

Keywords: early breast cancer; stage I; Asian; mammography; screening; mastectomy

Spectrum of very early breast cancer in a setting without organised screening

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Background: Within a setting without organised breast cancer screening, the characteristics and survival of very early breast cancer were determined.

Methods: All 4930 women diagnosed with breast cancer in University Malaya Medical Center, Malaysia from 1993 to 2011 were included. Factors associated with very early presentation (stage I) at diagnosis were identified. Tumour characteristics, management patterns, and survival of very early breast cancer were described, and where appropriate, compared with other settings.

Results: Proportion of women presenting with stage I breast cancer significantly increased from 15.2% to 25.2% over two decades. Factors associated with very early presentation were Chinese ethnicity, positive family history of breast cancer, and recent period of diagnosis. Within stage I breast cancers, median tumour size at presentation was 1.5 cm. A majority of stage I breast cancer patients received mastectomy, which was associated with older age, Chinese ethnicity, postmenopausal status, and larger tumours. Chemotherapy was administered in 36% of patients. Five-year age-adjusted relative survival for women with stage I breast cancer was 99.1% (95% CI: 97.6–99.6%).

Conclusions: The proportion of women presenting with very early breast cancer in this setting without organised screening is increasing. These women seem to survive just as well as their counterparts from affluent settings.

While breast cancer incidence rates have stabilised or even decreased in affluent western countries, the incidence of breast cancer in most Asian countries continues to escalate over the past few decades (Wang and Cao, 1996; Ravdin *et al*, 2007; Porter, 2008; Fontenoy *et al*, 2010). Furthermore, a substantial proportion of Asian patients with breast cancer are diagnosed at advanced stages compared with their western counterparts rendering survival rates to suboptimal levels in this part of the world (Anderson *et al*, 2011).

Early detection is associated with better survival probabilities, where the 5 and 10-year survival rates for women diagnosed with stage 0 or I breast cancer range between 90% and 100% (Owen *et al*, 2013; Ries and Esner, 2013). The two cornerstones of early detection are awareness of the disease, and both opportunistic and population-based screening. While population-based screening mammography is implemented in many affluent western countries, it is argued as not being cost-effective in most of Asia (Woo *et al*, 2007; Okonkwo *et al*, 2008; Kang *et al*, 2013) and had been offered

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Received 5 December 2013; revised 7 March 2014; accepted 15 March 2014

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only in high-income countries including Japan since 1987, Korea since 1999, and Singapore since 2003 (Kwong *et al*, 2008; Lim *et al*, 2010).

Given that Asia has seen rapid socio-economic development over recent times, it is conceivable that awareness of (breast) cancer in the population has increased, leading to more women presenting at earlier stages of breast cancer despite the absence of organised breast cancer screening programs. Malaysia is a middle-income country in South East Asia, which comprises three major ethnic groups, that is, Malays, Chinese, and Indians. It does not implement population-based mammography screening programme, but adopts opportunistic screening where mammography is targeted and offered to high-risk women. Clinical breast examination (CBE) by trained health professionals and self-breast examination (SBE) are also widely advocated, but as a measure to increase breast cancer awareness among women at risk rather than as a screening method.

We sought to determine the trends in presentation of very early breast cancer (stage I), and the associated factors in a Malaysia setting. Tumour characteristics, management patterns, and survival of very early breast cancer were described, and where appropriate, compared with other settings.

MATERIALS AND METHODS

Patients from the University Malaya Medical Centre (UMMC) Breast Cancer Registry were included in the study. The UMMC is an academic tertiary hospital situated in the city of Kuala Lumpur, Malaysia and caters to a predominantly middle class urban population. Since 1993, all patients with newly diagnosed breast cancer have been entered into a hospital-based breast cancer registry, and data on demographics, tumour profile, and treatment have been collected prospectively (Bhoo Pathy *et al*, 2011). This registry has received the approval of UMMC's Ethical Review Committee.

Staging of primary breast cancer in UMMC consisted of physical examination, blood tests, chest X-ray, and liver ultrasound. Diagnostic work-up for the presence of distant metastasis was performed in symptomatic patients, and those with clinical stage III disease by means of computed tomography scan of thorax, abdomen +/- pelvis, as well as bone scan. Testing for Human Epidermal Growth Factor Receptor 2 (HER2) status was only routinely done after 2005.

The current study comprises 4930 women who were newly diagnosed with invasive breast cancer between 1993 and 2011. Women with missing information on stage at diagnosis were excluded ($n = 307$; 6%).

Study variables. All breast cancers were restaged according to the 7th edition of TNM American Joint Committee on Cancer (AJCC) system. Very early presentation was defined as presentation with AJCC stage I breast cancer at initial diagnosis, whereas more advanced presentation comprise AJCC stage II, stage III, or stage IV breast cancers. Data on patient's socio-demographic characteristics included age at diagnosis, ethnicity (Malay, Chinese, Indian, and other races), marital status (unmarried and married), parity (nulliparous, 1–2 children, and 3 or more children), and year of diagnosis (1993–1997, 1998–2002, 2003–2007, and 2008–2011). Data on risk factors include menopausal status (premenopausal and postmenopausal), and family history of breast cancer in first- or second-degree relative (present and absent). As information on education and occupation was only sparsely available, these variables were not included in this study. Variables on tumour characteristics included pathologically determined tumour size (available as continuous values in cm), oestrogen receptor (ER) status (positive when >10% of tumour cells stained positive

during immunohistochemical (IHC) testing, negative), tumour grade (Scarff–Bloom–Richardson classification; grade 1, grade 2 and grade 3), lymphovascular invasion (LVI) (present and absent), and HER2 status (positive when IHC testing = 3+, negative when IHC testing = 1+ or 2+).

Loco-regional treatment data included type of surgery (no surgery, mastectomy, breast conserving surgery (BCS)) and radiotherapy (yes and no). Systemic treatment data comprised chemotherapy (yes and no), type of chemotherapy (regime), and endocrine therapy (yes and no). While details on targeted therapy were not available for a majority of the patients, the use of such therapies was very low during the study period.

Follow-up and outcome assessment. Patients were monitored *via* scheduled appointments in the specialist breast clinic. Vital status was verified through direct linkage with the National Registration Department in Malaysia. Follow-up time was calculated from the date of diagnosis, to the date of death, or end of follow-up in February 2012.

Statistical analysis. Patient characteristics were compared between those presenting very early, and at later stages, in an initial univariable logistic regression analysis using very early presentation as the outcome. Variables with P -values of <0.20 were entered into a stepwise backward logistic regression to determine factors that were independently and significantly associated with very early presentation.

The National Institutes of Health (NIH) Consensus Development Conference recommendations were used as a reference to assess the treatment patterns of very early breast cancers in this middle-income setting. In 1990, the NIH Consensus Development Conference on treatment of patients with early breast cancer had recommended BCS for the majority of women with stage I or stage II disease (National Institutes of Health, 1990). The NIH Consensus Development Conference also recommends administration of adjuvant chemotherapy for node-negative breast tumours when tumour size is greater than 1 cm, irrespective of hormone receptor status (Eifel *et al*, 2001). Therefore, chemotherapy administration rate in this subgroup of women was assessed. In instances when the treatment patterns differ with the recommendations, stepwise backward logistic regression analysis was used to determine the predictors of treatment to better understand factors influencing such treatment decisions.

As causes of death for a large proportion of patients were not available, relative survival rate (RSR) following diagnosis of stage I breast cancer was estimated using the Ederer II method for expected survival (Coleman *et al*, 2008). Relative survival is the ratio of all-cause survival observed in patients with very early breast cancer in the current study, to the survival that would have been expected had they been subjected only to the mortality rates of the general population (background mortality). It can be interpreted as net survival attributable to (very early breast) cancer, after adjustment for other causes of death. Expected survival was derived from a life table that contained the probabilities of death or the central death rates for the general population in Malaysia, by single age, sex, and calendar year between 1993 and 2012. These life tables were obtained from the National Statistics Departments in Malaysia.

Given that the breast cancer patients in this setting tended to be younger, their RSRs were adjusted for age using the standard cancer population 1 (Corazziari *et al*, 2004) to enable international comparisons. The age-adjusted relative survival of patients in this study was subsequently compared with their counterparts diagnosed with stage I breast cancer during the same calendar period from several affluent settings (Walters *et al*, 2013).

RESULTS

Median age at diagnosis was 51 years with an inter-quartile range of 44–60 years. The majority of patients were married (~86%), and approximately half were postmenopausal at diagnosis (Table 1).

Breast cancer stage at presentation. In this study, 1155 women presented with stage I (23.4%), 1926 with stage II (39.1%), 1278 with stage III (25.9%), and 571 with stage IV (11.6%) breast cancer at diagnosis. The proportion of patients presenting with very early breast cancer (stage I) in UMMC substantially increased over time; 15.2% between 1993 and 1997, 21.5% in 1998–2002, 24.8% in 2003–2007, and 25.2% in 2008–2011 ($P < 0.001$). Between 2000 and 2007, ~24% of our patients presented with stage I disease.

During the entire study period, only 176 patients with stage 0 (carcinoma *in situ*) were seen in UMMC, comprising 2.2% of total breast cancers seen between 1993 and 1997, 2.8% in 1998–2002, 3.2% in 2003–2007, and 4.4% in 2008–2011.

Factors influencing very early breast cancer presentation. Very early presentation was significantly associated with Chinese

ethnicity, having one or two children, positive family history of breast cancer, and recent calendar periods of diagnosis (Table 1). Age at diagnosis, marital status, and menopausal status were not associated with stage at presentation. Stepwise backward logistic regression showed that only ethnicity, family history of breast cancer, and period of diagnosis were significantly and independently associated with very early presentation (Table 1).

Tumour characteristics. The median tumour size at presentation in patients with stage I breast cancer was 1.5 cm, with an inter-quartile range of 0.8–2.0 cm (Table 2). Most patients presented with grade 2 tumours (55.0%) followed by grade 3 (26.4%) and grade 1 (18.6%) tumours. Lymphovascular invasion was present in 28%. Oestrogen receptor was positive in 70% of patients, whereas progesterone receptor was positive in 62% of patients. About 26% of patients had HER2-positive tumours.

Treatment patterns. Among patients subjected to surgery, 52.9% received mastectomy, whereas 47.1% underwent BCS (Table 2). Patients receiving mastectomy were more likely to be older, postmenopausal, of Chinese ethnicity, having three or more children, diagnosed in the most recent period, and have

Table 1. Factors associated with very early presentation of breast cancer in a setting without organised screening

Characteristics	Overall (N = 4930)	Very early presentation (stage I) ^a n = 1155	More advanced presentation (stage II–IV) ^b n = 3775	Univariable odds ratio for very early presentation (95% CI)	Multivariable odds ratio for very early presentation ^c (95% CI)
Age, n (%)					
< 50 years	2177 (100.0)	494 (22.7)	1683 (77.3)	1.00	—
50–64 years	1961 (100.0)	469 (23.9)	1492 (76.1)	1.07 (0.93–1.24)	—
≥ 65 years	792 (100.0)	192 (24.2)	600 (75.8)	1.09 (0.90–1.32)	—
Race, n (%)					
Chinese	3179 (100.0)	852 (26.8)	2327 (73.2)	1.00	1.00
Malay	1054 (100.0)	166 (15.7)	888 (84.3)	0.51 (0.43–0.61) ^d	0.52 (0.43–0.63) ^d
Indian	615 (100.0)	112 (18.2)	503 (81.8)	0.61 (0.49–0.76) ^d	0.62 (0.50–0.77) ^d
Others	82 (100.0)	25 (30.4)	57 (69.6)	1.20 (0.74–1.93)	1.21 (0.75–1.95)
Parity, n (%)					
Nulliparous	788 (100.0)	182 (23.1)	606 (76.9)	1.00	—
1–2 children	1313 (100.0)	341 (26.0)	972 (74.0)	1.17 (0.95–1.44)	—
≥ 3 children	2134 (100.0)	473 (22.2)	1661 (77.8)	1.04 (0.85–1.27)	—
Unknown	695	159	536		
Family history^e, n (%)					
Yes	779 (100.0)	228 (29.3)	551 (70.7)	1.43 (1.20–1.70) ^d	1.37 (1.15–1.63) ^d
No	3649 (100.0)	820 (22.5)	2829 (77.5)	1.00	1.00
Missing	502	107	395		
Year of diagnosis, n (%)					
1993–1997	448 (100.0)	68 (15.2)	380 (84.8)	1.00	1.00
1998–2002	985 (100.0)	212 (21.5)	773 (78.5)	1.51 (1.09–2.09) ^d	1.54 (1.13–2.11) ^d
2003–2007	1678 (100.0)	416 (24.8)	1262 (75.2)	1.82 (1.37–2.42) ^d	1.79 (1.35–2.38) ^d
2008–2011	1811 (100.0)	457 (25.2)	1354 (74.8)	2.00 (1.50–2.64) ^d	1.80 (1.36–2.38) ^d
Unknown	8	2	6		

Abbreviation: CI = confidence interval.

^aIncluded 1155 patients with stage I breast cancers.

^bIncluded 1926 patients with stage II, 1278 stage III, and 571 stage IV breast cancers.

^cUsing stepwise backward logistic regression. Variables entered on step 1 are those with P -values ≤ 0.20 in the Chi-square test: age at diagnosis, ethnicity, parity, family history, and year of diagnosis. The P -values for marital status and menopausal status were > 0.20 . Final model includes ethnicity, family history, and year of diagnosis.

^dStatistically significant.

^eHistory of breast cancer in first- or second-degree relative.

Table 2. Tumour characteristics and treatment patterns of patients with stage I breast cancer

Tumour characteristics/treatment patterns ^a	N, %
Size, median in cm	1.5 (0.8, 2.0) ^b
Grade	
Well differentiated	165 (18.6)
Moderately differentiated	488 (55.0)
Poorly differentiated	235 (26.4)
Unknown	267
Oestrogen receptor status	
Positive	765 (69.9)
Negative	329 (30.1)
Unknown	61
Progesterone receptor status	
Positive	587 (62.0)
Negative	360 (38.0)
Unknown	208
HER2 status	
Positive	259 (26.3)
Negative	725 (73.7)
Unknown	171
Lymphovascular invasion	
Present	254 (27.9)
Absent	658 (72.1)
Unknown	243
Surgery	
No surgery	37 (3.2)
Breast conserving surgery	527 (45.6)
Mastectomy	591 (51.2)
Radiotherapy^c	
Yes	459 (92.5)
No	37 (7.5)
Unknown	31
Endocrine therapy^d	
Yes	701 (95.4)
No	34 (4.6)
Unknown	30
Chemotherapy	
Yes	402 (35.6)
No	727 (64.4)
Unknown	26
Chemotherapy regime^e	
First generation	30 (8.8)
Second generation	290 (85.6)
Third generation	19 (5.6)
Unknown	63

Abbreviation: HER2 = Human Epidermal Growth Factor Receptor 2.

^aIncluded 1155 patients with stage I breast cancer.

^b25th and 75th percentile values.

^cIncluded patients receiving breast conserving surgery only.

^dIncluded patients with hormonal receptor-positive breast cancers only.

^eIncluded patients receiving chemotherapy only.

larger tumours. Following multivariable logistic regression, only age at diagnosis, postmenopausal status, Chinese ethnicity, and tumour size were independently and significantly associated with mastectomy (Table 3).

Overall, radiotherapy was administered in 50% of the patients. A vast majority of patients subjected to BCS in the present study had received adjuvant radiotherapy (92.5%).

Among 765 patients with positive ER status in the current study, 701 have received endocrine therapy (95.4%). Chemotherapy was administered in 36% of patients with stage I breast cancer. A majority of patients receiving chemotherapy were given second-generation regimes (fluorouracil, epirubicin, and cyclophosphamide), whereas the use of third generation (taxane-based) regimes was low. Of 615 women with node-negative breast cancers measuring >1 cm, 259 had received chemotherapy (42%), irrespective of their hormone receptor status. Chemotherapy administration was independently associated with younger age at diagnosis, larger tumour size, higher tumour grades, the presence of LVI, ER-negative, and PR-negative status (Table 4).

Survival. The 5-year crude and age-adjusted relative survival of patients with stage I breast cancer in the current study were 97.8% (95% CI: 95.6–99.6%) and 99.1% (95% CI: 97.6–99.6%) respectively.

In women diagnosed with stage I breast cancer between the year 2000 and 2007, the 3-year age-adjusted relative survival was 99.5%, 95% CI: 97.5–99.9%.

DISCUSSION

An increasing number of women with breast cancer in this Malaysian setting are presenting very early despite the absence of an organised breast cancer screening program. Factors associated with very early presentation are Chinese ethnicity, a positive family history of breast cancer, and recent calendar period of diagnosis. More than half of the patients with stage I breast cancer in the current study received mastectomy, in particular those who were older at diagnosis, postmenopausal, of Chinese ethnicity, and having larger tumours. The 5-year age-adjusted relative survival of patients with very early breast cancer in the current study is very high (99.1%, 95% CI: 97.6–99.6%).

Clinical breast examination by a trained health-care professional had been offered to Malaysian women aged 20–65 years attending primary health-care services since 2009. At the same time, women are taught the technique of BSE. Women who screen positive by CBE are referred for diagnostic mammography and other investigations and management at an appropriate facility. Since 2012, a targeted mammographic screening programme for women at high risk of breast cancer, that is, strong family history or known breast abnormalities, had been made available.

A recent study by the International Cancer Benchmarking Partnership Working Group had compared invasive breast cancer presentation by stage between several affluent western countries. Between the year 2000 and 2007, it was found that the proportion of stage I breast cancer was 41% in Canada, 29% in Denmark, 43% in Norway, 45% in Sweden, and 40% in United Kingdom (Walters *et al*, 2013). Analysis within the same period in the current study showed that ~24% of patients presented with stage I disease. It is not surprising that the proportion of patients presenting at very early stages in the current study setting is much lower compared to above settings with organised screening mammography programme. However, the proportion of stage I breast cancer patients diagnosed before 2007 in this study (~24%) is somewhat closer to the estimates of 29% in Denmark, where nation-wide breast cancer screening only started in 2007 (Walters *et al*, 2013). In this Malaysian setting where screening for breast cancer is

Table 3. Factors associated with mastectomy in patients with very early breast cancer^a

Characteristics	Mastectomy (n = 591)	Breast conserving surgery (n = 527)	Univariable odds ratio for mastectomy (95% CI)	Multivariable odds ratio for mastectomy ^b (95% CI)
Age, in years, median ^c	55 (48,64)	49 (43,56)	1.05 (1.04–1.06) ^d	1.02 (1.01–1.04) ^d
Race, n (%)				
Chinese	476 (57.6)	350 (42.4)	1.00	1.00
Malay	56 (35.9)	100 (64.1)	0.41 (0.29–0.59) ^d	0.41 (0.27–0.62) ^d
Indian	51 (45.9)	60 (54.1)	0.63 (0.42–0.93) ^d	0.55 (0.35–0.87) ^d
Others	8 (32.0)	17 (68.0)	0.35 (0.15–0.81) ^d	0.54 (0.21–1.40)
Marital status, n (%)				
Married	491 (54.3)	414 (45.7)	1.31 (0.92–1.85)	—
Not married	70 (47.6)	77 (52.4)	1.00	—
Not known	30	36	—	—
Parity, n (%)				
Nulliparous	86 (48.9)	90 (51.1)	1.00	1.00
1–2 children	162 (48.5)	172 (51.5)	0.99 (0.68–1.42)	0.77 (0.51–1.18)
≥3 children	283 (60.4)	175 (39.6)	1.69 (1.19–2.40) ^d	1.32 (0.87–2.00)
Unknown	60	90	—	—
Menopausal status, n (%)				
Premenopausal	198 (39.6)	302 (60.4)	1.00	1.00
Postmenopausal	355 (63.7)	202 (36.3)	2.68 (2.09–3.44) ^d	1.96 (1.27–3.02) ^d
Unknown	38	23	—	—
Year of diagnosis, n (%)				
1993–1997	37 (55.2)	30 (44.8)	1.00	—
1998–2002	89 (43.8)	114 (56.2)	0.63 (0.36–1.10)	—
2003–2007	215 (53.3)	188 (46.7)	0.93 (0.55–1.56)	—
2008–2011	248 (56.0)	195 (44.0)	1.03 (0.62–1.73)	—
Unknown	2	0	—	—
Tumour size, in cm, median ^c	1.5 (1.0,2.0)	1.4 (0.8,1.7)	1.21 (1.02–1.45) ^d	1.22 (1.01–1.48) ^d
Lymphovascular invasion				
Present	144 (57.4)	107 (42.6)	1.22 (0.91–1.64)	—
Absent	338 (52.4)	307 (47.6)	1.00	—
Unknown	109	113	—	—

Abbreviations: CI = confidence interval; HER2 = Human Epidermal Growth Factor Receptor 2.

^aIncluded patients with stage I breast cancer who underwent breast surgery.

^bUsing stepwise backward logistic regression. Variables entered on step 1 are those with *P*-values < 0.20 in the Chi-square (categorical variable) or Mann-Whitney *U* (continuous variable) test, i.e., age at diagnosis, ethnicity, marital status, parity, menopausal status, year of diagnosis, tumour size, and lymphovascular invasion. The *P*-values for family history, tumour grade, oestrogen receptor status, progesterone receptor status and HER2 status were > 0.20. Final model includes age at diagnosis, ethnicity, parity, menopausal status, and tumour size.

^c25th and 75th percentile values.

^dStatistically significant.

opportunistic, it was found that the proportion of patients with carcinoma *in situ* was extremely small. The increasing trend towards very early presentation observed in the current study hence largely reflects improved breast health literacy in the background population.

Ethnicity affects stage at breast cancer presentation in the United States, as well as in multiethnic Asian settings (Bhoo-Pathy *et al*, 2012). While socio-economic disparities between the ethnic groups may confound this association (Brawley, 2002), some argue that individuals of a particular ethnic group may share certain beliefs, attitudes, and behaviours (culture), thus impacting their health practices, and resulting in similar illness profiles within that ethnic group (Lannin *et al*, 1998). A recent study in Malaysia showed that a higher proportion of Chinese women had good knowledge of breast cancer as compared with Malay and Indian women (Hadi *et al*, 2010). This may partly explain the association

between Chinese ethnicity and very early breast cancer presentation in the current study. The positive association between family history of breast cancer and very early presentation seems to support the notion that women with affected family members are more likely to have higher breast cancer awareness and therefore, are more ready to engage in preventive and screening activities (Verkooijen *et al*, 2009). As expected, it was also observed that very early stage at presentation was more common in recent years, which could be due to a combination of improved socio-economic and education status, as well as implementation of health education, and early detection programmes (Devi *et al*, 2007; Dahlui *et al*, 2012). While it has been suggested that married women are more likely to present with earlier stages of breast cancer due to increased social support and social networks (Osborne *et al*, 2005), this was not apparent in this study, probably due to low numbers of unmarried patients.

Table 4. Factors associated with chemotherapy in patients with very early breast cancer^a

Characteristics	Chemotherapy (n = 402)	No chemotherapy (n = 727)	Univariable odds ratio for chemotherapy (95% CI)	Multivariable odds ratio for chemotherapy ^b (95% CI)
Age, in years, median ^c	47 (41,54)	55 (48,64)	0.93 (0.92–0.95) ^d	0.91 (0.90–0.93) ^d
Race, n (%)				
Chinese	285 (34.3)	545 (65.7)	1.00	—
Malay	71 (43.0)	94 (57.0)	1.44 (1.03–2.03) ^d	—
Indian	37 (33.6)	73 (66.4)	0.97 (0.64–1.48)	—
Others	9 (37.5)	15 (62.5)	1.15 (0.50–2.65)	—
Menopausal status, n (%)				
Premenopausal	242 (47.9)	263 (52.1)	1.00	—
Postmenopausal	134 (23.8)	428 (76.2)	0.34 (0.26–0.44) ^d	—
Unknown	26	36		
Year of diagnosis, n (%)				
1993–1997	17 (25.0)	51 (75.0)	0.68 (0.38–1.21)	1.36 (0.55–3.39)
1998–2002	72 (34.0)	140 (66.0)	1.04 (0.74–1.48)	0.79 (0.44–1.45)
2003–2007	167 (40.9)	241 (59.1)	1.41 (1.06–1.86) ^d	1.82 (1.20–2.76) ^d
2008–2011	145 (33.0)	294 (67.0)	1.00	1.00
Unknown	1	1		
Tumour size, in cm, median ^c	1.5 (1.0,2.0)	1.4 (0.6,1.8)	1.63 (1.34–1.97) ^d	1.46 (1.10–1.95) ^d
Grade, n (%)				
Well differentiated	18 (11.0)	145 (89.0)	0.05 (0.03–0.08) ^d	0.07 (0.03–0.14) ^d
Moderately differentiated	178 (37.6)	296 (62.4)	0.22 (0.15–0.31) ^d	0.30 (0.19–0.48) ^d
Poorly differentiated	166 (73.5)	60 (26.5)	1.00	1.00
Unknown	40	226		
Lymphovascular invasion, n (%)				
Present	150 (60.7)	97 (39.3)	3.90 (2.87–5.31) ^d	4.72 (3.08–7.22) ^d
Absent	183 (28.4)	462 (71.6)	1.00	1.00
Unknown	69	168		
Oestrogen receptor status, n (%)				
Positive	197 (26.3)	553 (73.7)	1.00	1.00
Negative	194 (61.0)	124 (39.0)	4.39 (3.33–5.80) ^d	2.65 (1.60–4.37) ^d
Unknown	11	50		
Progesterone receptor status, n (%)				
Positive	151 (26.3)	423 (73.7)	1.00	1.00
Negative	192 (55.3)	155 (44.7)	3.47 (2.62–4.60) ^d	1.73 (1.03–2.90) ^d
Unknown	59	149		
HER2 status				
Positive	113 (34.6)	138 (65.4)	1.55 (1.16–2.01) ^d	—
Negative	245 (45.0)	463 (55.0)	1.00	—
Unknown	44	126		
Abbreviations: CI = confidence interval; HER2 = Human Epidermal Growth Factor Receptor 2.				
^a Included 1129 stage I patients whose chemotherapy administration status were known.				
^b Using stepwise backward logistic regression. Variables entered on step 1 are those with P-values < 0.20 in the Chi-square (categorical variable), or Mann-Whitney U (continuous variable) test: age at diagnosis, ethnicity, menopausal status, year of diagnosis, tumour size, grade, lymphovascular invasion, oestrogen receptor status, progesterone receptor status, and HER2 status. The P-values for marital status, parity, and family history were > 0.20. Final model includes age at diagnosis, menopausal status, year of diagnosis, grade, lymphovascular invasion, oestrogen receptor status, and progesterone receptor status.				
^c 25th and 75th percentile values.				
^d Statistically significant.				

In the current study, a large proportion of women underwent mastectomy. Following the NIH Consensus Development Conference in 1990, BCS became the preferred choice of surgery for women with early breast cancer in western settings (Lazovich *et al*, 1999). A recent study among primarily stage I breast cancer

patients in the United States found that mastectomy rates were 38%, compared with 53% in this study (Mahmood *et al*, 2013). The finding that older age at diagnosis is more likely to be associated with mastectomy is in stark contrast to the study conducted in the United States, whereby the preponderance for mastectomy was

most pronounced in young patients (Mahmood *et al*, 2013). This difference may be driven by cultural factors in older Asian women who seem to accept mastectomy as a choice of therapy more readily, since almost all of them would have completed their families, breast fed their children, and are less concerned with their physical appearance (Wong *et al*, 2008; Gumus *et al*, 2010). However, in very affluent western settings, it may be that the young women are more likely to have undergone genetic testing, receive preoperative breast MRI (Mahmood *et al*, 2013), or offered immediate breast reconstruction (Greenberg *et al*, 2011), all of which are shown to be positively associated with mastectomy. In the current study, it is thought that postmenopausal women prefer mastectomy due to differences in their priority for sexuality and body image compared with their premenopausal counterparts. Chinese women were more likely to undergo mastectomy even after taking their age, menopausal status, and tumour sizes into account. This may be due to their smaller breast sizes compared with the Malays and the Indians, as well as fear of radiotherapy (Wong *et al*, 2008). The choice of mastectomy in Chinese women may also reflect their culturally driven inclination to be completely rid of breast cancer (Lee, 2002; Wong *et al*, 2008). The Chinese seem to view mastectomy as the best course of action to prevent recurrence and it was deemed to 'ensure a 100% cure' compared with other treatment options (Wong *et al*, 2008).

While the NIH guideline recommends chemotherapy administration for all patients with node-negative breast cancer with tumour sizes measuring > 1 cm irrespective of hormone receptor status, only 42% of such patients in the current study received chemotherapy (Eifel *et al*, 2001). However, divergence between consensus recommendations and clinical practice had been reported even in affluent western practices, raising the question of whether the recommendations are overly aggressive, or whether the clinicians are too conservative in their use of chemotherapy (Lu *et al*, 2003). A study based on the New Mexico Tumour Registry for instance revealed that only 11% of its patients with stage I breast cancer received adjuvant chemotherapy (Lu *et al*, 2003). This is most probably due to the fact that a higher proportion of patients in the above study were 65 years and older compared with the current study making them less likely to receive adjuvant chemotherapy. The finding that increasing age is inversely associated with the use of chemotherapy, independent of hormone receptor status, complements previous study results (Lu *et al*, 2003; Sukel *et al*, 2008), and maybe attributed to decreasing efficacy of adjuvant chemotherapy with age, and perhaps concerns of increasing chemotherapy-related toxicity in older women (Early Breast Cancer Trialists' Collaborative Group, 1998). In this cohort of Asian women with node-negative breast cancer, chemotherapy administration is associated with larger tumour size, higher tumour grade, the presence of LVI, and the absence of ER expression, similar to western practices (Lu *et al*, 2003; Sukel *et al*, 2008), and in line with the 2005 St Gallen Panel recommendation (Goldhirsch *et al*, 2005).

It appears that the survival of patients with stage I breast cancer in this study is similar to reported age-adjusted net survival rates in affluent western settings during the same calendar period (Walters *et al*, 2013). This reaffirms that very early presentation with breast cancer is associated with a high survival rate, be it in resource-limited or affluent settings. Nevertheless, breast cancer is more common in women with higher socio-economic status, that is, higher levels of education and income (Clarke *et al*, 2002) making life expectancies between the patients and the background population not entirely comparable. Since data on socio-economic status were not available for matching both in the breast cancer registry and in the Malaysian life tables, it remains possible that (relative) survival may have been overestimated in the current study due to mismatch in the socio-economic status between the breast cancer patients and the background population in Malaysia (Howlander *et al*, 2010).

As this study was conducted in a tertiary referral centre with oncology services, it is possible that we may have underestimated the proportion of patients with stage I breast cancer. This is in view that a substantial number of patients with stage I breast cancer would have been subjected to locoregional management without being considered for adjuvant chemotherapy, and hence not referred to our centre. On the other hand, patients with more advanced stages of breast cancer would have been more likely to be referred. Given that UMMC serves a predominantly middle-income urban population where a majority of breast cancer patients are of Chinese ethnicity, whereas the Malays form the majority of Malaysian population, our findings may not necessarily reflect the overall situation of very early breast cancer presentation in Malaysia.

This study provides an estimate of increases in early breast cancer presentation, which is largely independent of mass screening effect. Even though it used a hospital-based breast cancer registry, this is the best estimate, which is currently available from a middle-income country without organised breast cancer screening.

In conclusion, presentation of very early breast cancers is on the rise in this Asian setting without organised breast cancer screening. Women presenting with stage I breast cancer in this study seem to experience high survival rates similar to their counterparts from affluent western settings.

ACKNOWLEDGEMENTS

This study was financially supported by the Ministry of Education, Malaysia (High Impact Research Grant [UM.C/HIR/MOHE/06]).

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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