A Review of Breast Cancer Research in Malaysia

CH Yip, FRCS*, N Bhoo Pathy, MD, SH Teo, PhD*****

* Department of Surgery, Faculty of Medicine, 50603 Kuala Lumpur, ** Department of Social and Preventive Medicine, Faculty of Medicine, 50603 Kuala Lumpur, ***Cancer Research Initiatives Foundation (CARIF), Outpatient Centre, Subang Jaya Medical Centre, Subang, 47500 Selangor, Malaysia

SUMMARY

Four hundred and nineteen articles related to breast cancer were found in a search through a database dedicated to indexing all original data relevant to medicine published in Malaysia between the years 2000-2013. One hundred and fifty four articles were selected and reviewed on the basis of clinical relevance and future research implications. Overall, Malaysian women have poor survival from breast cancer and it is estimated that half of the deaths due to breast cancer could be prevented. Five-year survival in Malaysia was low and varies among different institutions even within the same disease stage, suggesting an inequity of access to optimal treatment or a lack of compliance to optimal treatment. Malaysian women have poor knowledge of the risk factors, symptoms and methods for early detection of breast cancer, leading to late presentation. Moreover, Malaysian women experience cancer fatalism, belief in alternative medicine, and lack of autonomy in decision making resulting in delays in seeking or avoidance of evidence-based medicine. There are ethnic differences in estrogen receptor status, HER2 overexpression and incidence of triple negative breast cancer which warrant further investigation. Malay women present with larger tumours and at later stages, and even after adjustment for these and other prognostic factors (stage, pathology and treatment), Malay women have a poorer survival. Although the factors responsible for these ethnic differences have not been elucidated, it is thought that pharmacogenomics, lifestyle factors (such as weight-gain, diet and exercise), and psychosocial factors (such as acceptance of 2nd or 3rd line chemotherapy) may be responsible for the difference in survival. Notably, survivorship studies show self-management programmes and exercise improve quality of life, highlighting the need to evaluate the psychosocial impact of breast cancer on Malaysian women, and to design culturally-, religiously- and linguistically-appropriate psycho-education programmes to help women cope with the disease and improve their quality of life. Research done in the Caucasian populations may not necessarily apply to local settings and it is important to embark on local studies particularly prevention, screening, diagnostic, prognostic, therapeutic and psychosocial research.

KEY WORDS: *breast cancer, Malaysia, review, genetics, screening, diagnosis, prognosis, treatment, outcome*

INTRODUCTION

Besides the articles searched through the database, we also conducted a literature review of articles indexed in PubMed from 1996 to 2014 on 30th April 2014 using the key words "breast cancer" "Malaysia" and reviewed 421 articles. Of these, 154 abstracts were considered relevant to clinical practice by the authors [a breast surgeon, a genetic epidemiologist and an epidemiologist] and full text articles were reviewed. The aim of this review article is to summarise what has already been published on breast cancer in Malaysia, to discuss the impact of the research findings to clinical practice, and to identify gaps in breast cancer research in Malaysia.

SECTION 1: REVIEW OF LITERATURE

INCIDENCE AND PRESENTATION OF BREAST CANCER

The National Cancer Registry (NCR) 2003-2005 reported an age-standardised rate (ASR) of 47.3 per 100 000. The incidence is highest in Chinese (59.9 per 100 000) followed by Indians (54.2 per 100 000) and Malays (34.9 per 100 000)[1]. The Penang Cancer Registry 2004-2008 reported an incidence of 48 per 100,000[2]. The International Agency for Research in Cancer (GLOBOCAN) 2012 estimated the ASR of breast cancer in Malaysia as 38.7 per 100,000 with 5410 new cases in 2012[3].

Malaysian women present at earlier age compared to women in Western countries. A collaborative study between two tertiary academic hospitals in Malaysia, and Singapore found that approximately 50% of women were diagnosed before the age of 50 years[4], whereas in most Western countries such as UK and Netherlands, 20% are diagnosed before age 50. Two factors account for the younger mean age at presentation in Malaysia. First, Malaysia has a younger demographic with median age of 26.1 years, compared with 39.8 years in United Kingdom[5]. Second, the current older population in Malaysia, experience lower-risk lifestyle factors (more children, more breast-feeding and lower urbanisation) and this cohort effect results in lower risk of post-menopausal breast cancer.

Malaysian women present at later stages compared to women in Western countries and Singapore[6-8] but presented at earlier stages compared to Indonesian women[9]. Presentation of breast cancer varies substantially not only among countries, but also within different settings in Malaysia. Table I summarises the stage at presentation, tumour size and age in different settings in Malaysia[2,8,10-13]. Delayed presentation remains very common[14] and a collaborative study in Malaysia, India and Hong Kong showed that inadequacies of health care infrastructures and standards, sociocultural barriers, economic realities, illiteracy, and the differences in the clinical and pathological attributes of this disease in Asian women compared with the rest of the world together result in significant proportion of late stage disease[15]. In Malaysia,

Corresponding Author: chenghar.yip@gmail.com

ethnicity, education level, socio-economic status and access to treatment centres in urban areas were found to be important factors influencing stage at presentation. By combining the hospital-based breast cancer databases in University Malaya Medical Centre (UMMC) and National University Hospital Singapore (NUHS) [5264 patients], it was found that the Malay ethnicity was significantly associated with larger tumours at presentation and later stages at presentation, compared to the Chinese and to a certain extent, the Indians[16]. Late stage at presentation of breast cancer had been attributed to a strong belief in traditional medicine, the negative perception of the disease, poverty and poor education, coupled with fear and denial[17]. In Sabah, patients who presented with advanced disease were also poor, non-educated and from rural areas[13].

LIFESTYLE AND GENETIC RISK FACTORS TO BREAST CANCER

A number of lifestyle and genetic factors cause an increased risk of breast cancer and these have been shown to increase risk of breast cancer in Malaysian women. Table II summarises results from case control studies involving Malaysian women[18-29]. Well-known risk factors such as nulliparity, family history, not breastfeeding and use of oral contraceptives are observed to be associated with an increased risk of breast cancer in Malaysian women, but other risk factors are not significantly associated (e.g. age at menarche and first childbirth). However, these studies are retrospective and may be underpowered to find statistically significant results. To date, no study has examined breast mammographic density and the extent to which ethnic-differences in breast mammographic density is associated with risk of breast cancer.

Genetic predisposition also play a role in the aetiology of breast cancer. Approximately 15% of breast cancer patients report family history of breast and ovarian cancer, and the most significant genetic predisposition genes identified are BRCA1 and BRCA2. Cohort studies have shown the prevalence of BRCA1 and BRCA2 among breast cancer patients of 2.7% and 5.4% respectively, which is consistent with other Asian ethnic groups 30-31. Large genomic rearrangements (LGRs) constitute 8% of BRCA1 and 4% of BRCA2 mutations, and a number of novel rearrangements have been reported, suggesting that comprehensive BRCA testing should include detection of LGRs[32,33].

Two algorithms to predict the presence of mutations, Manchester Scoring System and BOADICEA, were evaluated and found that the predictive power of these two models were significantly better for BRCA1 than BRCA2, and that the overall sensitivity, specificity and positive predictive value was lower in this population than previously reported in the Caucasian population[34]. Notably, breast cancers associated with BRCA1 mutations are more likely to be triple negative for estrogen, progesterone and HER2 receptors, and of higher grade; BRCA2 associated breast cancers were similar to non BRCA associated breast cancers[35]. These pathological characteristics are predictive of BRCA1 mutation status - twenty-eight percent of women with breast cancers negative for the estrogen, progesterone and HER2 receptors diagnosed younger than 35 years old were found to be BRCA1 carriers, while only 9.9% of women with non-TNBC and younger than 35 years were BRCA1 carriers. Addition of TNBC and PTEN status improved the sensitivity of the Manchester Scoring System[36].

Genetic counselling and genetic testing were accepted by 82% of women at high risk for hereditary breast and ovarian cancer (HBOC) syndromes. However, only 78% of carriers informed their families, and 11% of relatives came forward for predictive testing even when genetic counselling and testing were offered free[37]. Early experience of the genetic testing and risk management clinic for high risk breast and ovarian cancer families in UMMC showed that only 63.5% of eligible women chose to attend this clinic, 24% chose to have risk reducing mastectomy (RRM) while the rest chose breast surveillance. Sixty-three percent chose to have risk reducing salphingo-oophorectomy[38].

Of the high risk women who did not have germline BRCA mutations, four mutations in TP53 (5%) suggested that TP53 screening should be considered in women with early onset breast cancer (<35 years old)[39]. PALB2 mutations were also reported and screening with nine PALB2 mutations found two novel truncating mutations and ten missense mutations, and one additional PALB2 mutation indicating a low prevalence of PALB2 mutations[40]. A truncating mutation (1100delc) in the cell cycle checkpoint kinase -2 gene (CHEK2), a common moderate penetrance allele found in Caucasians, was not found in any of the cohort of 668 breast cancer patients, suggesting that screening for this allele should not be routinely conducted in Malaysia[41]. Other genes or genetic loci associated with breast cancer have also been reported including the human leukocyte antigen (HLA) types[42], and other loci of lower penetrance[43].

SCREENING AND EARLY DETECTION

One of the main determinants of survival from breast cancer is early detection, which in turn is dependent on disease awareness and uptake of screening (both opportunistic and population-based screening). However, breast cancer awareness is poor in Malaysian women and very few eligible women attend regular mammography screening. Table III summarises results of cross-sectional studies, utilising surveys and self-administered questionnaires, that have been carried out in the Malaysian community to assess knowledge of breast cancer and screening methods i.e. breast self-examination (BSE), clinical breast examination (CBE) and screening mammography[44-61]. Notably, even among high-risk women, a cross-sectional study of 131 women with a family history of breast cancer showed that 71% had poor knowledge about the risk factors for breast cancer[62] and women with a family history of breast cancer probably did not recognise their increased risk to cancer and so presented with same stage of disease as women with no family history of breast cancer[63]. Many studies have shown that symptom recognition remains an important public health issue in Malaysia, highlighting the pressing need to continue to educate women, their significant others, and primary health care workers[64].

To date, the only reported outreach programme, which was conducted over a 4-year period in Sarawak, showed that training health staff in hospital and rural clinics to improve their skills in early cancer detection, and raising public awareness through pamphlets, posters and sensitisation by health staff, resulted in a reduction in the proportion of stage 3 and stage 4 breast cancer from 60% in 1994 to 35% in 1998[65].

DIAGNOSIS AND PATHOLOGY

Mammography, ultrasounds, MRI and bone scans

Radiology is pivotal in the screening and diagnosis of breast cancer. The majority of mammography services have transitioned from screen-film to digital, but quality assurance continues to be an important challenge in Malaysia. A survey carried out by the Malaysian College of Radiology on 50 mammography units showed that although 86% passed the image quality test, only 12.5% complied with the ACR

(American College of Radiology) recommended view-box luminance[66]. Overall diagnosis was comparable between screen film mammography (SFM), computed radiography mammography (CRM) and full field digital mammography (FFDM), but FFDM improves the quality of mammography services by providing better workflow time and archiving system[67], and improving the detection of microcalcifications[68].

Breast mammographic density is higher in Asian women and may affect the sensitivity of mammographic screening. The majority of Malaysian women had dense breasts (59%) and age and parity were inversely related to breast density[69]. A number of dietary factors have been associated with mammographic density, but these require further validation[70]. There is currently no commonly accepted standards for quantifying breast mammographic density in Malaysia. However, a semi-automated technique for quantitative assessment of breast density from digitised mammograms correlated well with the Tabar pattern, with a kappa coefficient of 0.63[71], suggesting that both methods may be clinically useful.

Ultrasound is a useful adjunct to mammography in the assessment of breast lumps. To differentiate between benign and malignant lesions, conventional ultrasound has a sensitivity and specificity of 97%, and 61.4% alone, and 100% and 93% when combined with ultrasound elastography[72]. The validity of ultrasound in the assessment of a palpable mass found that ultrasound had a sensitivity of 100%, specificity of 85.7%, and accuracy of 81.3% for distinguishing a malignant mass from a benign mass in another study[73].

Magnetic resonance imaging of the breast is a relatively new diagnostic tool in Malaysia and should not be used for routine screening. A prospective study of SV (1)H MRS following dynamic contrast-enhanced magnetic resonance imaging (DCE-MRI) showed that there was good correlation between tCho peaks and malignancy[74]. The sensitivity of DCE-MRI alone in differentiating between malignant and benign breast lesions was 100% with a specificity of 66.7%[75].

Staging with bone scans are recommended in women with locally advanced or metastatic breast cancer, but the role in early Stage 1 and 2 breast cancer is equivocal. Notably, no patient with clinical Stage 0 or Stage 1, 4% with Stage 2, 9.5% with Stage 3 and 63% with Stage 4 disease had a positive bone scan, showing that there is little justification to perform a bone scan in early breast cancer[76].

Pathology

Diagnosis of breast cancer depends on team work between the radiologist, surgeon and pathologist. The three methods of biopsy are fine needle biopsy, core needle biopsy and excisional biopsy. The choice of diagnostic method depends on the expertise which is available. Fine needle aspiration cytology was the most common method of diagnosis (63.8% of cases) in UMMC followed by core needle biopsy and excisional biopsy[77]. For non-palpable breast lesions, a study of 38 cases in Hospital Kuala Lumpur showed that 26.3% of excisional biopsies after mammographic localisation with a hookwire were malignant[78], compared to 32.3% in 57 patients in UMMC[79]. For palpable breast masses, fine needle aspiration cytology on 676 palpable breast masses showed a sensitivity of 91.7%, specificity of 91.7%, with a false negative rate of 11%[80]. If the cytological suspicious / equivocal category was considered as test positive, the sensitivity of FNAC was further increased to 97.4% and the specificity to 92%[81].

Cytology tumour typing was accurate in 94.8%, cytology grading was accurate in 71% and evaluation of ER status in 92.5%[82]. Typical cytological pictures were described for invasive lobular83 as well as for mucinous carcinoma[84].

Breast cancer is a heterogenous disease and pathological assessment of the tumour is important for prognosis and treatment. Size, grade, lymph node status, ER PR and cerbB2 assessment should be done routinely and are essential for accurate decision making on treatment.

Breast specimens undergo shrinkage after fixation, losing more than a third of their original closest free margin, while the tumour itself does not shrink substantially[85]. Infiltrating ductal carcinoma was the commonest histology in all women, where it accounts for 74.6% of women diagnosed > 50 years old and 65.2% of women diagnosed <50 years old[86].

Table IV summarises the studies on molecular markers from various institutions in Malaysia[13, 87-93]. There are several notable points: first, the proportion of ER positive breast cancer has increased over time, probably due to the rapid urbanisation and changes in parity and breast feeding over time. Second, Malay women were more likely to be ER negative, probably because the cohort comprises women diagnosed at an earlier age of onset[87]. Finally, there is wide variation in proportion of HER2-positive and triple-negative breast cancer (TNBC) in the Malaysian population, which could be due to interlaboratory differences in quality assurance and standardisation of testing for the three molecular markers.

Consistent with studies in Caucasian populations, triple negative breast cancer is more likely to be associated with young age of diagnosis, high grade, dysregulation of TP53, high expression of EGFR, CK5/6 and c-KIT, and high Ki67 proliferation index[89,92]. Overexpression of HER2 was significantly associated with high tumour grade, PR negativity and lymphovascular invasion[88]. Tumours which are negative for the estrogen receptor but positive for progesterone receptor was found in 4.6% of cases and occurs at a younger age group with intermediate histopathological characteristics compared to the ER+PR+ and ER-PR- tumours, suggesting that it is likely to be a distinct entity and not a biological artifact[94], but this has not been replicated in other studies. A study in Sarawak on 1034 cases of female breast cancer suggest that there may be ethnic differences in the risk to different subtypes of breast cancer. Overall, the study reported 48% luminal A (ER+ PR+ HER2-) breast cancer, 12% triple positive (ER+PR+HER2+), 29% TNBC and 11% HER2 overexpressing subtypes (ER-PR-HER2+). The indigenous population had the highest incidence (37%) of TNBC compared to Chinese (23%) and Malays (33%), and this remain significant after adjusting for other variables including age. HER2 overexpression was more frequent among the Malays (29%) compared to Chinese (22%) and the indigenous population (21%)[93].

One study suggested that overexpression of p53, which was observed in 55.3% of tumours, may be a prognostic factor. With a median follow-up of 4 years, the median overall survival of tumours with wild type compared to p53 negative tumours was 3 years compared with 3.8 years while for disease-free survival, it was 2.5 years compared to 3.3 years[95]. However, the data was not adjusted to intrinsic subtypes of breast cancer or for treatment differences. Two other biomarkers which have been tested are PTEN and CA153. PTEN loss occurred in 48.3% of TNBC, and was significantly associated with younger age at diagnosis. Independent predictors of PTEN loss were late stage at presentation, cytokeratin 5/6 positivity and IGFBP2

expression. PTEN loss and high levels of IGFBP2 expression were associated with poorer survival, but neither of these trends were significant[96]. Elevated levels of CA153 was associated with a poorer survival, suggesting its potential role as a prognostic biomarker[97].

TREATMENT

Where possible, breast cancer patients should be treated by a multidisplinary team. Surgery remains the mainstay of breast cancer treatment, with chemotherapy, radiotherapy and hormone therapy as adjunctive therapy. Newer agents such as targeted therapy is also part of the armamentarium of treatment strategies.

Surgery

Over the past 10 years, there has been an increase in the number of general surgeons who subspecialise in breast surgery in Malaysia and improvements in surgery have been made. Conventional technology to use diathermy to cut and coagulate blood vessels compared with ultracision showed that the use of ultracision was able to reduce the amount of drainage annd number of drain days, hence allowing earlier discharge of patients[98]. Another randomised controlled trial comparing preemptive local infiltration with ropivacaine (PLA) with postoperative wound infiltration with ropivacaine (POW) found no difference in post-operative pain between the two groups[99].

Axillary lymph node status is the most important prognostic factor in breast cancer. Therefore, some form of axillary dissection is needed for accurate assessment of the axilla. Given that only 24 out of 53 (45.3%) with positive axillary nodes were palpable, surgeons should be aware that clinical and intraoperative assessment of the axilla is inaccurate and all patients require at least a Level 1-2 dissection[100]. However, this does not apply to small T1 tumours, where axillary dissection will result in over-treatment of up to 75% of cases, and therefore, a sentinel node biopsy is justified[101]. Multivariable analyses show that the predictors of lymph node metastases were lymphovascular invasion and tumour size. The degree of tumour free margins after surgery is also crucial in deciding subsequent management[85].

In metastatic breast cancer, mastectomy was previously not thought to improve survival. However, a study showed that breast surgery was associated with a 28% lower risk of death after adjustment for patient and tumour characteristics, metastatic profile and treatment[102].

Given that the majority of Malaysian women still present at late stage, mastectomy is an essential but disfiguring operation. Immediate reconstruction can help women feel whole again and reduce the negative impact on body image, but access, cost and fear of additional surgery remain significant barriers to reconstructive surgery. Only a third of patients undergoing mastectomy were offered immediate reconstruction[103].

Chemotherapy

Chemotherapy has been shown to improve survival in women with breast cancer in the adjuvant setting, but a major concern to patients is that their immune system may be compromised with chemotherapy. Anthracyclines are the most widely used anticancer agents for breast cancer and a study comparing the effect of FEC (5-fluorouracil, epirubicin, cyclophosphamide) and FAC (5-fluorouracil, adriamycin, cyclophosphamide) found no significant difference in the numbers of immune cells, percentages of lymphocytes subsets, Th/Cytotoxic-T-lymphocyte (Th/CTL) ratio, engulfment and killing abilities of polymorphonuclear cells (PMNs)[104], suggesting that the immune system is not a major target of epirubicin-chemotherapy. Three other side effects which are major concerns to patients are hypercalcemia, neutropenia and preservation of fertility. Hypercalcemia can occur in cancer patients with and without bone metastases and in a study of 1,023 breast cancer patients, 174 patients (17%) had increased calcium levels. Chemotherapy decreases calcium levels in breast cancer cases with hypercalcemia at cancer diagnosis, probably by reducing Parathyroid Hormone-Related Peptide (PTHrP) levels[105]. Neutropenia is a common side effect of chemotherapy, but with adjuvant taxane based chemotherapy for early breast cancer, febrile neutropenia was reported in 10% of cases and no treatment-related deaths were reported[106]. Chemotherapy-induced ovarian failure occured in 57% of women <35 years, 95% at 35-45 years and 97.9% at >50 years, but notably, this was reversible in 50% of women >35 years old[107].

Locally advanced breast cancer (LABC) is a common presentation in Malaysia, but may present clinical challenges in management of patients. Overall, neo-adjuvant chemotherapy gave a complete pathological response of 5.9-9.4%[108-109]. However, 17.6 - 25.1% of women defaulted part of the treatment, or did not receive optimal treatment, highlighting the importance of psychosocial support and counselling for this group of patients[108-109].

Pharmacogenomics

Although studies in other populations describe ethnic differences in pharmacogenomics, there have been few systematic studies on ethnic-differences in pharmacogenomic responses to chemotherapy in Malaysia.

One study showed ethnic differences in CYP3A4 and CYP2D6, which may in part explain the differences in antiemetic effects of granisetron and 5-HT receptor antagonist (e.g. tropisetron and dolasetron) respectively[110].

A retrospective study suggests that patients who were CYP2D6 IM (intermediate metabolisers) and homozygous CC genotype of C3435T have statistically significant higher risks of recurrence and shorter times to recurrence when treated with tamoxifen[111], but this needs to be validated through prospective studies.

Traditional and complementary medicine

Traditional and complementary medicine are often used by Malaysian women with breast cancer, with one study of 116 Malay women describing uptake of 64% and another study reporting 51%. The most common medicines in Malay women were dietary supplements, followed by praying and Malay traditional medicine[112]. In Sabah, where women were found to present late, ~20% of patients opted for traditional alternatives and defaulted treatment[13]. Women who defaulted treatment were significantly more likely to be non-Chinese[113].

To date, few traditional or complementary medicines have been robustly tested through randomised controlled trials. A study on Withania somnifera (Ashwagandha), an Indian traditional medication, in women undergoing either chemotherapy with oral Withana somnifera or chemotherapy alone, showed that patients in the control arm had a significantly higher fatigue score and poorer quality of life than the intervention arm[114]. Tocotrienols have potent antiproliferative and proapoptotic effects in vitro, but a double-blind, placebo-controlled pilot trial comparing adjuvant tocotrienol therapy in combination with tamoxifen with tamoxifen alone for five years in women with ER positive early breast cancer showed no effect on breast cancer specific survival[115].

OUTCOMES

Overall Survival

Survival from breast cancer has improved in the past 3 decades. The largest Malaysian population based study of 10,000 breast cancer patients diagnosed between Jan 2000 and Dec 2005 identified from the Health Informatics Centre, Ministry of Health Malaysia, the National Cancer Registry and the National Mortality Registry found that the 5-year overall survival rate was 49%[116]. However, overall 5-year survival of breast cancer patients in UMMC improved from 58% to 76% for patients diagnosed in 1993-1997 compared to 1998-2002 (11). The most likely explanation is the establishment of oncology services in the hospital in 1998. Survival analysis showed that stage, lymph node status, negativity for the estrogen receptor, tumour size and grade were the most important prognostic factors[117-118]. Notably, whereas several studies in Western settings had reported that lymph node ratio (LNR, i.e. the ratio of the number of positive nodes to the total number of nodes excised) was superior to the absolute number of nodes involved (pN stage), this did not improve prognostication in a Malaysian population[119]. Another prognostic factor is locoregional recurrence after mastectomy for breast cancer, which may predict distant recurrence and mortality. The overall post-mastectomy local recurrence rate was 16.4% and isolated local recurrence rate was 8.0% (42 of 522 patients). Race, age, size, stage, margin involvement, lymph node involvement, grade, lymphovascular invasion and ER status were associated with ipsilateral local recurrence (ILR)[120]. A number of studies have examined the prognostic value of new biomarkers but these studies have been limited by ascertainment bias, as patients were more likely to receive additional testing (e.g. HER2 testing) if they are at intermediate or high risk[121]. Investigating the prognostic value of new biomarkers in breast cancer using only patients with available biomarker status from hospital cancer registries may lead to invalid results. Compared with patients perceived as having low mortality risk, patients with high mortality risk were significantly less likely to be tested for HER2 status, whereas those with intermediate risk were more likely to be tested[121].

However, although survival is improving in Malaysia, overall survival continues to lag behind that of our neighbouring countries, particularly Singapore. A combined analysis of 5,264 patients treated in UMMC and National University Hospital Singapore (NUHS), showed 5-year overall survival of 82.5% in Stage 0 to Stage II breast cancer patients, and 30.2% in Stage III and IV patients (4). Malay women had significantly higher risk of all-cause mortality, independent of age, stage, tumour characteristics and treatment, compared to Indian and Chinese ethnicity in this and another Malaysian study [Indian: 10.0%, Chinese: 71.6%, Malay: 18.4%][16,122], but in another study, delayed time from diagnosis to treatment in Malay compared to Chinese women did not result in significant impact on survival[123].The combined Malaysia-Singapore database also showed that overall survival of breast cancer patients from Malaysia is much lower than that of Singaporean patients[8,12]. Table V summarises the 5-year survival data from different Malaysian institutions[8,11-12,116]. It is noteworthy that the survival in UMMC at each stage of diagnosis is better than that of Hospital Kuala Lumpur, suggesting that disparities in survival could arise from differences in compliance to treatment.

Notably, a limitation of the majority of studies conducted so far have been that they are single-institution-based studies that may not accurately provide an overall picture of presentation, management, and outcome of breast cancer in Malaysia. Recently, a multicentre retrospective observational study showed that the performance results, while acceptable for a middle income country, was below the 95% or higher adherence rates routinely reported by centres in developed countries[124]. Further multi-centre studies, such as the National Cancer Patient Registry-Breast cancer (NCPR-BC), would be useful for evaluating clinical management in Malaysia[125].

Another manifestation of the disparity in survival is in the over-optimistic prediction of survival from prognostic models. Prognostic models, such as Adjuvant! Online, which have been developed in Caucasian populations to guide decision making for adjuvant therapy in early breast cancers, has been found to significantly over-estimated the 10-year survival (70.3% predicted compared to 63.6% observed, difference of 6.7%)[126], thus highlighting the need to address the disparities in care.

Two groups of patients may have poorer survival, namely the elderly and pregnant women. Although there is limited information on the outcomes of elderly breast cancer patients, this group of patients tend to be undertreated and have poorer survival because of competing co-morbidities. Of one hundred and thirty six women with breast cancer aged 70 and older studied, the relapse free, cause specific survival and cumulative overall 5-year survival were 79.7%, 73.3% and 51.9% respectively[127]. Patients who develop breast cancer whilst pregnant were rare and they require a multidisciplinary approach involving an obstetrician, surgeon and oncologist. Experience with six patients in UMMC revealed that five patients refused any treatment during pregnancy and the outcome was poor, with all patients dying between 14 months and 52 months[128].

Biomarkers

To date, four pathological biomarkers have been evaluated in the Malaysian population for its prognostic value, namely HER2, TP53, PTEN and CA153. Consistent with studies in other populations, HER2 (cerbB-2 onco-protein) overexpression was associated with a shorter recurrence free survival and overall survival[129]. One study suggested that overexpression of p53, which was observed in 55.3% of tumours, may be a prognostic factor. With a median follow-up of 4 years, the median overall survival of tumours with wild type compared to p53 negative tumours was 3 years compared with 3.8 years while disease free survival was 2.5 years compared to 3.3 years[95]. However, the data was not adjusted to intrinsic subtypes of breast cancer or for treatment differences. Two other biomarkers which have been tested are PTEN and CA153. PTEN loss occurred in 48.3% of TNBC, and was significantly associated with younger age at diagnosis. Independent predictors of PTEN loss were late stage at presentation, cytokeratin 5/6 positivity and IGFBP2 expression. PTEN loss and high levels of IGFBP2 expression were associated with poorer survival, but neither of these trends was significant[96]. Elevated levels of CA153 was associated with a poorer survival, suggesting its potential role as a prognostic biomarker[97].

SURVIVORSHIP AND PSYCHOSOCIAL ISSUES

Physical and psychological impact of breast cancer diagnosis

With optimal treatment, survival from breast cancer is very good, with 5-year survival of over 80% reported from USA. However, breast cancer survivors may experience long-term side effects of treatment such as early menopause, infertility, and sexual function, and psychological issues such as fear of recurrence, sexuality and body image. Without appropriate social support, these physical and psychological issues can result in poor quality of life. Indeed, 17.6% of care givers of

breast cancer patients were diagnosed to have depressive disorders and this was associated with ethnicity, duration of caregiving, the patients' functional status, and the caregiver's education level 130. One solution for breast cancer patients is a 4-week patient self- management programme for breast cancer, which has been shown to improve the quality of life of breast cancer patients by enabling them to better manage the numerous medical emotional and role tasks[131], with the benefits experienced even after two years[132]. A shorter term solution of a one-month group psycho-education programme also improved well-being and reduced the proportion of depressed individuals from 23.5% to 2.9%[133]. Other avenues for support comes from the family and from survivor support groups. Family and support group interventions for survivorship strategies such as managing emotions, health, lifestyle and dietary practice are important[134-135].

To date, few studies have evaluated the psychosocial impact of a diagnosis of breast cancer and effects of treatment in the developing world and in Malaysia. In a study in Kelantan, the quality of life (QOL) of newly diagnosed breast cancer patients was satisfactory in both Malay and Chinese women, but Malay women had a lower QOL due to high general, as well as breast-specific, symptoms[136]. Three themes were found in a study of the live-in experiences of 20 of breast cancer patients (Chinese-10, Malays-10): uncertainty, transition from health to illness, and fatalism[137]. Several psychological tools developed in Caucasian countries to measure the coping mechanisms and psychosocial parameters in patients have been validated in Malaysia, including the COPE scale[138], the Malay version of the Breast Module (BR23)[139], the Malay version of the Breast Impact of Treatment Scale (MVBITS)[140], and the Malay version of the Hospital Anxiety and Depression Scale (HADS)[141].

Coping with treatment side effects

Few Malaysian studies have reported how Malaysian breast cancer patients cope with treatment-related side effects. One study used the validated questionnaire, Morrow Assessment of Nausea and Vomiting (MANE) and Osoba Nausea and Emesis Module (ONEM) to assess the impact of chemotherapy induced nausea and vomiting (CINV) on QOL and found that delayed CINV (3-5 days after chemotherapy) had a greater impact on QOL compared to acute CINV[142].

Lifestyle effects on survivorship

Some changes in lifestyles may improve survival. The majority of Malaysian breast cancer patients (72 of 116 women) considered diet as a contributing factor to breast cancer and 67 women changed their dietary habits, by increasing the consumption of fruits, vegetables, fish, low fat milk and soy products, and reducing red meat, seafood, noodles and poultry[143]. In other populations, weight loss after breast cancer and exercise have been linked to better outcomes. In Malaysia, 40% of women with breast cancer were overweight or obese, and significant weight gain was observed from time of diagnosis to study entry[144]. Women with more than 10% weight gain had the lowest servings of fruits and vegetables and the highest servings of dairy products[145]. Despite the many documented benefits of physical activity, the majority of survivors were not physically active, citing lack of time as the main barrier[146].

Many Malaysian women report the use of complementary and alternative medicine (CAM) to improve survivorship, despite scarce evidence of efficacy. Uptake of CAM was reported in 51-64% of women, to increase the body's ability to perform daily activities, enhance immune function and improve emotional well-being[112,147]. An in-depth interview with 11 Malaysian cancer survivors found that they sought CAM because of recommendation from family and friends, perceived benefit and compatibility, healer's credibility, reservations with western medicine and system delays[148].

Addressing reasons for delay in presentation and default in treatment

Given that some Malaysian breast cancer patients continue to delay in presentation and default treatment, a priority for Malaysian researchers has been the identification of the reasons for delay and the development of interventions to reduce delay and default. A qualitative study in the East Coast of Malaysia, where 72.6% of women delayed presentation for >3 months, found that the reasons for delay were poor awareness of breast cancer, fear of cancer consequences, belief in CAM, sanction by others, other priorities, denial of disease, the 'wait and see' attitude, and weaknesses in the health care system[149]. Other factors associated with delay were use of traditional medicine, breast ulcer, palpable axillary lymph nodes, false negative diagnostic test, non-cancer interpretation and negative attitude towards treatment[150]. A study in Hospital Kuala Lumpur, where 31.1% of women delayed presentation for >3 months, found that women who were divorced or widowed, or women who never performed BSE were more likely to delay[151]. Overall, six themes were identified in a qualitative study on the health seeking trajectories of' Malaysian women. First, women considered traditional- versus hospital-based treatment. Next, their experience with symptoms, with the healthcare system were important. Fourth, their psychological status were critical. Fifth, their interaction with a role model was pivotal and finally, their fear of removing the breast guided their decisions[152]. Four main operational constructs in delayed presentation were knowledge of disease and disease outcomes, knowledge of treatment and treatment outcomes, psychological and physical resources and support and finally, roles in decision making. Deconstructing why women present with advanced breast cancer and resist treatment provide clarity of the issues and opportunities for intervention[153].

One such intervention could be providing educational material for making decisions. Decision making experiences of women with breast cancer were explored through a qualitative study and identified four phases in the decision-making process: discovery (pre-diagnosis); confirmatory ('receiving bad news'); deliberation; and decision (making a decision) with the final treatment decision influenced mainly by women's own experiences, knowledge and understanding[154]. This should provide the basis for the formulation of decision aids adapted for use in the Malaysian population.

Another intervention is providing culturally-sensitive information for Malaysian patients. A comparison of the informational needs of women newly diagnosed with breast cancer in Malaysia compared to the UK showed that for Malaysian women, information about the likelihood of cure, sexual attractiveness and spread of disease were the most important information needs while sexual attractiveness ranked lower compared to in women in UK[155]. Breast cancer patients undergoing chemotherapy had high levels of informational needs and there were difference between what the patient needs and the nurse's perception of patient's needs[156].

Returning to work

Key barriers to return to work were physical-psychological after-effects of treatment, fear of potential environmental hazard, high physical job demand, intrusive negative thoughts and overprotective family. On the other hand, the key facilitators

were social support, employer support, and the need for financial independence[157].

SECTION 2: RELEVANCE OF FINDINGS FOR CLINICAL PRACTICE

Risk factors for breast cancer in the local population were similar to published data i.e. nulliparity, family history, lack of breast feeding, oral contraceptive pill, obesity, and physical activity. Of these, it is expected that there will be a surge in the number of breast cancer cases in the not too distant future, in view that obesity rates are increasing at an alarming rate in Malaysia. Malaysian women are becoming "Westernised' in terms of changes in their reproductive risk factors, which starts with the earlier attainment of menarche, women opting to postpone marriage and pregnancies to a later age and having less number of children. Dietary changes may also play a role in the expected rise in the incidence of breast cancer.

Breast cancer associated with genetic mutations constitute a small percentage, between 5-10% of breast cancers. Nonetheless, they form an important group especially with increasing awareness about family history as a risk for breast cancer. The prevalence of BRCA1 and BRCA2, as well as less well known mutations such as TP53, PALB2 and CHEK2 in Malaysian women with breast cancer is reported, together with the clinical and pathological features. The results of the initial studies led to the establishment of a high risk management clinic, and early results of genetic testing and counselling revealed societal and cultural barriers to testing and preventative therapy. As Malaysia moves towards being a developed nation, development of facilities for genetic counselling, testing and preventative therapy are required.

Malaysian women, especially Malay women, present with late stages of the disease. Generally, there is a lack of breast awareness with a low uptake of breast self- examination, clinical breast examination and mammographic screening. These three methods appear to complement each other. Based on existing evidence, the Ministry of Health and NGOs will need to design community education programmes on modification of risk factors for breast cancer, signs and symptoms of breast cancer, and methods to detect breast cancer early.

Diagnostic radiology is important in the evaluation of a breast symptom. Screen film mammogram and digital mammogram are equally good in diagnosing breast cancer, although Full Film Digital Mammography (FFDM) seems to be superior in detecting microcalcifications and the quality of mammography by improving workflow. There are still a number of hospitals that are providing screen film mammography, which is cheaper and replacing all units with FFDM is probably not necessary. Ultrasound is a useful adjunct to mammography especially in younger women and combination of ultrasound elastography with conventional ultrasound is better in differentiating benign from malignant breast lumps, and may reduce the number of benign biopsies. MRI is also useful to differentiate malignant from benign breast lumps. Mammographic breast density is related to ethnicity, parity, age and diet, and is important because it reduces the sensitivity of mammography as well as increase risk to breast cancer. It is important that there is a standardisation of radiological breast reporting, and that density is reported as well, although there is no agreed method of reporting breast density.

Fine Needle Aspiration Cytology (FNAC) is the cheapest and quickest method of obtaining a diagnosis of breast cancer but requires the services of an experienced cytopathologist. In good hands, FNAC is able to determine the histological type, grade and ER status of the cancer. ER PR and HER2 are important in the management of breast cancer as it will classify breast cancer into four distinct subtypes i.e. Luminal A, Luminal B, Triple negative breast cancer, and HER2 overexpressing, with different prognostic implications. Other markers such as p53 have been assessed but their role is not as well-defined. While there is not much variation in the ER positive rate, TNBC and HER2 positive rates appear to vary widely in different local studies. However, some of these studies involve very small numbers of patients, and there may be interlaboratory variation in standardisation and reporting. It is important to develop and implement guidelines on collection of samples, laboratory standardisation and reporting of breast cancer.

Research on management of breast cancer is limited with only a significant study showing that mastectomy can improve survival in metastatic breast cancer; however, this is a retrospective study and a prospective study to confirm the findings is needed before becoming standard of care. CYP2D6 polymorphisms may play a role in tamoxifen resistance; however, the study was in a small number of women, and current guidelines do not require the evaluation of CYP2D6 polymorphisms before starting tamoxifen.

Survival analysis in different hospitals in Malaysia also show that there appear to be a great variation in survival rates among different hospitals in Malaysia, as well as between the three ethnic groups, with Malays having the poorest survival independent of pathological features, age and treatment. What is striking is that in HKL, the 5-year overall survival for Stage 1 and Stage 2 breast cancer was 58% and 53%, which is very low, when Stage 1 breast cancer in other studies have a survival of more than 90%. However, details of treatment were not available in the study from HKL, making it difficult to disentangle the impact of management patterns on survival. The two main determinants of survival are early detection and access to optimal treatment. Since the survival by stage differs so widely in different settings, access to optimal treatment may be an issue in some hospitals.

Breast cancer survivorship is a neglected area in Malaysia, and certainly the implementation of a sort of self-management/ psycho-education programme and education on lifestyle changes particularly weight control and exercise is needed. There is a need for psycho-oncologists to evaluate the psychosocial impact of breast cancer on women, and to design psycho-education programmes to help women cope with the disease and to improve quality of life. Women with breast cancer have multiple unmet needs that need to be addressed, whether in terms of education or support. Health care professionals need to work together to determine how best to support and improve quality of life. The reasons for delayed presentation has also been well studied. While some of the delays are due to patient delay, health care system delays contribute to this as well. Doctors also need to be educated on the symptomatology of breast cancer, and have better communication skills in breaking bad news. Poor decision making skills was also a reason for delay.

SECTION 3: FUTURE RESEARCH DIRECTION

Further research is required on the different presentation of breast cancer with different outcomes in the three ethnic groups in Malaysia, (summarised in Table VI) particularly on why

Malays have a poorer survival which is independent of pathology, stage and treatment. A hypothesis would be different lifestyles after completion of treatment for breast cancer and perhaps different pharmacogenomics in response to chemotherapy and hormone therapy.

It is generally accepted that breast cancer risk factors, which have mainly been studied in Western populations are similar worldwide. However, the presence of gene-environment or gene-gene interactions may alter their importance as causal factors across populations. Also, risk assessment models developed in the West such as the Gail Model has not been validated in Malaysia, and perhaps a large study can be done to determine if this model works in Malaysian women, and if not, then another model specific to the local population can be developed. Since risk factors is known to differ according to subtypes of breast cancer, a large study looking at risk factors, particularly the reproductive risk factors in different subtypes of breast cancer are warranted.

Breast cancer genetic research is expensive and not many centres have enough research money or even expertise to carry out this type of research. Future research should focus on identifying mutations specific to Asians that are neither BRCA1 nor BRCA2, and this is currently ongoing with the UM-CARIF group and need to be strengthened. Collaboration within the Asian region is also important since more patients will be needed to identify any novel mutations. Qualitative research into barriers to testing and preventative surgery need to be carried out.

Intervention studies are required to determine the appropriate early detection method which is not only effective but also economically feasible in Malaysia. Based on findings from Sarawak, it is felt that a well-designed randomised controlled trial, for example on CBE, with downstaging of breast cancer as a short-term outcome, and reduction of breast cancer mortality as a long-term outcome within a defined population would be more impactful than conducting a series of small questionnaire studies focussing on knowledge. Local information on the efficacy of screening is also lacking. Opportunistic mammogram screening programmes are available in government and private hospitals. There are no published results on the efficacy of opportunistic mammography screening in the local population.

The quality of breast imaging reporting depends more on the radiologist than technology, and future research on quality assurance of the radiology reporting is indicated. There are no local studies on the sensitivity and specificity of diagnostic mammography in the diagnosis of breast cancer. The study on validity of ultrasound was very small, in 70 patients of whom only eight had cancer. The role of MRI in the local setting, where breast density is higher than in western settings needs more study.

Breast density is an area of research that is fairly new, and local institutions are embarking on various aspects of breast density research. Not only lifestyle and genetic determinants of breast density are being studied but also the accurate methods of determining breast density. Results of these studies will add to the information about breast density and the risk of breast cancer.

The majority of breast cancer pathology research focuses on the associations of pathological variables with clinical characteristics, and may not be applicable to the clinical outcome. Since the distribution of the four subtypes of breast cancer (based on immunohistochemistry assessment of ER, PR and HER2) seem to vary considerably from one study to another i.e. in different labs, it may be due to problems with quality assurance and standardisation of reporting. Future research in the area of quality control and standardisation of testing, and perhaps quantification of ER and PR and its relationship to response to treatment may have more impact on patient management. Identification of new prognostic markers will require the availability of tissue samples with corresponding clinical data and outcomes, which are available in some centres.

There are not many controversial issues in the surgical treatment of breast cancer. However there have been no large local studies on breast conserving surgery versus mastectomy, or on the performance of sentinel lymph node biopsy in the local population. Well-designed clinical trials on different chemotherapy regimes are lacking, and studies tend to involve very small numbers. There is a need to establish multicentred trials on chemotherapy and hormone therapy, as well as a need for investigator initiated trials, particularly in natural products, and traditional products that are commonly used locally. The outcomes in these trials should not be only focussed on treatment effectiveness, but also on adverse effects, and patient-orientated outcomes such as quality of life. Pharmacogenomics is an emerging field and the multiethnic population in Malaysia would be ideal for studying genetic polymorphisms affecting pharmacodynamics, and pharmacokinetics.

We should also aim to get a sufficient number of our multi-ethnic patients enrolled in large scale international clinical trials, to enable appropriate conclusions to be made on the effectiveness of new anticancer therapies in Asians.

Future research would be to determine which of the lifestyle variables would contribute to improved survival from breast cancer. A prospective breast cancer cohort study is currently ongoing in UMMC (MyBCC study). This study looks at the quality of life, nutrition and weight changes, return to work, physical activity and its relationship to recurrence and survival. Similar studies should also be conducted in other settings such as rural regions as lifestyle might be different. Studies on the prevalence of long-term side effects of treatment such as premature menopause, menopausal symptoms, osteoporosis, infertility, sexuality, lymphoedema, fatigue, chronic pain and upper limb dysfunction is lacking, and cognitive deficits are areas for future research.

Future research would also be to determine what interventions would work in improving quality of life and ensuring that women do not delay treatment. A national study on delay in treatment is underway in UM, as well as a collaborative study with international research group to identify reasons for delay. There is a need for research on decision making processes in women with breast cancer as this is one of the areas identified as a reason for delay.

Breast cancer prediction rules including diagnostic, and prognostic rules which may be very useful in aiding clinical practices are increasingly shown to be 'setting specific'. The rules must therefore be validated in Malaysian women before implementing them in clinical care. In instances when they are not found to be accurate, it may even be necessary to build new 'Malaysian-specific' prediction models using a large cohort of Malaysian breast cancer patients.

The NCPR therefore will need to be strengthened, and eventually be used as a research resource like the SEER (Surveillance Epidemiology and End Results) database in USA. Finally it is important to remember that research done in the western counties may not apply to local settings and hence it is important to embark on local studies in all domains of research in breast cancer[158].

Table I: Stage at presentation of breast cancer in different institutions in Malaysia

Author (ref)	Institution	No	Stage 0 (%)	Stage 1 (%)	Stage 2 (%)	Stage 3 (%)	Stage 4 (%)	Size of tumour (cm,‡)	Mean Age
Penang Cancer Registry 2004-2008(2)	Penang	1091	NA	23.5	46.1	17.3	13.1	NA	NA
Hisham *et al* 2003(10)	HKL 1998-2001	774	NA	40		60		5.4	50
Taib *et al* 2011 (11)	UMMC 1993-97	423	NA	17.3	48.7	17.5	16.6	4.5	49
	UMMC 1998-2002	965	NA	21.5	48.8	17.7	12	4.4	49
Leong *et al* 2007 (13)	Queen Elizabeth Hosp KK	186	4.8	12.9	30.1	36.6	15.6	NA	51
Ibrahim *et al* 2012 (12)	HKL 2005-09	868	NA	14.6	43.8	25.6	16.0	5.0	NA
Saxena *et al* 2012 (8)	UMMC 1993-2007	3321	2.9	21.6	42.4	22.3	10.8	3	50
	NUH Singapore 1993-2007*	2141	10	24.7	42.9	24.4	7.9	2.2	50

‡ Mean tumour size is presented except the study by Saxena which presented median
*Singapore data for comparison

Table II: Risk factors for breast cancer

Author (Ref)	Controls (n)	Cases (n)	Recruitment	Factors that reduce risk	Factors that increase risk	Factors that are not significant
Matalqah *et al* (18)	150	150	Penang General Hospital	Low fat diet, education >11 years, breast feeding, being employed	Family history, benign breast disease, menstrual irregularity, use of oral contraceptive (OCP)	
Razif *et al* (19)	216	216	HKL and UKMMC	Higher number of life births	Family history	Age at first child birth and menarche not significant
Norsa'adah *et al* (20)	147	147	Kelantan		Nulliparity, overweight, family history, use of OCP	
Hejar *et al* (21)	89	85	Chinese, HKL and UMMC	Breast feeding		
Kamarudin *et al* (22)	203	203	HKL	Exercise, low fat diet, longer duration of breast-feeding		
Rejali (23)	62	62	Malaysian hospital	Higher intake of selenium	Nulliparity, exposure to cigarette smoke, use of OCP	
Shahar *et al* (24)	70	138	Klang Valley	Higher intake of selenium	Abdominal obesity, physical inactivity, low serum adiponectin	
Sulaiman *et al* (25)	382	382	Kuala Lumpur			Total fat and fat subtypes not associated
Suzana *et al* (26)	64	127	Klang Valley	Higher intake of selenium, vit A, vit E		
Sharhar *et al* (27)	57	139	Klang Valley		Poor antioxidant status and oxidative stress measured by higher levels of malondialdehyde (MDA)	
Shahril *et al* (28)	382	382	Kuala Lumpur	Higher Healthy Eating Index-2005 (HEI-2005) score		
Ho *et al* (29)	37 pre-menopausal 68 post-menopausal	36 pre-menopausal 66 post-menopausal	Kuala Lumpur		Higher serum progesterone and testosterone levels in postmenopausal women	

Table III: Breast awareness studies in Malaysia

Author (ref)	No	Recruitment	Age	Findings
Al-Dubai 2011 (44)	250	Random, Shah Alam	Mean age 28 years old	Did not know symptoms and signs of breast cancer Poor awareness of mammography
Kanaga *et al* 2010 (45)	125	Urban and rural areas	19-60 years old	Awareness of breast cancer and screening procedures increase with higher education and urban living
Abdul Hadi *et al* 2010 (46)	384	Penang	19-60 years old	Serious knowledge deficits about breast cancer and unaware of screening guidelines, ethnicity, education and employment status were significantly related to knowledge
Dunn *et al* 2011 (47)	816	Data from the Malaysian Non communicable Disease Surveillance-1	Above 40 years old	Malay women less likely than Chinese and Indian women to undergo mammography, but were more likely to undergo BSE. Education level and urban residence positively associated with each screening method among Chinese women but not among Malay women
Al-Dubai 2012 (48)	222	Urban area, Shah Alam	Mean age 28.5 years	55% of women practise BSE. Women >45 yrs, Malay, married and higher education level were more likely to practise BSE
Akhtari-Zavare *et al* 2013 (49)	252	Female undergraduates UPM	Mean age 22 years old	37% practise breast self examination (BSE), motivation and self-efficacy higher in those who practise BSE
Al-Naggar 2011 (50)	251	Female undergraduates MSU	Majority >20 yrs	55% practised BSE, barriers to BSE were lack of knowledge, not having symptoms and being afraid of being diagnosed with breast cancer
Al-Naggar *et al* 2012 (51)	250	Random sampling, mainly urban	Mean age 34.7 yrs	47.2% practise BSE, and race, marital status, residency, belief that breast cancer can be detected early, belief that early detection improves the chance of survival, and family history significantly influenced the practice of BSE
Rosmawati *et al* 2010 (52)	86	Suburban area in Trengganu	Mean age 40 yrs old	Proportions of women with good scores for knowledge, attitude and practice for BSE was 38.4%, 73.3% and 7% respectively. Not knowing the correct method for BSE, lack of knowledge about signs and symptoms of breast cancer, lack of support from friends and family were related to poor practices
Dahlui *et al* 2013 (53)	959	Rural areas,	NA	Knowledge about breast cancer and screening varied by ethnicity, location and type of support received. Women below 50 years old, of Malay ethnicity and who had secondary education scored better than those who were older, of Chinese ethnicity and had primary education. The uptake of BSE was 59%, CBE 61% and mammography screening was 6.8%
Dahlui *et al* 2011 (54)	718	Female staff, UM	35 years and above	41% practised BSE regularly, 47% had undergone CBE and 23% had had a mammogram. Those who had CBE were more likely to do BSE, while of the 19% who felt a breast lump on BSE, 87% went on to have a CBE
Dunn *et al* 2010 (55)	816	Data from the Malaysian Non communicable Disease Surveillance-1	Above 40 yrs old	Women who perform BSE were more likely to have undergone mammography screening in all ethnicities, suggesting that previous work on the efficacy of BSE in developed countries may not apply to nations with limited resources
Dahlui *et al* 2012 (56)	381	Suburban district Selangor	20-60 yrs old	58.5% of women practised BSE, uptake of mammogram was only 14.6%. Significant predictors of BSE were good knowledge of breast cancer, being married and attending CBE, while predictors of CBE was being married, good knowledge of breast cancer and good social support
Al-Naggar *et al* 2012 (57)	200	Shah Alam	65.5% under 50 years old	Only 15% of women had a mammogram. Barriers to mammographic screening were lack of time, lack of knowledge, not knowing where to go for a mammogram, and fear of the result
Rosmawati *et al* 2010 (58)	86	Suburban area in Trengganu	45.5 yrs	Only 10.5% had a mammogram done, and knowledge pertaining to mammographic screening was poor
Parsa *et al* 2010 (59)	425	Female teachers	Mean age 37 yrs	Only 13.6 % ever had a mammogram while 25% ever had a CBE. Having a perceived susceptibility for breast cancer, regular CBE's were predictors for having a mammogram
Chan *et al* 2011 (60)	Case control comparing 27 women who defaulted mammography appointments with 73 controls	Ipoh GH	NA	Women from lower socioeconomic groups and rural areas were more likely to default their mammogram appointment
Abdullah *et al* 2011 (61)	534	Female staff UMMC	40 years and above	20% of personnel did not undertake mammography screening although there is no cost incurred and the procedure is fully accessible to them. Barriers are negative perception of the procedure, low confidence with radiologist/radiographers in detecting abnormality; lack of coping skills in dealing with expected results and pain during procedure

Table IV: Molecular markers in breast cancer

Author (Ref)	Institution	No	Period	ER positive rate, %	HER2 positive rate, %	Triple negative breast cancer, %
Yip *et al* 2011 (87)	UMMC	279 1041 1757	1994-98 1999-2003 2004-2008	54.5 56.4 58.4	- - -	- - -
Tan *et al* 2009 (88, 89)	UMMC	996	2005-2007	-	30.3	17.0
Leong *et al* 2007 (13)	Sabah	186	2005-2006	59.1	-	-
Teoh *et al* 2011 (90)	Penang	NA	2005-2006	55.8	24	15
Chng *et al* 2012 (91)	HUSM, Kota Baru	94	2006-2010	53.2	24.5	22.3
Kanapathy *et al* 2012 (92)	Private hospital KL	340	2002-2006	-	37.2%	12.4
Devi *et al* (93)	Sarawak	1034	2003-	57	23	29

Table V: Outcomes - 5 year survival

Author (ref)	Institution	No	Overall 5 year survival, %	Stage 1, % (95% CI)	Stage 2, % (95% CI)	Stage 3, % (95% CI)	Stage 4, % (95% CI)
Taib *et al* 2011 (11)	UMMC 1993-97 UMMC 1998-2002	423 965	58.4 (54-63) 75.7 (73-79)	81.7 95.2	72.4 87.5	39.9 55.6	12.8 18.7
Ibrahim *et al* 2012 (12)	HKL 2005-09	868	43.5	58 (54.2-61.8)	52.7 (50.2-55.1)	39 (35.8-42.6)	19.8 (17-22.7)
Abdullah *et al* 2013 (116)	Data from Health Informatics, NCR, National Registration Dept 2000-2005	10 230	49.4 (NA)	NA	NA	NA	NA
Saxena *et al* (8)	UMMC 1993-2007	3320	69 (67-71.1)	93 (91.9-94.1)	79 (77.8-80.3)	52 (49.4-54.6)	12 (6.8-17.1)
	NUH Singapore 1993-2007*	2141	80 (79-80.9)	98 (97-99)	85 (83.7-86.3)	66 (62.5-69.6)	23 (16.6-29.5)

*Singapore data for comparison

Table VI: Molecular markers in breast cancer

Author	Time period	Institution	Presentation and survival	Malays	Chinese	Indians
Taib *et al* (112)	1993-1997	UMMC	No	85	261	67
			Prevalence (%)	21	63	16
			Stage 1 (%)	11	21	10
			Stage 2 (%)	49	48	58
			Stage 3 and 4 (%)	40	31	32
			Survival (%)	47.5	63	57.4
Ibrahim *et al* (10)	2005-2009	HKL	No	501	218	149
			Prevalence (%)	58	25	17
			Stage3-4 (%)	46	36	34
			5 year survival (%)	39.7	48.2	47.2
			(95% CI)	(37.3-42.1)	(44.4-52.0)	(43.2-51.2)
N Bhoo Pathy *et al* (13)	1990-2007	UMMC and NUH Singapore combined	No	968	3767	529
			Prevalence (%)	18.4	71.6	10
			Median size (mm)	35	25	30
			Lymph node involved (%)	53.6	42.9	48.9
			Metatastic (%)	16	9	4
			5 year survival (%)	58.5	75.8	68
			(95% CI)	(55.2-61.7)	(74.4-77.3)	(63.8-72.2)

Note: This review contains articles published from 1996 and 2014, however the literature outside year 2000-2013 were not thoroughly searched.

ACKNOWLEDGEMENT

I would like to sincerely thank the Director General of Health, Malaysia for his permission to publish this paper. I wish to thank Clinical Research Centre team for their contribution and support.

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