World J Surg (2012) 36:2838–2846
DOI 10.1007/s00268-012-1746-2

World Journal of Surgery

Breast Cancer in South East Asia: Comparison of Presentation and Outcome Between a Middle Income and a High Income Country

Nakul Saxena · Mikael Hartman · Nirmala Bhoo-Pathy · Jennifer N. W. Lim · Tar-Ching Aw · Philip Iau · Nur Aishah Taib · Soo-Chin Lee · Cheng-Har Yip · Helena M. Verkooijen

Published online: 28 August 2012

Abstract
Background There are large differences in socio-economic growth within the region of South East Asia, leading to sharp contrasts in health-systems development between countries. This study compares breast cancer presentation and outcome between patients from a high income country (Singapore) and a middle income country (Malaysia) in South East Asia.
Methods Within the Singapore Malaysia Breast Cancer Registry we identified all consecutive patients diagnosed with breast cancer between 1993 and 2007 at the National University Hospital in Singapore (high income country, $n = 2{,}141$) and the University of Malaya Medical Center in Kuala Lumpur, Malaysia (middle income country, $n = 3{,}320$). We compared demographics, tumor characteristics, treatment patterns, and survival between patients from both countries.
Results In Malaysia, patients were less often diagnosed with in situ breast cancer (adjusted odds ratio [ORadj] 0.2; 95 % confidence interval [95 % CI] 0.1–0.3), more likely to be diagnosed with late stage (III and IV) disease (ORadj for stage III 1.6; 95 % CI 1.3–2.0; ORadj for stage IV 1.2; 95 % CI 1.1–1.4) as compared to patients from Singapore. Univariate analysis showed that Malaysian patients were at a 72 % increased risk of death as compared to Singaporeans. After adjusting for other prognostic factors, the risk decreased by only 5 % (ORadj 1.67, 95 % CI 1.44–1.92).

N. Saxena · M. Hartman (✉) · H. M. Verkooijen
Saw Swee Hock School of Public Health, National University of Singapore, MD3 16 Medical Drive, Singapore 117597, Singapore
e-mail: mikael_hartman@nuhs.edu.sg

M. Hartman · P. Iau
Department of Surgery, Yong Loo Lin School of Medicine, National University of Singapore, MD3 16 Medical Drive, Singapore 117597, Singapore

N. Bhoo-Pathy
National Clinical Research Centre, Level 3, Dermatology Block, Hospital Kuala Lumpur, Jalan Pahang, 50586 Kuala Lumpur, Malaysia

N. Bhoo-Pathy
Julius Center for Health Sciences and Primary Care, University Medical Center, PO Box 85500, 3508 GA Utrecht, The Netherlands

J. N. W. Lim
Leeds Institute for Health Sciences, Faculty of Medicine and Health Sciences, University of Leeds, Charles Thackrah Building, 102 Clarendon Road, Leeds LS2 9LJ, United Kingdom

T.-C. Aw
Department of Community Medicine, United Arab Emirates University, PO Box 17666, Al-Ain, United Arab Emirates

N. A. Taib · C.-H. Yip
Department of Surgery, Faculty of Medicine, University of Malaya, 50603 Lembah Pantai, Kuala Lumpur, Malaysia

S.-C. Lee
Department of Hematology Oncology, National University Cancer Institute, National University Health System Singapore, Singapore 119228, Singapore

H. M. Verkooijen
Department of Radiology, University Medical Center Utrecht, PO Box 85500, 3508 GA Utrecht, The Netherlands

Conclusions Differences in way of presentation (except stage and tumor size) and treatment of breast cancer patients from the two countries are small. The overall survival of breast cancer patients from Malaysia is much lower than that of Singaporean patients.

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 income and middle income countries [1, 2]. Over recent decades, South East Asia has seen large differences in socio-economic growth, leading to sharp contrasts in health systems developments between countries [2].

Compared to Western countries, where breast cancer incidence rates have stabilized or even decreased over the last two decades [3–5], most Asian countries have seen a rapid rise in breast cancer incidence [6–10]. 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 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 [11]. Classified as a high income Asian country, Singapore sees a 95 % literacy rate and a life expectancy at birth of 81 years [12]. Rapid economic growth and low unemployment rates [12] have converted Singapore from a developing to a developed country within three decades [13], 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 [14]. Current healthcare provision in Singapore is considered at par with that from other developed countries [14].

Like Singapore, Malaysia also comprises three major ethnic groups—i.e., Malay (~54 %), Chinese (~26 %), and Indians (~8 %) [15], with a life expectancy at birth of 74 years [15]. An upper middle income country [16], Malaysia has seen sustained economic growth over the past few years, with an increasing proportion of people falling into the middle class category [17]. 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 [18].

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) [19–23]. Incidence rates of breast cancer in Singapore (developed country) and Malaysia (less developed country) are 60.0 and 46.2 per 100,000 populations, respectively [24, 25]. 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 [20, 26].

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

Materials and methods

Data for this study were obtained from the Singapore Malaysia Breast Cancer Hospital Based Registry [27]. 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 was started in 1995 and contains information on 2,449 consecutive breast cancer patients diagnosed between 1990 and 2007. From the NUH registry we selected 2,141 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 [27, 28]. 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, nodal status (pN0, pN1, pN2, pN3, and unknown), regional nodes examined (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 neoadjuvant 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 by logistic regression analysis. Age at diagnosis and tumor size (as continuous variables) were presented as a median and compared with the Mann-Whitney *U*-test.

The 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 with the chi square test.

Kaplan-Meier analysis and the log rank 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 Malaysia as compared to those treated in Singapore. To gain 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 (HR) representing the relative risk of death of patients from Malaysia as compared to those from Singapore. The second model presented HR 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 type, radiotherapy, chemotherapy, and hormone therapy.

All analyses were performed with SPSS version 16, and a p value <0.05 was considered significant.

Results

The median follow-up for the Malaysian and Singaporean patients was 5.1 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 0.1–0.3) and more likely to be diagnosed with advanced disease [(22.3 versus 14.4 %, respectively, for stage III; ORadj 1.6; 95 % CI 1.3–2.0); 10.8 versus 7.9 %, respectively, for stage IV; ORadj 1.2; 95 % CI 1.1–1.4)] as compared to Singaporean patients (Table 1). The tumor size of Malaysian patients was larger than that of Singaporean patients (median tumor size 30 mm compared to 22 mm; p <0.001). Malaysian patients were more likely not to undergo surgery for stage I–III disease (9.0 versus 0.6 %, respectively; p value <0.001) (Table 2). Malaysian patients with invasive, non metastatic disease were less likely to receive radiotherapy (RT) following BCS as compared to the Singaporean patients (78.0 versus 89.8 %, respectively; p value <0.001) (Fig. 1). Malaysian women were just as likely to receive chemotherapy for estrogen receptor (ER) negative lymph node (LN) positive disease (87.6 % compared to 90.1 %; 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.

A total of 209 (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 to 80.0 %; log rank test p <0.001) (Fig. 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 3).

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. 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), 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 1.44–1.92) (Table 5). Patients diagnosed in both countries receiving incomplete locoregional treatment or no surgery for invasive disease had a similar risk of death, whereas Malaysian patients receiving chemotherapy or presenting with node negative disease had a significantly higher risk of death than their Singaporean counterparts (Table 6).

Discussion

This study highlights important differences in survival between breast cancer patients from tertiary hospitals in Singapore (high income country) and Malaysia (middle

Table 1 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, (years)[a]				
median (range)	50 (21–95)	50 (22–93)		
<40	480 (14.5 %)	282 (13.2 %)	1	1
40–59	2060 (62.0 %)	1398 (65.3 %)	0.8 (0.7–1.0)	1.0 (0.8–1.2)
≥60	780 (23.5 %)	461 (21.5 %)	0.9 (0.8–1.1)	1.3 (0.9–1.7)
Ethnicity				
Chinese	2112 (63.7 %)	1663 (77.7 %)	1	1
Malay	733 (22.1 %)	242 (11.3 %)	2.3 (2.0–2.7)	2.0 (1.6–2.4)
Indian	423 (12.7 %)	112 (5.2 %)	2.9 (2.3–3.6)	2.7 (2.0–3.6)
Other	52 (1.6 %)	124 (5.8 %)	0.3 (0.2–0.4)	0.3 (0.2–0.5)
Estrogen receptor status[b,c]				
Negative	1188 (44.2 %)	747(42.1 %)	1	1
Positive	1495 (55.8 %)	1027 (57.9 %)	0.9 (0.8–1.0)	1.1 (0.8–1.3)
Unknown	542	165	0.8 (0.4–1.4)	0.1 (0.1–0.2)
Progesterone receptor status[b,c]				
Negative	1044 (50.6 %)	770 (43.7 %)	1	1
Positive	1019 (49.4 %)	992 (56.3 %)	0.7 (0.6–0.8)	0.7 (0.6–0.8)
Unknown	1162	177	2.1 (1.8–2.4)	2.6 (1.9–3.0)
Stage				
In situ	95 (2.9 %)	202 (10.0 %)	0.3 (0.2–0.4)	0.2 (0.1–0.3)
I	718 (21.6 %)	502 (24.7 %)	1	1
II	1406 (42.4 %)	870 (42.9 %)	1.1 (0.9–1.3)	0.8 (0.6–1.0)
III	736 (22.3 %)	293 (14.4 %)	1.7 (1.4–2.0)	1.6 (1.3–2.0)
IV	351 (10.8 %)	162 (7.9 %)	1.5 (1.2–1.8)	1.2 (1.1–1.4)
Unknown	14	112	0.1 (0.1–0.2)	0.1 (0.1–0.2)
Cell differentiation[b–e]				
Good	232 (10.2 %)	239 (13.9 %)	0.6 (0.5–0.8)	0.4 (0.3–0.9)
Moderate	1130 (49.8 %)	769 (44.7 %)	1	1
Poor	902 (40 %)	724 (41.2 %)	0.8 (0.7–1.0)	0.5 (0.4–0.8)
Unknown	961	207	3.1 (2.6–3.7)	2.9 (2.2–3.8)
Tumor size[b–d]				
Median (range), (mm)	30 (2–370)	22(3–200)		
0.1 to 2 (cm)	947 (30.2 %)	587 (44.4 %)	0.6 (0.5–0.7)	0.9 (0.7–1.1)
2.1 to 5 (cm)	1432 (45.7 %)	571 (43.2 %)	1	1
>5 (cm)	755 (24.1 %)	163 (12.4 %)	1.8 (1.5–2.2)	1.5 (1.1–1.9)
Unknown	91	618	0.1 (0.1–0.2)	0.1 (0.1–0.2)
Regional nodes examined[c]				
0	19 (0.5 %)	154 (7.9 %)	0.1 (0.1–0.2)	0.1 (0.1–0.2)
1–3	70 (2.2 %)	128 (6.6 %)	0.3 (0.2–0.4)	0.3 (0.2–0.4)
4–9	570 (17.7 %)	241 (12.4 %)	1.4 (1.2–1.7)	1.5 (1.2–1.8)
≥10	1861 (57.7 %)	1160 (59.8 %)	1	1

Table 1 continued

Variable	Country		Unadjusted or (95 % CI)	Adjusted or (95 % CI)
	Malaysia (n = 3,320)	Singapore (n = 2,141)		
Unknown	707 (21.9 %)	256 (13.2 %)	1.7 (1.4–2.0)	5.8 (3.1–10.8)
Regional nodes positive[b–d] (nodal status)				
pN0	1,383 (53.0 %)	856 (55.7 %)	1	1
pN1	634 (24.3 %)	373 (24.3 %)	1.0 (0.9–1.2)	0.8 (0.6–0.9)
pN2	342 (13.2 %)	199 (13.1 %)	1.0 (0.8–1.2)	0.7 (0.5–0.9)
pN3	246 (9.5 %)	107 (6.9 %)	1.4 (1.1–1.8)	1.1 (0.8–1.5)
Unknown	620	404	0.9 (0.8–1.1)	0.1 (0.1–0.3)

[a] Mann-Whitney U-test p value >0.05

[b] Valid proportions have been calculated

[c] Excluding in situ patients

[d] Logistic regression model adjusted for age, ethnicity, *ER* estrogen receptor status, and *PR* progesterone receptor status. All other *OR* odds ratios are adjusted for age, ethnicity, ER status, PR status, and stage

[e] Mann-Whitney U-test p value <0.001. *95 % CI* 95 % confidence interval

Table 2 Treatment administered to nonmetastatic invasive breast cancer 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 (10.9–37.9)	20.6 (11.4–50.2)
Mastectomy	1,963 (68.6 %)	1155 (69.4 %)	1	1
Breast conserving	641 (22.4 %)	500 (30.0 %)	1.0 (0.9–1.5)	0.6 (0.5–1.0)
Radiotherapy				
No	1,355 (47.4 %)	754 (45.3 %)	1	1
Yes	1,505 (52.6 %)	911(54.7 %)	0.9 (0.8–1.0)	0.9 (0.7–1.0)
Chemotherapy				
No	1,061 (37.2 %)	635 (38.1 %)	1	1
Yes	1,799 (62.8 %)	1,030 (61.9 %)	1.0 (0.9–1.1)	1.4 (1.3–1.7)
Hormone therapy				
No	1,189 (41.6 %)	540 (32.4 %)	1	1
Yes	1,671 (58.4 %)	1125 (67.6 %)	0.6 (0.5–0.7)	0.5 (0.7–1.0)
Neoadjuvant chemotherapy[a]				
No	2,662 (93.1 %)	1,481 (90.9 %)	1	1
Yes	198 (6.9 %)	150 (9.1 %)	0.7 (0.5–1.0)	0.3 (0.2–0.4)
Unknown	2	36	0.1 (0.1–0.2)	0.1 (0.1–0.2)

[a] Valid proportions have been calculated. All ORs are adjusted for age, ethnicity, ER status, PR status, and stage

income country). Despite only small differences in way of presentation and access to treatment, Malaysian patients were more than 60 % more likely to die within the first 5 years after diagnosis than the Singaporean patients. 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 [29–34]. Although incidence rates of breast cancer are lower in middle income countries than in high income countries, 55 % of breast cancer deaths occur in low income countries, a finding that can be attributed to two major determinants: namely, late stage at presentation and inadequate treatment [35, 36]. In a comparative study of 12

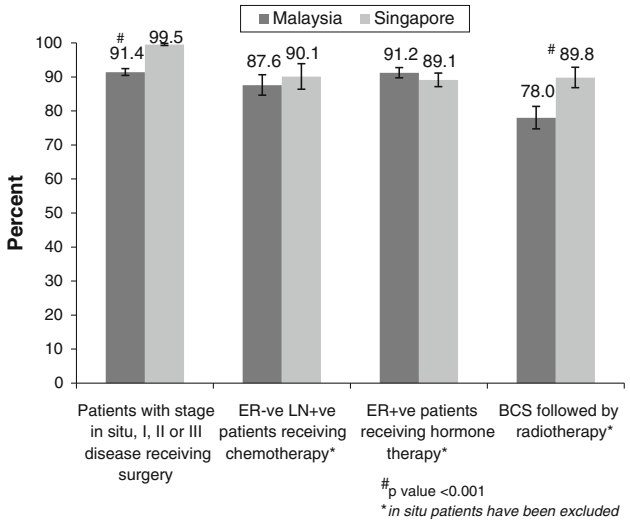
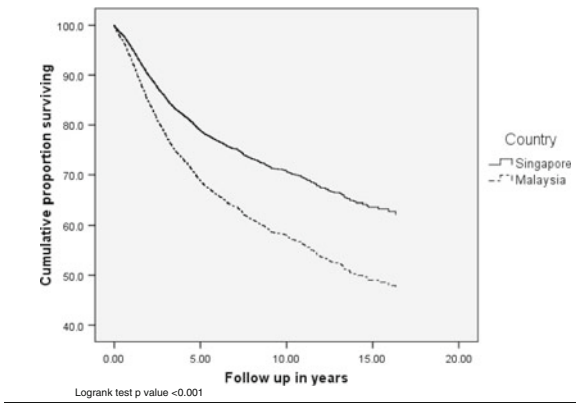


Fig. 1 Country stratified differences in proportion of stage in situ, I, II, and III patients receiving surgery; ER negative LN positive patients receiving chemotherapy; ER positive patients receiving hormone therapy; and patients receiving BCS followed by radiotherapy (excluding metastatic cases and cases with unknown stage)



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

Fig. 2 Life table estimates for Malaysia and Singapore (excluding in situ patients)

countries in Africa, Asia, and Central America, differences in cancer outcome correlated with level of development of health services [37].

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 reluctance to approach physicians due to cultural taboos are more prevalent [25, 38].

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

Large differences in breast cancer survival rates between Singaporean and Malaysian patients highlight a scope for improvement in the management of breast cancer in

Table 3 Five-year overall survival estimates for Malaysia and Singapore (excluding in situ patients)

Country 5 year survival estimate	Malaysia (n = 3,225) (%)	Singapore (n = 2,227) (%)
Overall	69.0 (67.0–71.1)	80.0 (79.0–80.9)
By year		
1993–2000	62.0 (59.4–64.5)	79.0 (77.5–80.5)
2001–2007	73.0 (71.8–74.6)	81.0 (80.1–82.9)
By stage		
Stage I	93.0 (91.9–94.1)	98.0 (97.0–99.0)
Stage II	79.0 (77.8–80.3)	85.0 (83.7–86.3)
Stage III	52.0 (49.4–54.6)	66.0 (62.5–69.6)
Stage IV	12.0 (6.8–17.1)	23.0 (16.6–29.5)

Table 4 Stepwise modeling for Cox regression analysis

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, distant metastasis, and ER status
D	Hazard ratio adjusted for variables in "c" plus surgery type, radiotherapy, chemotherapy, and hormone therapy

Table 5 Cox regression models for all-cause mortality for invasive breast cancer patients

	Total	Singapore	Malaysia
Number of patients	5,164	1,939	3,225
Number of deaths	1,606	423	1,183
Hazard ratio (95 % CI)[a]		1 (ref)	1.72 (1.54–1.93)
Hazard ratio (95 % CI)[b]		1 (ref)	1.71 (1.53–1.92)
Hazard ratio (95 % CI)[c]		1 (ref)	1.71 (1.51–1.94)
Hazard ratio (95 % CI)[d]		1 (ref)	1.67 (1.44–1.92)

[a, b, c, d] Models described in Table 4

Table 6 Subgroup analysis—multivariate Cox regression models for all cause mortality (excluding in situ patients)

Subgroups	Singapore	Malaysia
Estrogen receptor positive		
HRadj[a]	1(ref)	1.72 (1.38–2.14)
Estrogen receptor negative		
HRadj[a]	1(ref)	1.65 (1.33–2.05)
No surgery[i]		
HRadj[b]	1(ref)	0.99 (0.37–2.62)
Surgery given[i]		
HRadj[b]	1(ref)	1.81 (1.53–2.15)
Stage I and II		
HRadj[c]	1(ref)	1.65 (1.36–1.99)
Stage III and IV		
HRadj[c]	1(ref)	1.57 (1.33–1.86)
Incomplete locoregional treatment[g,i]		
HRadj[d]	1(ref)	0.88 (0.45–1.70)
Complete locoregional treatment[h,i]		
HRadj[d]	1(ref)	1.84 (1.55–2.20)
Node negative[i]		
HRadj[e]	1(ref)	2.00 (1.42–2.81)
Node positive[i]		
HRadj[e]	1(ref)	1.65 (1.34–2.04)
Chemotherapy not given[i]		
HRadj[f]	1(ref)	1.66 (1.20–2.29)
Chemotherapy given[i]		
HRadj[f]	1(ref)	1.73 (1.42–2.11)

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

[b] Only stage I, II, and III patients included

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

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

[e] 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

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

[g] Cox model adjusted for age, ethnicity, year of diagnosis, tumor size, grade, nodal status, ER status, radiotherapy, surgery type, hormone therapy

[h] 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

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

Malaysia. Several factors, such as differences in population structure (life expectancy) [39, 40], low access to screening [41, 42], lower socio-economic status [26, 43], low access to high-quality healthcare [25], poor treatment compliance [44–46], poor lifestyle after diagnosis [47], and lack of knowledge of the disease and its outcome [48] among Malaysians could explain the disparities in survival between patients from Malaysia and Singapore. Several studies have shown that type of treatment received is associated with breast cancer survival [49–52], but from our study, it is unlikely that differences in treatment would explain the overall 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.

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 endpoint, as no data on cause of death were available. Third, because this is a hospital-based study rather than a population-based study, extrapolating 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 [28]. The 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 [27]. The presentation of breast cancer in the rural Malaysian settings for instance, may be more advanced than in our study [27]. Another limitation of our study is that some prognostic factors, such as co-morbidity, body mass index, HER2/neu status, and local/systemic recurrence were largely missing and hence their impact on our results will be difficult to gauge.

Conclusions

Differences in way of presentation (except stage and tumor size) and treatment of breast cancer patients from Singapore and Malaysia are small. Patients from Malaysia present slightly more often with advanced stage disease 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 could explain the higher mortality risk of Malaysian breast cancer patients.

Acknowledgments The Malaysian data were supported by HIR Grant UM.C/HlR/MOHE/06 from the Ministry of Higher Education, Malaysia. Nirmala Bhoo-Pathy was funded by the European Union through a PhD fellowship grant (AsiaLink program MY/AsiaLink/044[128–713]). This work was funded by the NUS Initiative to Improve Health in Asia (NIHA) Grant. Official Project Number: NIHA-2011-1-001. The authors are grateful to Kimberley S. K. Chua, Senior Research Coordinator at the National University Hospital, Singapore, for her help in data collection and verification.

Conflict of interest All authors indicate no potential conflict of interest.

References

1. Yip CH (2009) Breast cancer in Asia. Methods Mol Biol 471: 51–64
2. Yip CH, Cazap E, Anderson BO et al (2011) Breast cancer management in middle-resource countries (MRCs): consensus statement from the Breast Health Global Initiative. Breast 20(Suppl 2):S12–S19
3. Ravdin PM, Cronin KA, Howlader N et al (2007) The decrease in breast-cancer incidence in 2003 in the United States. N Engl J Med 356:1670–1674
4. Wang PP, Cao Y (1996) Incidence trends of female breast cancer in Saskatchewan, 1932–1990. Breast Cancer Res Treat 37:197–207
5. Fontenoy AM, Leux C, Delacour-Billon S et al (2010) Recent trends in breast cancer incidence rates in the Loire-Atlantique, France: a decline since 2003. Cancer Epidemiol 34:238–243
6. Takiar R, Srivastav A (2008) Time trend in breast and cervix cancer of women in India—(1990–2003). Asian Pac J Cancer Prev 9:777–780
7. Medina VM, Laudico A, Mirasol-Lumague MR et al (2010) Cumulative incidence trends of selected cancer sites in a Philippine population from 1983 to 2002: a joinpoint analysis. Br J Cancer 102:1411–1414
8. Sim X, Ali RA, Wedren S et al (2006) Ethnic differences in the time trend of female breast cancer incidence: Singapore, 1968–2002. BMC Cancer 6:261
9. Seow A, Koh WP, Chia KS et al. (2004) Trends In Cancer Incidence In Singapore 1968–2002 Singapore Cancer Registry, Singapore
10. Hirabayashi Y, Zhang M (2009) Comparison of time trends in breast cancer incidence (1973–2002) in Asia, from cancer incidence in five continents, Vols IV–IX. Jpn J Clin Oncol 39:411–412
11. Ministry of Health http://www.moh.gov.sg/mohcorp/statistics.aspx?id=5524. Accessed July 2011
12. World Bank. Country Classification http://data.worldbank.org/country/singapore. Accessed July 2011
13. Department of Statistics Singapore http://www.singstat.gov.sg/stats/latestdata.html. Accessed July 2011
14. Lim M-K (2009) Health Care Reforms in Singapore: Six Countries, Six Reform Models: The Health Care Reform, World Scientific Publishing Co. Pte. Ltd
15. Malaysia. US Department of State (2010) http://www.state.gov/r/pa/ei/bgn/2777.htm
16. World Bank. Country classification. http://data.worldbank.org/country/malaysia. Accessed July 2011
17. Barraclough S (1997) The growth of corporate private hospitals in Malaysia: policy contradictions in health system pluralism. Int J Health Serv 27:643–659
18. Francis T (2009) Health care in Malaysia: the dynamics of provision, financing and access. In: Barraclough S (ed) Heng Leng Chee SB. Routledge, London
19. Newman LA, Mason J, Cote D et al (2002) African-American ethnicity, socioeconomic status, and breast cancer survival. Cancer 94:2844–2854
20. Kogevinas M Pearce N, Susser M et al., eds. (1997) Social Inequalities and Cancer. IARC Scientific Publications no. 138, Lyon, France
21. Webster TF, Hoffman K, Weinberg J et al (2008) Community- and individual-level socioeconomic status and breast cancer risk: multilevel modeling on Cape Cod, Massachusetts. Environ Health Perspect 116:1125–1129
22. Barbone F, Filiberti R, Franceschi S et al (1996) Socioeconomic status, migration and the risk of breast cancer in Italy. Int J Epidemiol 25:479–487
23. Ferlay J, Shin H-R, Bray F et al (2010) Estimates of worldwide burden of cancer in 2008: GLOBOCAN 2008. Int J Cancer 127: 2893–2917
24. Singapore Cancer Registry Report (2010) Trends in cancer incidence in Singapore 1968–2007. http://www.nrdo.gov.sg/
25. Yip CH, Taib NA, Mohamed I (2006) Epidemiology of breast cancer in Malaysia. Asian Pac J Cancer Prev 7:369–374
26. Bouchardy C, Verkooijen HM, Fioretta G (2006) Social class is an important and independent prognostic factor of breast cancer mortality. Int J Cancer 119:1145–1151
27. Pathy NB, Yip CH, Taib NA et al (2011) Breast cancer in a multi-ethnic Asian setting: results from the Singapore-Malaysia Hospital-based breast cancer registry. Breast 20(Suppl 2):S75–S80
28. Lim SE, Back M, Quek E et al (2007) Clinical observations from a breast cancer registry in Asian women. World J Surg 31:1387–1392
29. Sant M, Allemani C, Capocaccia R et al (2003) Stage at diagnosis is a key explanation of differences in breast cancer survival across Europe. Int J Cancer 106:416–422
30. Gondos A, Bray F, Brewster DH et al (2008) Recent trends in cancer survival across Europe between 2000 and 2004: a model-based period analysis from 12 cancer registries. Eur J Cancer 44: 1463–1475
31. Pineda MD, White E, Kristal AR et al (2001) Asian breast cancer survival in the US: a comparison between Asian immigrants, US-born Asian Americans and Caucasians. Int J Epidemiol 30: 976–982
32. Moller H, Sandin F, Bray F et al (2010) Breast cancer survival in England, Norway and Sweden: a population-based comparison. Int J Cancer 127:2630–2638
33. Redaniel MT, Laudico A, Mirasol-Lumague MR et al (2010) Breast cancer survival in different country settings: comparisons between a Filipino resident population, Filipino-Americans and Caucasians. Breast 19:109–114
34. Li CI, Malone KE, Daling JR (2003) Differences in breast cancer stage, treatment, and survival by race and ethnicity. Arch Intern Med 163:49–56
35. Kamangar F, Dores GM, Anderson WF (2006) Patterns of cancer incidence, mortality, and prevalence across five continents: defining priorities to reduce cancer disparities in different geographic regions of the world. J Clin Oncol 24:2137–2150
36. Curado MP, Voti L, Sortino-Rachou AM (2009) Cancer registration data and quality indicators in low and middle income countries: their interpretation and potential use for the improvement of cancer care. Cancer Causes Control 20:751–756
37. Sankaranarayanan R, Swaminathan R, Brenner H et al (2009) Cancer survival in Africa, Asia, and Central America: a population-based study. Lancet Oncol 11:165–173
38. Dahlui M, Ramli S, Bulgiba AM (2011) Breast cancer prevention and control programs in Malaysia. Asian Pac J Cancer Prev 12: 1631–1634
39. Eley JW, Hill HA, Chen VW et al (1994) Racial differences in survival from breast cancer. Results of the National Cancer

Institute Black/White Cancer Survival Study. JAMA 272: 947–954
40. Ooi SL, Martinez ME, Li CI (2011) Disparities in breast cancer characteristics and outcomes by race/ethnicity. Breast Cancer Res Treat 127:729–738
41. Schopper D, de Wolf C (2009) How effective are breast cancer screening programmes by mammography? Review of the current evidence. Eur J Cancer 45:1916–1923
42. Kuhl CK, Schrading S, Leutner CC et al (2005) Mammography, breast ultrasound, and magnetic resonance imaging for surveillance of women at high familial risk for breast cancer. J Clin Oncol 23:8469–8476
43. Kaffashian F, Godward S, Davies T et al (2003) Socioeconomic effects on breast cancer survival: proportion attributable to stage and morphology. Br J Cancer 89:1693–1696
44. Lee-Feldstein A, Anton-Culver H, Feldstein PJ (1994) Treatment differences and other prognostic factors related to breast cancer survival. Delivery systems and medical outcomes. JAMA 271: 1163–1168
45. Early Breast Cancer Trialists' Collaborative Group (2005) Effects of chemotherapy and hormonal therapy for early breast cancer on recurrence and 15-year survival: an overview of the randomised trials. Lancet 365:1687–1717
46. Chong HY, Taib NA, Rampal S et al (2011) Treatment options for locally advanced breast cancer—experience in an Asian tertiary hospital. Asian Pac J Cancer Prev 11:913–917
47. Holmes MD, Chen WY, Feskanich D et al (2005) Physical activity and survival after breast cancer diagnosis. JAMA 293: 2479–2486
48. Taib NA, Yip CH, Low WY (2011) Recognising symptoms of breast cancer as a reason for delayed presentation in Asian Women—the psycho-socio-cultural model for breast symptom appraisal: ppportunities for intervention. Asian Pac J Cancer Prev 12:1601–1608
49. Schonberg MA, Marcantonio ER, Li D et al (2009) Breast cancer among the oldest old: tumor characteristics, treatment choices, and survival. J Clin Oncol 28:2038–2045
50. Early Breast Cancer Trialists' Collaborative Group (2011) Effect of radiotherapy after breast-conserving surgery on 10-year recurrence and 15-year breast cancer death: meta-analysis of individual patient data for 10 801 women in 17 randomised trials. Lancet 378:1707–1716
51. Nakul S, Mikael H, Zakir H et al (2011) Impact of older age on presentation, management and outcome of breast cancer in the multi-ethnic Asian population of Singapore. J Geriatric Oncol 2: 50–57
52. Krell J, James CR, Shah D et al (2011) Human epidermal growth factor receptor 2-positive breast cancer relapsing post-adjuvant trastuzumab: pattern of recurrence, treatment and outcome. Clin Breast Cancer 11:153–160