RESEARCH COMMUNICATION

The Impact of Mammographic Breast Cancer Screening in Singapore: A Comparison Between Screen-detected and Symptomatic Women

Wei Vivian Wang[1*], Su Ming Tan[2], Wai Leng Chow[1]

Abstract

Background: Breast cancer is the leading cause of cancer death amongst Singapore women. There are few studies evaluating the impact of mammographic screening among Asian women. This study aimed to examine differences in disease stage at presentation and outcome between breast cancer patients who were detected by screening (screen-detected) and those who presented symptomatically (symptomatic) from the experience of a regional hospital in Singapore. We also sought to identify the demographic profile of patients who were less likely to be screen detected. Methods: Retrospective data fpr female patients diagnosed with primary breast cancer and treated from January 2002 - December 2008 were analyzed. Univariate and multivariate analyses were performed to examine the profile of symptomatic as opposed to screen-detected patients and factors that influence presentation at an early disease stage. Survival and recurrence rates were computed by Kaplan-Meier method and compared by log rank test. Results: The study population consisted of 82 screen-detected and 679 symptomatic patients. The screen-detected patients were more likely to present at an earlier stage and have better overall cancer-specific survival as compared to symptomatic patients. Malay women and those without a family history of breast cancer were less likely to be detected by screening. Conclusions: Mammographic screening appeared to enable the detection of oncologically more favorable lesions and conferred better overall cancer-specific survival in Singapore women. There is possibly room for more targeted education efforts to reach out to Malay women and those without a family history of breast cancer to enable earlier disease detection among these individuals through regular breast cancer screening.

Keywords: Breast cancer - disease presentation - mammography screening - survival - Singapore

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Introduction

Breast cancer remained the most common malignancy and the leading cause of cancer death amongst Singapore women for the period 2003-2007. The age-standardised incidence rate had increased almost 3 folds from 20.0 (1968-72) to 60.9 per 100,000 per year (2003-07) (Singapore National Registry of Diseases Office, 2011). The increasing breast cancer incidence together with positive results from the Singapore Breast Screening Pilot Project (Ng et al., 1998; Tan et al., 1999; Wee, 2002; Wang, 2003) led to the launch of BreastScreen Singapore (BSS). This is a nationwide government-subsidised breast screening program using mammography which started in January 2002 (Jara-Lazaro et al., 2010). BSS targets at women in the age group of 50–69 years who are encouraged to be screened biennially (Wang, 2003). Prior to the launch of BSS, there was much public education in the various media to heighten the awareness of breast cancer and breast cancer screening. Subsequent to the launch, regular annual nationwide campaigns were conducted to continue to educate the public about the importance of screening.

Extensive studies (Tabár et al., 1985; Feig, 1988; Fletcher et al., 1993; McCann et al., 1997; The Swedish Organised Service Screening Evaluation Group, 2006) in Western populations have shown that mammography screening reduces breast cancer mortality both in and outside controlled trial environment. However there are few studies (Leung et al., 2007; Chuwa et al., 2009) evaluating the impact of screening amongst Asian women. These studies commonly report that screening was associated with oncologically more favorable tumors at presentation but did not quantify the impact by adjusting for other known influencing factors on disease presentation, such as race, age at presentation and parity. This study is the first one looking at the adjusted impact of screening over seven years since the launch of BSS from the perspective of a regional hospital serving the eastern part of Singapore.

In particular, we seek to understand the difference in disease stage at presentation and outcome (i.e. cancer

*[1]Center for Health Services Research, Singapore Health Services Pte Ltd, [2]Breast Service, Department of General Surgery, Singapore Changi General Hospital, Singapore *For correspondence: wei.wang@nus.edu.sg*

specific death and recurrence) between breast cancer patients who were detected by screening (screen-detected patients) and those who presented symptomatically (symptomatic patients) while taking other influencing factors on disease presentation into consideration. We also seek to identify the demographic profile of women whose cancer were less likely to be screen detected in order to facilitate a more targeted effort in promoting screening.

Materials and Methods

Retrospective data of female patients diagnosed with primary breast cancer and treated at the Department of Surgery, Changi General Hospital (CGH) in Singapore during the period January 2002 to December 2008 was extracted from its breast cancer registry. CGH is a regional hospital serving as a major healthcare provider for approximately 1.3 million people living in the eastern part of Singapore (Singapore Changi General Hospital, 2011).

Patients who had received prior treatment in the form of chemotherapy, hormonal therapy or radiotherapy, and those presenting with recurrent disease were excluded. Staging was done using the American Joint Committee on Cancer (AJCC) staging system for breast cancer (sixth edition)(Singletary & Connolly, 2006). Histological grade was assessed by the Elston-Ellis modification of the Bloom-Richardson grading method (Elston & Ellis, 1991).

Disease-free survival was defined as the time from the date of primary treatment to the date for first recurrence, be it local or distant, or both. Follow-up time was defined as the time from the date of treatment to the date of death or, if still alive, last follow-up.

Statistical analyses were performed with disease stage at presentation, cancer-specific death and disease recurrence as primary end points. Chi-square test and Mann-Whitney U-test were used to compare categorical and continuous variables respectively between screen-detected and symptomatic patients. Survival and recurrence rates were computed by Kaplan-Meier method and compared by log rank test. Multivariate logistic regression analysis was performed to determine the profile of symptomatic patients and the adjusted impact of the screening on disease stage at presentation. All tests of significance were two-tailed with a p-value cutoff of 0.05. Statistical analyses were carried out using SPSS v.15.0 (Chicago, IL).

Results

Subjects' characteristics

A total of 761 patients were included in the analysis. The majority of the patients (71.0%) were Chinese. The proportion of Malays and that of other races were slightly higher that those in the general population, but overall our study population can still be considered comparable to and representative of the general population (Figure 1) (Singapore Department of Statistics, 2010). The median age at presentation was 53 years old, and 64% of all patients were between 40-65 years old, which is also the target age group of BSS. Only 82 (10.8%) of all patients had cancer detected through screening (screen-detected patients), while 679 (89.2%) presented with symptoms (symptomatic patients).

The median follow-up time among all patients was 30 months (range: 0-84 months). The 5-year overall survival rate of this cohort was 87.5% (95% CI: 83.8%-91.2%). A total of 73 patients had disease recurrence, of whom 23 (30.1%) had only local recurrence, 39 (50.7%) had only distant recurrence and 11 (15.1%) patients had both. The 5-year disease-free survival rate was 77.3% (95% CI: 71.2%-83.4%).

Comparison between screened patients and symptomatic patients

Table 1 compares the difference in demographic characteristics between symptomatic and screen-detected patients. Univariate analysis showed that the screen-detected patients had significantly more Chinese, more patients between the ages of 40-65 years and more patients with a family breast cancer history. The symptomatic patients had significantly more patients with four or more children, more divorced/ separated/ widowed patients and more of them had breast fed. After adjusting for age, marital status, breast feeding experience and number of children, Malay women were found to be less likely to be detected by screening compared to Chinese women, while patients with a family history of breast cancer were found to be more likely to be detected by screening (Table 2).

Clinically (Table 3), lesions in the screen-detected patients were found to be of a lower stage (99% vs 70% stage 0-2). Only one patient, although screen-detected, had eight positive nodes and thus presented with T1N2M0,

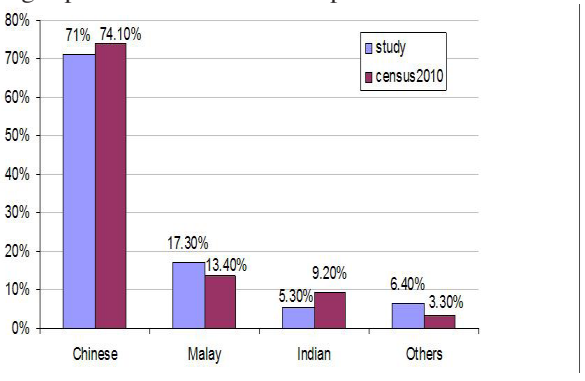

Figure 1. Ethnic Composition of the Study Population vs. the General Population in Singapore

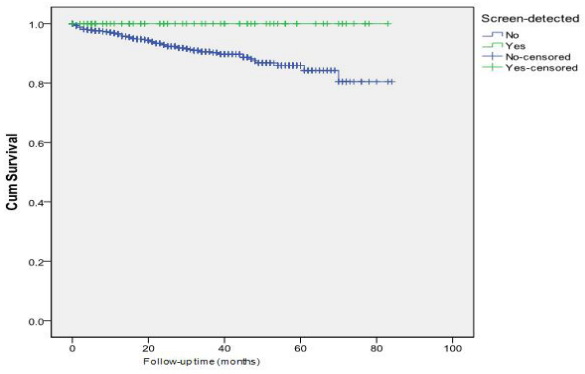

Figure 2. Kaplan-Meier Crude Survival Curves by Different Detection Modes

Table 1. Demographic Characteristics of Symptomatic and Screened Patients

Characteristics	Symptomatic (N=679)	%	Screen-detected (N=82)	%	p-value
Race					0.004*
Chinese	470	69.2%	70	85.4%	
Malay	128	18.9%	4	4.9%	
Indian	36	5.3%	4	4.9%	
Others	45	6.6%	4	4.9%	
Age at presentation					
Mean (SD)	55.3 (14.2)		53.4 (10.4)		0.238
Median (range)	53(16-93)		52(37-82)		
Age group at presentation					0.009*
below 40 years	80	11.8%	3	3.7%	
40-49 years old	199	29.3%	34	41.5%	
50-65 years old	225	33.1%	32	39.0%	
66 years and above	175	25.8%	13	15.9%	
Marital status					0.038*
Divorced/Separated/Widowed	84	13.4%	4	5.1%	
Single	82	13.1%	16	20.3%	
Married	459	73.4%	59	74.7%	
Number of children					0.002*
No Children	104	17.3%	18	23.4%	
1-3 Children	374	62.3%	56	72.7%	
4-11 Children	122	20.3%	3	3.9%	
Breast feeding					0.003*
Yes	283	47.6%	23	29.9%	
No	311	52.4%	54	70.1%	
Oral Contraceptive					0.32
Yes	112	18.6%	18	23.1%	
No	489	81.4%	59	76.6%	
Menopause					0.554
Yes	364	54.1%	41	50.6%	
No	309	45.9%	40	49.4%	
Family breast cancer history					0.001*
Yes	67	11.0%	19	24.1%	
No	544	89.0%	60	75.9%	
Significant medical history[a]					0.55
Yes	376	59.0%	45	55.6%	
No	261	41.0%	36	44.4%	

*denotes statistical significance (p-value<0.05); [a]Significant medical history includes Hypertension, Diabetes, Ischaemic heart disease, Cardiovascular accidents, Chronic obstructive lung disease

stage 3A disease. Ductal carcinoma in situ (DCIS) lesions comprised 38% in the screen-detected patients as compared to 8% in the symptomatic patients. For invasive cancers, the median size in the screen-detected patients was 11 mm (range 2-30 mm) compared to 26 mm (range 1-195 mm) for the symptomatic patients. The screen-detected patients also had a lower incidence of nodal involvement (20% vs 47%) and vascular invasion (16% vs 44%) but a higher rate of breast conservation surgery (40% vs 19%) as compared to the symptomatic patients. All p-values are below 0.001.

Table 4 shows the differences in outcomes between the two groups. The median follow-up time was 30 months in symptomatic patients, and 26 months in screen-detected patients. Although the symptomatic group had more patients with disease recurrence, there was no statistically significant difference in disease-free survival between the two groups. There were five women in the screen-detected group that developed recurrences. Of these, three were local recurrences and two with distant recurrences. One of these presented with stage 2B disease and developed pleural metastasis at 56 months, while the other had stage 1 disease and developed bone metastasis at 37 months.

There was no death case observed in the screen-detected patients. They had better cancer-specific overall survival than the symptomatic patients (p=0.007) (Figure 2). Due to the short follow-up time for most of screen-detected patients, we were not able to accurately estimate the 5-year cancer-specific overall survival rate for them.

Adjusted impact of screening and other influential factors on stage at presentation

Univariate analysis (data not shown) showed that early stage at presentation was significantly associated with being Chinese, younger age at presentation, having one to three children, no experience of breast feeding and menopause, and being screen-detected out of all the factors listed in Table 1. In the multivariate analysis (Table 5) , after adjusting for the abovementioned factors, screening was found to be the only significant factor that was associated with presentation at an early stage, as compared to a symptomatic patient (OR=25.3, p=0.001).

Discussion

Breast cancer is the leading cause of cancer among

Table 2. Tumor and Treatment Characteristics and Outcomes of Symptomatic and Screened Patients

Characteristics	Symptomatic (N=679)	%	Screen-detected (N=82)	%	p-value
Stage					<0.001*
0	51	7.8%	31	38.3%	
1	132	20.2%	33	40.7%	
2A	174	26.6%	15	18.5%	
2B	98	15.0%	1	1.2%	
3A	64	9.8%	1	1.2%	
3B	30	4.6%	0	0.0%	
3C	37	5.7%	0	1.2%	
4	67	10.3%	0	1.2%	
Early or advanced stage					<0.001*
Early (Stage 0-2)	455	69.7%	80	98.8%	
Advanced (Stage 3&4)	198	30.3%	1	1.2%	
Tumor histology type					<0.001*
Ductal carcinoma in situ (DCIS)	51	7.8%	31	38.3%	
Invasive cancer	602	92.2%	50	61.7%	
Histologic Grade					0.001*
1&2	283	45.4%	47	66.2%	
3	341	54.6%	24	33.8%	
Tumor size (invasive cancer only)					<0.001*
≤ 10mm	55	10.2%	22	45.8%	
> 10mm	485	89.8%	26	54.2%	
Nodal involvement (invasive cancers only)					<0.001*
Yes	269	47.1%	10	20.4%	
No	302	52.9%	39	79.6%	
Vascular invasion					<0.001*
Yes	253	43.8%	8	16.0%	
No	324	56.2%	42	84.0%	
Type of operation					<0.001*
Mastectomy	509	75.2%	49	59.8%	
Breast conservation	125	18.5%	33	40.2%	
None	43	6.4%	0	0.0%	
Recurrence					0.127
Yes	68	12.5%	5	6.5%	
No	477	87.5%	72	93.5%	
Death from breast Cancer					0.006*
Yes	55	8.4%	0	0.0%	
No	599	91.6%	82	100.0%	
Current status					<0.001*
Alive, cancer free	527	80.2%	80	97.6%	
Alive, with cancer	60	9.1%	2	2.4%	
Dead	70	10.7%	0	0.0%	
Follow-up time	(in months)				
median	30	-	26	-	
25th -75th percentile	13-45		9.8-53.3		
Overall survival (months)					0.007*
1 year survival (95% CI)	96.50%(94.9%-98.1%)		100% (96.3%-100%)		
2 year survival (95% CI)	92.90% (90.5%-95.3%)		100% (96.3%-100%)		
5 year survival (95% CI)	84.30% (79.2%-89.4%)		-		
DFS (months)					
Mean (95% CI)	71.9(69.2-74.7)		75.8(69.9-81.7)		0.220
1 year survival (95% CI)	96.50% (94.9%-98.1%)		98.20% (94.7%-100%)		
2 year survival (95% CI)	90.60% (87.9%-93.3%)		93.30% (85.7%-100%)		
5 year survival (95% CI)	76.6% (70.1%-83.1)		83.30% (68.0%-98.6%)		

*denotes statistical significance (p-value<0.05)

women in Singapore. While there is much published on the effects of breast screening on women in the western population, there is little data on breast screening among Asian women. In our study, we found that mammographic screening appeared to enable the detection of oncologically more favorable lesions and conferred better cancer-specific overall survival among Singapore women. Univariate analysis also suggests that there is possibly room for more targeted education efforts to reach out to Malay women and those without family history of breast cancer to attend breast cancer screening.

In the Western countries, response rates to mammographic screening are well over 75% with screen-detected tumors forming up to 30% of all treated breast cancers (Sant et al., 2006; Smigal et al., 2006; The Swedish Organised Service Screening Evaluation Group, 2006). In contrast, the Singapore Health Surveillance Survey 2007 (SHSS) (Singapore Ministry of Health, 2011)

found that only 40.9% of Singaporean women aged 50–69 years reported that they had undergone a mammographic screening within the previous 2 years.

Changi General Hospital is not a screening centre, but a referral centre for symptomatic patients in the eastern part of the country. However, there are patients who present specifically for screening, as well as some who were offered opportunistic screening. This accounts for the low proportion (10.8%) who were screen detected. Nonetheless, this is consistent with a national report by Singapore Health Promotion Board (Thilagaratnam, 2009), which examined regional differences in breast cancer screening patterns in women 50-69 years in Singapore. It was found that the eastern part of Singapore had the lowest overall screening rate (18% in the general target women) in BSS, compared to other areas of the island (21 - 22%). The same report also found that the eastern region also had the lowest assessment attendance (i.e. going for assessment at designated tertiary hospitals due to abnormal Pap smear results (Thilagaratnam, 2009) rate at 16% in the lower socioeconomic group, compared to 77% in the northern part of the island and about 30% in the rest of the island.

SHSS (Singapore Ministry of Health, 2011) also found that a higher proportion of Chinese women (62.7%) and Indian women (56.9%) had undergone mammography at least once compared to their Malay counterparts (52.9%). This is consistent with the present study where Malay breast cancer patients were less likely to be detected by screening. Our study also showed that screen detected patients had a higher incidence of family history of breast cancer. Having a relative with breast cancer could heighten one's awareness of the disease and result in an increased motivation to undergo screening. This result mirrors the findings of a survey done on women in the eastern part of Singapore, where Malay respondents and those who did not know anyone with breast cancer were less likely to go for screening mammogram (Thilagaratnam, 2009).

Although mammographic screening in Western populations has been shown to reduce mortality by up to 45% in women aged 50 years and above (Tabár et al., 1985; Feig, 1988; Fletcher, et al., 1993; McCann, et al., 1997; The Swedish Organised Service Screening Evaluation Group, 2006), there has not been any similar finding demonstrated in Asian women so far. Our study found that mammographic screening results in the early detection of oncologically more favorable lesions in Singapore women and is the first to suggest that screening also confers a higher overall survival in Asian women.

The finding of early detection by screening mirrors the findings from the Singapore Breast Screening Project (Ng, et al., 1998) and an earlier study by Chuwa et al based on the experience of a tertiary hospital in the central part of Singapore (Chuwa, et al., 2009). Studies in Hong Kong (Leung, et al., 2007) and United Kingdom (McCann et al., 1997; Yassin et al., 2003) also showed that screen-detected lesions were significantly smaller and associated with less frequent lymph node involvement than those detected symptomatically. However, these findings did not take into account other potential influencing factors on disease presentation (Largent et al., 2005; Ali et al., 2008; Echeverria et al., 2009; Macleod et al., 2009) such as race, age at diagnosis, marital status, parity, breastfeeding and menopausal status. Our study demonstrated that detection by screening is indeed an independent influential factor on a favorable disease stage at presentation after adjusting for those factors above.

Our study is the first that assessed the impact of screening over seven years since the launch of the first and only national breast cancer screening program, BreastScreen Singapore (BSS) (Jara-Lazaro et al., 2010) from the perspective of a regional hospital in the eastern part of Singapore. This is not a study evaluating the effectiveness of the BSS program as our population of interest is that of the disease population. Nevertheless, since Singapore is a small city country, all the public education campaigns on breast cancer and screening should have a similar impact across the island including the eastern region where CGH is serving. Therefore, the findings that Malay women and those without family history of breast cancer are less likely to attend breast cancer screening in our study may provide relevant and timely views on how BSS and the associated education programs have influenced the total disease population in Singapore.

There are however, some limitations to our study. SHSS (Singapore Ministry of Health, 2011) and a local survey of Asian women (Sim et al., 2009) both showed that lower education level is associated with the low response to mammographic screening. However, due to the lack of socioeconomic data in the registry, we were unable to adjust for factors such as education level, income and occupation when assessing the impact of screening on disease stage at presentation and identifying the profile of symptomatic patients. Our study is also limited by the relatively short follow-up period since the national breast cancer screen program was only launched in 2002. A longer follow-up with more events would provide a more insightful comparison on the overall 5-year survival rate between screen-detected and symptomatic patients, and allow us further understand the impact of screening detection on survival by adjusting for the potential influence of certain clinicopathological variables (such as tumor size, histological grade and nodal involvement). Lastly, the sample sizes of the two groups were not equal (82 screen-detected vs. 679 symptomatic patients) and such an unbalanced comparison inevitably introduced statistical errors. However, despite the unbalanced sample sizes, the standard deviations in the present study were similar in the groups and hold up to the requirements of the statistical tests.

In conclusion, mammographic screening results in the early detection of oncologically more favorable lesions in Asian women and our study is the first to suggest that screening also confers a higher overall survival in Asian women. We also found that Malay women and those without family history of breast cancer are less likely to have their cancer detected by screening. Screening outreach efforts could be more targeted toward these at particular risk groups to encourage screening and earlier disease presentation particularly in the eastern part of Singapore.

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