REVIEW

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Risk-Stratified Breast Cancer Screening in Malaysia: Challenges and Opportunities

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Abstract

Introduction: Breast cancer is the commonest cancer among Malaysian women. Current clinical practice guidelines (CPG) by the Ministry of Health, Malaysia comprise recommendations based on a risk stratification approach. **Aim:** This paper reviewed and reflected on the challenges and uncertainties that needed to be considered regarding the implementation and delivery of risk-stratified breast cancer screening in Malaysia. **Methods:** Our iterative writing, discussions and reflections revolved around the results of key relevant literature search from the Ministry of Health Malaysia website, PubMed, and Google Scholar, and on feedback from local clinical experts in the field of breast cancer screening practice. The articles related to risk-stratified breast cancer screening, genetic testing, screening guidelines for the Malaysia population, and articles published in English were included in this narrative review. **Result:** Further infrastructure and workforce capacity building is needed in order to achieve successful wider implementation e.g.; genetic counselling and testing services are limited in Malaysia. Furthermore, there is a need to elicit Malaysian women's views and evaluate their acceptance of risk-stratified breast cancer screening. The primary healthcare setting is an obvious potential avenue to introduce and deliver initial risk assessment and stratification. However, the workload and willingness of Malaysian primary healthcare doctors to practice risk-stratified screening is yet to be explored to have a better understanding on their perspective. **Conclusion and recommendation:** Identifying a valid and appropriate risk model tailored to the population profile and needs of Malaysian women and conducting a pilot project of risk-stratified screening, guided by implementation science would provide lessons and insights for policymakers, health service managers, and public and primary health care professionals. The results of these activities would increase the likelihood that decisions and plans would lead to the successful implementation in Malaysia of a sustainable and effective breast cancer screening strategy that incorporates a patient-sensitive, risk-stratified approach.

Keywords: Breast cancer- Risk-stratified breast cancer screening- Malaysia- Primary healthcare

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Breast cancer in Malaysia

Breast cancer is the commonest cancer in the Malaysian population and approximately one out of five cancer patients have breast cancer (19% of all cancer) [1]. Age-standardised incidence rates of breast cancer among Malaysian women have been increasing and were 34.1 in 2016 [1]. Late-stage diagnosis has been increasing also – the most recent report estimated that 47.9% of women were diagnosed at Stage III and IV even though cancer screening, prevention, and control programmes have been implemented in Malaysia [1-3]. Furthermore, the onset of breast cancer among Malaysian women is early and approximately half of patients are diagnosed before the age of 50 years [4].

Gene mutations and breast cancer

Globally, *BRCA1* and BRCA 2 are common mutations that indicate an important genetic susceptibility to developing breast cancer [5]. Among Asian familial breast cancer patients, the prevalence of *BRCA1*/2 has been estimated to be 8.0% to 31.8% and 2.8% to 21.4% among early onset breast cancer patients [6]. Generally, the prevalence of *BRCA1* mutation is more common than *BRCA2* mutation except for Asian women where equal prevalence has been reported [7]. However, in addition to *BRCA1* and *BRCA2*, it has been reported that the mutation of the Apolipoprotein B mRNA-editing enzyme, the catalytic polypeptide-like (APOBEC3B) and tumor suppressor gene (*TP53*) are associated with breast cancer and observed more commonly among Asian

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women than European women [8, 9]. A recent study in Thailand identified the significance of PALB2 and ATM genetic mutations among breast cancer patients as well as *BRCA1* and *BRCA2* [10]. The pathogenic mutations of genes (*BRCA1, BRCA2, PALB2, APOBEC3B*, and *TP53*) were reported to be associated with the occurrence of breast cancer among Malaysian and Singaporean women [11] and screening for *BRCA1*, *BRCA2*, *TP53*, and PALB2 genes using blood and saliva samples is currently available in Malaysia [12].

General population screening for breast cancer

Screening plays a crucial role in terms of earlier detection and management, improving survival and maintaining, at least, the quality of life of breast cancer patients. Clinical breast examination (CBE) and mammogram tests are recommended and encouraged as an opportunistic screening strategy [13]. Malaysian women between 50- and 74-years old are encouraged to undergo regular biennial mammogram screening [14]; and that in the general (average risk) population CBE are recommended once every three years (for women aged between 20- and 39-years old), and annually (for women aged 40-years old and above) [15]. Mammograms are provided in Malaysian government clinics and hospitals for an affordable nominal charge, and in private hospitals, there are subsidized programmes organized by the National Population and Family Development Board (NPFDB) Malaysia [16, 17]. However, screening uptake is underutilized and needs to be improved alongside screening guideline adherence by healthcare providers [18, 19].

Assessment of risk for breast cancer and screening high-risk populations

Risk assessment is a crucial component in the process of determining a woman's likelihood of developing breast cancer and to plan targeted screening [20]. The Malaysian Ministry of Health (MoH) clinical guidelines and recommendations have evolved over time and have been updated periodically with new evidence. The current and third edition of the MoH Management of Breast Cancer (Clinical Practice Guidelines) includes a risk assessment and screening recommendations based on risk stratification [14]. The risk assessment considers various factors including family history, age at diagnosis of breast cancer in relatives, bilateral breast cancer in relatives, and having male relatives with breast cancer [21]. People with hereditary cancer syndromes have a higher risk of developing cancer [22]. Therefore, genetic testing should be considered for people with one or more hereditary cancer syndrome along with appropriate pre- and post-test counselling [14]. However, ideally, any risk assessment model should be tailored to the Malaysian population and validated in terms of its predictive accuracy [14].

A version of risk stratification that affords an opportunity to categorize women with no personal history of breast cancer as having an average-, moderate-, or high-risk has been introduced in Malaysia [23, 14]. The risk stratification was adapted from UK National Institute for Health and Clinical Excellence (NICE) guidelines (2018) by the Ministry of Health Malaysia (MOH) [14] though it is unclear whether or not the model has been tested and validated in Malaysia. Table 1 describes the features of the MOH Malaysia risk stratification.

The adapted guidelines suggest that high-risk women with no genetic mutation variant or women with a low chance of being a genetic mutation (BRCA, *TP53*) carrier should consider undergoing an annual mammogram when they are between 30- and 39-years old; and the guidelines recommend clearly, an annual mammogram for women between 40- and 59-years old, and biennially for women 60-years old and above. Annual magnetic resonance imaging is recommended in addition to a mammogram for women (30-49 years-old) with pathogenic variants in *BRCA1*, *BRCA2*, and PALB2 whilst receipt of an annual mammogram is recommended for women aged between 40- and 69-years old and biennially at 70-years old and above (Figure 1) [14]. Furthermore, risk reduction measures such as removal of both breasts or chemoprevention such as tamoxifen and their treatment consequences should be discussed with high-risk women [14].

Health professionals including radiologists and breast cancer specialists play important roles with respect to the implementation and sustainability of a screening programme and guidelines [24, 18]. Cancer genetic clinics and counselling are essential services for women suspected

Table 1. Risk Stratification of Malaysian Women with No Personal History of Breast Cancer [14]

Risk category	Lifetime risk of developing breast cancer	Factors
Average risk	<17%	
Moderate risk	17% to <30%	*"Women with pathogenic/ likely pathogenic variants in PALB2 regardless of family history of breast cancer and, individuals with pathogenic/ likely pathogenic variants in ATM and CHEK2 and at least one first degree relative affected by breast cancer."* *"Individuals with pathogenic/ likely pathogenic variants in ATM or CHEK2 and no close family history of breast cancer is considered to be of low moderate risk of breast cancer."*
High risk	At least 30%	*"Pathogenic/ likely pathogenic variants in PALB2 and strong family history of breast cancer, or individuals where BOADICEA or other risk prediction tools suggest a high-risk based on family history of breast cancer"*
High risk with pathogenic variant		*"Known BRCA1 or BRCA2 carrier"*

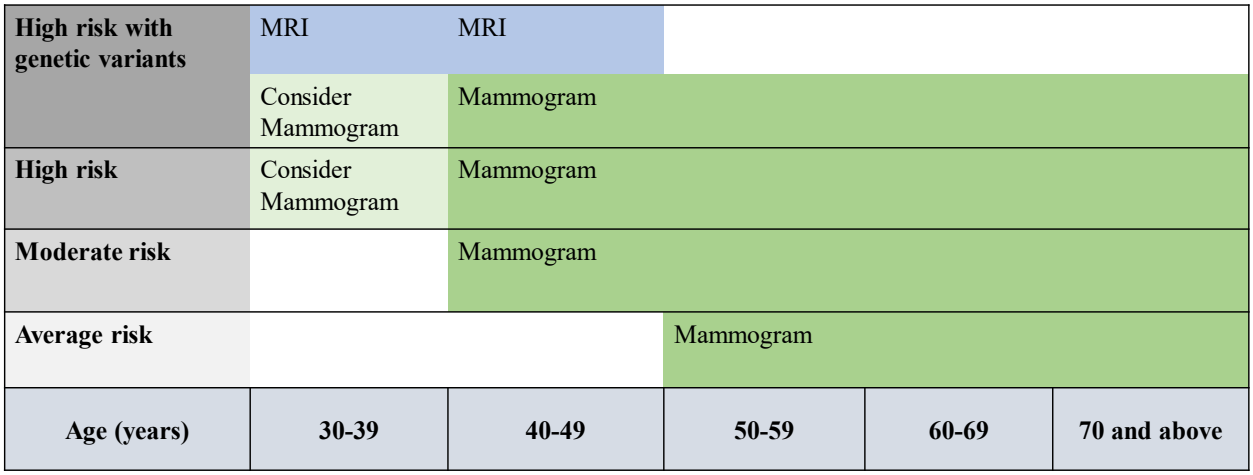

Figure 1. Breast Cancer Screening Recommendation According to Risk Category [14]

of having hereditary breast or ovarian cancer [14]. A risk stratification approach requires an infrastructure that, necessarily, includes these kinds of services as well as user-friendly lay information.

Risk communication and implementation of genetic testing

Effective communication strategies and techniques are essential in order to convey information about health risks in a way that people comprehend, and that will encourage them to undergo screening [25]. A risk-stratified approach aims to provide and enhance evidence-based and research-informed decision-making that will personalise or tailor breast cancer screening decision pathways and increase patient benefits and reduce harm [26]. However, there is a risk of causing anxiety and worry to high-risk women, and, so, effective risk communication by well-trained professionals is crucial to minimize distress [27, 28]. The Genetic Counselling Society Malaysia (GCSM) was initiated in 2019 [29] and, currently, genetic risk assessment and counselling services are provided in Kuala Lumpur Hospital, Penang Hospital, Universiti Sains Malaysia Hospital in Kubang Kerian, Canselor Tuanku Muhriz Hospital in Cheras and University Malaya Medical Centre, Kuala Lumpur [30]. The clinics offer a risk assessment to all eligible women; and women who are deemed to be high risk and to need genetic testing are referred to Cancer Research Malaysia [12]. However, the fact that there were only 11 clinical geneticists in Malaysia in 2022 means that genetic counselling services are very limited [30].

Compared to countries with more developed economies and health systems, Malaysian women were less informed about genetic testing and how this test information can be used to predict cancer risk [31]. Despite the lack of information, there appeared to be a moderate level of interest among women to take a genetic test, ranging from 41.7% (age 40 to 60 years) [32] to 67.9% (age 19 to 26 years) [31]. Regarding healthcare professionals, nurses reported positive attitudes about testing and were recorded as having adequate knowledge about BRCA genetic testing in Malaysia [33]. Indeed, willingness to pay for genetic testing in the general population was reported to be a median of USD 48.31 (Malaysian Ringgit, MYR 200.00), which included women who indicated that they would be willing to share the cost with a health insurance company [32]. The estimated cost to the MOH Malaysia for providing breast cancer genetic testing is USD 325 (MYR1500) [34], which is much higher than the amount that is indicated in the willingness-to-pay study. However, the cost of breast cancer genetic testing as indicated by a risk stratification approach is not covered by health insurance schemes in Malaysia, like other countries in Asia in general [35, 36]. In Malaysia, genetics testing facilities are limited and breast cancer genetic testing is provided by Cancer Research Malaysia [12].Therefore, unsurprisingly, priority is given to women who have a high probability of having the BRCA mutation [37]. Although the cost-effectiveness of genetic testing for risk stratification in Malaysia has not been evaluated, a systematic review of ten cost-effectiveness simulation modelling studies from the USA, Spain, Germany, Netherlands, and China reported that risk-based screening was cost-effective compared to no screening and age-based screening strategies [38].

Risk-stratified screening is at an initial stage of implementation in most countries. The eventual findings from current ongoing clinical trials are likely to be beneficial in terms of informing decisions about, for example, the effectiveness, benefits and any harms of risk-stratified screening [39-41]. Breast cancer risk-assessment models such as the Gail model, the Contraceptive and Reproductive Experience (CARE) model, the Breast and Ovarian Analysis of Disease Incidence and Carrier Estimation Algorithm (BOADICEA) and the Vermont model have been tested in European and USA country populations [42-45]. Prediction accuracy has been tested for BOADICEA among Chinese cohort and found to be fairly accurate for women with personal and family history of breast or ovarian cancer, while the prediction was found to be unreliable for those without family history [46]. Each model has strengths and limitation. The Gail model, which is the most widely used model, is developed in 1989 to estimate women's risk of developing breast cancer and it appears to have moderate discriminative ability [47, 48]. However, risk prediction was uncertain with respect to African American women. The CARE model was

developed in 2007 and had been applied to estimate the risk of developing breast cancer among African American women [49, 43]. The BOADICEA model estimates the risk of developing breast cancer and ovarian cancer among women with higher than average population risk, specifically, women with a family history of breast cancer and genetic mutation status [50-52]. The Vermont model (developed from the Vermont Breast Cancer Surveillance System) [53]. Assessing Vermont model among elderly women was reported that it did not predict well for women aged 70 years and above [44]. Gail model is widely used and having a good calibration, however, further validation is necessary till a well-fitted model with a better predictive for Malaysian women is established [54]. The ongoing pilot of a risk-stratified screening programme in Singapore incorporates the Gail model [55]. There may be merit in the proposal that, before implementing a risk-stratified screening strategy in Malaysia consideration should be given to the application of a suitable risk prediction model, and the balance of potential benefits and harms including false-positive, over-diagnosis, and management.

Ethical considerations of risk-stratified screening

It is important to take into account ethical considerations regarding the implementation of risk-stratified screening [56].There is a need to ensure the equity and fair access to risk-stratified screening including genetic testing for high-risk individuals and access to breast radiologists and breast surgeons. Many countries like the UK recognise that there is a need to develop awareness about risk-stratified screening, perhaps, via community leaders and healthcare practitioners, as well as developing culturally appropriate messages and utilizing media campaigns. There is recognition too that primary healthcare has the potential to incorporate, integrate, and deliver risk assessment and screening, including taking a saliva sample, and providing risk-reducing medication for high-risk women [57]. Equity of access for minority ethnic groups may be improved via community engagement programmes [57]. The resources that are currently available and accessible to the high-risk group of women in Malaysia need to be expanded in order to achieve wider coverage [24]. Autonomy, informed consent, transparency, and effective communication should be ascertained during the consultation with healthcare provider and women [57]. In the UK, consideration is being given to increasing the duration of screening for low-risk women, while more frequent screening might be offered to high-risk women [57]. Therefore, it is important to evaluate the acceptability by women from different risk groups of programme content and delivery [57]. The ethical implementation and conduct of risk-stratified screening is characterised by respect for the individual rights of women, equitable access, and the promotion of the well-being of women.

Opportunities and potential challenges

Risk-stratified screening will convey a focused and personalized screening plan for individual women. The application of artificial intelligence algorithms to integrate clinical data and radiological findings is a promising advancement for the future [58]. Structural and organizational challenges remain issues of concern, especially in low- and middle-income countries [59] like Malaysia.

The primary healthcare setting would appear to be the most appropriate service venue to introduce risk assessment, stratification, and guidance regarding the pathway to breast cancer screening [59]. However, it is important to recognise and respond to the challenges. For example, primary healthcare doctors in Spain reported anticipated concerns about risk communication with women, patient resistance to reduce screening for low-risk women, and the organizational transformation and appropriate resources that would be required to implement a programme of risk-based breast cancer screening [60]. Furthermore, the requirement for training to identify breast cancer risk, provide prevention advice, communicate risk, and manage the workflow in primary healthcare settings has been highlighted as practical considerations [59]. Studies in the United States suggested that it is feasible to conduct a risk assessment of a patient during the time when a patient is waiting meet their doctor [61, 62]. Coordination is needed regarding further genetic testing and the initiation of risk-reducing medication by specialists such as oncologists and breast surgeons [63]. On a more positive note, primary healthcare in Malaysia has been shown to provide comprehensive, coordinated, and continuity of care in private and public sectors [64]. Training to provide cancer screening and care in primary healthcare was introduced in Malaysia [65]. However, the willingness of Malaysian primary healthcare doctors to practice risk-stratified screening is uncertain and requires considered attention and consultation. Further studies should investigate for workload and willingness to implement risk-stratified at the primary healthcare that might require considered attention and implementation support.

In Singapore, a pilot personalised risk-stratified breast cancer screening programme was initiated in 2021 [55]. To the best of our knowledge, this pilot programme is the first comprehensive risk-based mammogram screening programme in Asia [55]. The incidence of breast cancer among Singaporean women is much higher compared to Malaysia with an incidence rate of 72.6 [66] vs 43.1 per 100,000 population [1] respectively. Participants in the pilot programme in Singapore appear (so far) to accept risk-stratified screening. Women indicated a need for clear communication about their risk category, follow-up support for high-risk women, and guidance about actionable steps in relation to lifestyle behaviours [67]. Conducting a pilot project of this kind, preferably guided by implementation science, would provide lessons and insights for policymakers, health service managers, and public and primary health care professionals to the extent that decisions and plans for a sustainable and effective breast cancer screening strategy that incorporates as risk-stratified approach in Malaysia would be based on evidence from the local setting as well as curated international best-available evidence.

Author Contribution Statement

MNNH lead the literature search and review. MDo and TTS supervised and guided the process. MNNH prepared the first draft of the manuscript. TTS and MDo amended and refined the manuscript. All authors contributed to, reviewed, and approved the final manuscript.

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Ethical consideration

This manuscript is the review of previously published articles, reports, and documents. Therefore, ethical approval is not applicable to this review.

Conflict of interest

All authors declare that they have no conflicts of interest.

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