COMMENTARY

A Commentary on Delayed Presentation of Breast Cancer in Singapore

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Abstract

Breast cancer is the most common cancer in Singaporean women and the rate of increase in incidence is one of the highest in the world. In view of the significant contribution of delayed presentation to the disease burden in South East Asia, we reviewed the incidence of late presentation of breast cancer and the contributing factors in Singapore. Disease presentation was analysed using studies based on the Singapore Cancer Registry 2004-2008 and with data from women with breast cancer at the National University Hospital (NUH) in Singapore 1990-2007. Available literature from Singapore on factors contributing to delayed presentation was reviewed and presented here. The overall age-standardized 5-year relative survival for Singaporean women was 70% with only half diagnosed with localized cancer. Of all women diagnosed at NUH close to 20% presented at Stages III and IV. Given the magnitude of the problem of women presenting with more advanced stages of breast cancer, the National University of Singapore has joined a collaborative team with the University of Leeds (UK), the University of Malaya, and University of UAE to set up the UK-SEA-ME Psychosocial-Cultural Cancer Research Network to better understand late presentation.

Keywords: Breast cancer - delayed presentation - late stage - Singapore

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Introduction

Breast cancer is the most common malignancy affecting women worldwide and is the leading cause of cancer-related mortality (Hortobagyi et al., 2005). More than 1-2 million cases are diagnosed every year, affecting 10-12% of the female population and accounting for 500,000 deaths per year worldwide (Benson et al., 2009). Breast cancer is also the most common cancer affecting Singaporean women with an incidence of 29.2% (Figure 1), an age-standardized incidence rate (ASR) of 59.5 per 100,000 person-years in 2004-2008 and a lifetime risk in Singapore females of 1 in 20. The rate of increase in incidence in Singapore is one of the highest in the world at 5.7% per year in pre-menopausal women and 3.9% per year in post-menopausal women (Seow et al., 1996), in contrast to the United States at 1.5% per year.

Ethnic disparity in incidence, mortality and survival is evident in the United States, where breast cancer is predominantly a postmenopausal disease in the Caucasian American population (Anderson et al., 2002; Smigal et al., 2006) in contrast to a premenopausal disease in Asian or non-Caucasian populations (de Waard et al., 1979; Matsuno et al., 2007; Kwong et al., 2008). An increased proportion of late-stage breast cancers at presentation is an important reason accounting for worse outcomes in Afro-American women compared with Caucasian American women in the US. This could be explained by delayed diagnosis reflecting the socioeconomic status, cultural beliefs, access to healthcare (Hunter et al., 1993), and the proportion of estrogen receptor (ER) – negative tumors in the Afro-American women (Anderson et al., 2002). Similar to the presentation of late-stage breast cancers in Afro-American women, late presentation of the disease contributes significantly to the burden of breast cancer in this region, i.e. Singapore, Malaysia, Indonesia and the Philippines. Recently published data from the National University Hospital of Singapore Breast Cancer Registry between 1990 and 2002 reflects a profile of breast cancer in Singapore that differs from that seen in the West: patients present at a younger age, with more advanced stage and fewer estrogen-positive tumors (Lim et al., 2007). In this study population, the most frequent stage at diagnosis is Stage II, accounting for 55% of the women in the registry. The distribution of stage in Singapore as a whole is less well known. Data from National University Hospital suggest that stage 3 and 4 breast cancer account for more than 20% of all women diagnosed with the disease.

Methodology

For this commentary we reviewed disease presentation using the Breast Cancer Registry of the National University Hospital (NUH), one of two tertiary teaching hospitals in

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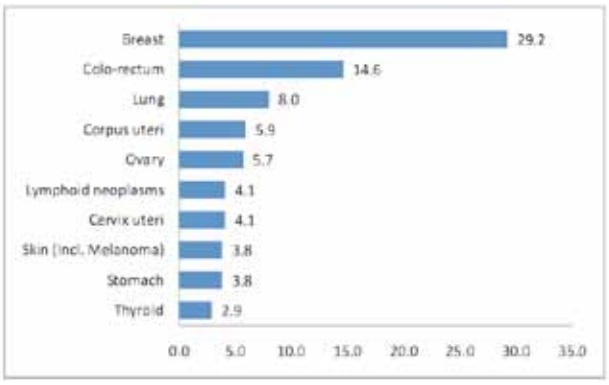

Figure 1. Ten Most Frequent Cancers in Singapore Females (%), 2004 – 2008 (Singapore Cancer Registry 2004 – 2008)

Singapore (Lim et al., 2007; Bhoo Pathy et al., 2011). The Breast Cancer Registry was established in 1995, through prospective data collection on demographics, tumor characteristics, treatment and follow up of all patients presenting with invasive or in situ breast cancer. Data from 1990 to 1995 was collected retrospectively from medical records. The Breast Cancer Registry has been approved by the NUH Institutional Ethics Review Board. Additionally we included results from the Singapore Cancer Registry and a limited number of available studies on breast cancer presentation in Singapore.

1990-2007 NUH BC Registry

Data on 2,449 breast cancer patients from the National University Hospital Breast Cancer Registry is presented in Table 1. Close to 14% of all women are diagnosed before the ages of 40 years and more than 30% have estrogen-negative tumors. In the NUH study population, the most frequent stage at diagnosis is Stage II. Less than one-quarter of women were identified as Stage I at diagnosis, and 20% of patients present at Stages III and IV.

2004-2008 Singapore Cancer Registry database

According to 2004 – 2008 data from the Singapore Cancer Registry, breast cancer remains the most frequent cause of cancer death in Singapore females, with an age-standardized rate of 13.7 per 100 000 per year (Figure 1) (Tan et al., 2009). Stage at presentation was the single most important determinant of breast cancer survival according to the authors (Peto et. al., 2000). The overall age-standardized 5-year relative survival for Singaporean women was 70% (Tan et al., 2009), and only half of the Singaporean cohort in this study was diagnosed with localized cancer, again reflecting the higher proportion of patients presenting with late-stage disease.

Table 1. Patient and Tumor Characteristics and Treatment for 2,449 Patients Diagnosed with Breast Cancer between 1990 and 2007 at NUH

Variable		Numbers (%)
Age in years	Median (range)	49 (22-93)
	<40	336 (13.7%)
	40 to 59	1579 (64.5%)
	≥ 60	534 (21.8%)
Ethnicity	Chinese	1919 (78.4%)
	Malay	258 (10.5%)
	Indian	126 (5.1%)
	Other	146 (6.0%)
Histology	Ductal	2030 (82.9%)
	Lobular	103 (4.2%)
	Mucinous	48 (2.0%)
	Other	157 (6.4%)
	Unknown	111 (4.5%)
Estrogen Receptor Status	Negative	798 (32.6%)
	Positive	1068 (43.6%)
	Unknown	583 (23.8%)
Progesterone Receptor Status	Negative	819 (33.4%)
	Positive	1033 (42.2%)
	Unknown	597 (24.4%)
Stage	0	222 (9.1%)
	I	544 (22.2%)
	II	1015 (41.4%)
	III	324 (13.2%)
	IV	184 (7.5%)
	Unknown	160 (6.5%)
Grade	Good diff	258 (10.5%)
	Moderate diff	814 (33.2%)
	Poor diff	781 (31.9%)
	Unknown	596 (24.3%)
Tumor size	1 to 2 cm	686 (28.0%)
	2.1 to 5 cm	621 (25.4%)
	>5 cm	167 (6.8%)
	Unknown	975 (39.8%)
Lymphovascular invasion	No	306 (12.5%)
	Yes	1662 (67.9%)
	Unknown	481 (19.6%)
Regional nodes positive	0	977 (39.9%)
	1-3	385 (15.7%)
	4-9	208 (8.5%)
	≥10	109 (4.5%)
	Unknown	770 (31.4%)
Surgery	None	158 (6.5%)
	Mastectomy	1575 (64.3%)
	Breast Conserving	716 (29.2%)
Radiotherapy	No	1333 (54.4%)
	Yes	1116 (45.6%)
Chemotherapy	No	1237 (50.5%)
	Yes	1212 (49.5%)
Hormone therapy	No	1102 (45.0%)
	Yes	1347(55.0%)
Neoadjuvant chemotherapy	No	2111 (86.2%)
	Yes	243 (9.9%)
	Unknown	95 (3.9%)

Comparison Findings

In a comparison in outcome among breast cancer patients diagnosed in Singapore and a western population (Stockholm, Sweden) Chia et al. (2005) noted the following. From 1980 to 1989, premenopausal Singaporean women had a 26% increased risk of death compared with women from Stockholm, adjusted for stage and year of follow-up. In post-menopausal women, this risk was higher, at 48%. From 1990 to 1999, this risk of death decreased to 19% and 22% for pre- and post-menopausal women respectively, when compared with the Swedish cohort. This difference is likely explained by the improved living standards in Singapore during the period of economic restructuring where there was presumably better education, improved awareness of the disease and better healthcare including

breast screening – albeit opportunistic. The low risk of death in Sweden can be attributed to affordable primary healthcare services, heavily subsidized tertiary healthcare and a nationwide mammographic screening program that was established in the 1980s.

In the United States, close to half of all women with breast cancer are diagnosed at Stage I, with a median tumor size of ≤ 2cm at presentation (Osteen et al., 1994). In the profiling of breast cancer patients using data from the National University Hospital of Singapore Breast Cancer Registry from 1990 to 2002 (Lim et al., 2007), when compared to the United States, the absence of a nationwide screening program during this period may account for the difference in presentation of breast cancer patients when compared to the United States, however, the underlying mechanism explaining the younger age of onset and smaller proportion of ER-positive tumors is not clear, although a birth cohort effect likely contributes to the variation in age of onset (Chia et al., 2005). In another study examining the differences in breast cancer incidence between Singapore and Swedish women, the overall breast cancer incidence rates in both countries begin to rise at 30 years of age and start diverging 5-10 years later; this increase plateaus after age 50 at nearly 100 per 105 person-years in women above 80 years of age; in contrast, it continues to rise slowly in Sweden to nearly 350 per 105 person-years in the same age group. This study illustrates a different temporal pattern for Singapore with incidence rates rising among younger women (<45) from 1983 to be similar to Swedish rates. Throughout the 25-years of the study, the divergent incidence rates in women above 50 years of age persisted (Chia et al., 2005). When these results were adjusted for birth cohort effects, i.e. women born at different time periods experiencing markedly different risks of disease, the age effects became remarkably similar in the two countries, suggesting that the differences in cross-sectional age-specific rates is accounted for by birth cohort effects whereby there was possibly increased exposure to risk factors or an increase in screening pick-up rate for the particular cohort (Chia et al., 2005).

Amongst Asian countries, the rate of estrogen receptor (ER) positivity was low, with only 51% of premenopausal and 60% of postmenopausal patients testing ER positive. The hormonal profile reported in Singapore is remarkably similar to that observed in a study of Chinese breast cancers from Hong Kong (Chow et al., 2000), where ER positivity was 53% and 61.6% in pre- and postmenopausal women, respectively. In contrast, more than 60% of premenopausal and 80% of postmenopausal Caucasian patients stain positive for ER (Lim et al., 2007).

Mortality rates for breast cancer have fallen in many industrialized nations since 1990, having previously been stable or increasing for several consecutive decades (Beral et al., 1995; Peto et al., 2000; Jatoi, et al., 2003). The improvement in outcome has been attributed mainly to the introduction of mammographic screening programs, increased awareness leading to early diagnosis, and the widespread use of adjuvant systemic therapies including tamoxifen (Berry et al., 2005).

At the National University Hospital, five-year relative survival estimates between the Singapore and SEER populations in the US were comparable for patients with stage I disease (Manuscript on review). Five-year survival rates of patients from National University Hospital were 50.2% and 13.6% for stages III and IV respectively. The trend in breast cancer patients is towards earlier presentation, with approximately 20% presenting with stage I and II in 1990-1994 and more than 40% by 2005-2007 (Bhoo Pathy et al., 2011). Despite the shift towards earlier diagnosis, the current status of delayed presentation of breast cancer in Singapore is worrying and the reasons are multi-factorial. The underlying mechanisms can be divided into the following categories – socioeconomic background, self-perception, disease perception, concerns regarding diagnosis and treatment, and attitude towards alternative therapies.

Possible Reasons for Delayed Presentation

a) Knowledge of cancer

A local survey done to assess the prevalence of lack of knowledge about cancer showed that misconceptions about cancer, resulting from limited cancer knowledge, are prevalent (Ong et al., 2010). 35% of participants thought that cancer was fatal; 49% thought that cancer would always relapse and 71% thought that cancer was always physically painful. A worrying 33% thought that cancer screening was only for symptomatic individuals (Ong et al., 2010).

b) Barriers to screening

A prospective study done in Singapore to investigate attitudes as barriers to breast screening profiled women who were more likely to attend free breast screening (Straughan et al., 2000). These women came from higher income households with educational achievements, had fewer perceived barriers, perceived that cancer was curable and preventable, that they were important to their family members, and tended to be less fatalistic.

i) Education: Straughan et al illustrated that socioeconomic and cultural background and therefore education level and attitudes of fatalism are inter-related. Belief in the efficacy of screening tests for early cancer detection is primarily embedded in the western biomedical model. Only 41% of eligible women with limited cancer knowledge went for screening mammography compared to 68% of eligible women with high cancer knowledge (Straughan et al., 2000). Well-educated women tend to be of a higher socioeconomic class, are usually more cosmopolitan in their outlook and less traditional in their beliefs. This appears to correlate with greater acceptance of cancer screening and adoption of western medical practice and treatment.

ii) Patient perceptions: Women with more perceived barriers were less likely to attend breast cancer screening. Straughan et al identified five perceived barriers (Straughan et al., 2000): time, domestic responsibilities, logistics, pain and embarrassment. The first three are physical, while the last two are psychological barriers. Physical barriers can

be alleviated by making screening more convenient for the target population, e.g. bringing screening sites nearer to them, increasing the availability of time slots when screening can be performed. Psychological barriers are harder to overcome. Perceptions of pain and notions of modesty are subjective and often, they are affected by cultural perceptions. Asian women are, in general, more private in their perception of their bodies and are less receptive to revealing their private parts, even to health care providers. Measures to circumvent this issue include matching the gender of patients and healthcare providers to alleviate embarrassment for the patient. Greater effort can be taken to explain and reassure patients to reduce anxieties regarding pain.

Women who perceived themselves to be important to their family members were more likely to accept breast cancer screening. This reinforces the fact that health-screening behavior is highly 'social' in nature (Straughan et al., 2000), i.e. whether a woman goes for breast screening is influenced by her perceived importance in her family. Family support contributes positively to women accepting breast cancer screening in two ways. Firstly, family members serve as messengers; women are more likely to accept advice from their trusted family members. Secondly, with a perceived importance to the family, women are more likely to accept breast cancer screening so as to sustain their health status to continue contributing to the family.

iii) Treatment issues/concerns: Concerns regarding the diagnosis and treatment of breast cancer are one of the contributing factors to delayed presentation. Singapore women are generally concerned about events following the diagnosis of breast cancer. Tightly linked to tradition, these women are fearful of mastectomy, and chemo-radiotherapy that will bring about intolerable side effects. One solution would be to increase public awareness of breast cancer and the various modalities for treatment. In addition, emphasis needs to be placed on the impact that diagnosis of early breast cancer has on its treatment and five-year survival. Furthermore, negative thoughts about mastectomy and chemo-radiotherapy adverse effects (e.g. alopecia, mouth ulcers, intractable nausea and vomiting) might result in these women seeking alternative therapies (e.g. Traditional Chinese Medicine), thereby delaying treatment or even a definitive diagnosis. Southeast Asian patients are known to have a strong belief in traditional medicine (Hisham et al., 2004; Moore et al., 2010). When it comes to treatment, it is usual in Chinese tradition to involve her family members, some of whom might advise a trial of alternative therapy before considering western medicine. This could potentially lead to a delay in appropriate therapeutic intervention thereby decreasing the survival probabilities for patients from this region.

Conclusion

In conclusion, few factors outrank stage at presentation as a prognostic factor. The later stage at presentation, the larger proportion diagnosed in the premenopausal population and the lower rate of ER positivity denotes a different profile of breast cancer patients in Singapore compared to the West. In order to reduce the burden of disease it is critical to diagnose women at an earlier stage. The mechanism for achieving fewer women presenting with advanced disease is likely multi-factorial, requiring the input of many disciplines. Given the magnitude of the problem of women presenting with more advanced stage of breast cancer, a collaborative team including the University of Leeds (UK), the National University of Singapore, the University of Malaya, and University of UAE have set up the UK-SEA-ME Psychosocial-Cultural Cancer Research Network to better understand late presentation.

Identifying factors that influence detection of early breast cancer in the Singapore population is the primary goal of our collaboration with WUN where we hope to gain important insights from future multi-disciplinary studies in Singapore as well as from our collaborators in UK, Malaysia and the United Arab Emirates.

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