the survival differences were substantially reduced. Further, type of treatment, after adjusting for disease characteristics, did not influence survival in the elderly, but did so for the young patients.

Bias

Bias is any systematic error in the design, conduct or analysis of a study that results in a mistaken estimate of an exposure’s effect on the outcome. The two major biases encountered in epidemiology studies are slecetion bias and information bias. When the way in which cases and controls or exposed and non exposed individuals are selected such that an association between the exposure and outcome is seen, and if , in reality, no such association exists, then the apparent association is a result of selection bias. The

nature of this selection potentially affects the generalizability of the study. Information bias can occur when the means for obtaining the information from a study subject are inadequate as a result, some of the information obtained regarding the exposure and/or outcome is incorrect. This could lead to misclassification of study subjects thereby introducing a misclassification bias.

Internal Validity

Internal validity refers both to how well a study was run (research design, operational definitions used, how variables were measured, what was/wasn't measured), and how confidently one can conclude that the observed effect(s) were produced solely by the independent variable of interest and not extraneous ones.

External Validity

External validity is the ability the apply the results obtained from a study beyond the study population. To do so, we must know to what extent the study population is representative of all patients with the disease in question (breast cancer in our case).

For Survival Analysis

Mortality

Mortality rate is a measure of the number of deaths (all cause or breast cancer specific) in a population, scaled to the size of that population, per unit of time. Mortality rate is typically expressed in units of deaths per 1000 individuals per year; thus, a mortality rate of 9.5 (out of 1000) in a population of 100,000 would mean 950 deaths per year in that entire population. The term "mortality" is also sometimes inappropriately used to refer to

the number of deaths among a set of diagnosed hospital cases for a disease or injury, rather than for the general population of a country or ethnic group. This disease mortality statistic is more precisely referred to as "case fatality".

Survival

Survival rate refers to the percentage of people in a study or treatment group who are alive for a certain period of time after they were diagnosed with or treated for a disease, such as breast cancer. The survival rate is often stated as a five-year survival rate, which is the percentage of people in a study or treatment group who are alive five years after diagnosis or treatment. Also called overall survival rate. It is important to note that while mortality may be high, survival of the patients might be extremely good.

Prognosis

Prognosis is a medical term for predicting the likely outcome of an illness, often involving a detailed description.A complete prognosis includes the expected duration, the function, and a description of the course of the disease. Prognostic indicators are situations or conditions, or characteristics of a patient, that can be used to estimate the chance of recovery from a disease or the chance of the disease recurring.

Time to event and censoring

Time to event data arise when interest is focused on the time elapsing before an event is experienced. They are known generically as survival data, since death is often the event of interest, particularly in cancer and heart disease. Timetoevent data consist of pairs of observations for each individual: (i) a length of time during which no event was

observed, and (ii) an indicator of whether the end of that time period corresponds to an event or just the end of observation. Participants who contribute some period of time that does not end in an event are said to be ‘censored’. Their event-free time contributes information and they are included in the analysis. Time-to-event data may be based on events other than death, such as recurrence of a disease event (for example, time to the end of a period free of epileptic fits) or discharge from hospital.

Life tables and Kaplan Meier Method

A life table is a table which shows the survival probability of a group of patients wherein the survival time is divided into a certain number of intervals. For each interval we can then compute the number and proportion of cases that entered the respective interval "alive," the number and proportion of cases that failed in the respective interval (i.e., number of terminal events, or number of cases that "died"), and the number of cases that were lost or censored in the respective interval. This statistical method is similar to the Kaplan Meier method of estimating survival.

The Kaplan Meier Product-Limit method has been considered as a gold standard for many years when it comes to graphical displays of survival data. A Kaplan-Meier analysis allows estimation of survival over time, even when patients drop out or are studied for different lengths of time. For each interval of time (say 1 year), survival probabilities are calculated as number of patients surviving / number of patients at risk. Patients who have died or lost to follow up (censored) are not counted in the denominator. Probability of surviving to any point is estimated from the cumulative probability of surviving each of the preceding time intervals (calculated as the product of

preceding probabilities)[160]. The advantage of the Kaplan Meier Product-Limit method over the life table method for analyzing survival and failure time data is that the resulting estimates do not depend on the grouping of the data (into a certain number of time intervals).

Comparing the proportion surviving after computing the survival curves for two sets of patients would only give us a comparison at some arbitrary time point. In order to compare the total survival experience between two sets of patients, the logrank test is more useful [161]. The logrank test is used to test the null hypothesis that there is no difference between the populations inthe probability of an event (here a death) at any time point. The analysis is based on the times of events (here deaths). For each such time we calculate the observed number of deaths in each group and the number expected if there were in reality no difference between the groups.If a survival time is censored, that individual is considered to be at risk of dying in the time interval of the censoring but not in subsequent weeks. This way of handling censored observations is the same as for the Kaplan-Meier survival curve. The logrank test is based on the same assumptions as the Kaplan Meier survival curve namely, that censoring is unrelated to prognosis, the survival probabilities are the same for subjects recruited early and late in the study, and the events happened at the times specified. Since the logrank test is purely a test of significance it cannot provide an estimate of the size of the difference between the groups or a confidence interval.

Relative survival

Relative survival is defined as the ratio of the proportion of observed survivors in

cohort of cancer patients to the proportion of expected survivors in the background population with same age and period distribution[156]. The formulation is based on the assumption of independent competing causes of death. The relative survival adjusts for the general survival of the Singapore population for that race, sex, age and year. Thus the relative survival is a net survival measure representing cancer survival in the absence of other causes of death.

Relative survival provides an estimate of the excess mortality in the patient pool directly or indirectly associated with cancer (in our study, breast cancer) [156, 162]. It thus gives an estimate of the disease related deaths (excess deaths) in the patient population after assuming that the general population is free from that particular disease (breast cancer in this case).

Excess mortality can be represented in the following manner:

Excess mortality = Observed Mortality – Expected Mortality

A major advantage of relative survival is that information on cause of death is not required. This eliminates problems associated with the inaccuracy or non-availability of death certificates. We obtain a measure of excess mortality experienced by patients diagnosed with breast cancer irrespective of whether the excess mortality is directly or indirectly attributable to the cancer.

The central issue in estimating relative survival is defining a “comparable group from the general population.” If not all the excess mortality is due to breast cancer, it would lead to an overestimation of excess mortality.

Statistical Tests

Student's t-test

Student's t-test, is a method of testing hypotheses about the mean of a small sample drawn from a normally distributed population when the population standard deviation is unknown. The null hypothesis states that there is no effective difference between the observed sample mean and the hypothesized or stated population mean, i.e., any measured difference is due only to chance.It is most commonly applied when the test statistic follows a normal distribution.

Mann Whitney U test

The Mann-Whitney U Test is used to compare differences between two independent groups when the dependent variable is either (a) ordinal or (b) interval but not normally distributed. The Mann-Whitney U test is often viewed as the nonparametric equivalent of Student's t-test. Like the parametric Student's t-test, the non- parametric Mann-Whitney U test (1) is used to determine if a difference exists between two "groups," however you define "groups"; (2) is ideally dependent on random selection of subjects into their respective group. The major difference between the Mann-Whitney Test and Student's t-Test involves the concept of normal distribution:

Mann-Whitney is a nonparametric test.

Normal distribution of data is not necessaryfor use of this test.

Chi Square Test

The chi-square test is used to determine whether there is a significant difference between the expected frequencies and the observed frequencies in one or more categories. The chi square test tests the null hypothesis that there is no significant difference in the number of observed and expected frequencies in each category.

The Chi square value for a given contingency table can be calculated as follows:

$X^2 = (O - E)^2 / E$

Where O is the Observed Frequency in each category

E is the Expected Frequency in the corresponding category

df is the "degree of freedom" (n-1) where n is the number of categories

X^2 is Chi Square.

Logistic regression analysis

Logistic regression is used to predict the probability of occurrence of an event in a group of patients by fitting the data to a logistic function curve. Logistic regression is useful in describing the relationship between one or more independent variables (ethnicity, tumor characteristics, treatment etc in our studies) and a binary response variable (dead or alive, young or old and so on). The goal of logistic regression is to correctly predict the category of outcome for individual cases using the most parsimonious model. To accomplish this goal, a model is created that includes all predictor variables that are useful in predicting the response variable. Several different options are available during model creation. Variables can be entered into the model in the order specified or logistic

regression can test the fit of the model after each coefficient is added or deleted, called stepwise regression. Backward stepwise regression is usually preferred method of exploratory analyses, where the analysis begins with a full or saturated model and variables are eliminated from the model in an iterative process. The fit of the model is tested after the elimination of each variable to ensure that the model still adequately fits the data.When no more variables can be eliminated from the model, the analysis has been completed.

The output of a logistic regression analysis is an "odds ratio". An odds ratio is a measure of effect size that describes the strength of an association between two binary data values. It is the ratio of the odds of an event occurring in one group to the odds of an event occurring in another group.

Hosmer Lemeshow test

The Hosmer–Lemeshow test is a statistical test for goodness of fit (calibration) for logistic regression models. It tests the null hypothesis that there is no significant difference in the observed mortality risk and model predicted mortality risk [163].If the Hosmer and Lemeshow Goodness-of-Fit test statistic is .05 or less, we accept the null hypothesis that there is no difference between the observed and model-predicted values of the dependent. (This means the model predicted values significantly differ from what they ought to be, which is the observed values). If the H-L goodness-of-fit test statistic is greater than .05, as we want for well-fitting models, we fail to reject the null hypothesis that there is no difference, implying that the model's estimates fit the data at an acceptable level.

Concordance (c) statistic

The c statistic is used to determine the descriminative power of a model. Discrimination refers to the ability to distinguish high risk subjects from low risk subjects.The interpretation of the c statistic is equivalent to the area under the receiver operating characeristic curve for a binary outcome variable (dead or alive) [164], that is, a c statistic of 0.5 indicates no discrimination above chance, whereas a c statistic of 1.0 indicates perfect discrimination. For this thesis, the c statistic was computed to determine whether one prognostic model was superior in predicting survival to another.

Net Reclassification Index (NRI)

The Net Reclassification Index assesses the ability of a model including a new prognostic marker to more accurately reclassify individuals into higher or lower risk strata. The NRI is the difference in proportions of patients moving up and down risk strata (high, moderate and low risk of mortality) among patients with the event of interest versus those without. The NRI is similar to the simple percentage reclassified but distinguishes between movements in the correct direction (up for case patients (deaths) and down for control patients (survivors) [165].

The NRI is calculated as follows:

$P_{up,event}$ = number of events moving up / number of events

$P_{down,event}$ = number of events moving down / number of events

$P_{up,nonevent}$ = number of nonevents moving up / number of non events

$P_{down,nonevent}$ = number of nonevents moving down / number of non events

$$NRI = (P_{up,event} - P_{down,event}) - (P_{up,nonevent} - P_{down,nonevent})$$

Where "up" refers to the patients moving up in the risk stratas based on the new model when being compared to the old model and "down" refers to the patients moving down in the risk stratas based on the new model when being compared to the old model. For this thesis, "event" refers to "dead" while nonevent refers to "alive".

Cox proportional hazards regression analysis

Survival analysis examines and models the time it takes for events to occur. Survival analysis focuses on the distribution of survival times. Although there are well known methods for estimating unconditional survival distributions, most interesting survival modeling examines the relationship between survival and one or more predictors, usually termed "covariates".

Proportional Hazard model is a type of survival analysis model in statistics. Survival models can be viewed as consisting of two parts: the underlying hazard function, often denoted $\lambda 0(t)$, describing how the hazard (risk) changes over time at baseline levels of covariates; and the effect parameters, describing how the hazard varies in response to explanatory covariates[166, 167].The effect of covariates estimated by any proportional hazards model is called the "Hazard Ratio".

Throughout this thesis, for all survival analysis, the outcome of interest was overall survival. All multivariate Cox proportional hazard analysis was applied (a) to calculate adjusted mortality risks for the patient groups of interest and (b) to identify which combination of factors best predicted overall survival. For this we entered all variables univariately associated with overall survival with a p-value <0.2 into the model and used stepwise backward regression and maximum likelihood method to find the optimal fit.

Hazard ratios

A hazard is the rate at which an event happens, so that the probability of an event happening in a short time interval is the length of the time multiplied by the hazard. Although the hazard may vary with time, the assumption in proportional hazard models for survival analysis, is that the hazard in one group is a constant proportion of the hazard in the other group which means that in a regression type of setting, the survival curves for the groups must have a hazard function that is proportional over time (i.e., constant relative hazard). This proportion is the hazard ratio. Thus the hazard ratio is an expression of the hazard or chance of an event occurring in one arm as a ratio of the hazard of the event occurring in the other arm.

Chapter 4 Comparison of presentation and outcome of Singaporean breast cancer patients with Malaysian and SEER breast cancer patients

Comparison of presentation and outcome of breast cancer patients between a middle income country (Malaysia) and a high income country (Singapore)

(Accepted for publication as "Breast cancer in South East Asia: Comparison of presentation and outcome between a middle income and a high income country." in the World Journal of Surgery 2012)

Introduction:

Asia is the world's largest and most populous continent comprising over 60% of the world's population. Except for a few countries (Singapore, Taiwan, Hong Kong, Japan, South Korea, Israel, Saudi Arabia, and Macau) that are classified as high-income countries, the rest of Asia includes low- and middle-income countries [7, 29]. Over the past decades, South East Asia has seen large differences in socio-economic growth, leading to sharp contrasts in health-systems developments between countries [29].

Compared to Western countries where breast cancer incidence rates have stabilized or even decreased over the last two decades [168-170], most Asian countries have seen a rapid rise in breast cancer incidence [4-6, 40, 171]. With the Westernization of Asian countries, changes in dietary pattern and increased exposure to environmental and reproductive risk factors among Asian women, it is quite likely that in the near future, the majority of the breast cancer patients will be of Asian descent.

Singapore is a newly industrialized Asian country where approximately 75% of the population is Chinese, 14% is Malay and 9% is Indian [172]. Classified as a high income Asian country, Singapore sees a 95% literacy rate and a life expectancy at birth of 81 years [173]. Rapid economic growth and low unemployment rates[173] have converted Singapore from a developing to a developed country within three decades [174] with rising standards of living and advanced healthcare facilities. Healthcare systems in Singapore have undergone major reforms from the early 1960s (when decentralization took place) to the early 1980s where the National Health Plan outlined a 20 year plan to modernize healthcare facilities and raise medical standards[175]. Current healthcare provision in Singapore is considered at par with that from other developed countries[175].

Like Singapore, Malaysia also comprises of three major ethnic groups i.e., Malay (~54%), Chinese (~26%) and Indians (~8%) [176] with a life expectancy at birth of 74 years [177]. An upper middle income country [177], Malaysia has seen sustained economic growth over the past few years with an increasing proportion of people falling in the middle class category [178]. Although healthcare systems in Malaysia have undergone significant improvements over the last three decades, there are still gaps in terms of resource allocation, funding and infrastructure that need to be filled before Malaysian healthcare can be considered at par with that from other developed countries [179].

Several studies in the West have shown that breast cancer occurs more frequently in developed countries and among women with a high socioeconomic status (SES) [3, 75-78]. Incidence rates of breast cancer in Singapore (developed country) and Malaysia (less

developed country) are 60.0 and 46.2 per 100,000 respectively[35, 180]. Survival after breast cancer, on the other hand, is generally lower in low income countries and in women with a low SES or educational level [76, 181].

This study compares breast cancer presentation, treatment and outcome of patients from two neighboring countries in South East Asia with different levels of development.

Methods:

Data for this study was obtained from the Singapore Malaysia Breast Cancer Hospital Based Registry [1]. This registry combines data from two hospital based registries, i.e., the National University Hospital (NUH) breast cancer registry, (Singapore, high income country) and the University of Malaya Medical Center (UMMC) hospital based registry, (Kuala Lumpur, Malaysia, middle income country).

The NUH breast cancer registry started in 1995 and contains information on 2,449 consecutive breast cancer patients diagnosed between 1990 and 2007 (data for patients diagnosed from 1990-1995 was collected retrospectively).From the NUH registry we selected2,141 patients diagnosed between 1993 and 2007. The UMMC breast cancer registry started in 1993 contains information on 3,320 patients diagnosed between 1993 and 2007. Details on both these registries are described elsewhere [1, 38]. In both centers, patients were monitored through follow-up in the specialist outpatient clinics. Data on mortality were obtained from the hospitals' medical records, as well as active follow-up through the patients' next-of-kin. Follow up for each patient was calculated from the date of diagnosis to the date of death or end of follow up (July 2010 for NUH patients and November 2010 for UMMC patients).

For individual patients, the registry provides information on age at diagnosis, ethnicity (Chinese, Malay, Indian and other), Estrogen Receptor (ER) and Progesterone Receptor (PR) status (if ≥10% of epithelial tumor cells expressing receptors, negative and unknown), stage (*in situ*, I, II, III, IV and unknown), differentiation (good, moderate, poor, unknown), tumor size (continuous), nodal status (pN0, pN1, pN2, pN3 and unknown), regional nodes (0, 1-3, 4-9 and 10 or more). Treatment variables included type of surgery (mastectomy, breast conserving surgery [BCS] and no surgery), radiotherapy (yes/no), chemotherapy (yes/no), hormone therapy (yes/no) and noeadjuvant chemotherapy (yes, no and unknown).

Statistical analysis:

Demographics, tumor characteristics and treatment received by patients at the National University Hospital (Singapore) (n=2,141) or the University of Malaya Medical Center (Kuala Lumpur, Malaysia) (n=3,320) were compared using logistic regression analysis. Age at diagnosis and tumor size (as continuous variables) were presented as a median and compared with Mann Whitney U test.

Proportion of patients receiving adequate (standard) treatment (defined as surgery for patients with stage *in situ*, I, II or III, chemotherapy for patients with ER negative lymph node positive invasive tumors, hormone therapy for patients with ER positive tumors and radiotherapy for patients treated with breast conserving surgery) were compared between the two institutions using the Chi Square Test.

Kaplan Meier analysis and logrank test were used to compare overall survival between countries and Cox regression analysis was used to estimate the adjusted relative risk of all cause mortality for patients treated in Singapore as compared to those treated in

Malaysia. In order to get insight into the factors contributing to survival disparities, we entered all variables, univariately associated with survival, into a multivariate Cox model in a stepwise manner. The first model consisted of crude Hazard Ratios (HRs) representing the relative risk of death of patients from Malaysia as compared to those from Singapore. The second model presented hazard ratios adjusted for age at diagnosis, year of diagnosis and ethnicity. The next model was additionally adjusted for tumor characteristics (i.e. tumor size, grade, nodal status and ER status) and the final model was additionally adjusted for type of surgery, radiotherapy, chemotherapy and hormone therapy.

All analysis were performed using SPSS Version 16 and any p value <0.05 was considered significant.

Results:

The median follow up for the Malaysian and Singaporean patients was 5.1 years and 6.1 years respectively. Malaysian and Singaporean patients presented at similar ages (median age 50 years for both countries). Malaysian patients were less likely to be diagnosed with *in situ* breast cancer than patients from Singapore (Adjusted Odds Ratio (ORadj) 0.2; 95% CI 0.1 to 0..3) and more likely to be diagnosed with advanced disease [(22.3% vs 14.4% respectively for stage III; ORadj 1.6; 95% CI 1.3 to 2.0); 10.8% vs 7.9% respectively for stage IV; ORadj 1.2; 95% CI 1.1 to 1.4)] as compared to Singaporean patients (Table 4.1a). The tumor size at presentation for the Malaysian patients was larger than that of Singaporean patients (median tumor size 30mm compared to 22mm, p <0.001). Malaysian patients were more likely not to undergo surgery for stage I-III disease (9.0% vs 0.6% respectively; p value <0.001) (Table4.1b).Malaysian patients with

invasive, non-metastatic disease were less likely to receive radiotherapy (RT) following BCS as compared to the Singaporean patients (78.0% vs 89.8% respectively, p value <0.001) (Figure 4.1). Malaysian women were just as likely to receive chemotherapy for estrogen receptor (ER) negative lymph node (LN) positive disease (87.6% compared to90.1%, p value >0.05) and hormone therapy for ER positive disease (91.2% compared to 89.1%, p value >0.05) as the Singaporean patients.

Table 4.1a Patient and tumor characteristics by place of diagnosis and the likelihood of these characteristics being associated with being diagnosed in Malaysia as determined by logistic regression.

Variable	Country		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
	Malaysia (N=3,320)	Singapore (N= 2,141)		
Age at diagnosis in years[b]				
Median (Range)	50 (21 to 95)	50 (22 to 93)		
<40	480 (14.5%)	282 (13.2%)	1	1
40-59	2060 (62.0%)	1398 (65.3%)	0.8 (0.7 to 1.0)	1.0 (0.8 to 1.2)
≥60	780 (23.5%)	461 (21.5%)	0.9 (0.8 to 1.1)	1.3 (0.9 to 1.7)
Ethnicity				
Chinese	2112 (63.7%)	1663 (77.7%)	1	1
Malay	733 (22.1%)	242 (11.3%)	2.3 (2.0 to 2.7)	2.0 (1.6 to 2.4)
Indian	423 (12.7%)	112 (5.2%)	2.9 (2.3 to 3.6)	2.7 (2.0 to 3.6)
Other	52 (1.6%)	124 (5.8%)	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.5)
Estrogen Receptor Status*^				
Negative	1188 (44.2%)	747(42.1%)	1	1
Positive	1495 (55.8%)	1027 (57.9%)	0.9 (0.8 to 1.0)	1.1 (0.8 to 1.3)
Unknown	542	165	0.8 (0.4 to 1.4)	0.1 (0.1 to 0.2)
Progesterone Receptor Status*^				
Negative	1044 (50.6%)	770 (43.7%)	1	1
Positive	1019 (49.4%)	992 (56.3%)	0.7 (0.6 to 0.8)	0.7 (0.6 to 0.8)
Unknown	1162	177	2.1 (1.8 to 2.4)	2.6 (1.9 to 3.0)
Stage				
In Situ	95 (2.9%)	202 (10.0%)	0.3 (0.2 to 0.4)	0.2 (0.1 to 0.3)
I	718 (21.6%)	502 (24.7%)	1	1
II	1406 (42.4%)	870 (42.9%)	1.1 (0.9 to 1.3)	0.8 (0.6 to 1.0)
III	736 (22.3%)	293 (14.4%)	1.7 (1.4 to 2.0)	1.6 (1.3 to 2.0)
IV	351 (10.8%)	162 (7.9%)	1.5 (1.2 to 1.8)	1.2 (1.1 to 1.4)
Unknown	14	112	0.1 (0.1 to 0.2)	0.1 (0.1 to 0.2)
Cell differentiation*^a#				
Good	232 (10.2%)	239 (13.9%)	0.6 (0.5 to 0.8)	0.4 (0.3 to 0.9)
Moderate	1130 (49.8%)	769 (44.7%)	1	1
Poor	902 (40%)	724 (41.2%)	0.8 (0.7 to1.0)	0.5 (0.4 to 0.8)

Unknown	961	207	3.1 (2.6 to 3.7)	2.9 (2.2 to 3.8)
Tumor Size*^[a]				
Median (Range) in mm	30 (2 to 370)	22(3 to 200)		
0.1 to 2 cm	947 (30.2%)	587(44.4%)	0.6 (0.5 to 0.7)	0.9 (0.7 to 1.1)
2.1 to 5 cm	1432 (45.7%)	571 (43.2%)	1	1
>5 cm	755 (24.1%)	163 (12.4%)	1.8 (1.5 to 2.2))	1.5 (1.1 to 1.9)
Unknown	91	618	0.1 (0.1 to 0.2)	0.1 (0.1 to 0.2)
Regional nodes examined^				
0	19 (0.5%)	154 (7.9%)	0.1 (0.1 to 0.2)	0.1 (0.1 to 0.2)
1-3	70 (2.2%)	128 (6.6%)	0.3 (0.2 to 0.4)	0.3 (0.2 to 0.4)
4-9	570 (17.7%)	241 (12.4%)	1.4 (1.2 to 1.7)	1.5 (1.2 to 1.8)
≥10	1861 (57.7%)	1160 (59.8%)	1	1
Unknown	707 (21.9%)	256 (13.2%)	1.7 (1.4 to 2.0)	5.8 (3.1 to 10.8)
Regional nodes positive*^[a] (Nodal Status)				
pN0	1383 (53.0%)	856 (55.7%)	1	1
pN1	634 (24.3%)	373 (24.3%)	1.0 (0.9 to 1.2)	0.8 (0.6 to 0.9)
pN2	342 (13.2%)	199 (13.1%)	1.0 (0.8 to 1.2)	0.7 (0.5 to 0.9)
pN3	246 (9.5%)	107 (6.9%)	1.4 (1.1 to 1.8)	1.1 (0.8 to 1.5)
Unknown	620	404	0.9 (0.8 to 1.1)	0.1 (0.1 to 0.3)

* Valid proportions have been calculated
^ Excluding *In situ* patients
[a] Logistic regression model adjusted for age, ethnicity, ER status and PR status. All other ORs are adjusted for age, ethnicity, ER status, PR status and stage.
[#] Mann Whitney U test p value <0.001
[b] Mann Whitney U test p value >0.05

Table 4.1b Treatment administered to stage I, II and III patients from Malaysia and Singapore and the likelihood of treatment being associated with being diagnosed in Malaysia as determined by logistic regression.

Variable	Country		Unadjusted OR (95% CI)	Adjusted OR (95% CI)
	Malaysia (N=2,860)	Singapore (N= 1,665)		
Surgery Type				
No surgery	256 (9.0%)	10 (0.6%)	19.9 (10.9 to 37.9)	20.6 (11.4 to 50.2)
Mastectomy	1963 (68.6%)	1155 (69.4%)	1	1
Breast Conserving	641 (22.4%)	500 (30.0%)	1.0 (0.9 to 1.5)	0.6 (0.5 to 1.0)
Radiotherapy				
No	1355 (47.4%)	754 (45.3%)	1	1
Yes	1505 (52.6%)	911(54.7%)	0.9 (0.8 to 1.0)	0.9 (0.7 to 1.0)
Chemotherapy				
No	1061 (37.2%)	635 (38.1%)	1	1
Yes	1799(62.8%)	1030(61.9%)	1.0 (0.9 to 1.1)	1.4 (1.3 to 1.7)
Hormone Therapy				
No	1189 (41.6%)	540 (32.4%)	1	1
Yes	1671 (58.4%)	1125 (67.6%)	0.6 (0.5 to 0.7)	0.5 (0.7 to 1.0)
Neoadjuvant Chemotherapy*				
No				
Yes	2662 (93.1%)	1481(90.9%)	1	1
Unknown	198 (6.9%)	150 (9.1%)	0.7 (0.5 to 1.0)	0.3 (0.2 to 0.4)
	2	36	0.1 (0.1 to 0.2)	0.1 (0.1 to 0.2)

* Valid proportions have been calculated
All ORs are adjusted for age, ethnicity, ER status, PR status and stage

Two hundred and nine (10.8%) Singaporean patients and 610 (18.9%) Malaysian patients with invasive breast cancer received incomplete locoregional treatment defined as no surgery or BCS without RT or ER negative LN positive without chemotherapy or ER positive without hormone therapy.

The 5 year overall survival for Malaysian patients was substantially lower than that of Singaporean patients (69.0% compared to80.0%, logrank test p <0.001) (Figure 4.2). Overall survival estimates for both countries improved with calendar time with the improvement in survival being stronger for Malaysia (5 year survival estimates for Malaysians diagnosed between 1993-2000 and 2001-2007 were 62.0% and 73.0% respectively while for the Singaporeans, estimates were 79.0% and 81.0% respectively) (Table 4.2).

Univariate Cox regression analysis showed that besides country of diagnosis (i.e. Singapore or Malaysia), age at diagnosis, period of diagnosis, ethnicity, ER status, PR status, type of surgery, radiotherapy, chemotherapy, hormone therapy, regional nodes examined, nodal status, cell differentiation (grade), tumor size and receipt of neoadjuvant chemotherapy were significantly associated with risk of all cause mortality.

Table 4.2 Five year overall survival estimates for Malaysia and Singapore patients (excluding *in situ* patients)

Country / 5 year survival estimate	Malaysia (N= 3,225)	Singapore (N=1,939)
Overall	69.0% (67.0% to 71.1%)	80.0% (79.0% to 80.9%)
By Year		
1993-2000	62.0% (59.4% to 64.5%)	79.0% (77.5% to 80.5%)
2001-2007	73.0% (71.8% to 74.6%)	81.0% (80.1% to 82.9%)
By Stage		
Stage I	93.0% (91.9% to 94.1%)	98.0% (97.0% to 99.0%)
Stage II	79.0% (77.8% to 80.3%)	85.0% (83.7% to 86.3%)
Stage III	52.0% (49.4% to 54.6%)	66.0% (62.5% to 69.6%)
Stage IV	12.0% (6.8% to 17.1%)	23.0% (16.6% to 29.5%)

Figure 4.1 Country stratified differences in proportion of: Stage *in situ*, I, II and III patients receiving surgery, ER negative LN positive patients receiving chemotherapy, ER positive patients receiving hormone therapy, patients receiving BCS followed by radiotherapy and ER positive LN positive patients receiving chemotherapy. (Excluding metastatic cases and cases with unknown stage)

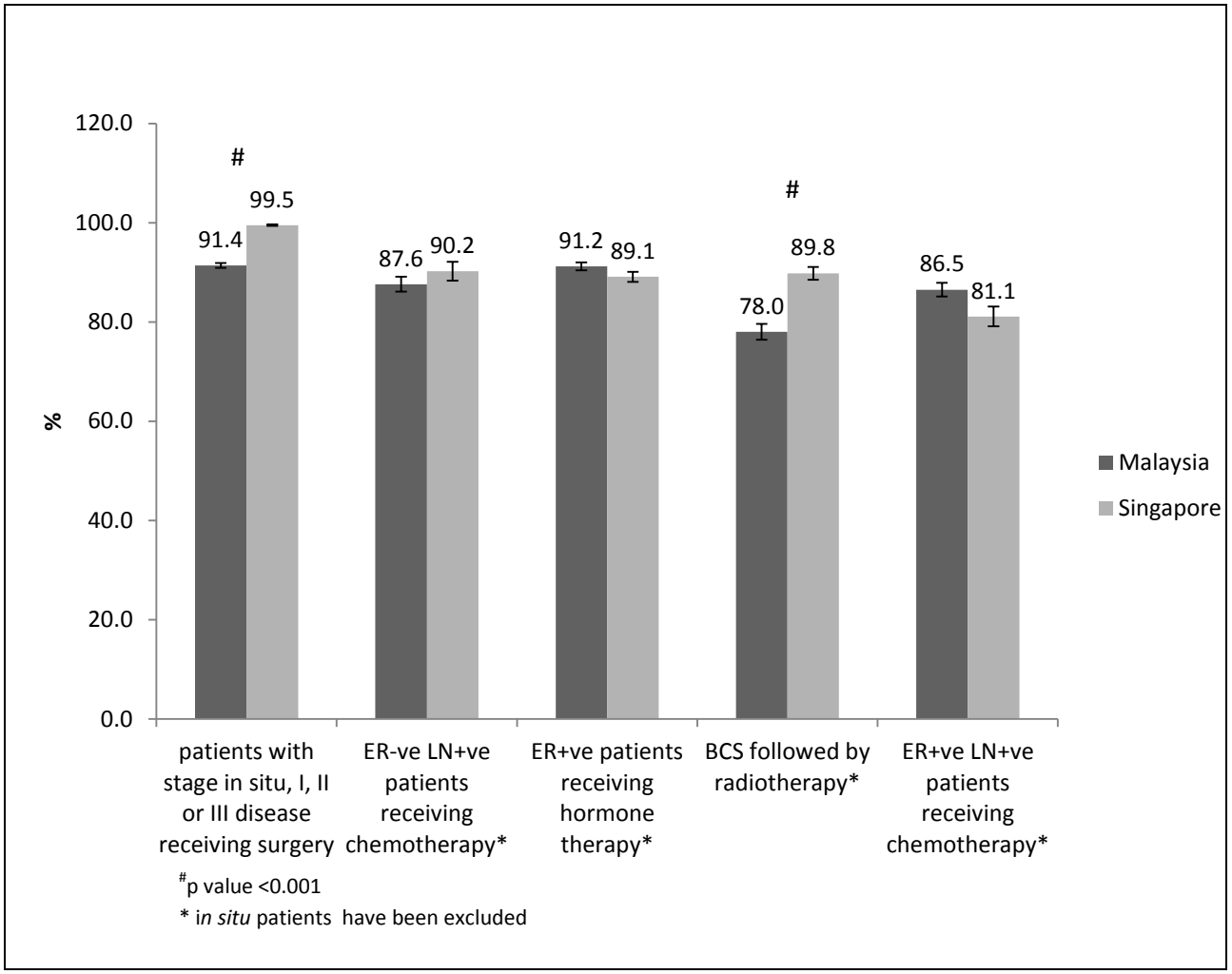
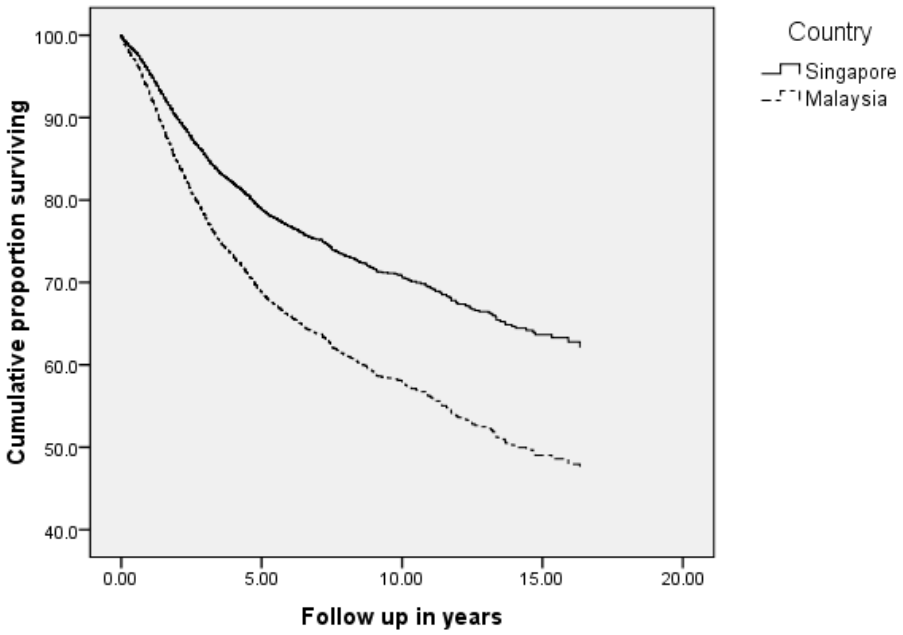


Figure 4.2 Kaplan Meier survival curves for Malaysia and Singapore (excluding *in situ* patients)



Logrank test p value <0.001

Country	Interval(years)	1	2	3	4	5	6	7	8	9	10
Malaysia	Number at risk	3,225	2,965	2,710	2,466	2,020	1,641	1,313	1,076	826	624
	Number of deaths	257	255	213	145	104	60	33	36	22	12
Singapore	Number at risk	1,939	1,788	1,578	1,465	1,359	1,171	996	791	593	417
	Number of deaths	52	97	74	51	62	28	17	19	10	1

Multivariate Cox regression analysis showed that country of diagnosis remained independently and significantly associated with survival, even after adjusting for tumor characteristics and treatment in a stepwise manner (Table 4.3a), with patients diagnosed and treated in Malaysia having a 67% higher mortality risk than patients diagnosed in Singapore (Adjusted Hazard Ratio [HRadj]1.67, 95% CI 1.44 to 1.92) (Table 4.3b). Patients diagnosed in both countries receiving incomplete locoregional treatment or no

surgery for invasive disease had similar risk of death while Malaysian patients receiving chemotherapy or presenting with node negative disease had a significantly higher risk of death as compared to their Singaporean counterparts (Table 4.3c).

Table 4.3a Stepwise modeling for Cox Regression analysis for all cause mortality of Malaysian patients compared to Singaporean patients

Model	Hazard Ratios adjusted for stated variables
a	Unadjusted Hazard Ratio representing relative risk of death of Malaysian patients as compared to Singaporean patients
b	Hazard Ratio adjusted for, year of diagnosis, age and ethnicity
c	Hazard Ratio adjusted for variables in 'b' plus tumor size, grade, nodal status and ER status
d	Hazard Ratio adjusted for variables in 'c' plus surgery type, radiotherapy, chemotherapy and hormone therapy

Table 4.3b Cox regression models for all cause mortality of Malaysian patients compared to Singaporean patients (excluding *in situ* patients)

	Total	Singapore	Malaysia
Number of patients Number of deaths	5164 1606	1939 423	3225 1183
Hazard Ratio (95% CI)[a]		1 (ref)	1.72(1.54 to 1.93)
Hazard Ratio (95% CI)[b]		1 (ref)	1.71 (1.53 to 1.92)
Hazard Ratio (95% CI)[c]		1 (ref)	1.71 (1.51 to 1.94)
Hazard Ratio (95% CI)[d]		1 (ref)	1.67 (1.44 to 1.92)

Discussion:

This study highlights important differences in survival between breast cancer patients from tertiary hospitals in Singapore (high income country)and Malaysia (middle income country), Despite only small differences in way of presentation and access to treatment,

Malaysian patients more than 70% likely to die within the first five years after diagnosis. This increased risk was not explained by more advanced staging and less optimal treatment.

Breast cancer survival disparities between countries have been well documented and studies have shown that patients from countries with enhanced diagnostic facilities and up to date treatment options have better survival rates [182-187]. Although incidence rates of breast cancer are lower in middle income countries as compared to high income countries, 55% of breast cancer deaths occur in low income countries and this can be attributed to two major determinants namely, late stage at presentation and inadequate treatment [188, 189]. In a comparative study of 12 countries in Africa, Asia and Central America, differences in cancer outcome correlated with level of development of health services [190].

Differences in presentation between Singaporean and Malaysian patients could be a result of a higher level of health systems development in Singapore, where screening is more commonplace and diagnostic and healthcare facilities are advanced as compared to Malaysia. However, social and cultural factors are likely to play a role as well. In Malaysia, factors like lower awareness about the disease and or inhibition to approach physicians due to cultural taboos are more prevalent [35].

Like for presentation, we only found small differences in treatment patterns between patients from the two countries. Singaporean patients were more likely to receive standard treatment (radiotherapy in case of treatment with BCS, and surgery for non metastatic disease) as compared to the Malaysians. However, the differences were small.

Table 4.3c Subgroup analysis - Multivariate Cox regression models for all cause mortality for Malaysian patients compared to Singaporean patients (excluding *in situ patients*)

Subgroups	Singapore			Malaysia		
		N	N death		N	N death
Estrogen Receptor Positive HRadj[a]	1(Ref)	1048	178	1.72 (1.38 to 2.14)	1540	387
Estrogen Receptor Negative HRadj[a]	1(Ref)	771	192	1.65 (1.33 to 2.05)	1212	460
No Surgery^ HRadj[b]	1(Ref)	127	78	0.99 (0.37 to 2.62)	478	375
Surgery given^ HRadj[b]	1(Ref)	2014	349	1.81 (1.53 to 2.15)	2842	815
Stage I and II HRadj[c]	1(Ref)	1372	175	1.65 (1.36 to 1.99)	2124	468
Stage III and IV HRadj[c]	1(Ref)	455	208	1.57 (1.33 to 1.86)	1087	707
Incomplete locoregional treatment*^ HRadj[d]	1(Ref)	245	103	0.88 (0.45 to 1.70)	632	400
Complete locoregional treatment#^ HRadj[d]	1(Ref)	1896	324	1.84 (1.55 to 2.20)	2688	790
Node negative^ HRadj[e]	1(Ref)	936	79	2.00 (1.42 to 2.81)	1432	212
Node positive^ HRadj[e]	1(Ref)	681	193	1.65 (1.34 to 2.04)	1222	542
Chemotherapy not given^ HRadj[f]	1(Ref)	1021	187	1.66 (1.20 to 2.29)	1294	435
Chemotherapy given^ HRadj[f]	1(Ref)	1120	240	1.73 (1.42 to 2.11)	2026	755

[a] Cox model adjusted for age, ethnicity, year of diagnosis, tumor size, grade, nodal status, surgery type, radiotherapy, chemotherapy, hormone therapy, distant metastasis

[b] Cox model adjusted for age, ethnicity, year of diagnosis, tumor size, grade, nodal status, ER status, radiotherapy, chemotherapy, hormone therapy, distant metastasis

[c] Cox model adjusted for age, ethnicity, year of diagnosis, grade, ER status, radiotherapy, chemotherapy, Surgery type, hormone therapy

[d] Cox model adjusted for age, ethnicity, year of diagnosis, tumor size, grade, nodal status, ER status

[e] Cox model adjusted for age, ethnicity, year of diagnosis, tumor size, grade, ER status, radiotherapy, chemotherapy, Surgery type, hormone therapy,

[I] Cox model adjusted for age, ethnicity, year of diagnosis, tumor size, grade, nodal status, ER status, radiotherapy, Surgery type hormone therapy,
[*] Incomplete locoregional treatment defined as no surgery or breast conserving surgery without radiotherapy or ER negative lymph node positive without chemotherapy or ER positive without hormone therapy
[#] Complete locoregional treatment defined as mastectomy or breast conserving surgery followed by radiotherapy or ER negative lymph node positive with chemotherapy or ER positive with hormone therapy.
^ Only stage I, II and III patients included

Large differences in breast cancer survival rates between Singaporean and Malaysian patients highlight a scope for improvement in the management of breast cancer in Malaysia. Several factors such as differences in population structure (life expectancy) [191, 192], low access to screening [57, 67], lower socioeconomic status [181, 193], low access to high quality healthcare[35], poor treatment compliance[120, 194], poor lifestyle after diagnosis [195]among Malaysians could explain the disparities in survival compared to Singaporean patients. While mortality risks of patients who did not receive standard treatment (incomplete locoregional treatment or no surgery) were similar in both groups, Malaysian patients receiving complete locoregional treatment had 84% increased risk of mortality compared to Singapore patients. This could be due to differences in treatment regime administered to patients from the two countries, especially the choice of chemotherapeutic agents, or perhaps even the extent of surgery. Also differences in compliance with treatment may explain part of the difference. However, details of chemotherapeutic agents or duration of therapy were not available and hence gauging the impact of differences in chemotherapy regimen on survival could not be made. Several studies have shown that type of treatment received is associated with breast cancer survival [32, 107, 196, 197] but from our study, it is unlikely that differences in receipt of treatment between patients from the two countries would explain the survival differences as the stepwise adjusted Hazard Ratios (adjusting for demographic characteristics

followed by adding tumor characteristics and finally treatment to the Cox model) did not differ significantly from the unadjusted HR.

Another possible explanation for the survival differences could be due to differences in screening practices between the two countries. Singapore has implemented a structured screening program for all women aged 50 years to 69 years from 2002 [55], although the response rate for the same is not too high. In contrast, Malaysia practices only opportunistic screening[198]. Thus large number of *in situ* patients from Singapore as compared to Malaysia, suggests that lead time bias (artificial prolonging of survival time due to early detection) could also account for longer survival for Singaporean patients when compared to Malaysian patients.

We acknowledge that our study suffers from several shortcomings, including a relatively short follow up time for patients from both countries.In addition, we assessed all cause mortality as our end point as no data on cause of death was available. Thirdly, being a hospital based study rather than a population based study, extrapolate these findings to the general population of the respective countries might not be feasible. However, the catchment area of NUH, Singapore, which treats an estimated 10% of breast cancer cases in Singapore, sees patients with demographics that are not different from other areas of the country [38]. UMMC in Kuala Lumpur, Malaysia, serves a predominantly middle income urban population and hence our findings may not necessarily reflect the overall situation of breast cancer in Malaysia [1], for example, the presentation of breast cancer in the rural Malaysian settings for instance, may be more advanced than in our study [1]. Another limitation of our study is that some prognostic factors, such as co-morbidity, body mass index (BMI), HER2/neu status, and local/systemic recurrence were largely

missing and hence their impact on our results will be difficult to gauge. Also, the impact of certain factors such as SES, treatment compliance and education level on the differences in survival between Singaporean and Malaysian patients was not assessed.

Conclusion:

Differences in way of presentation and treatment of patients with breast cancer were small except for certain tumor characteristics like tumor size and stage at presentation between Singaporean and Malaysian patients. Patients from Malaysia present slightly more often with advanced stage and unfavorable characteristics. The overall survival of breast cancer patients from Malaysia is much lower than that of Singaporean patients. Poorer compliance with treatment, unfavorable life style factors and competing risks can potentially explain the higher mortality risk of Malaysian breast cancer patients and these factors need to be further explored.

Differences in outcome between Singaporean and Surveillance Epidemiology and End Results (SEER;USA) breast cancer patients

Introduction:

Breast cancer incidence rates are on the rise in South East Asia, where in some countries rates have tripled over the last three decades [5, 16, 40]. Although incidence rates of breast cancer are still higher in Western countries than Asian countries, rates in Asia are increasing more sharply. Hence it is quite likely that in the near future, a majority of breast cancer patients will be of Asian origin.

Differences in breast cancer survival rates between countries have been studied extensively [39, 182, 183, 199, 200] and several studies have compared the breast cancer survival rates of Asian and Western countries [39, 186, 201-203]. Some of these studies showed poorer survival rates for Asian women when compared to their Western counterparts [186, 204, 205] while other studies concluded otherwise [201, 206, 207].

Patterns in breast cancer survival are a composite effects of a multitude of factors including predominantly the severity of disease and administration of adequate treatment [208]. Differences in breast cancer survival rates between countries can be attributed to differences in socioeconomic background, health insurance systems, access to early detection, access to and compliance with standard treatment [209-211], variation in tumor biology and lifestyle after treatment [186, 212, 213].

This study aims to highlight differences in presentation and survival of breast cancer patients diagnosed in a tertiary teaching hospital in Singapore compared to those in the US and quantifies the excess mortality among Singaporean patients.

Methods:

For this study we used data from the Breast Cancer Registry of a tertiary teaching hospital in Singapore and the SEER registry [214].

The Breast Cancer Registry of the tertiary teaching hospital in Singapore was established in 1995, through prospective data collection on demographics, tumor characteristics, treatment and follow up of all patients presenting with invasive or *in situ* breast cancer. Data from 1990 to 1995 was collected retrospectively from medical records. Vital status information for a majority of the patients was determined through long term follow up clinics. For those patients that did not undergo regular follow up at the hospital, contact was made via telephone or letter annually. Women were followed until death or end of follow up (31st December 2007), whichever came first. The hospital Breast Cancer Registry has been approved by the respective Institutional Ethics Review Board.

We included all 2,302 patients diagnosed with invasive breast cancer between 1990 and 2007 at the tertiary teaching hospital in Singapore. From the SEER registry, we selected female patients diagnosed with invasive breast cancer during the same period (1990-2007) [214]. The SEER database is a compilation of data on cancer patients (incidence, survival, demographics, cancer site, morphology, stage and follow up) from eighteen geographic areas of the United States, which together represent approximately 26 percent of the US population [215].

Variables of interest included: Age at diagnosis (categorized into <40 years, 40 to 59 years and ≥ 60 years), stage at presentation (I, II, III and IV) and ethnicity [Chinese and

non Chinese (i.e., Malays, Indians and others) for Singapore and non Hispanic Whites and Blacks for US].

Statistical Analysis:

Age and stage at presentation were compared between the Singaporean and SEER patients using the Chi Square test. Five year relative survival estimates were computed according to country, stage, age and ethnicity, using the Singapore population mortality data and the US background population mortality data respectively. For details on relative survival, refer to chapter 3.

In addition, relative survival estimates were computed for Singaporean patients by stage and receipt of treatment (Standard treatment: Breast Conserving Surgery (BCS) + Radiotherapy (RT) or Mastectomy +/- RT or Estrogen Receptor (ER) positive + Hormone therapy or ER negative Lymph Node (LN) positive + Chemotherapy. Non Standard treatment: BCS alone or no surgery or ER positive without Hormone therapy or ER negative LN positive without Chemotherapy). Relative survival is defined as the ratio of the proportion of observed survivors in cohort of cancer patients to the proportion of expected survivors in the background population with same sex, age and period distribution [156].

In order to estimate the excess mortality among Singaporean patients within 5 years of diagnosis, we applied the 5 year relative survival rates of the SEER patients to the Singaporean patients.We adopted an approach used by Abdel-Rehman et al and Richards et al [216, 217] and applied the following formulae to calculate the excess mortality in Singapore [216, 217] :

Excess mortality = Observed mortality – Expected mortality

Observed mortality = (complement of 5 year Relative Survival Rate for Singapore) X number of patients

Expected mortality = (complement of 5 year Relative Survival Rate for SEER) X number of patients

Results:

The median age of the 2,302 Singaporean breast cancer patients was 50 years (range 22 years to 93 years) and for the 624,942 SEER patients was 61 years. Patients and tumor characteristics and treatment received by Singaporean patients are listed in table 4.4. A higher proportion of Singaporean patients presented with late stage disease as compared to SEER patients (9.1% compared to 4.9% for stage IV disease respectively, $p < 0.001$) (Table 4.5).

Ethnic distribution of the two countries followed a similar pattern with each country having an ethnic majority (Non-Hispanic Whites (83.7%) for the USA and Chinese (77.7%) for Singapore) and other ethnic minorities (Blacks, Hispanic Whites, Asia Pacific islanders for USA and Malays and Indians for Singapore).

Table 4.4 Patient and tumor characteristics and treatment received by patients at a tertiary teaching hospital in Singapore

Variable	Number (%) (Total N = 2,302)
Ethnicity	
Chinese	1789 (77.7%)
Malay	257 (11.2%)
Indian	117 (5.1%)
Other	139 (6.0%)
Estrogen Receptor Status	
Negative	799 (34.7%)
Positive	1085 (47.1%)
Unknown	418 (18.2%)
Progesterone Receptor Status	
Negative	828 (36.0%)
Positive	1042 (45.3%)
Unknown	432 (18.8%)
Cell differentiation	
Good	261 (11.3%)
Moderate	818 (35.5%)
Poor	796 (34.6%)
Unknown	427 (18.5%)
Tumor Size	
Median (Range) in mm	23 (3 to 200)
0.1 to 2 cm	605 (26.3%)
2.1 to 5 cm	583 (25.3%)
>5 cm	1025 (44.3%)
Unknown	89 (3.9%)
Regional nodes examined	
0	199 (8.6%)
1-3	136 (5.9%)
4-9	273 (11.9%)
≥10	1226 (53.3%)
Unknown	468 (20.3%)
Regional nodes positive (Nodal Status)	
pN0	935 (40.6%)
pN1	393 (17.1%)
pN2	214 (9.3%)
pN3	111 (4.8%)
Unknown	649 (28.2%)
Surgery Type	
No surgery	164 (7.1%)
Mastectomy	1531 (66.5%)
Breast Conserving	607 (26.4%)
Radiotherapy	
No	1259 (54.7%)
Yes	1043 (45.3%)
Chemotherapy	
No	1062 (46.1%)
Yes	1240 (53.9%)
Hormone Therapy	
No	962 (41.8%)
Yes	1340 (58.2%)
Neoadjuvant Chemotherapy	
No	1949 (84.7%)
Yes	249 (10.8%)
Unknown	104 (4.5%)

Table 4.5 Distribution of age and stage at diagnosis for Surveillance Epidemiology and End Results (SEER) and Singaporean patients

	SEER, United States (n= 624,952)	**Tertiary teaching hospital in Singapore (n=2,302)**	**Chi Sq test P value**
Stage*			<0.001
I	182,586 (48.7%)	570 (26.7%)	
II	146,984 (39.3%)	1039 (48.7%)	
III	26,868 (7.1%)	331 (15.5%)	
IV	18,495 (4.9%)	195 (9.1%)	
Unknown	250,039	167	
Age			<0.001
Median	61 years	50 years	
0 to 39 years	34,982 (5.5%)	316 (13.7%)	
40 to 59 years	251,387 (40.2%)	1469 (63.8%)	
≥60 years	338,603 (54.3%)	517 (22.5%)	
* indicates valid proportions have been calculated (i.e., not considering unknowns)			

After a median follow up of 2.4 years, five year relative survival estimates for stage I diseasewere comparable for the two populations (99.6% for Singapore and 100% for SEER) (Table 4.6) . However, for more advanced stages, five year relative survival probabilities were lower for Singapore patients than for SEER patients (81.3% compared to 87.8% for stage II, 50.2% compared to 60.0% for stage III and 13.6% compared to 21.7% for stage IV respectively). Age stratified five year relative survival esimates were also poorer for Singaporean patients as compared to SEER patients for each age stratum (73.9% compared to 81.6% for patients <40 years at diagnosis, 77.2% compared to 88.5% for patients aged 40 to 59 years and 68.2% compared to 89.4% for patients aged ≥60 years respectively) (Table 4.6). For Singaporean patients receiving standard treatment, the 5 year overall relative survival estimate was 78.4% compared to 26.6% for the patients not receiving non standard treatment (Table 4.6). Analysis based on stage stratification and receipt of treatment showed large differences in relative survival

estimates with patients within each stage strata having substantially higher survival rates when treated with standard treatment as compared to those treated withnon standard treatment. Also, patients receiving standard treatment have survival rates similar to SEER patients especially for late stage (stage III and IV) disease (Table 4.6).

Table 4.6 Five year relative survival estimates by stage and age for SEER, USA and a tertiary teaching hospital in Singapore.

	(5 year relative survival estimates)					
	SEER, United States	**Tertiary teaching hospital, Singapore**				
	Overall	Overall	Standard treatment	**N**	Non standard treatment	N
Stage						
All stages*	88.8% (88.6% to 88.9%)	73.8% (70.5% to 77.1%)	78.4% (75.5% to 81.0%)	1921	26.6% (18.5% to 35.5%)	214
I	100%	99.6% (96.1% to 101.6%)	100% (96.6% to 101.8%)	542	84.7% (27.7% to 99.0%)	28
II	87.8% (87.5% to 88.0%)	81.3% (77.5% to 84.6%)	82.8% (79.0% to 86.0%)	989	39.5% (16.0% to 63.0%)	50
III	60.0% (50.3% to 60.7%)	50.2% (41.9% to 58.1%)	52.8% (44.1% to 60.9%)	313	7.6% (1.0% to 38.2%)	18
IV	21.7% (21.0% to 22.4%)	13.6% (7.7% to 21.4%)	18.8% (8.6% to 32.3%)	77	9.9% (3.7% to 20.0%)	118
Age (years)						
0 to 39	81.6% (81.4% to 81.8%)	73.9% (66.9% to 79.6%)	76.4% (68.7% to 82.4%)	281	33.4% (12.5% to 56.1%)	35
40 to 59	88.5%(88.4 % to 88.6%)	77.2% (74.0% to 80.1%)	80.8% (77.4% to 83.8%)	1301	21.4% (11.9% to 32.8%)	168
≥60	89.4% (89.3% to 89.5%)	68.2% (61.1% to 74.6%)	72.3% (64.3% to 79.3%)	414	34.4% (18.5% to 52.8%)	103
*Excluding stage unknown Standard treatment: BCS +RT or Mastectomy +/- RT or ER positive + Hormone therapy or ER negative LN positive + Chemotherapy Non Standard treatment: BCS alone or no surgery or ER positive w/o Hormone therapy or ER negative LN positive w/o Chemotherapy						

Non-Hispanic White SEER patients had the highest five year relative survival probabilities while the Non Chinese (Singaporean) had the worst survival estimates (Figure 4.3). These differences persisted after stage stratification (Table 4.7).

Table 4.7 Five year relative survival estimates by ethnicity for SEER, USA and a tertiary teaching hospital in Singapore.

Ethnicity / **Stage**	**SEER, United states**		**Tertiary teaching hospital in Singapore**	
	White (n=523,399)	**Black (n= 54,832)**	**Chinese (n=1,724)**	**Non Chinese (n=504)**
All stage	89.7% (89.5% to 89.8%)	76.5% (75.9% to 77.0%)	77.8% (74.8% to 80.5%)	62.2% (55.6% to 68.2%)
Stage I	100%	96.8% (96.0% to 97.5%)	99.8% (95.8% to 101.7%)	98.8% (81.9% to 101.4%)
Stage II	88.6% (88.4% to 88.9%)	80% (79.1% to 80.8%)	83.3% (79.1% to 86.9%)	72.9% (62.8% to 80.9%)
Stage III	62.6% (61.8% to 63.4%)	44.5% (42.6% to 46.4%)	53.1% (43.3% to 62.1%)	41.9% (25.9% to 57.2%)
Stage IV	23.1% (22.3% to 23.9%)	14.0% (12.5% to 15.6%)	14.2% (7.0% to 24.1%)	11.4% (3.5% to 24.6%)

Figure 4.3 Relative survival curves for women diagnosed with breast cancer in Singapore or USA between 1990 and 2007 by ethnicity.

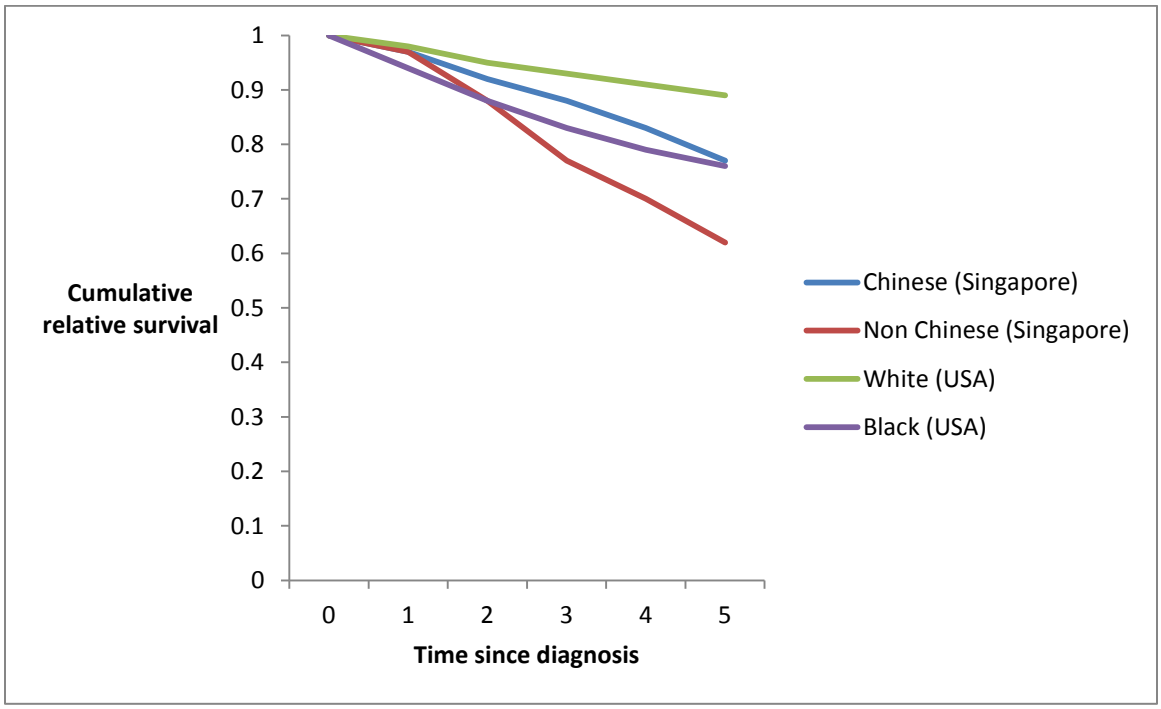
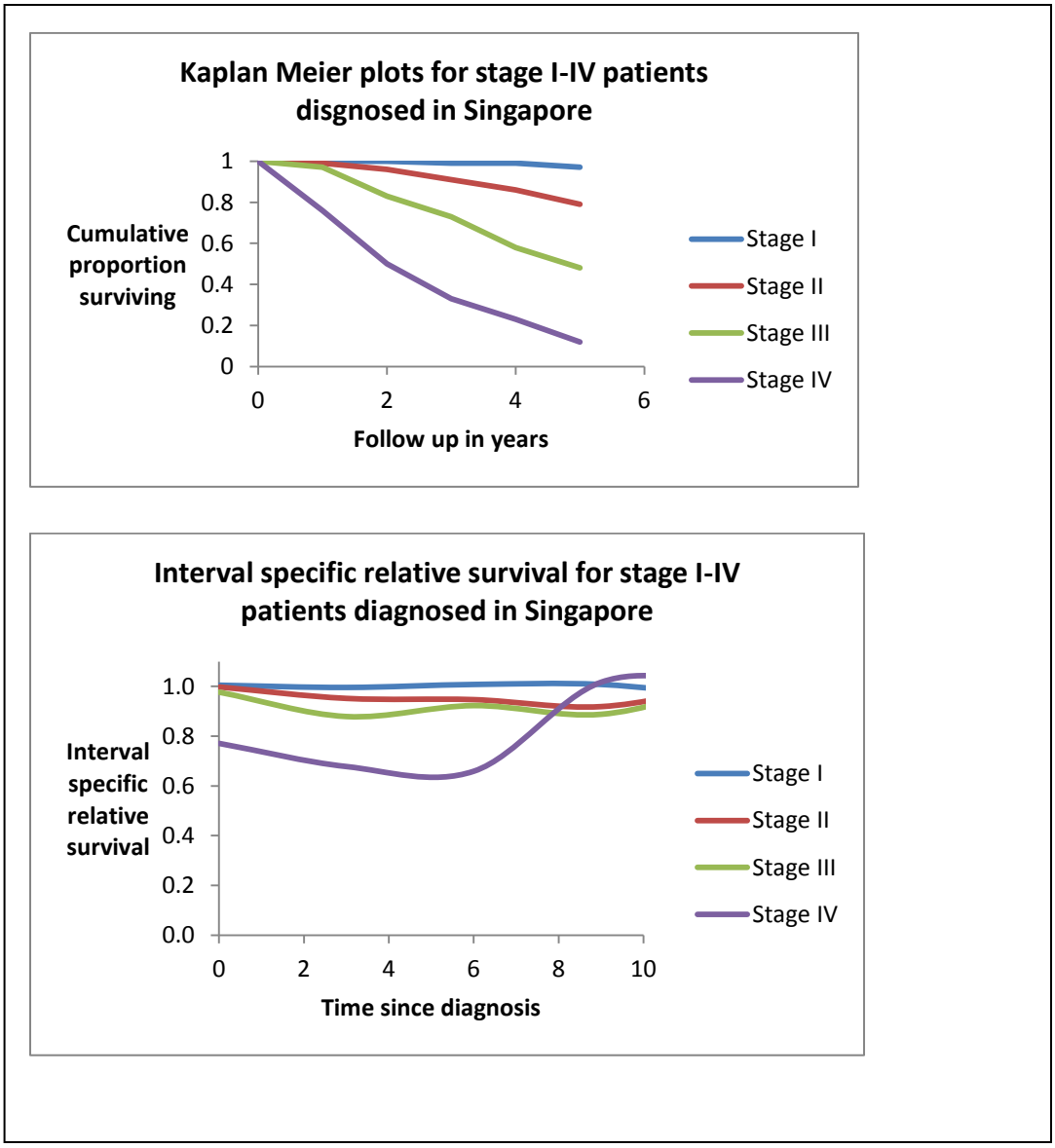


Figure 4.4 shows the Kaplan Meier survival plots for the patients diagnosed at in Singapore stratified by stage. Increasing stage decreases overall survival probability. Additionally, by plotting the conditional (interval specific) relative survival against the time since diagnosis, one can estimate the instantaneous relative survival rate after having survived for a certain number of years. The curve for stage IV patients, for example, reaches an interval specific relative survival rate of 1 following eight years from the date of diagnosis suggesting that if a woman with stage IV disease survives for eight years, her instantaneous survival rate will the same as that of a matched woman in the general population.

Table 4.8 Excess mortality at five years among Singaporean patients.

Variable	Number of cases diagnosed with breast cancer in Singapore	Observed mortality 5 years from diagnosis (Using the Singapore 5 year RSR)	Expected mortality 5 years from diagnosis (Using the SEER 5 year RSR)	Excess mortality (as per formula in text)
Stage				
I	543	2	0	2
II	1015	194	126	68
III	324	165	132	33
IV	184	168	152	16

Figure 4.4 Kaplan Meier plots and interval specific relative survival plots for stage I-IV breast cancer patients diagnosed in Singapore.



For women with stage II, III and IV disease in Singapore, we observed differences in estimated excess mortality (computed using Singaporean patients' 5 year RSRs) and expected excess mortality (computed using the SEER patients' 5 year RSRs) (Table 4.8) indicating that some deaths within each stage strata could be reduced if Singapore achieved similar stage-specific relative survival as the USA. Had the SEER stage-specific survival rates been reached in Singapore, 410 instead of an estimated 529 breast cancer deaths would have been observed (reduction of 22.4%).

Discussion:

This study shows marked differences in breast cancer presentation and survival between Singaporean and SEER patients with Singaporean patients being more likely to be diagnosed at a younger age and at a later stage compared to the US patients. Singaporean patients had poorer overall 5-year RSRs as well as poorer outcome for late stage disease and for all age groups. Ethnic differences in survival were similar between the two countries with the ethnic minorities having poorer outcome as compared to the ethnic majority in their respective country. The excess mortality among Singaporean breast cancer patients when compared to the SEER patients was more than 20%.

Differences in age at presentation can be explained by the fact that the Singaporean population is predominantly young with only 18% of the breast cancer cases being diagnosed above the age of 65 years in the last two decades [32, 40]. In contrast, nearly 50% of all breast cancer cases in USA occur in women aged 65 years or more [218, 219]. In addition, postmenopausal breast cancer risk is relatively low among Singaporean

patients as compared to their Western counterparts likely due to differences in reproductive patterns, hormone replacement therapy use, screening and lifestyle [220].

Later stage at presentation for the Singaporean patients could reflect the decreased awareness of the Singaporeans regarding breast cancer and its treatment as well as limited knowledge about the benefits of early detection. Cultural issues among South East Asian women such as fatalism and cultural taboos preventing women from being screened may also explain the difference in stage at presentation [30]. In Singapore, the prevalence of cancer misconceptions and limited knowledge about cancer warning signs and screening are widespread [221] and uptake of mammography screening is low as compared to the US [55] .

Crude overall differences in outcome between American and Singaporean patients were large with the Singaporean patients having poorer five year relative survival estimates for each stage (except stage I) and all age groups. Very young age at breast cancer diagnosis carries a poor prognosis. Since almost 14% of the patients diagnosed at the tertiary teaching hospital in Singapore were below the age of 40 years as compared to 5.5% from the SEER database, some of the observed survival difference may be explained by differences in age distribution [222, 223]. Differences in survival between older patients from the two countries can in part be explained by the fact that older Asian patients may be more likely to decline treatment due to cultural and financial reasons [32]. Additionally, 34.7% of the Singaporean patients presented with estrogen receptor (ER) negative tumors whose survival is known to be poor when compared to ER positive patients [224]. In comparison 18.6% of the SEER breast cancer patients (diagnosed between 1990 and 2001) presented with ER negative tumors [225]. This difference in ER

status at presentation could also explain the difference in survival between patients from the two countries. Several other possible explanations for the survival disparities between patients from the two regions could be the variations in disease aggressiveness [226], suboptimal and lower compliance with treatment for Singaporean patients, differences in health seeking behavior, differences in life style factors after cancer, and financial and cultural reasons inhibiting Singaporean patients to opt for optimal treatment. South East Asian patients are known to have a strong belief in traditional medicine [30, 227] and when it comes to treatment, the patient usually involves her family members. This in turn could lead to a delay in appropriate therapeutic intervention, increasing disease severity and thus affecting the survival probabilities for patients from this region. Lead time bias due to more prevalent screening in the West compared to Singapore could also account for the better survival rates among SEER patients compared to Singaporean patients[57]. These differences in survival highlight a scope for improvement in the management and healthcare of breast cancer in South East Asia.

Differences in survival between ethnic groups of the two countries were similar and these differences showed that the ethnic minorities (Blacks for USA and Non Chinese for Singapore) had poorer survival probabilities than the ethnic majorities. Studies in the West have shown that ethnic minorities have worse outcome after breast cancer diagnosis [228, 229]. The ethnic distribution of Singapore is such that almost 30% of the population is constituted of ethnic minorities, namely Malays and Indians. Ethnic minorities are often of a lower socioeconomic status (SES) and low SES is associated with poor outcome for breast cancer patients[181]. As our study seems to suggest that the ethnic

minorities do perform poorly, this rather large proportion of ethnic minority patients in Singapore could also contribute substantially towards the difference in survival between Singaporean and SEER patients.

Singapore is a developed country with healthcare facilities and access to chemotherapy, biological therapy and surgical interventions being at par with other developed countries [175]. However, lack of disease awareness and benefits of adherence to treatment need to be addressed in order to decrease the annual number of cancer related deaths even though the annual number of new cases is stable or rising [217]. The fall in deaths from breast cancer as seen in many countries [230] can be attributed to improved survival from a combination of earlier diagnosis [231], improved screening [57] and better treatment [232]. Among Singaporean patients, there is room for improvement in the management of breast cancer as evidenced from the fact that 22.4% of the excess mortality among Singaporean patients could have been reduced had the SEER survival rates been reached. This excess mortality among Singaporean patients can be largely attributed to the large proportion (9.2%) of the patients receiving non standard treatment.

We do acknowledge that it is not only stage at presentation that impacts survival and several factors like tumor characteristics, treatment and patients' attitude towards the disease all affect survival, but, a shift in stage at presentation towards earlier stages would account for a proportion of deaths being avoided nonetheless.

We acknowledge that our study suffers from several limitations. The tertiary teaching hospital in Singapore sees about 10% of all breast cancer patients in Singapore and using data from a hospital based registry in Singapore might not allow us to generalize the

findings to the general population of the country. Secondly, our study is limited by short follow up time of the patients. Thirdly, complete information on ER status for the SEER patients was not available. However, the reported difference in proportion between ER negative patients from the two countries was large suggesting that Singaporean patients in general do present with more ER negative disease than the SEER patients. We do acknowledge that residual confounding could also partly explain the differences in survival between the two countries. The increased diagnostic intensity in USA as compared to Singapore will capture 'healthier' patients within the early stage strata (stage I and II) resulting in better survival of American patients. However, this effect is likely to be very small. Lastly, the impact of certain factors on survival such as SES, treatment compliance and cultural and financial barriers to treatment among Singaporean patients was not assessed due to lack of data availability.

Conclusion:

Singaporean breast cancer patients tend to present at an earlier age and with late stage disease as compared to their American counterparts. A stage shift by early detection could significantly reduce the burden of the disease in Singapore. In order to reduce the excess mortality among Singaporean patients, their within stage survival differences need to be reduced. This can be partly achieved by improving the patients' treatment and creating awareness regarding compliance to treatment and its benefit in terms of survival. Possible benefit of early detection and broadening health seeking behavior among Singaporean breast cancer patients are issues that need to be addressed and the possible reasons for excess mortality are questions worth exploring in future research.

Chapter 5 Breast cancer among elderly Singaporean women

Impact of older age on presentation, management and outcome of breast cancer in the multi-ethnic Asian population of Singapore

(Published as "Impact of older age on presentation, management and outcome of breast cancer in the multi-ethnic Asian population of Singapore." In the Journal of Geriatric Oncology 2011)

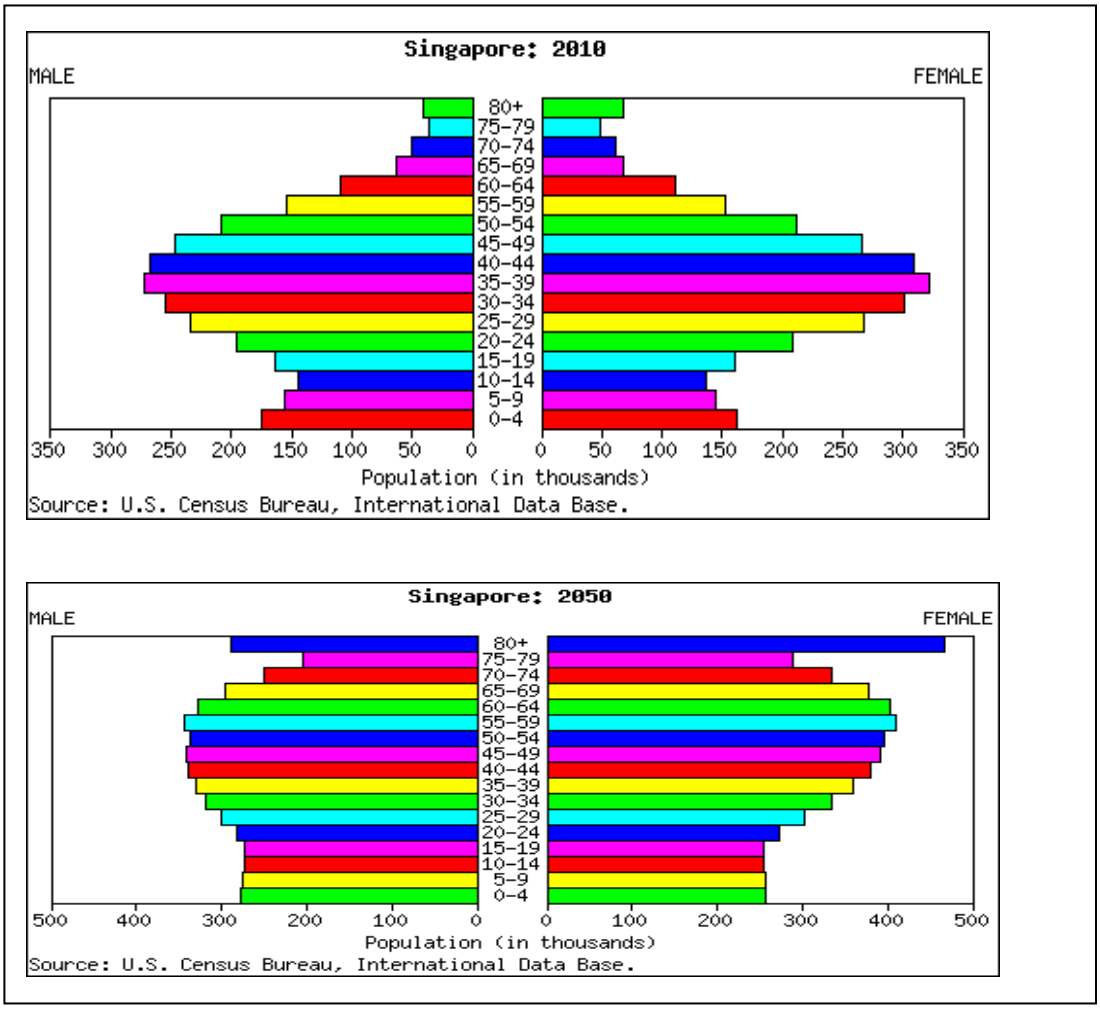
Introduction

Breast cancer is the most common type of cancer and the most common cause of cancer death among women worldwide [233]. Breast cancer is a disease of the elderly [15, 16] with a majority of Caucasian patients being over 65 years of age at diagnosis [17, 18]. In contrast to Europe and the US, where breast cancer incidence rates have stabilized or even decreased, Asian breast cancer rates are increasing dramatically [144, 188, 234]. With the Westernization of Asian countries, one can expect this trend to continue and it is not unthinkable that in the relatively near future, the majority of breast cancer patients will be of Asian ethnicity. In Singapore, breast cancer incidence rates have tripled over the past three decades [5] and today a Singaporean woman has a lifetime risk of 1 in 20 to develop breast cancer [38]. Singapore has seen a shift in peak age of incidence from the mid forties to late fifties [37]. With the increasing incidence of breast cancer in general, the shift towards the older age groups and the aging population (Figure 5.1), it is crucial to have a good understanding of breast cancer in older Asian women.

Elderly patients are more likely to receive non standard treatment [235]. Reasons for this include the higher prevalence of co-morbid conditions, the assumption among clinicians

that breast cancer in older women is less aggressive than that in younger women and their limited life expectancy, thereby decreasing the perceived benefit of adequate treatment. Since older women are less likely to participate in clinical trials [236], little evidence exists on optimal treatment for elderly women.

Figure 5.1 Past and predicted age distribution of Singaporean females.



Several observational studies have suggested that non standard treatment of older breast cancer patients strongly impairs their outcome [107, 219, 237]. Until now, characteristics of older patients, the degree of non standard treatment and the impact on outcome have

hardly been studied in an Asian setting. The purpose of this study was to examine differences in tumor characteristics, treatment and survival among older and younger female breast cancer patients in Singapore.

Patients and Methods

For this study we used data from the Breast Cancer Registry of the National University Hospital (NUH), one of two tertiary teaching hospitals in Singapore [38]. The Breast Cancer Registry was established in 1995, through prospective data collection on demographics, tumor characteristics, treatment and follow up of all patients presenting with invasive or *in situ* breast cancer. Data from 1990 to 1995 was collected retrospectively from medical records. The Breast Cancer Registry has been approved by the NUH Institutional Ethics Review Board. NUH followed a standard management protocol, based on international guidelines, throughout the study period.

In this study we included all women diagnosed with primary invasive or *in situ* (ductal carcinoma in situ only) breast cancer between 1990 and 2007 aged 40 years or above (N = 2195). Variables of interest included age at diagnosis (continuous), year of diagnosis (1990-1995, 1996-2000, 2001-2005, 2006-2007), ethnicity (Chinese, Malay, Indian, others), stage (0, I, II, III, IV, unknown) [238], estrogen receptor (ER) and progesterone receptor (PR) status (positive, i.e., >10% of the tumor cells expressing ERs or PRs, negative or unknown), lymphovascular invasion (LVI) (yes, no, unknown), histology (ductal, lobular, mucinous, others, unknown), tumor grade (good, moderate, poor, unknown), number of lymph nodes excised and number of positive lymph nodes (0, 1-3, 4-9, ≥ 10 nodes in accordance with the TNM nodal staging classification [238]). Tumor

characteristics were based on surgically removed specimens. For patients not undergoing surgery, tumor characteristics were determined from core biopsy specimens. Treatment variables in the study were surgery (mastectomy, breast conserving surgery, no surgery) radiotherapy (yes, no), chemotherapy (yes, no) and hormone therapy (yes, no).

We divided patients into two age categories <65 years and ≥ 65 years at diagnosis and compared sociodemographic and tumor characteristics and treatments received. To assess the level of standard/adequate treatment we compared the proportion of invasive breast cancer patients treated with surgery, the proportion receiving radiotherapy following breast conserving surgery (BCS), the proportion of estrogen receptor (ER) positive patients receiving hormonal therapy, the proportion of ER negative and lymph node (LN) positive patients receiving chemotherapy and the proportion of women with invasive breast cancer who underwent axillary clearance. These analyses were repeated after excluding stage IV patients. This was done to minimize discrepancies as there are no "standard treatment" guidelines for patients with stage IV disease.

Statistical analysis

We performed univariate logistic regression analysis to identify sociodemographic, tumor and treatment characteristics that were significantly associated with older age. Subsequently we applied multivariate logistic regression analysis to identify which factors were independently and significantly associated with older age.

We calculated relative survival rates (RSRs) to estimate the excess mortality among the patient population due to breast cancer [239]. Population mortality data for Singapore was used to compute these estimates. Relative survival is defined as the ratio of the proportion of observed survivors in a cohort of cancer patients to the proportion of

expected survivors in the background population with same age and period distribution [156]. The formulation is based on the assumption of independent competing causes of death. The relative survival adjusts for the general survival of the Singapore population for that race, sex, age and year. Thus the relative survival is a net survival measure representing cancer survival in the absence of other causes of death.

With Cox proportional hazard analysis we determined the association between type of locoregional treatment (i.e., mastectomy, BCS plus radiotherapy, BCS alone or no surgery) and overall risk of death for the younger and older age groups adjusting for other prognostic factors and after testing for proportionality.

Relative survival analyses were carried out using STATA (version 10) and all other analyses were carried out using SPSS (version 16).

Results

Of the 2195 patients in our study, 1869 (85.1%) patients were 40 to 64 years old and 326 (14.9%) patients were 65 years or older. In general, older patients had more missing information on the various patient and tumor characteristics than younger patients (Table 5.1).

Patient and tumor characteristics and treatment

In univariate analysis, ethnicity, stage, LVI, ER status, number of lymph nodes excised were associated with older age. In multivariate analysis we found that older patients were more likely to present with advanced stage disease (stage IV) than their younger counterparts (odds ratio [OR], 1.6; 95% CI, 1.0 to 2.6) and less likely to present with early stage disease (stage 0 OR, 0.2; 95% CI, 0.1-0.6 and stage I OR, 0.7; 95%CI, 0.5 to 1.0).

Table 5.1 Patient and tumor characteristics by age and the likelihood of these characteristics being associated with old age as determined by logistic regression.

Variable	≥ 65 yrs n=326	< 65 yrs n=1869	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Ethnicity*				
Chinese	277 (85%)	1473(78.8%)	1	1
Malay	20 (6.1%)	197(10.5%)	0.5(0.3-0.9)	0.5(0.3-0.9)
Indian	13 (4%)	105(5.6%)	0.7(0.4-1.3)	0.7(0.4-2.5)
Others	16 (4.9%)	94(5%)	0.9(0.5-1.6)	0.7(0.3-1.2)
Stage*^				
0	15(4.6%)	194(10.4%)	0.5(0.2-0.8)	0.2(0.1-0.6)
1	58 (17.8%)	454(24.3%)	0.8(0.5-1.1)	0.7(0.5-1.0)
2	117 (35.9%)	760(40.7%)	1	1
3	38 (11.7%)	240(12.8%)	1.0(0.6-1.5)	1.0(0.6-1.5)
4	53 (16.3%)	123(6.6%)	2.7(1.9-4.0)	1.6(1.0-2.6)
Unknown	45 (13.8%)	98(5.2%)	2.9(1.9-4.4)	1.7(1.0-3.0)
Lymphovascular invasion*				
Yes	179(54.9%)	1035(68.9%)	1	1
No	78(23.9%)	221(11.8%)	1.9(1.3-2.8)	2.4(1.4-4.2)
Unknown	69(21.2%)	343(18.4%)	1.3(0.9-1.8)	1.1(0.7-1.8)
Histology*				
Ductal	248(76.1%)	1562(83.6%)	1	1
Lobular	12(3.7%)	88(4.7%)	0.6(0.3-1.3)	0.5(0.2-1.1)
Mucinous	9(2.8%)	33(1.8%)	1.7(0.8-3.9)	1.5(0.7-3.5)
Other	25(7.7%)	121(6.5%)	1.5(0.9-2.4)	1.4(0.9-2.3)
Unknown	32(9.8%)	65(3.5%)	2.6(1.5-4.3)	1.3(0.7-2.4)
Number of positive lymph nodes*#+				
0 nodes	116(63%)	777(59.5%)	1	1
1-3 nodes	34(18.4%)	279(22.2%)	0.7(0.4-1.1)	0.7(0.5-1.2)
4-9 nodes	22(12.0%)	155(11.7%)	0.9(0.5-1.5)	0.9(0.5-1.6)
>=10 nodes	12(6.6%)	87(6.6%)	0.9(0.4-1.8)	1.0(0.5-2.1)
Unknown	142(43.6%)	553(26.9%)	1.3(1.0-1.8)	0.5(0.1-1.5)
Tumor Size*+				
<2 cm	73(22.4%)	562(30.1%)	0.7(0.5-1.0)	0.6(0.4-0.9)
2-5 cm	86(26.4%)	450(24.1%)	1	1
>5 cm	16(4.9%)	114(6.1%)	0.7(0.3-1.3)	0.7(0.3-1.4)
Unknown	151(46.3%)	743(39.7%)	1.0(0.7-1.3)	0.6(0.4-1.0)
ER Status*#				
Negative	67 (28.8%)	628(44.0%)	1	1
Positive	165 (71.2%)	797(56.0%)	1.9(1.3-2.6)	2.6(1.7-3.8)
Unknown	94 (28.8%)	444(23.8%)	1.8(1.2-2.5)	2.8(0.4-19.3)
PR Status				
Negative	97 (29.8%)	639(34.2%)	1	1
Positive	133 (40.8%)	775(41.5%)	1.0(0.7-1.3)	0.6(0.4-0.9)
Unknown	96(29.4%)	455(24.3%)	1.1(0.8-1.6)	0.4(0.1-2.9)
Grade+				
Good	43 (13.2%)	200(10.7%)	1	1
Moderate	99 (30.4%)	640(34.2%)	0.6(0.4-0.9)	0.8(0.5-1.2)
Poor	91 (27.9%)	587(31.4%)	0.6(0.4-1.0)	0.9(0.6-1.5)
Unknown	93 (28.5%)	442(23.6%)	0.8(0.5-1.2)	0.7(0.4-1.2)

***** Variable is significant.

Valid percentage has been calculated (i.e., not considering "unknown").

^ Unadjusted and Adjusted OR included stage 4 patients.

All other Odds Ratios (ORs) and confidence intervals (CIs) have been calculated after excluding stage IV patients.
[+] Logistic regression model adjusted for ethnicity, year of diagnosis, lymphovascular invasion, histology, ER and PR status.
All other ORs are adjusted for ethnicity, year of diagnosis, lymphovascular invasion, histology, ER and PR status, stage.

Older patients were more likely to present with ER positive tumors (OR, 2.6; 95% CI, 1.7 to 3.8). Tumor grade, histology, progesterone receptor status and number of positive lymph nodes were not independently associated with older age.

Elderly patients were less likely to undergo breast conserving surgery than younger patients (OR, 0.4; 95% CI, 0.3 to 0.7) (Table 5.2) and this difference was more pronounced for stage 1 disease (Figure 5.1). Types of surgical treatment as well as receipt of adjuvant treatment were significantly associated with age, with older patients being less likely to receive BCS, radiotherapy and chemotherapy (Table 5.2). There were 217 patients treated with neoadjuvant chemotherapy (38 elderly and 179 young patients). Sixty percent (60%) of these elderly patients proceeded to undergo surgery as compared to 85% of the younger patients receiving neoadjuvant chemotherapy. Of the patients not receiving radiotherapy (247 elderly and 983 young patients), 62% of the elderly and 46.8% of the young patients received hormonal therapy ($p<0.001$).

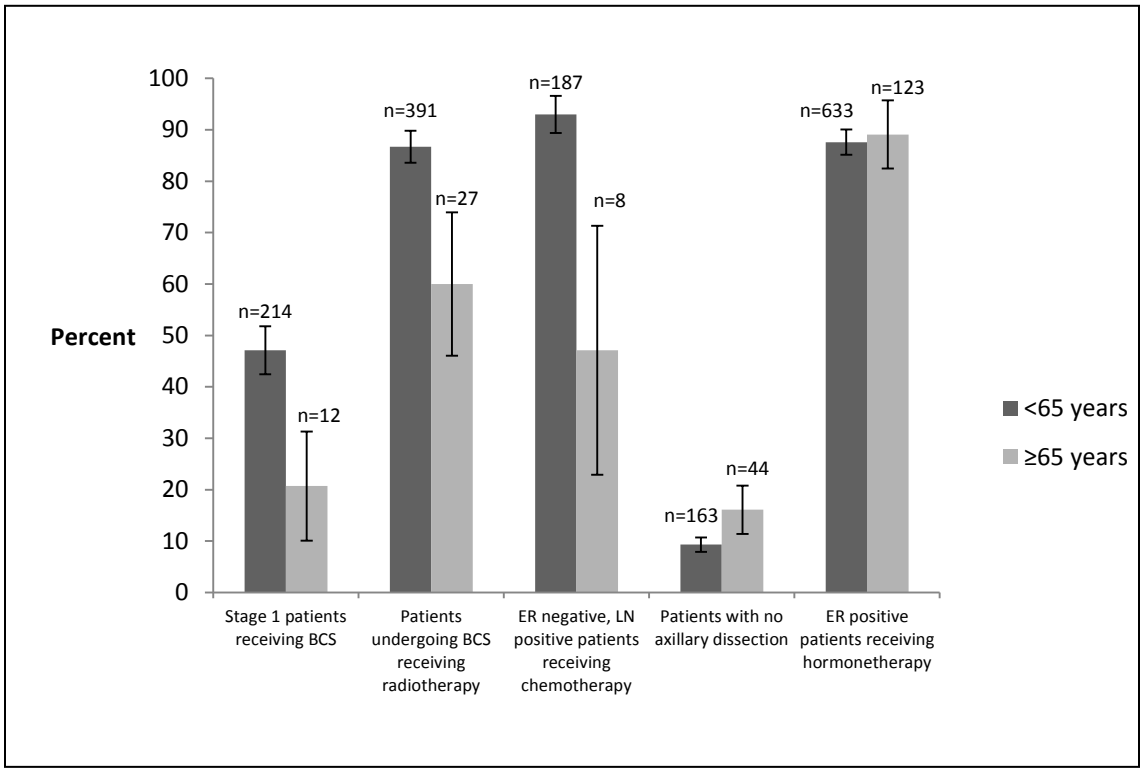
Table 5.2 Treatment for patients stratified by age and the likelihood of treatment being associated with old age as determined by logistic regression.

Variable	≥ 65 yrs n =326	< 65 yrs n=1869	Unadjusted OR (95%CI)	Adjusted OR (95%CI)
Surgery type*				
Mastectomy	216 (66.3%)	1191(63.7%)	1	1
BCS	59 (18.1%)	579(31.0%)	0.5(0.3-0.7)	0.4(0.3-0.7)
No surgery/Unknown	51 (15.6%)	99(5.3%)	3.3(1.9-5.6)	1.0(0.4-2.0)
Radiotherapy*				
No	247(75.8%)	983(52.6%)	1	1
Yes	79(24.2%)	886(47.4%)	0.3(0.2-0.5)	0.3(0.2-0.5)
Chemotherapy*				
No	275(84.4%)	906(48.5%)	1	1
Yes	51(15.6%)	963(51.5%)	0.1(0.1-0.2)	0.08(0.05-0.12)
Hormone therapy*				
No	114(35%)	851(45.5%)	1	1
Yes	212(65%)	1018(54.5%)	2.3(1.7-3.1)	2.8(1.9-4.0)
Number of lymph nodes excised*				
0 nodes	78(23.9%)	221(11.8%)	1.7(0.9-3.0)	2.0(1.1-3.8)
1-3 nodes	21(6.4%)	138(7.4%)	1	1
4-9 nodes	30(9.2%)	204(10.9%)	0.9(0.5-1.7)	0.9(0.5-1.8)
>=10 nodes	128(39.3%)	963(51.5%)	0.8(0.5-1.3)	0.9(0.5-1.5)
Unknown	69(21.2%)	343(18.4%)	1.1(0.6-1.9)	1.0(0.5-2.0)

* variable is significant.
All ORs and CIs have been calculated after excluding stage IV patients.
All ORs are adjusted for ethnicity, year of diagnosis, lymphovascular invasion, histology, ER and PR status, stage.

Older patients with non-metastasized invasive breast cancer were less likely to undergo axillary dissection as compared to the younger patients (Figure 5.2). Among the patients with stage 1-3 disease treated with breast conserving surgery, 54.7% of older women received radiotherapy as compared to 83.3% of younger women ($p < 0.001$).

Figure 5.2 Age stratified differences in proportion of: stage 1 patients receiving BCS, patients receiving BCS and radiotherapy, ER negative LN positive patients receiving chemotherapy and ER positive patients receiving hormonal therapy, all patients presenting with invasive breast cancer (excluding stage IV patients).

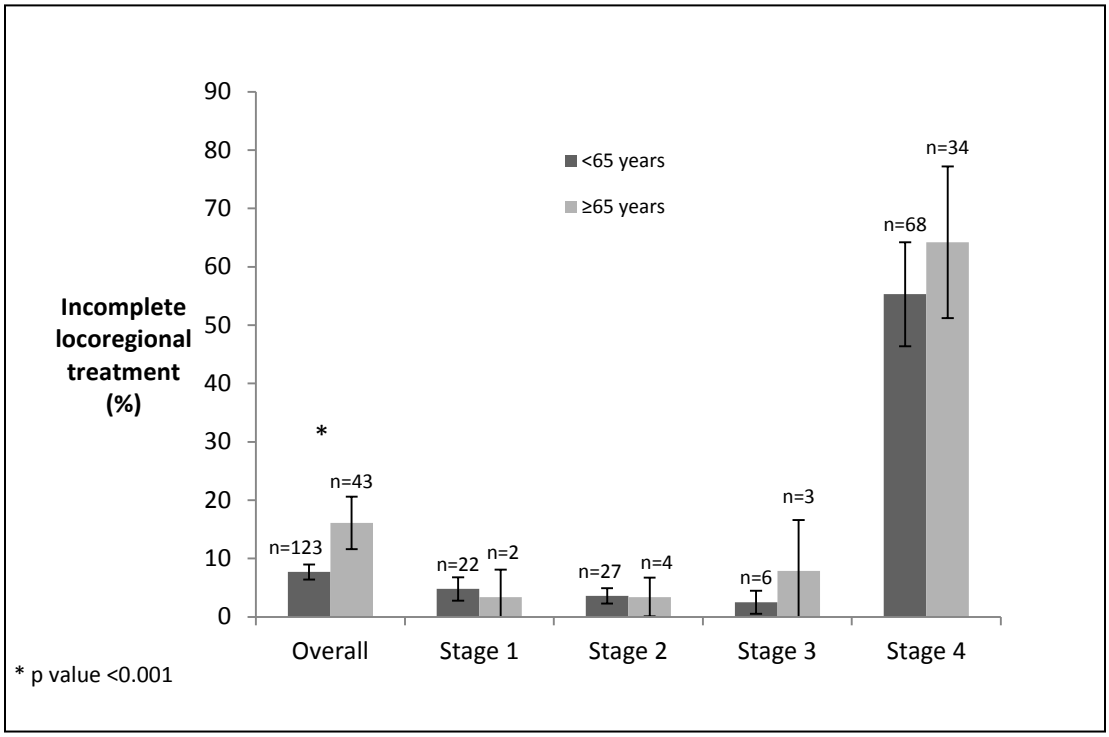


Similarly older women with ER negative, lymph node positive breast cancer were less likely to receive chemotherapy than younger patients (OR, 0.06; 95% CI, 0.01-0.2). In contrast, among women with ER positive tumors, equal proportions of old and young patients received hormonal therapy (88.7% vs 86.8% respectively).

A quarter of the elderly patients did not receive standard locoregional treatment (defined as tumorectomy without radiotherapy or no surgery) as compared to 10.9% of the younger patients ($p < 0.001$) (Figure 5.3). This difference disappeared after stratification

by stage and the far majority of older and younger women underwent surgery for stage I-III disease.

Figure 5.3 Patients with invasive breast cancer treated with tumorectomy without radiotherapy or no surgery according to stage and age.



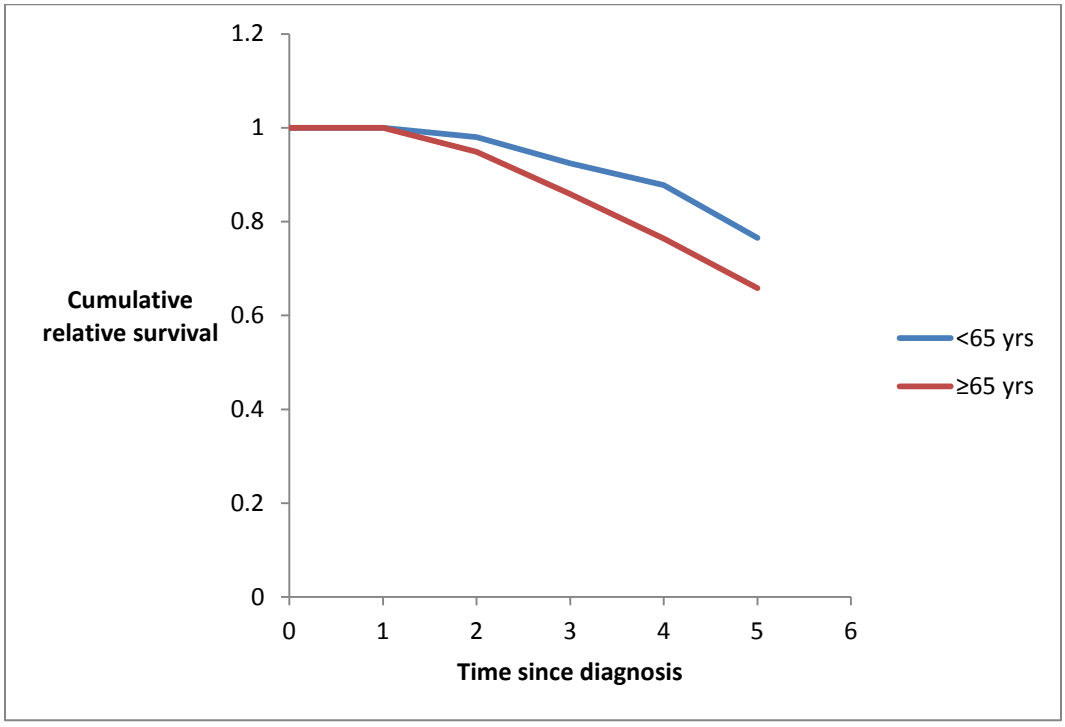
Relative survival

Overall, the median follow up time was 2.33 years (8 days to 15.7 years). Older patients' 5 and 10 year relative survival (RS) was lower than that of younger patients (65.8% vs 76.5% for 5 year RS and 48.5% vs 60.6% for 10 year RS respectively) (Figure 5.4). After stratification by stage, the differences in 5 and 10 year relative survival between the two age groups were substantially reduced (Table 5.3).

Table 5.3 Relative survival estimates by stage and age.

	5 Year Relative Survival		10 Year Relative Survival	
	<65 Years	**≥ 65 Years**	**<65 Years**	**≥ 65 Years**
Overall	**76.5%** (73.4% - 79.3%)	**65.8%** (56.0% - 74.8%)	**60.6%** (55.6% - 65.3%)	**48.5%** (32.1% - 65.9%)
Stage 1	**100%** (97.0% - 101.3%)	**98.2%** (68.0% - 111.7%)	**97.6%** (88.2% - 101.6%)	**99.9%** (58.6% - 140.5%)
Stage 2	**82.9%** (78.6% - 86.6%)	**77.7%** (61.7% - 90.3%)	**60.3%** (52.8% - 67.1%)	**61.5%** (33.3% - 87.9%)
Stage 3	**46.0%** (36.0% - 55.6%)	**40.6%** (19.6% - 63.3%)	**24.3%** (10.9% - 40.8%)	**20.7%** (3.9% - 51.6%)
Stage 4	**12.7%** (6.1% - 21.8%)	**23.0%** (8.1% - 44.6%)	**10.1%** (3.9% - 19.8%)	**7.1%** (0.5% - 22.9%)

Figure 5.4 Relative survival curves by age



Age	Interval (years)	1	2	3	4	5
<65 years	Number at risk	1860	1614	1126	725	567
	Number of deaths	39	85	51	45	38
≥65 years	Number at risk	323	266	179	109	83
	Number of deaths	26	30	23	10	11

(Age adjusted estimates: 5 year cumulative relative survival: 72.1%, 10 year cumulative relative survival: 55.8%)

The risk of death among both age groups was highest in women who did not undergo any surgical intervention (Table 5.4), the relative risk being higher for the younger breast cancer patients.

Table 5.4 Hazard ratios for all cause mortality by various surgical treatment options for all patients with invasive breast cancer (excluding stage IV patients).

Treatment type	Overall adjusted HRs	Adjusted HRs by age	
		<65 yrs	≥ 65 yrs
BCS + RT	1 (reference)	1(reference)	1(reference)
Mastectomy	1.8(1.2-2.6)	1.8 (1.2-2.9)	1.2 (0.5-3.1)
BCS alone	3.4(1.7-7.1)	4.5 (1.8-11.4)	1.0(0.2-3.8)
No surgery	6.3(3.4-11.8)	6.7 (3.1-14.8)	2.4 (0.7-8.6)

BCS: Breast Conserving Surgery, RT: Radiotherapy, HR: Hazard Ratio.
Adjusted for: Ethnicity, ER status, grade, stage and number of regional nodes positive.
P values for overall and <65 yrs groups were <0.001.

Patients receiving breast conserving surgery followed by radiotherapy had the lowest risk of death for both age groups.

Discussion:

This study shows important differences in tumor characteristics and treatment between older and younger breast cancer patients in the Asian setting. Older women were more likely to be diagnosed at advanced stages and had more often ER positive tumors. Older patients were less likely to receive standard treatment and had overall lower relative survival estimates.

In general, our findings are in concordance with other studies on elderly women, most of which were conducted in the West [240-242]. Similar to what has been reported in Caucasian studies, our results emphasize that there is room for improvement in the

management of Asian elderly breast cancer patients. First of all a lower proportion of breast cancer in the elderly was detected at an early stage while a large proportion presented with distant metastases. This could be the result of patient delay, reduced awareness among the elderly [221] or higher prevalence of fatalistic views. Other explanations could be the fact that breast screening in Singapore is relatively new and attendance rates are low [55]. Older women could be more hesitant to undergo mammographic screening for cultural or personal issues and this could have led to a decrease in the detection of early breast cancers. Presenting with advanced disease could reflect the elderly patients' attitude towards the disease and possible fear or anxiety of treatment. Since older women were less likely to present with lymphovascular invasion and had similar grade distribution, it is unlikely that increased aggressiveness of breast tumors caused the advanced stage at diagnosis.

There is a large volume of evidence showing that elderly patients are less likely to receive standard treatment for breast cancer [236, 243-246]. In Caucasian populations it has been observed that older women are less likely to be treated surgically, even though they tolerate mastectomy and breast conserving surgery just as well as younger patients [247]. Omission of surgery for older women has been associated with increased risk of local recurrence and death from breast cancer [107]. We noted that non-standard locoregional treatment (tumorectomy without radiotherapy or no surgery was associated with an increased risk of death, and this effect was stronger in younger women. The far majority of patients in our study underwent surgery and mastectomy was the most common form of surgery for both age groups. Even though elderly patients were overall less likely to receive surgical treatment than younger patients, stage stratification showed

that they were just as likely as younger patients to receive surgery for stage I-III disease. It was difficult to gauge the impact of chemotherapy for LN positive patients or BCS for stage 1 disease on survival (for each age group) as the number of elderly patients were too small within each subgroup.

Optimal adjuvant treatment regimens for older breast cancer patients are still debated. Studies have shown diminishing benefits of chemotherapy with increasing age [232] and the underrepresentation or even exclusion of elderly patients in clinical trials has led to a huge gap in available evidence in this field. In our study, use of hormonal treatment was similar among the younger and older age groups but older women were less likely to receive chemotherapy for ER negative, lymph node positive tumors. This could reflect physicians' decision not to administer radiotherapy or chemotherapy, taking into account toxicity profiles of the drugs and patient co-morbidities. Other explanations for the omission of adjuvant treatment include the patient or family members' wish not to treat [219, 237] based on financial or cultural reasons, lack of social healthcare system in Singapore and the fact that very few people have health insurance. Transportation to hospitals and clinics in our opinion would not be a major deterrent as distances are fairly short in Singapore and public transport is efficient and reliable.

Relative survival analysis showed that elderly breast cancer patients had lower 5 and 10 year overall relative survival rates indicating more breast cancer related deaths occurred in the elderly patients. These survival differences were mainly attributed to differences in stage distribution as they practically disappeared after stratification by stage. This is in contrast to the Caucasian setting where age differences in survival persist after stage stratification [223, 248]. Lead time bias could also account for the differences in survival

as the elderly patients are less likely to undergo mammographic screening resulting in a lower number of breast cancer cases being detected early as compared to younger patients.

Adequate loco-regional treatment (i.e., breast conserving surgery followed by radiotherapy or mastectomy) is associated with a reduced risk of local recurrence [249] and all cause mortality [107]. We found that patients underwent inadequate loco-regional treatment, i.e. breast conserving surgery without radiotherapy or no surgery at all were at a significantly increased risk of death as compared to patients who underwent adequate loco-regional treatment. The association between overall mortality and type of breast cancer treatment was present in both age groups but the increment in risk with inadequate loco-regional treatment was higher for younger patients suggesting that under treatment may be especially detrimental in younger age groups. It was difficult to gauge the differences in survival between patients receiving chemotherapy for LN positive patients or BCS for stage 1 disease on survival for each age group as the number of elderly patients were too small within each subgroup. Residual confounding is very likely to play a role, as unmeasured factors like co-morbidity or general health status may have influenced the decision not to operate or irradiate.

We acknowledge that our study has several limitations. Firstly, being a hospital based study rather than a population based study, extrapolation of our findings to the general population might not be appropriate. The National University Hospital treats an estimated 10% of breast cancer cases in Singapore [38]. The demographics of the patients and catchment area that NUH serves are not different from other areas of the country [38]. Thus, even though extrapolation of our results to the general population might not be

appropriate, the NUH data did give a good idea of Singaporean breast cancer patient and tumor characteristics. Secondly, our study is also limited by the small sample size of elderly patients and limited follow up time. However, the small proportion of elderly patients in our study can be partly explained by the fact that Singapore has an age distribution that is predominantly young with a majority of the population being below the age of 65 years. Also, the Singapore Cancer Registry data showed that during the period of 1990-2002, 18% of the female breast cancer patients were ≥65 years of age at diagnosis[40]. Hence we would expect a larger proportion of patients to be diagnosed under the age of 65 years. Although the proportion of elderly patients in our study was 15%, we did manage to display important differences in tumor characteristics and treatment between the old and young patients. Thirdly, lack of co-morbidity data and patient background information such as residential status, educational level and family income could have led to residual confounding. The impact of this missing information on treatment decisions and patient survival will be difficult to gauge. Lastly, being an observational study, there was the possibility of selection bias.

Conclusion:

Our study shows that older Asian breast cancer patients are diagnosed at later stages than younger women. However our results suggest that older age in itself is not independently associated with impaired survival.

Chapter 6 Lymph node ratio as a prognostic indicator

Does the axillary lymph node ratio have any added prognostic value over pN staging for Singaporean and Malaysian breast cancer patients?

(Accepted for publication as "Does the axillary lymph node ratio have any added prognostic value over pN staging for South East Asian breast cancer patients? in PLOS ONE 2012)

Introduction

Axillary lymph node status is one of the most important prognostic factors for breast cancer [19-21] . Traditionally, axillary lymph node status is classified according to the American Joint Committee on Cancer (AJCC) breast cancer staging system, which is based on the number of positive axillary lymph nodes [250] where pN0 indicates zero positive nodes, pN1 1-3 positive nodes, pN2 4-9 positive nodes and pN3: ≥10 positive nodes. This pN stage is restricted by the number of nodes excised [251] which in turn depends upon the surgical approach to axillary dissection, the expertise of the surgeon as well as the pathologists' experience and thoroughness. Variation in these factors can lead to large differences in the number of lymph nodes retrieved across institutions thereby influencing staging.

Increasing evidence suggests that the Lymph Node Ratio (LNR) (the ratio of the number of positive nodes to the total number of nodes excised), is a superior prognostic indicator compared to the absolute number of nodes involved [22-26]. However some studies have shown no difference in prognostic value for LNR over pN [252]. Vinh Hung *et al* showed that LNR, categorized as low > 0 and <0.2, intermediate 0.2 to 0.65 and high risk >0.65

to 1, was better at predicting breast cancer specific mortality than pN staging [22]. This conclusion was based on the fact that confidence intervals for the adjusted hazard ratios did not overlap for the intermediate and high risk LNR groups but did so for the pN2 and pN3 groups. A study from Korea showed no overall difference between LNR and pN staging in categorizing poor, intermediate and good survivors, except for certain subgroups, i.e. women aged <35 years, HER2 over expressing and triple negative tumors[26]. Other studies conducted in different populations also suggested that LNR was a significant and independent predictor of outcome for breast cancer patients [10, 23-25, 142].

Prognostication, however, is a multivariable process, as the outcome of a disease is determined by a variety of (sometimes interacting) factors, and breast cancer is no exception. In addition to axillary lymph node status, prognosis is determined by a variety of factors, including, age, tumor size, grade, receptors status and treatment. Despite the large number of studies that have addressed LNR, not one has assessed the added prognostic value of LNR over pN in predicting overall survival after breast cancer.

Methods:

Data for this study was obtained from the Singapore Malaysia Hospital based Breast Cancer Registry [1]. This registry combines data from the National University Hospital (NUH) breast cancer registry, Singapore and the University of Malaya Medical Center (UMMC) breast cancer registry, Kuala Lumpur, Malaysia.

The NUH breast cancer registry started in 1995 and contains information on 2,449 consecutive breast cancer patients diagnosed between 1990 and 2007. The UMMC breast

cancer registry started in 1993 contains information on 3,320 patients diagnosed between 1993 and 2007. Details on both these registries are described elsewhere [1, 38]. In both centers, patients were monitored through follow-up in the specialist outpatient clinics. Data on mortality were obtained from the hospitals' medical records and by linkage with the respective death registries. Follow up for each patient was calculated from the date of diagnosis to the date of death or end of follow up (July 2010 for NUH patients and November 2010 for UMMC patients). Both the registries had approval from their respective ethics review boards.

We selected women diagnosed with non metastatic primary invasive breast cancer, with information on the number of excised and the number of positive axillary lymph nodes. Patients receiving neoadjuvant chemotherapy (N=312), patients with a node negative (pN0) axilla (N=2352), patients with missing information on exact number of lymph nodes involved (N=664), with *in situ* breast cancer (N=317) and stage IV disease (N=535) were excluded. In total 1589 patients were included for analysis.

Information recorded for each patient included age at diagnosis, ethnicity (Chinese, Malay, Indian or others), year of diagnosis, place of diagnosis (Singapore, Kuala Lumpur), date of death or date of last contact . Tumor characteristics included tumor size (<2 cm, 2-5 cm, >5 cm, unknown), estrogen (ER) and progesterone receptor (PR) status (positive i.e., ≥10% of epithelial tumor cells expressing receptors, negative and unknown), grade (good, moderate, poor, unknown). In terms of axillary dissection, we collected information on total number of axillary nodes examined and number of positive axilary nodes. LNR was categorized into three categories including, low (>0 and <0.2), intermediate (0.2 to 0.65) and high risk (>0.65 to 1) groups as previously reported [22].

Statistical analysis

Life table analysis was performed to calculate survival probabilities for the three pN categories and the three LNR categories. After testing for proportionality, we performed univariate Cox proportional hazards analysis to identify variables that were significantly associated with all cause mortality. For details on Cox proportional hazards analysis, refer to chapter 3. Multivariate Cox proportional hazard analysis was applied (1) to calculate adjusted mortality risks and (2) to identify which combination of factors, including pN or LNR that best predicted overall survival. Internal validation of the models was done by bootstrap resampling. From the final model, adjusted Hazard Ratio for pN were derived and by replacing pN with LNR, we obtained adjusted HRs for the three LNR categories.

In order to ascertain the added prognostic value of LNR over pN, we compared the discriminative capacity of the two models. Discrimination indicates how well the model is able to distinguish between patients who will experience the outcome (death) and those who will not. Discrimination was assessed by the Concordance (c) statistic, the interpretation of which is equivalent to the area under the receiver operating characeristic curve, that is, a c statistic of 0.5 indicates no discrimination above chance, whereas a c statistic of 1.0 indicates perfect discrimination. Comparison of c statistics between the model including LNR with the one including pN staging tells whether one model is better in discriminating between poor and good survivors, and thus superior in predicting survival. Model calibration—the agreement between predicted risks and observed mortality risks—was assessed by comparing the predicted survival and the observed survival at 3-year follow-up.

After a recent publication suggested that LNR is particularly informative in subgroups of patients (i.e. patients with unfavorable tumor characteristics and younger patients) we performed subgroup analyses by age (<60 years and ≥60 years), receptor status (ER- vs ER+) and grade (1, 2 and 3) [26].

Finally, the c statistic has been criticized for being insensitive in comparing models and for having little direct clinical relevance. Therefore, we calculated the Net Reclassification Improvement (NRI), which assesses the ability of a model including a new prognostic marker to more accurately reclassify individuals into higher or lower risk strata. The NRI is the difference in proportions of patients moving up and down risk strata (high, moderate and low risk of mortality) among patients with the event of interest versus those without (in our case patients who died within 3 years of follow up versus those who survived). The NRI is similar to the simple percentage reclassified but distinguishes between movements in the correct direction (up for case patients (deaths) and down for control patients (survivors) [165]. Based on their individual survival probabilities we categorized patients into lower tertile, middle tertile and upper tertile for risk of death at 3 years of follow up.

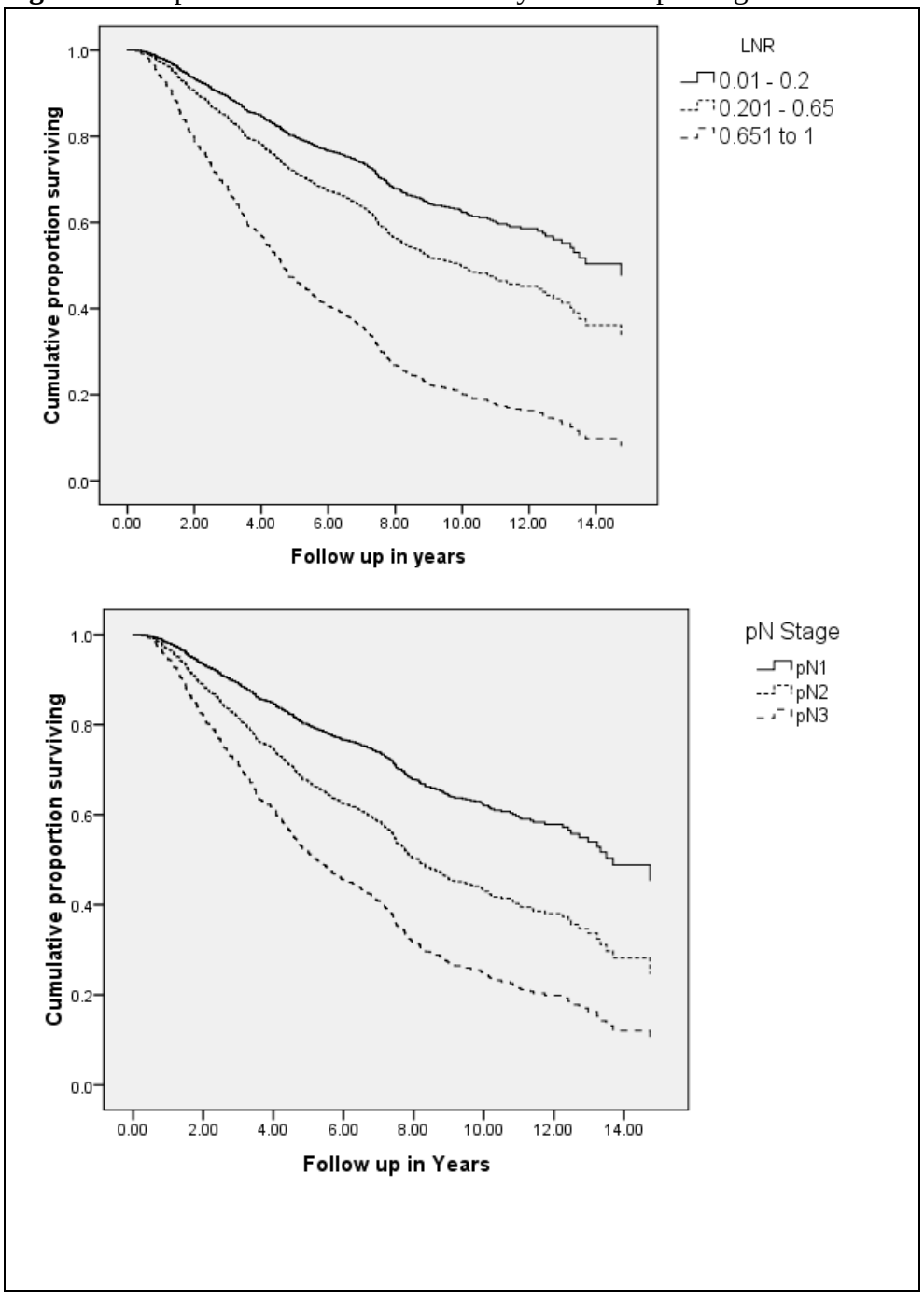
All analysis were performed using STATA version 11.

Results

According to the LNR classification, 758 (47.7%) patients were categorized as low risk (>0 and <0.2), 574 (36.1%) as intermediate risk (0.2 to 0.65) and 257 (16.2%) as high risk (>0.65 to 1)LNR. For classic pN staging, 879 (55.2%) were pN1, 447 (28.1%) pN2 and 263 (16.7%) pN3 (Table 6.1). Five year survival probabilities for the patients

stratified by LNR were 79%, 70% and 43% for low, intermediate and high risk groups respectively (Table 6.2). Five year survival probabilities for the patients stratified by pN classification were 79%, 65% and 48% for pN1, pN2 and pN3 respectively (Figure 6.1).

Figure 6.1 Kaplan Meier survival curves by LNR and pN stage.



In univariate Cox regression analysis, age at diagnosis, place of diagnosis, year of diagnosis, ethnicity, receptor status (ER and PR), treatment, grade, stage, tumor size, pN staging were independently and significantly associated with all cause mortality (Table 6.1). After multivariate analysis, a model consisting of pN, age, tumor size, tumor grade, chemotherapy, radiotherapy, and surgery, gave the best fit. Taking pN1 patients as a reference, adjusted mortality risks (Hazard Ratios) were 1.9 (95%CI, 1.5 to 2.3) for pN2 patients and 3.0 (95%CI, 2.4 to 3.7) for pN3 patients. Similarly, compared to patient classified as low risk LNR (>0 and <0.2), those with intermediate risk LNR had an HRadj of 1.5 (95%CI, 1.2 to 1.9) and those with high risk LNR an HRadj of 3.2 (95%CI, 2.6 to 4.0) (Table 6.2).

Both models (including pN and LNR respectively) were well calibrated (p-value Hosmer Lemeshow test 0.67 and 0.83 respectively). In terms of discriminating ability, both models performed equally well, as shown by the c statistic for model including LNR of 0.73 (95% CI 0.71 to 0.76) and c statistic for the model including pN stage of 0.72 (95% CI 0.70 to 0.75). The substantial overlap between the two 95% confidence intervals indicated that LNR did not provide any added prognostic value when compared to pN staging in predicting all cause mortality.

Table 6.1 Patient, tumor characteristics and treatment along with the unadjusted Hazard Ratio for all cause mortality for Malaysian and Singaporean patients.

Variable	N (%)	Unadjusted HR (95% CI)	P value of unadjusted HR
Age in years			<0.001
Median (Range)	50 (22 to 87)		
<40 years	225 (14.2%)	1	
40 to 49 years	569 (35.8%)	0.7 (0.5 to 0.9)	
50 to 59 years	470 (29.6%)	1.0 (0.8 to 1.3)	
≥ 60 years	325 (20.5%)	1.2 (0.9 to 1.6)	
Ethnicity			0.005
Chinese	1064 (67.0%)	1	
Malay	303 (19.1%)	1.5 (1.1 to 1.9)	
Indian	176 (11.1%)	1.2 (1.0 to 1.5)	
Other	46 (2.9%)	0.8 (0.4 to 1.6)	
ER status*			<0.001
Negative	662 (44.0%)	1	
Positive	844 (56.0%)	0.5 (0.4 to 0.7)	
Unknown	83	0.8 (0.5 to 1.1)	
PR Status*			<0.001
Negative	596 (45.7%)	1	
Positive	706 (54.3%)	0.4 (0.3 to 0.6)	
Unknown	287	0.8 (0.6 to 1.0)	
Grade*			<0.001
Low	89 (6.2%)	0.4 (0.2 to 0.7)	
Moderate	699 (49.1%)	1	
High	635 (44.6%)	1.4 (1.1 to 1.6)	
Unknown	166	1.0 (0.7 to 1.4)	
Tumor size*			<0.001
≤2 cm	381 (26.0%)	0.5 (0.4 to 0.7)	
2.1-5 cm	868 (59.3%)	1	
>5 cm	214 (14.6%)	1.6 (1.3 to 2.0)	
Unknown	126	0.8 (0.6 to 1.1)	
Radiotherapy			<0.001
No	430 (26.9%)	1	
Yes	1159 (72.9%)	0.7 (0.5 to 0.8)	
Chemotherapy			<0.001
No	246 (15.5%)	1	
Yes	1343 (84.5%)	0.5 (0.4 to 0.6)	
Hormone Therapy			<0.001
No	560 (35.2%)	1	
Yes	1029 (64.8%)	0.5 (0.4 to 0.6)	
Regional nodes examined			0.151
Median	15		
1-3	18 (1.1%)	1.8 (0.9 to 3.3)	
4-9	249 (15.7%)	1.0 (0.8 to 1.2)	
≥10	1322 (83.2%)	1	
Regional nodes positive (pN Stage)			<0.001
Median	3		
1-3	879 (55.2%)	1	
4-9	447 (28.1%)	1.7 (1.4 to 2.1)	
≥10	263 (16.7%)	3.3 (2.6 to 4.1)	
Lymph Node Ratio			<0.001
Median	0.22		
0.01-0.2	758 (47.7%)	1	
0.201-0.65	574 (36.1%)	1.5 (1.2 to 1.8)	
0.651-1	257 (16.2%)	3.6 (2.9 tp 4.5)	
* indicates valid proportions have been calculated (i.e., not considering unknown)			

Subgroup analysis showed that LNR was superior to pN staging in categorizing patients' risk of death for patients aged 60 years and above, patients with ER negative tumors and patients with high grade tumors, as for these subgroups, 95% confidence intervals (CIs) for intermediate and high risk LNR groups did not overlap while they did for the pN2 and pN3 categories. However, in terms of discriminating capacity, models including LNR performed similarly well as models including pN, as attested by the c statistics and largely overlapping 95% CIs (Table 6.3). There was no significant difference in risk stratification between LNR and pN staging for women <60 years, ER positive and low / moderate grade tumors (Table 6.3).

Table 6.2 Survival probabilities and Hazard Ratios for all cause mortality by pN classification and Lymph Node Ratio(LNR)

Variable	N (%)	N Dead	5 year Survival Probability (95% CI)	Unadjusted HR (95% CI)	Adjusted HR* (95% CI)	c statistic (95% CI)
pN Stage						0.72
pN1	879 (55.2%)	256	79.0% (75.6% to 82.4%)	1	1	
pN2	447 (28.1%)	198	65.0% (59.0% to 71.0%)	1.7 (1.4 to 2.1)	1.9 (1.5 to 2.3)	(0.70 to 0.75)
pN3	263 (16.7%)	151	48.0% (43.2% to 52.8%)	3.3 (2.6 to 4.1)	3.0 (2.4 to 3.7)	
LNR						0.73
Low	758 (47.7%)	213	79.0% (75.4% to 82.6%)	1	1	
Intermediate	574 (36.1%)	228	70.0% (65.2% to 74.8%)	1.5 (1.2 to 1.8)	1.5 (1.2 to 1.9)	(0.71 to 0.76)
High	257 (16.2%)	164	43.0% (33.0% to 53.0%)	3.6 (2.9 to 4.5)	3.2 (2.6 to 4.0)	
*Each model is adjusted for: age, radiotherapy, ethnicity, surgery type, grade and tumor size and stratified by ER Status Both models were internally validated using bootstrap resampling.						

Based on individual predicted survival probabilities (from both pN staging and LNR models), when patients were categorized into lower tertile, middle tertile, and higher tertile for risk of death, the LNR model additionally classified 8.0% (n=49) of patients with the event (death) into higher risk groups and 4.5% (n=29) of the patients with the event into low risk groups. Among the patients without the event (alive), an additional 5.6% (n=52) of patients were classified into lower risk groups while 5.7% (n=53) of the patients without the event were classified into high risk groups than the model with pN

staging So overall, the model including LNR reclassified 3.2% more patients in the correct risk groups than the model including pN, but the Net Reclassification Improvement was not significant (NRI = 3.2%, p value 0.08) (Table 6.4).

Table 6.3 Stratified analysis to check the added prognostic value of LNR over pN within specific subgroups.

Patients ≥ 60 years of age at diagnosis (N=325)				
	N (%)	**Unadj HR (95% CI)**	**AdjHR[a] (95% CI)**	**C statistic (95% CI)**
pN stage				0.75 (0.70 to 0.81)
pN1	175 (53.8%)	1	1	
pN2	89 (27.4%)	2.8 (1.8 to 4.1)	2.7 (1.8 to 4.1)	
pN3	61 (18.8%)	4.2 (2.7 to 6.3)	4.2 (2.6 to 6.7)	
Lymph Node Ratio				0.76 (0.71 to 0.80)
Low ≤0.20	147 (45.2%)	1	1	
Intermediate >0.20 to ≤0.65	112 (34.5%)	1.6 (1.0 to 2.4)	1.8 (1.1 to 2.7)	
High >0.65	66 (20.3)	5.2 (3.4 to 7.8)	4.5 (2.8 to 7.0)	
Patients with ER negative tumors at diagnosis (N=662)				
	N (%)	**Unadj HR (95% CI)**	**AdjHR[b] (95% CI)**	**C statistic (95% CI)**
pN stage				0.84 (0.80 to 0.87)
pN1	339 (51.2%)	1	1	
pN2	206 (31.1%)	2.0 (1.5 to 2.6)	2.0 (1.5 to 2.7)	
pN3	117 (17.7%)	3.1 (2.3 to 4.3)	3.0 (2.1 to 4.1)	
Lymph Node Ratio				0.85 (0.81 to 0.88)
Low ≤0.20	304 (45.9%)	1	1	
Intermediate >0.20 to ≤0.65	233 (35.2%)	1.4 (1.0 to 1.9)	1.5 (1.1 to 2.0)	
High >0.65	125 (18.9%)	3.7 (2.7 to 4.9)	3.5 (2.5 to 4.8)	
Patients with high grade tumors at diagnosis (N=635)				
	N (%)	**Unadj HR (95% CI)**	**AdjHR[c] (95% CI)**	**C statistic (95% CI)**
pN stage				0.76 (0.72 to 0.80)
pN1	320 (50.4%)	1	1	
pN2	180 (28.3%)	1.6 (1.2 to 2.1)	1.7 (1.2 to 2.3)	
pN3	135 (21.3%)	2.6 (1.9 to 3.5)	2.6 (1.9 to 3.5)	
Lymph Node Ratio				0.76 (0.72 to 0.81)
Low ≤0.20	286(45.0%)	1	1	
Intermediate >0.20 to ≤0.65	229 (36.1%)	1.3 (1.0 to 1.7)	1.4 (1.1 to 1.8)	
High >0.65	120 (18.9%)	2.9 (2.1 to 3.1)	2.7 (2.0 to 3.7)	

Table 6.3 Contd.

Patients < 60 years of age at diagnosis (N=1264)				
	N (%)	**Unadj HR (95% CI)**	**AdjHR[a] (95% CI)**	**C statistic (95% CI)**
pN stage				0.71 (0.68 to 0.74)
pN1	704 (55.7%)	1	1	
pN2	358 (28.3%)	1.5 (1.2 to 1.9)	1.6 (1.3 to 2.1)	
pN3	202 (16.0%)	2.7 (2.1 to 3.4)	2.6 (2.0 to 3.5)	
Lymph Node Ratio				0.70 (0.66 to 0.72)
Low ≤0.20	612 (48.5%)	1	1	
Intermediate >0.20 to ≤0.65	462 (36.5%)	1.4 (1.1 to 1.7)	1.6 (1.2 to 2.2)	
High >0.65	190 (15.0%)	2.9 (2.2 to 3.6)	2.9 (2.2 to 3.9)	
Patients with ER positive tumors at diagnosis (N=844)				
	N (%)	**Unadj HR (95% CI)**	**AdjHR[b] (95% CI)**	**C statistic (95% CI)**
pN stage				0.74 (0.71 to 0.79)
pN1	485 (57.5%)	1	1	
pN2	222 (26.3%)	1.5 (1.1 to 2.1)	1.6 (1.2 to 2.3)	
pN3	137 (16.2%)	2.9 (2.1 to 3.8)	2.9 (2.1 to 4.1)	
Lymph Node Ratio				0.75 (0.70 to 0.77)
Low ≤0.20	423 (50.1%)	1	1	
Intermediate >0.20 to ≤0.65	307 (36.4%)	1.6 (1.2 to 2.0)	1.8 (1.3 to 3.4)	
High >0.65	114 (13.5%)	2.6 (1.9 to 3.6)	2.9 (2.0 to 4.2)	
Patients with moderate andlow grade tumors at diagnosis (N=788)				
	N (%)	**Unadj HR (95% CI)**	**AdjHR[c] (95% CI)**	**C statistic (95% CI)**
pN stage				0.70 (0.66 to 0.73)
pN1	463 (58.8%)	1	1	
pN2	213 (27.0%)	1.9 (1.4 to 2.5)	2.0 (1.5 to 2.7)	
pN3	112 (14.2%)	3.1 (2.3 to 4.3)	3.3 (2.4 to 4.6)	
Lymph Node Ratio				0.69 (0.66 to 0.73)
Low ≤0.20	400 (50.8%)	1	1	
Intermediate >0.20 to ≤0.65	281 (35.7%)	1.8 (1.3 to 2.3)	1.9 (1.4 to 2.5)	
High >0.65	107 (13.6%)	3.4 (2.3 to 3.7)	3.4 (2.4 to 4.8)	

[a] Model adjusted for age at diagnosis, chemotherapy, radiotherapy, surgery type, grade and tumor size and stratified by ER status
[b] Model adjusted for age at diagnosis, chemotherapy, , surgery type and tumor size
[c] Model adjusted for age at diagnosis, chemotherapy, radiotherapy, surgery type and tumor size and stratified by ER status
All models were internally validated using bootstrap resampling.

Although a majority of the patients (~83%) did have at least ten lymph nodes examined, about 17% of the patients had less than 10 nodes removed during axillary dissection. We performed a subgroup analysis to assess the added prognostic value of LNR for patients with less than 10 nodes and for this subset of patients, pN staging was better at classifying patients into risk categories as compared to LNR (Table 6.5).

Table 6.4 Risk reclassification table at 3 years of follow up based on models including pN stage and LNR respectively.

			Model with LNR			
Model with pN	For patients with the event (Dead)		Lower tertile	Middle tertile	Higher tertile	Total
		Lower tertile	127	24		151
		Middle tertile	23	335	25	383
		Higher tertile		6	65	21
		Total	150	365	90	605
	For patients without the event (alive)	Lower tertile	405	45		450
		Middle tertile	48	396	8	452
		Higher tertile		4	16	20
		Total	453	445	24	922
Net Reclassification Index (NRI) = 3.2% (p value 0.08)						

Table 6.5 Multivariate Cox regression analysis for all cause mortality for patients with less than ten nodes retrieved.

	N (%)	**Unadj HR (95% CI)**	**AdjHR[a] (95% CI)**	**C statistic (95% CI)**
pN stage				0.71
pN1	209 (78.3%)	1	1	(0.65 to 0.78)
pN2	58 (21.7%)	2.8 (1.9 to 4.1)	2.9 (1.8 to 4.6)	
Lymph Node Ratio				0.70
Low ≤0.20	91 (31.4%)	1	1	(0.65 to 0.77)
Intermediate >0.20 to ≤0.65	119 (44.6%)	1.1 (0.7 to 1.8)	1.1 (0.6 to 1.8)	
High >0.65	57 (21.3%)	3.3 (2.0 to 5.4)	1.2 (1.8 to 5.5)	
[a]Model adjusted for age at diagnosis, chemotherapy, radiotherapy, surgery type, grade and tumor size and stratified by ER status				

Several cut off points for LNR were explored but no new cut off points were established for our cohort of patients.

Discussion

This study shows that pN staging is comparable to LNR in predicting overall survival of women with breast cancer, with the exception of patients aged 60 years or more, patients with ER negative tumors and patients with high grade tumors. Here, LNR was superior in

categorizing patients into intermediate and high risk strata as compared to pN stage. However, in combination with other prognostic factors, LNR did not provide any additional prognostic information over pN staging, neither for the entire cohort, nor for the subgroups of older women and those with ER negative of grade 3 tumors. The observation that LNR was not superior to the pN staging was seen in other Asian studies as well [26]. A non significant Net Reclassification Index for the LNR model compared to the pN model suggested that replacement of pN by LNR would not lead to better classification of patients into appropriate risk strata.

The number of lymph nodes retrieved and examined is highly dependent on surgical expertise, the institution's protocol and the pathologists' experience [253]. Removal of at least ten axillary lymph nodes is considered adequate for reliable lymph node staging [254-256]. In the current study, 17% of the patients had less than 10 nodes removed during axillary dissection. For this subset of patients, pN staging was better in categorizing patients into different risk strata as compared to LNR but there was no significant difference in the discriminative power of the two multivariate models (one with LNR and one with pN).

The implications of our study have been put into a different light by recent studies, which have indicated that full axillary clearance following a positive sentinel node biopsy does not affect survival in certain (low risk) categories of breast cancer patients [118, 257]. These studies may induce a shift towards less axillary clearances following sentinel node biopsy in the future. However, in many low and middle income countries, sentinel node biopsies are not routinely available. Also, Asian women present with more advanced disease, larger tumor sizes, more nodal metastasis and more high grade tumors, and

therefore complete axillary dissection, and complete staging of the axilla, is still very relevant in the South East Asian setting [258].

We acknowledge that our study suffers from several shortcomings, including a relatively short follow up time. In addition, we assessed all cause mortality as our end point as no data on cause of death was available. This could have led to a mixing of effects as this analysis allowed for competing risks of death. Also, additional information on HER2 / NEU receptor status, socioecomonic status and comorbidity could have allowed for a deeper understanding of the association.

Conclusion

Among South East Asian breast cancer patients, both the Lymph Node Ratio and the pN staging system seem to be equally good at predicting all cause mortality. LNR may be better than pN in dividing tumors into high vs low risk for certain subgroup of patients, but LNR has no added prognostic value over pN staging in addition to other prognosticators.

Prognostic value of axillary lymph node status after neoadjuvant chemotherapy.

(Published as "Prognostic value of axillary lymph node status after neoadjuvant chemotherapy. Results from a multicenter study." in the European Journal of Cancer 2011)

Introduction

Administration of neoadjuvant chemotherapy to women with locally advanced breast cancer serves not only to convert inoperable to operable disease, but also to increase the likelihood of breast conservative surgery [259-263]. Neoadjuvant chemotherapy may however modify the yield of involved axillary lymph nodes and may lead to an underestimation in prognostic value provided by nodal status [142, 264].

The number of positive lymph nodes is one of the most important prognostic factors for breast cancer [19-21] and to date, the American Joint Committee on Cancer (AJCC) staging system is based on the number of positive axillary lymph nodes [250] (ypN0: zero positive nodes, ypN1: 1-3 positive nodes, ypN2: 4-9 positive nodes, ypN3: ≥10 positive nodes). The number of positive lymph nodes (ypN stage) is however restricted by the number of nodes excised [251] which in turn depends upon the surgical approach to axillary dissection, physiological variations between patients as well as the effect of neoadjuvant chemotherapy. Variation in these factors leads to large differences in the number of lymph nodes retrieved across surgeons as well as institutions thereby influencing staging. Thus if a surgeon systematically excised only 8 axillary lymph nodes, patients can never be classified as ypN3, potentially resulting in under-staging and under-treatment of the patient. Several studies have suggested that the ratio of the number

of positive nodes to the total number of nodes excised, known as the lymph node ratio (LNR), is a superior prognostic indicator than the absolute number of nodes [22-25]. Being a ratio, the LNR accounts for the discrepancies that might arise due to differences in the technique of axillary dissection across institutions.

In this study, we evaluated the prognostic value of lymph node status in patients treated with neoadjuvant chemotherapy and assessed whether LNR was superior to the absolute number of lymph nodes involved in predicting overall survival.

Patients and Methods

For this study we combined data from three sources, i.e. the National University Hospital (NUH) Breast Cancer Registry in Singapore, University of Malaya Medical Centre (UMMC) Hospital Based Registry in Kuala Lumpur, Malaysia and the population-based Geneva Cancer Registry, Switzerland.

The NUH Breast Cancer Registry was described previously [38]. In summary, this registry was established in 1995, through prospective data collection on demographics, tumor characteristics, treatment and follow up of all patients presenting with invasive or *in situ* breast cancer. Data from 1990 to 1995 was collected retrospectively from medical records. Vital status information for a majority of the patients was determined through long term NUH follow up clinics. For those patients that did not regularly follow up at NUH, contact was made via telephone of letter annually. Death information was obtained from the physician and hospital records and Hospice Associations. Patients were followed to death or end of follow up (31st December, 2008), whichever came first. The Breast Cancer Registry has been approved by the NUH Institutional Ethics Review

Board. The UMMC Hospital Based Registry has been prospectively compiling patient and tumor characteristics for all patients diagnosed with breast cancer starting from 1993. Mortality data was updated by direct linkage with the Malaysian National Registry Department. This registry has been approved by the UMMC Institutional Ethics Review Board. Patients were followed to death or end of follow up (31st April, 2010), whichever came first.

The Geneva Cancer Registry records information on all newly diagnosed cancer cases arising in the Swiss canton of Geneva (population approximately 430,000). The registration is based on several sources of information and is extremely accurate, as attested by its low percentage (<2%) of cases recorded from death certificates only [265]. Patients were followed to death or end of follow up (31st December, 2008), whichever came first. All hospitals, pathology laboratories, and private practitioners in the canton are requested to report all cancer cases. Trained tumor registrars systematically abstract data from medical and laboratory records. Physicians regularly receive inquiry forms to complete missing clinical and therapeutic data. The Geneva Cancer Registry regularly assesses survival, taking as reference date the date of confirmation of diagnosis or the date of hospitalization (if it preceded the diagnosis and was related to the disease). In addition to passive follow-up (standard examination of death certificates and hospital records), active follow-up is performed yearly using the files of the Cantonal Population Office (office in charge of the registration of the resident population).

For the current study, we selected women diagnosed with primary invasive breast cancer, receiving neoadjuvant chemotherapy followed by surgery and with information on the number of excised and the number of positive axillary lymph nodes. Patients with distant

metastases and patients not undergoing surgery were excluded from the study. All cause mortality of the selected patients was assessed. From the 2545 patients in the NUH breast cancer registry databse, 156 (6.1%) patients received neoadjuvant chemotherapy and of these, 136 (5.3%) with complete information on excised and positive lymph nodes were included in the analysis. Similarly, from the 1001 patients diagnosed in Kuala Lumpur , 71 (7.0%) underwent neoadjuvant chemotherapy for locally advanced disease and of these 51 (5.0%) patients with complete information on excised and positive lymph node were included in the analysis. Of the 5236 patients in the Geneva Cancer Registry, 133 (2.5%) received neoadjuvant chemotherapy and for 127 (2.4) patients we had complete information on . In total, 314 patients were included for analysis.

Information recorded for each patient included age at diagnosis, ethnicity (Asian versus Caucasian/other), nationality, year of diagnosis, place of diagnosis (Singapore, Geneva or Kuala Lumpur), date of death or date of last contact . Tumor characteristics included tumor size based on prechemotherapy and was categorized into less than 2 cm, 2 to 5 cm, greater than 5 cm and unknown, stage (based on prechemotherapy - 1, 2, 3, unknown), estrogen (ER) and progesterone receptor (PR) status (positive i.e., ≥10% of immune-reactive neoplastic cells expressing receptors, negative and unknown), differentiation (good, moderate, poor, unknown -based on the Scarff-Bloom-Richardson grading scheme [85]), were recorded for all patients. Treatment information included adjuvant radiotherapy (no, yes), adjuvant hormonal therapy (no, yes) and adjuvant chemotherapy (no, yes). Axillary dissection information included number of regional nodes examined and number of positive regional nodes. All excised axillary noded were embedded for analysis. Information on chemotherapy regimens was not available for the

Geneva patients. Patients from Kuala Lumpur center received FEC (ie 5-fluorouracil 500 mg/m2, epirubicin 75 mg/m2 and cyclophosphamide 500 mg/m2) given IV every 3 weeks for 3 cycles as neoadjuvant chemotherapy. A majority of the patients from Singapore received anthracyclines-containing combination chemotherapy with or without taxanes as neoadjuvant treatment. None of the patietns in our study underwent sentinel lymph node biopsy.

For the purpose of comparability with the current ypN classification system, LNR was categorized into four categories including zero (0), low (>0 and <0.2), intermediate (0.2 to 0.65) and high risk (>0.65 to 1) groups based on previous findings [22]. These cut off points were earlier identified as most optimal cut off levels and internallly validated in a population based study (13). Additionally, using three cut off points gave us four categories for LNR which facilitated comparison to the four ypN groups.

Statistics:

After testing for proportionality, we performed a univariate Cox proportional hazard analysis to identify variables that were significantly associated with all cause mortality. Subsequently we performed multivariate Cox proportional hazard analysis, to look at the association between overall mortality and LNR and ypN respectively using two different models with similar adjustments. The first model had LNR as one the independent variables and the second model had ypN staging as one of the independent variables.

We entered all the significant variables (as per table 6.9) into a multivariate Cox model. Using backward stepwise selection, we eliminated variables that did not contribute significantly to the fit of the model and continued until the model consisted of variables

that were significantly associated with all cause mortality. Using this procedure, only LNR or ypN, age, PR status, place of diagnosis and radiotherapy were significantly associated with all cause mortality.

The reference category for the models were low risk LNR group and ypN1 group respectively as these categories contained the highest number of patients. By using large groups as reference categories, we increased the stability of our models. The interpretation of our findings would not have changed had we used the "zero" categories as the references for the two models.

Life tables were computed to gauge the survival probability for the group of patients stratified by the different LNR cutoffs and ypN classification.

Statistical analyses were performed with STATA (version 10) and SPSS (version 16).

Results

The median age of the 314 patients was 48 years (Table 6.6) and the majority (75.5%) had at least 10 axillary lymph nodes examined. All patients had undergone an axillary clearance. A large proportion of the patients (88.4%) received adjuvant radiotherapy and virtually all patients (98.8%) received adjuvant (completion) chemotherapy , which is standard procedure in the respective countries. The median number of involved nodes was two (range: 0 to 41 nodes) and the median LNR was 0.16 (range: 0-1.0) (Table 6.7).

Table 6.6 Patient and tumor characteristics for patients treated with neoadjuvant chemotherapy

Place of diagnosis / Variable	Singapore N=136	Geneva N=127	Kuala Lumpur N=51	Combined N=314
Age				
Median	48 years	49 years	48 years	48 years
Lower-upper quartile	25-81 years	24-86 years	26-66 years	24-86 years
<50 years	77 (56.6%)	66 (52.0%)	33 (64.7%)	176 (56.1%)
≥50 years	59 (43.4%)	61 (48.0.%)	18 (35.3%)	138 (43.9%)
Year of Diagnosis				
1990-2000	14 (10.3%)		43 (84.3%)	57 (18.1%)
2001-2007	122 (89.7%)	127 (100%)	8 (15.7%)	257 (81.9%)
Ethnicity				
Asian	125 (91.9%)	-	50 (98%)	175 (55.7%)
Caucasian and other	11 (8.1%)	127 (100%)	1(2%)	139 (44.3%)
Estrogen Receptor status*				
Negative	61 (46.9%)	47 (37.0%)	18 (46.1%)	126 (42.5%)
Positive	69 (53.1%)	80 (63.0%)	21 (53.9%)	170 (57.5%)
Unknown	6	-	12	18
Progesterone Receptor Status*				
Negative	67 (51.5%)	68 (53.5%)	2 (33.3%)	137 (52.0%)
Positive	63 (48.5%)	49 (46.5%)	4 (66.7%)	126 (48.0%)
Unknown	6	-	45	51
Grade*				
Good	16 (12.8%)	14 (11.2%)	2 (5.0%)	32 (11.2%)
Moderate	46 (36.8%)	68 (56.8%)	18 (45.0%)	132 (46.4%)
Poor	63 (50.4%)	37 (32.0%)	20 (50.0%)	120 (42.4%)
Unknown/not reported	11	8	11	30
Clinical tumor size (pre chemotherapy)*				
<2 cm	2 (2.3%)	10 (11.3%)	2 (4.0%)	14 (6.3%)
2-5 cm	17 (20%)	52 (59.0%)	9 (18.0%)	78 (35.0%)
≥ 5 cm	66 (77.7%)	26 (29.7%)	39(78.0%)	131 (58.7%)
Unknown/ not reported	51	39	1	91
Clinical Stage (pre chemotherapy)				
I				
II	3 (2.2%)	3 (2.4%)	-	6 (1.9%)
III	32 (23.5%)	57 (44.9%)	3 (5.9%)	92 (29.3%)
Unknown/ not reported	97 (71.3%)	55 (43.3%)	48 (94.1%)	200 (63.7%)
	4 (2.9%)	12 (9.4%)	-	16 (5.1%)
Adjuvant Radiotherapy				
No	18 (13.2%)	14(11.0%)	4 (7.8%)	36 (11.6%)
Yes	118 (86.8%)	113(89.0%)	47 (92.2%)	278 (88.4%)
Adjuvant Hormone therapy				
No	55 (40.4%)	44(34.6%)	20 (36.7%)	117 (38.1%)
Yes	81 (59.6%)	83(65.4%)	31 (63.3%)	197 (61.9%)
Adjuvant Chemotherapy				
No	4 (3%)	-	-	4 (1.3%)
Yes	132 (97%)	-	51 (100%)	183 (58.2%)
Unknown	-	127 (100%)	-	127 (40.5)

* indicates valid proportion has been calculated (i.e., not considering "unknown")

When using the LNR classification, 88 patients were categorized as zero, 91 as low risk (>0 and <0.2), 82 as intermediate risk (0.2 to 0.65) and 53 as high risk (>0.65 to 1) LNR. For classic ypN staging, 88 were ypN0, 126 ypN1, 58 ypN2 and 42 ypN3. Five year survival probabilities for the patients stratified by LNR were 84%, 69%, 53% and 37% for zero, low (>0 and <0.2), intermediate (0.2 to 0.65) and high risk (>0.65 to 1) groups respectively (Table 6.8). In comparison to this, the 5 year survival probabilities for the patients stratified by ypN classification were 84%, 64%, 57% and 30% for ypN0, ypN1, ypN2 and ypN3 respectively (Figure 6.2).

Table 6.7 Axillary nodal status of the patients treated with neoadjuvant chemotherapy

Place of diagnosis / Variable	Singapore N=136	Geneva N=127	Kuala Lumpur N=51	Combined N=314
Regional nodes examined				
Median	13	14	10	13
1-3	2 (1.5%)	2 (1.6%)	7 (13.7%)	11 (3.5%)
4-9	27 (19.9%)	24 (18.9%)	15 (29.4%)	66 (21.0%)
≥10	107 (78.7%)	101 (79.5%)	29(56.9%)	237 (75.5%)
Regional nodes positive (ypN stage)				
Median	2	2	2	2
0	44 (32.4%)	34 (26.8%)	10 (19.6%)	88 (28.0%)
1-3	48 (35.3%)	57 (44.9%)	21 (41.2%)	126 (40.1%)
4-9	25 (18.4%)	22 (17.3%)	11 (21.6%)	58 (18.5%)
≥10	19 (14%)	14 (11%)	9 (17.6%)	42 (13.4%)
LNR				
Median	0.14	0.13	0.38	0.16
0	44 (32.4%)	34 (26.8%)	10 (19.6%)	88 (28.0%)
0.01-0.2	37 (27.2%)	44 (34.6%)	10 (19.6%)	91 (29.0%)
0.201-0.65	33 (24.3%)	33 (26.0%)	16 (31.4%)	82 (26.1%)
0.651-1	22 (16.2%)	16 (12.6%)	15 (29.4%)	53 (16.9%)

In univariate analysis, place of diagnosis, year of diagnosis, ethnicity, receptor status (ER and PR), hormone therapy, differentiation, stage, tumor size, ypN staging and LNR were independently and significantly associated with all cause mortality (Table 6.9).

Figure 6.2 Kaplan Meier survival curves by LNR and ypN stage (in the neoadjuvant setting).

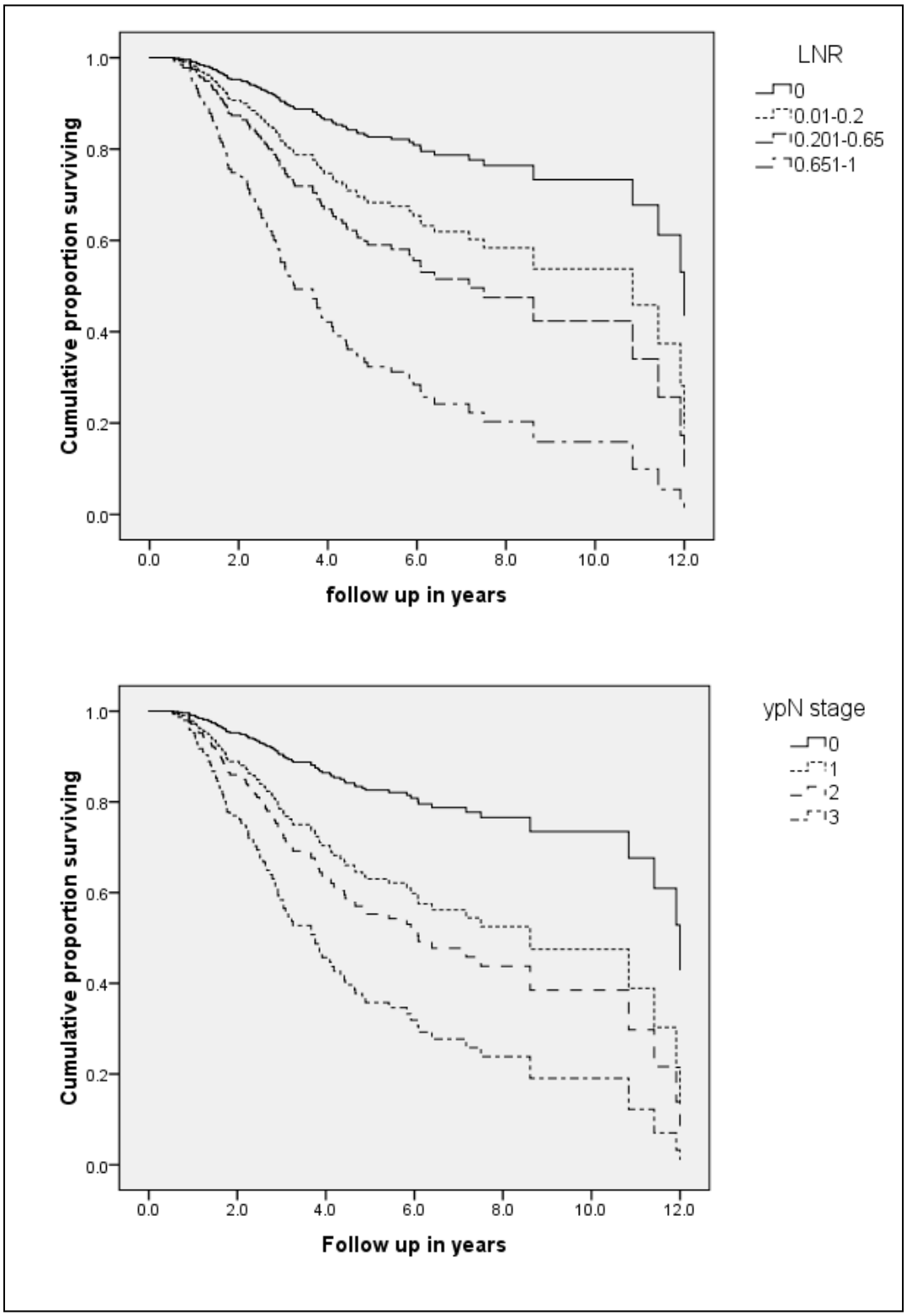


Table 6.8 Survival probabilities by LNR and ypN classification (neoadjuvant pathological lymph node status).

Variable	1 year survival probability (95% CI)	3 year survival probability (95% CI)	5 year survival probability (95%CI)
LNR			
0	1.00 (0.98-1.02)	0.89 (0.86-0.91)	0.84 (0.81-0.87)
Low ≤0.20	0.99 (0.97-1.00)	0.82 (0.64-1.00)	0.69 (0.67-0.71)
Intermediate >0.20 and ≤0.65	0.99 (0.97-1.00)	0.76 (0.74-0.77)	0.53 (0.51-0.54)
High >0.65	0.91 (0.90-0.92)	0.55 (0.54-0.56)	0.37 (0.35-0.38)
ypN			
0	1.00 (0.98-1.02)	0.89 (0.86-0.91)	0.84 (0.81-0.87)
ypN1	0.97 (0.96-0.98)	0.78 (0.77-0.79)	0.64 (0.62-0.65)
ypN2	0.97 (0.96-0.98)	0.74 (0.72-0.75)	0.57 (0.55-0.59)
ypN3	0.98 (0.95-1.00)	0.59 (0.57-0.61)	0.30 (0.29-0.31)

Compared to patient classified as low risk LNR (>0 and <0.2), those with LNR zero had an adjusted mortality (adjusted hazard ratio [HRadj]) of 0.4 (95%CI, 0.2 to 0.9), those with intermediate risk LNR had an HRadj of 1.2 (95%CI, 0.7 to 2.2) and those with high LNR an HRadj of 2.7 (95%CI, 1.5 to 5.0) Similarly, ypN classification adjusted mortality risks for ypN0 patients was HRadj 0.3 (95%CI, 0.2 to 0.7) , for ypN2 patients was HRadj 1.1 (95%CI, 0.6 to 2.0) and for ypN3 patients was HRadj 2.2 (95%CI, 1.3 to 3.8) compared to ypN1 patients (Table 6.10).

Almost a quarter (N= 77) of the patients had less than 10 lymph nodes excised.We performed a subgroup analysis to determine whether LNR had better prognostic value than ypN for this subset of patients. Compared to patient classified as low risk LNR (>0 and <0.2) (N=10), the HRadj for LNR zero (N=28) was 0.1 (95% CI, 0.02 to 0.9), intermediate risk LNR (N=24) was 0.8 (95%CI, 0.2 to 3.7) and high risk LNR (N=15) was 3.6 (95%CI 0.8 to 15.0).

Table 6.9 Univariate Cox Regression analysis for variables associated with all cause mortality for patients treated with neoadjuvant chemotherapy.

Variable	Unadjusted HR (95% CI)	P value
Place of Diagnosis		<0.001
Singapore	1	
Geneva	0.2 (0.1-0.4)	
Kuala Lumpur	1.2 (0.7-2.0)	
Age (continuous)	1.02 (1.00-1.04)	0.048
Ethnicity*		<0.001
Chinese	1	
Malay	1.9 (1.1-3.3)	
Indian	1.3 (0.7-2.6)	
Caucasian and other	0.3 (0.1-0.5)	
ER status		0.032
Negative	1	
Positive	0.6 (0.3-0.9)	
Unknown	1.1 (0.5-2.2)	
PR status		0.002
Negative	1	
Positive	0.5 (0.3-1.0)	
Unknown	1.7 (1.0-2.7)	
Radiotherapy		0.102
No	1	
Yes	0.6 (0.3-1.1)	
Hormone Therapy		0.002
No	1	
Yes	0.5 (0.3-0.7)	
Grade		0.011
Good	1	
Moderate	2.5 (0.7-8.2)	
Poor	4.2(1.3-13.8)	
Unknown	2.1(0.5-7.9)	
Tumor size		<0.001
<2 cm	1	
2-5 cm	2.2(0.2-18.5)	
>5 cm	4.3(0.6-31.9)	
Unknown	1.7(0.2-12.6)	
Stage		0.015
1	0.1 (0.05-0.5)	
2	1	
3	2.6 (1.4-4.7)	
Unknown	2.9 (1.1-7.8)	
Regional nodes examined		0.632
1-3	1.5 (0.6-3.9)	
4-9	1.0 (0.6-1.7)	
≥ 10	1	
LNR		<0.001
0	0.5 (0.2-1.0)	
Low , ≤0.20	1	
Intermediate, >0.20 and ≤0.65	1.4 (0.8-2.5)	
High, >0.65	3.0 (1.7-5.4)	
ypN stage		<0.001
0	0.4 (0.2-0.7)	
1	1	
2	1.3 (0.7-2.2)	
3	2.4 (1.4-4.0)	

Similarly, when compared to ypN1 patients (N=36), the HRadj for ypN0 patients (N=28) was 0.1 (95%CI, 0.01 to 0.5) and for ypN2 patients(N=13) was 2.1 (95%CI, 0.7 to 6.1). Even though it seems that LNR may have some added value over ypN in identifying patients at highly increased risk of death, the number of patients in our study was too limited to allow firm conclusions for this subset of patients.

Table 6.10 Hazard ratios for LNR and ypN classification for all cause mortality

Variable	**Unadjusted HR (95%CI)**	**Adjusted HR (95%CI)**	**P value for adjusted HR**
LNR			<0.001
0	0.5 (0.2-1.0)	0.4 (0.2-0.9)	
Low , ≤0.20	1	1	
Intermediate, >0.20 and ≤0.65	1.4 (0.8-2.5)	1.2 (0.7-2.2)	
High, >0.65	3.0 (1.7-5.4)	2.7 (1.5-5.0)	
ypN			<0.001
0	0.4 (0.2-0.7)	0.3 (0.2-0.7)	
ypN1	1	1	
ypN2	1.3 (0.7-2.2)	1.1 (0.6-2.0)	
ypN3	2.4 (1.4-4.0)	2.2 (1.3-3.8)	
HR- Hazard Ratio HRs adjusted for Age, PR status, Place of diagnosis and Radiotherapy.			

Discussion

The results of this study show that axillary nodal status of patients treated with neoadjuvant chemotherapy is strongly associated with overall mortality. Both the absolute number of positive lymph nodes involved (current ypN staging) as well as the LNR are among the strongest prognostic factors in this patient category. LNR and ypN classification were comparable in predicting mortality in this group of patients.

The past few decades has seen a rapid rise in the role and complexity of neoadjuvant chemotherapy for breast cancer [266]. Neoadjuvant chemotherapy enables doctors to *in vivo* monitor the response to chemotherapy [267], although it is not associated with

improved survival as compared to adjuvant chemotherapy [267, 268]. The broader use of neoadjuvant chemotherapy has led to challenging complexities in breast cancer staging. Clinical staging, i.e., preoperative staging based on clinical and radiographic examination and pathological staging, i.e., postoperative staging based on lymph node involvement and tumor size might vary significantly for patients who have responeded well to neoadjuvant chemptherapy [269]. It is unclear whether the initial clinical staging or the final pathological staging is more meaningful in terms of prognosis and treatment options for patients receiving neoadjuvant chemotherapy [269] and the effect of neoadjuvant chemotherapy on lymph node involvement is still uncertain. The number of lymph nodes retrieved and examined is highly dependent on surgical expertise, the institution's protocol and the pathologists' experience [253]. Removal of at least 10 axillary lymph nodes is considered adequate for reliable lymph node staging [254-256]. In the neoadjuvant setting, certain studies have shown that patients undergoing neoadjuvant chemotherapy have a significantly lower number of lymph nodes excised compared to patients undergoing surgery without preoperative chemotherapy [270, 271] while another study concluded otherwise [251]. Since the number of positive lymph nodes is one of the most important and well established prognostic factors in patients treated with primary surger it is important for us to elucidate its role in the neoadjuvant setting.

To date only one comprehensive study has looked at the prognostic value of the lymph node ratio in the neoadjuvant setting [142]. This study concluded that the LNR was an independent prognostic factor for relapse free and overall survival. Another study (only presented in abstract form [272]) also looked into the prognostic value of the LNR in the

neoadjuvant setting and also concluded that LNR was a significant prognostic factor for overall survival and superior to ypN.

Our research indicates that patients with higher LNR had a poorer survival probability which was in accordance with other studies [22, 24, 143, 273]. On comparing the current ypN classification and LNR, we did not notice substantial differences in hazard ratios for all cause mortality. Even though it seems that for patients with less than 10 lymph nodes removed, LNR may have some added value over ypN in identifying patients at highly increased risk of death, the number of patients in our study was too limited to allow firm conclusions for this subset of patients.

Patients from Singapore and Kuala Lumpur presented with larger tumors that were more often poorly differentiated as compared patients from Geneva. Although the median number of positive nodes for the three centers was the same, a greater proportion of patients from the Singapore and Kuala Lumpur center were categorized into the ypN2 and ypN3 categories than patients from the Geneva center. This could suggest that larger tumor size led to greater number of lymph nodes being involved as seen from the Singapore and Kuala Lumpur centers which is in accordance with previous studies [274].

This is one of the first studies indicating that lymph node status, be it ypN or LNR, is of prognostic value in patients treated with neoadjuvant chemotherapy. Even though several studies in the non-neoadjuvant setting have shown that the LNR is a superior prognostic indicator than the current ypN staging [22-25], our findings do not support this.

We acknowledge that our study suffers from several shortcomings, including a limited number of patients and a relatively short follow up time. In addition, we assessed all

cause mortality as our end point as no data on cause of death or local recurrence were available. Lastly, the lack of information on variables like HER2/ NEU receptor status and socio-economic status left room for residual confounding. During our period of study, the South East Asian institutes (Kuala Lumpur and Singapore) followed a different pattern of chemotherapy administration as compared to the regimens adopted in Western countries. Although the chemotherapy regimens have now been redesigned in these institutes, we do agree that the difference in chemotherapy regimens could limit our findings.

The strength of this study lies in the fact that it is an international multicenter study. Data from the three registries were merged, justified by the similar distribution of age and tumor characteristics. Secondly, detailed information on treatment and tumor characteristics was available.

Conclusion

This international multicentre study shows that lymph node status after neoadjuvant chemotherapy is informative. In the neoadjuvant setting, lymph node ratio does not seem to be superior to the ypN classification.

Chapter 7 Conclusion

This thesis looks at clinical outcomes of breast cancer patients from Singapore and Malaysia. Although outcome of Singaporean breast cancer patients was better than the Malaysian counterparts, there is still some way to go before Singaporean patients can achieve survival rates observed in the SEER population.

Elderly Singaporean patients present with advanced stage disease and are less likely to receive adequate treatment compared to the younger patients. Elderly patients were also more likely to have poorer relative survival overall but this difference substantially reduced after stage stratification.

Based on the results from the LNR studies, it is clear that cut off points for LNR established in Geneva, Switzerland do not add any prognostic value over the current pN staging system for Singaporean and Malaysian patients. Further work looking at factors such as SES, education, treatment compliance, method of breast cancer detection, housing type and cultural and financial barriers and their impact on survival need to be addressed.

The overall burden of breast cancer is shifting substantially to vulnerable populations in ill-prepared developing countries. In the past few decades, Asia has seen rapid economic growth resulting in increasing life expectancies, declining mortality from infectious diseases and Westernization of lifestyles. A consequence of such changes has been an increase in breast cancer incidence across Asia with rates increasing by up to 30% in the last decade for countries like India and China. Singapore has seen a threefold increase in incidence rate from 1968 to 2007. These alarming statistics added to the fact that Asia is

the most populous of continents seems to suggest that a majority of new breast cancer cases will arise from Asia in the near future.

With the growing global heath inequalities, very little attention is being paid to the rising toll of cancer patients in developing countries. Today, a person's odds of surviving after cancer diagnosis or even receipt of appropriate treatment, including basic palliative care, is strongly correlated with where that person live [275]. With the globalization of breast cancer, it is essential for us to focus on Asian women, who are relatively understudied. It is common practice among both clinicians and researchers to superimpose findings conducted in the Western populations, onto other ethnic groups. This might not be a rational approach given the differences in life expectancy, socioeconomic status, lifestyles, culture, diet and health beliefs among Western and Asian women as these factors may contribute towards breast cancer incidence and prognosis.

Conducting clinical research in Asia is not only about gaining knowledge but also about transforming daily clinical practice and guiding policy makers to perform heath transformation and rethink their funding priorities. With the rapid industrialization of most Asian countries, breast cancer will soon be one of the leading causes of death overtaking infectious diseases in Asia and it is essential for governments in developing Asian countries to be equipped for this. An estimated 1.7 million cases of breast cancer will arise in 2020 with a majority of the cases being from developing countries [14]. Experts have warned that most of these nations will not be prepared to face this crisis as they do not have the infrastructure in place to prevent cancer, diagnose it early or provide long term treatment [275].

Although breast cancer incidence is lower in Asian countries as compared to the West, this should not be an excuse for inaction [12]. Branding breast cancer as "low priority" [276] will not benefit any nation and affirmative action needs to be taken immediately. Although international expert groups like Breast Health Global Initiative [12] and CanTreat International [275] have been lobbying to improve cancer prevention and control in developing countries, it should be the governments that proactively take action to combat cancer. Action in breast cancer prevention should encompass all areas such as improving early detection, imparting knowledge about the disease to the general population, providing access to adequate treatment and long term follow up as well as palliative care when necessary. The aim of this approach is to improve the survival rates and quality of life of Asian patients with breast cancer.

Breast cancer in Asian women – what can clinicians and researchers do?

National breast cancer registries are needed to facilitate health services planning and policy making. Where such registries don't exist yet or are in their infancy, hospital based registries could be used as a guide to establish the population based registries.

The Singapore Malaysia Breast Cancer Working Group hospital based Breast Cancer Registry was a first step in achieving the goal mentioned above [1]. To date, the registry contains information on over 6000 consecutive patients from two tertiary teaching hospitals namely, National University Hospital, Singapore and University of Malaya Medical Center, Kuala Lumpur, Malaysia. Over the past two years, members of this working group have performed various studies, among others, determining the prognostic factors for survival in Asian women with breast cancer [277, 278], validating prognostic

classification systems such as Lymph Node Ratio [32] and Adjuvant! Online [139] for Asian women, studying the impact of age on presentation, management and outcome of breast cancer among South East Asian women [32, 278].

Further studies focusing on studying the economic burden of the disease in South East Asia as well as improving patient quality of life and overall healthcare need to be conducted with special attention being paid to better understanding the root cause for poor survival in developing Asian countries. Studies looking at patients' outlook towards the disease and treatment selection and adherence and how this impacts survival, what underlying cultural beliefs lead women to present at late stages with large tumors – factors associated with delayed presentation among Asian women, possible explanations and implications of delayed treatment or non compliance to treatment due to cultural or financial factors are all vital for improving outcome of breast cancer patients from South East Asia.

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