MUTATION PROFILE OF BREAST CANCER IN MALAYSIAN PATIENTS

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Abstract

Background: Breast cancer (BC) is the most common cancer in women globally. In low- and middle-income countries, the use of appropriate breast cancer genetics services for screening and personalized treatments is severely lacking. This review is aimed to assess and summarize the reported mutation profiles of Malaysian BC patients.

Methods: A literature search was performed in PubMed and Google Scholar from 2002 to 2019 using a set of keywords and MESH terms.

Results: Data from 14 eligible studies are presented here. A total of 28 genes were studied in Malaysian BC patients in which 445 genetic alterations (229 deleterious, 209 variants with unknown clinical significance (VUC), and seven protective variants) have been reported, with 73 being novel (16% novel). The frequency ranged from 0.2% to 76% for VUC and 2.1 to 15% for deleterious variations. Only $BRCA1$, $BRCA2$, $PALB2$, $APOBEC3B$, and $P53$ have been associated with BC risk in Malaysian patients. Nine of these studies were conducted using the overlapped source of patients, which may limit the generalizability of the findings to the whole population of Malaysia.

Conclusion: Information on the genetic basis of BC in the Malaysian population is scant. Multidisciplinary efforts with appropriate sample selection techniques and study design with multicenter collaboration are needed to address this issue. Out of thirteen high- and moderated-penetrance pathogenic mutations for BC, only five have been linked to Malaysians’ BC susceptibility. The findings from this review is valuable for decision-makers, researchers, and physicians, to enhance the research plans and utility of genetic services for screening and prevention.

Keywords: Breast Cancer, BRCA, Gene profiling, $PALB2$, $P53$

Introduction

BC is a multifactorial disease caused by multiple genetic and environmental factors and their interaction. A case-control study in Malaysia shows that breastfeeding, soy intake, and physical activity are modifiable risk factors for breast cancer (1). The standardized incident rate of BC in Malaysia during the year 2003 was 46.2 per 100,000 with the Chinese having the highest incidence (59.9/100,000), followed by Indians (52.2/100,000) and the lowest in Malays (34.9/100,000). This rate in Malaysia is comparable with the Philippines and Singapore but much higher than those in Japan, China, Thailand, and India (2). Approximately 50 % of BC cases in Malaysia are diagnosed below the age of 50 and 16.8 % below the age of 40 (3).

Malaysia has three main racial groups, i.e., Malays (65 %), Chinese (26 %), and Indians (8 %). The presence of genetic admixtures has been reported among different ethnicities in Malaysia (4-6). One of the lowest survival rates for BC in Asia has been reported among Malaysian patients. On the other hand, genetic studies have reported some unique genetic variations in Malaysians that are linked to the
diseases such as periorbital hyperpigmentation, obesity, metabolic risk factors, and high lipidemia (7, 8).

Risk-stratified screen for BC patients improves the accuracy of diagnosis as well as treatment plans. The first BC predisposition gene to be identified was \textit{BRCA1}, located on chromosome 17q21. With the advancement of sequencing, studies investigating the association between BC risk and common genetic variants are rapidly increasing. BC cases are mostly sporadic, but around 5\% to 10\% of all breast and ovarian cancer cases are assumed to be inherited via the high penetrance germline mutations such as \textit{BRCA1} and \textit{BRCA2} (9). The results from a large-scale meta-analysis of mutations identified in panels of BC and ovarian cancer-related genes have provided strong evidence of cancer predisposition genes for both BC and ovarian cancer (10). In this study, a comprehensive meta-analysis of results from forty-eight NGS multi-gene panel-based studies was carried out to evaluate the association of these two types of cancer and any pathogenic variants in BC or ovarian cancer predisposition genes. The role of 37 genes was assessed, and it was found that 13 of these genes (e.g., \textit{CDKN2A} and \textit{PALB2}) were significantly associated with an increased risk of BC. However, this meta-analysis acknowledged very limited genes that have been studied in a small number of studies on Asian populations. Another meta-analysis included both Asian and European populations, has reported that only a small portion of Asian BC patients carried the common genetic variants in 183 identified loci for BC. In this meta-analysis, 28 loci, which were not previously reported, were identified in both Asians and Europeans (11).

Though there have been remarkable developments in identifying the genetic basis of both sporadic and familial BC, still about 50\% of the genetic risk factors playing a role in the etiology of BC remains unidentified. Guidelines for BC screening is continuously improving and are mainly based on risk factors such as personal or family history of cancer as well as genetic risks. A very recent guideline from the American Society of Breast Surgeons offers genetic testing to each BC patient either newly diagnosed or with a personal history (12).

Knowing that Asians have a lower age of onset of BC, it can be assumed that inherited predisposition to BC is more significant (13). On the other hand, because of different environmental exposures as well as the presence of distinctive linkage disequilibrium in each population, it is vital to detect genetic alteration associated with BC in each population, which consequently may improve understanding of BC etiology (14). Despite evidence on the usefulness of BC genetics services for the management of carriers of some mutations, recommendation for the use of such services is uncommon in low- and middle-income countries. Therefore, this review was aimed to identify, assess and summarize the reported mutation profiles of Malaysian BC patients.

**Methodology**

**Selection of literature**


**Inclusion criteria**

Selected articles were targeted in human studies in Malaysia, which included breast cancer patients. Any type of study design, including case series, case report, and cohort study, was considered if patients were Malaysians. This study did not proceed with meta-analysis; thus, no specific statistical test was done. Inclusion criteria were patients diagnosed with breast cancer with or without ovarian cancer and have molecular genetic analysis. Studies on patients with breast metastases from primary tumors other than breast carcinoma were excluded.

**Quality assessment and data extraction**

To identify relevant studies, all titles and abstracts of the studies were reviewed by two reviewers from July to August 2019. Any disagreement for the exclusion or inclusion of an article was resolved by discussion for stronger arguments. Quality assessment was done using arbitrary scoring (Supplementary Table 1). Data were extracted from eligible studies by two reviewers independently. These data included author, year of publication, study design, sample size, patient characteristics, assessment method, the finding of studies, ethnicity, and biological samples.

**Results**

A total of 7026 articles were found in different databases using keywords and filters, i.e., year (2002-2019). Thirty-five articles that met the inclusion and exclusion criteria were viewed accordingly (Figure 1). Finally, 14 articles were selected for this review. The characteristics of patients, sample size, methodology, and findings, are summarized in Table 1.

There were 14 studies (7 case-control and 7 cohorts), which met the inclusion criteria (13, 15-27). Except for two studies investigating the tumor tissue (20, 23), the remaining focused on germline mutations.

A total of 28 genes were studied in Malaysian BC patients in which 445 genetic alterations (229 deleterious and 209 variants with unknown clinical significance (VUC) and seven protective variants) reported, with 73 being novel mutations/variations (16\% novel). The frequency ranged from less than 1\% to 76\% for VUC and 2.1 to 15\% for deleterious variations. The deleterious mutations were reported only in \textit{BRCA1/2}, \textit{PALB2}, and \textit{P53}. Nine of these
Using Keywords such as: Breast cancer, gene, polymorphism, BRCA, SNP, HER2, Malaysia

**Table 1: Characteristics of selected studies**

<table>
<thead>
<tr>
<th>Study</th>
<th>Sample size</th>
<th>Gene</th>
<th>Patient Characteristic</th>
<th>Method</th>
<th>Finding</th>
</tr>
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<tbody>
<tr>
<td>(Balraj et al., 2002)</td>
<td>30</td>
<td>BRCA1 (germline mutation)</td>
<td>Group 1 early onset of BC, Group 2: BC patients with two or more 1st or second-degree relatives with BC and/or ovarian cancers</td>
<td>Direct sequencing</td>
<td>A frameshift mutation (result in a premature stop codon) and 8 polymorphisms (3 silent + 1 in IVS + 4 missense)</td>
</tr>
<tr>
<td>(Thirthagiri et al., 2008)</td>
<td>187</td>
<td>BRCA1 &amp; BRCA2</td>
<td>BC patients (BC alone or with the presence of ovarian cancer), early-onset and families with breast cancer</td>
<td>DNA sequencing and MLPA</td>
<td>27 deleterious mutations (14 in BRCA1 (5 del, 1 ins, 8 SNPs) and 13 in BRCA2 (7 del + 3 ins + 3 SNPs), 47 SNPs with uncertain clinical effect (16 in BRCA1 and 31 in BRCA2). Out of all these, 37 novel (13 in BRCA1 mutations and 24 in BRCA2).</td>
</tr>
<tr>
<td>(Toh et al., 2008)</td>
<td>37</td>
<td>BRCA1 &amp; BRCA2</td>
<td>Patients with early-onset of BC, with no history of familial BC and/or ovarian cancer</td>
<td>Direct sequencing</td>
<td>14 BRCA1 and 17 BRCA2 sequence alterations, 8 of them novel (3 BRCA1 and 5 BRCA2)</td>
</tr>
<tr>
<td>(Lee et al., 2012)</td>
<td>100</td>
<td>BRCA1, BRCA2 &amp; TP53</td>
<td>Patient with early-onset BC (≤ 35 years), with or without family history</td>
<td>DNA sequencing</td>
<td>17 deleterious mutations (11 BRCA1 &amp; 6 BRCA2), 7 polymorphisms in TP53 (4 in exon, 3 in introns) (2 novels in TP53)</td>
</tr>
<tr>
<td>(Phuah et al., 2013)</td>
<td>3411 (1528 cases &amp; 1883 control)</td>
<td>PALB2 germline mutations</td>
<td>Familial and non-familial BC patients</td>
<td>Direct sequencing</td>
<td>3 novel truncating mutations and 10 missense mutations</td>
</tr>
<tr>
<td>(Chin et al., 2016)</td>
<td>80</td>
<td>CYP2D6 Tumor DNA &amp; Germline DNA</td>
<td>Patient with BC, in any age group.</td>
<td>DNA sequencing</td>
<td>6 SNPs (7 alleles)</td>
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Table 1: Characteristics of selected studies (Continued)

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<thead>
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<th>Study</th>
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<th>Gene</th>
<th>Patient Characteristic</th>
<th>Method</th>
<th>Finding</th>
</tr>
</thead>
<tbody>
<tr>
<td>(Mohamad et al., 2015) (21)</td>
<td>59 for sequencing &amp; 1148 for screening (878 cases &amp; 270 control)</td>
<td>CHEK2</td>
<td>non-BRCA carriers, high risk BC patients with early-onset BC, family history of BC or ovarian cancer, both male and female, invasive BC patients</td>
<td>Genotyping analysis</td>
<td>4 polymorphisms</td>
</tr>
<tr>
<td>(Chong et al., 2016) (22)</td>
<td>331 (71 cases &amp; 260 control)</td>
<td>CYP2E1, STK15 and XRCC1</td>
<td>Patient with BC</td>
<td>PCR-RFLP Known variation screening and confirmed with sequencing</td>
<td>CYP2E1 rs3813867 SNP had significantly increased higher BC risk in Malaysian women STK15 rs2273535 appeared to protect against breast cancer in Malaysian Chinese.</td>
</tr>
<tr>
<td>(Ng et al., 2016) (13)</td>
<td>108</td>
<td>ATM, BRCA1, BRCA2, BARD1, BRIP1, CDH1, CHEK2, NF1, MRE11A, NBN, RAD50, PALB2, PTEN, STK11, TP53</td>
<td>BC alone or with the presence of ovarian cancer, in any age group, both Male and female.</td>
<td>DNA sequencing</td>
<td>18 deleterious mutations/variants in BRCA1 &amp; BRCA2 (8 of them novel), 15 deleterious mutations/variants in other genes (7 of them novel)</td>
</tr>
<tr>
<td>(Wen et al., 2016) (23)</td>
<td>2893 (1451 cases and 1442 controls)</td>
<td>APOBEC-3B</td>
<td>Patient with BC, only female</td>
<td>Copy number variation analysis &amp; Microarray analysis</td>
<td>germline APOBEC3B deletion was associated with BC</td>
</tr>
<tr>
<td>(Lai et al., 2017) (24)</td>
<td>3603 (2110 cases &amp; 1493 control)</td>
<td>BRCA1 &amp; BRCA2</td>
<td>Patient with BC, any age group, with or without family history</td>
<td>MassARRAY genotyping</td>
<td>69 polymorphisms (24 BRCA1 &amp; 45 BRCA2). Only 32 variants (7 BRCA1 and 25 BRCA2) were present in both cases and controls</td>
</tr>
<tr>
<td>(Yang et al., 2017) (25)</td>
<td>467</td>
<td>germline BRCA1, BRCA2, PALB2, TP53</td>
<td>Invasive BC</td>
<td>MLPA</td>
<td>34 polymorphisms (13 BRCA1, 15 BRCA2, 4 PALB2, and 2 TP53). 8 novel</td>
</tr>
<tr>
<td>(Wen et al., 2018) (26)</td>
<td>5384 (2575 cases and 2809 control)</td>
<td>BRCA1, BRCA2</td>
<td>Patient with BC, any age group, with or without family history</td>
<td>Sanger sequencing,</td>
<td>121 in cases (55 BRCA1 &amp; 66 BRCA2) &amp; 11 in controls (5 in BRCA1 and 6 in BRCA2)</td>
</tr>
<tr>
<td>(Chahil et al., 2015) (27)</td>
<td>80 cases and 80 control</td>
<td>MMP9, CCL2, VEGFA, DDR2, XPC, MCM3AP, ERCC2, IL16</td>
<td>BC patients with or without family history</td>
<td>Illumina GoldenGate Assay</td>
<td>80 cases and 80 controls in each of genes (MMP9, CCL2, VEGFA, DDR2, XPC, MCM3AP, ERCC2, IL16)</td>
</tr>
</tbody>
</table>

Studies were conducted using the same source of patients in one medical center. These 28 genes were BRCA1 and BRCA2, TP53, PALB2, CYP2D6, CHEK2, APOBEC-3B, CYP2E1, STK15, BARD1, PTEN, CDH1, MRE11A, RAD50, ATM, BRIP1, NF1, NBN, STK11, XRCC1, MMP9, VEGFA, XPC, CCL2, DDR2, MCM3AP, and ERCC2.

Discussion
There is still limited information regarding BC predisposition genes in the Malaysian population. Identifying the germline susceptibility gene variants in BC may help to stratify the individuals at risk of BC. However, due to the multifactorial...
nature of BC and the influence of lifestyle, diet, and environmental exposures, it is vital for each population to investigate the potential variants among its own BC patients. This review found 14 studies that have examined candidate genes for BC susceptibility variations among Malaysian women. When pooling the findings of all these studies, there is no substantial evidence that any of the identified variations are significantly associated with BC risk in Malaysian patients. Nevertheless, there have been a few statistically significant associations between BC risk and reported variations in a few studies (20, 23, 24, 27). Chong et al. (22) have reported that heterozygous c1/c2 genotype or the presence of c2 allele in CYP2E1 (rs3813867) was associated with increased BC risk. Wen et al. (23) found a significant association between BC risk and germline APOBEC3B deletion in Malaysian BC cases. Single-variant analysis in the study by Lai et al. (24) suggests that BRCA1 p.Arg762Ser may be associated with BC risk in Malaysian patients. Chahil et al. (27) reported that AC genotype in rs13181 (ERCC2 gene) was significantly associated with reduced risk of BC in a cohort of Malaysian patients.

None of these associations have been reported by more than one study. Low statistical power due to small sample size as well as using the same group of patients in a single medical center may explain this observation. In a few case and control studies which have reported significant association, the magnitude is low. An SNP in CYP2E1 significantly increased the risk of BC among all three ethnic groups in Malaysia (1.8-fold higher) (22). In the same study, an SNP in STK15 reported protecting against BC in Malaysian Chinese. The multigenic nature of BC presents a fundamental challenge for using individual SNPs to predict the risk of cancer. However, a recent study has shown that the combined effect of SNPs to calculate polygenic risk score offer robust risk discrimination to stratify patients into distinct categories (28).

While there are a number of genome-wide association studies (GWAS) for BC in Europe and other western countries, these type of studies have rarely been conducted in South East Asia, including Malaysia. A few regional or global GWAS, which included Malaysian patients, have found some novel variations among them (5, 11, 29, 30). These studies included patients from mainland China, South Korea, Japan, Hong Kong, Taiwan, and Malaysia. The study by Shu et al. (11) reported the association for 78 of the 166 previously reported risk variants (P < 0.05) in Asian women. Further, the results from 54 studies participating in the Consortium of Investigators of Modifiers of BRCA1/2 have shown 11q22.3 as a new modifier locus in BRCA1 carriers (30). In another GWAS by Michailidou et al. (29), with more than 120,000 cases from different countries, including Malaysia and European countries, 15 new susceptibility loci for BC were identified. In this study, two regions in SETBP1 on 18q12.3 and RNF115 and PD2K1 on 1q21.1 were proposed as susceptible genes for BC. However, a study among minorities in the USA has suggested that the implementation of validated transcriptome-wide association studies might be an efficient method for understanding the genetics underpinning BC outcomes in diverse populations (31).

Available data showed that BC patients from different ethnicities in Malaysia have different variations profile, and unsurprisingly different responses to treatment (20). A study by Han et al. (32), which evaluated the genetic variants in high and moderate-penetrance genes associated with BC risk in Asians, has included BC patients from Malaysia. They have found some novel risk variants in BRCA1, BRCA2, PALB2, and CHEK2. In another GWAS on East Asians, susceptibility loci were identified at 1q32.1, 5q14.3, and 15 (ZC3H11A, ARRDC3, and PRC1 genes) (5).

The study by Wen et al. (23) reported that APOBEC3 deletion was associated with BC risk with odds ratios of 1.23 for one-copy deletion and 1.38 for two-copy deletion compared to women with no deletion. This finding agrees with a meta-analysis that reported a correlation between APOBEC3 deletion and increased BC risk (33). In this study, stratified analysis by ethnicity indicated a stronger and more stable relationship in Asians. This study concluded that APOBEC3 copy number variations might be an ideal screening test for BC.

BRCA1 and BRCA2, which have high penetrance, account for 15 % of the extra-familial risk in European BC women (34). Results from a large consortia on investigating the modifiers of BRCA1 and BRCA2 have found that carriers of these mutations may have different phenotypes due to differential allelic expression with the presence or absence of a modifier (30). The study by Ng et al. (13) in Malaysian BC patients also reported these two genes as the most common predisposition genes in their cohort. For BC patients from Sarawak in East Asia, a prevalence of 2.8 % germline mutation for BRCA1 has been reported (25). Among other high penetrance genes in European descents, including P53, CDH1, LKB1, and PTEN, only P53 has been reported as a predisposed gene in Malaysian BC patients, but it was very rare (18, 25). Among moderate-penetrance genes, for instance, CHEK2, PALB2, and ATM, only PALB2 has been reported in Malaysian BC patients but with a low prevalence and a specific mutation profile (19). CHEK2 was found to be very rare in this population (21).

**Conclusion**

In conclusion, out of thirteen high- and moderated-penetrance pathogenic mutations for BC, only five (BRCA1, BRCA2, PALB2, APOBEC3B, and P53) have been linked to BC susceptibility in Malaysians. Evidently, information on the genetic basis of BC in the Malaysian population is scant. Only a few medical centers have attempted to study the genetic basis of BC patients in Malaysia, and they are mostly located in the capital. Multidisciplinary efforts with appropriate sample selection techniques, sample size, and study design with multicenter collaboration are needed to address this issue. More research is required to explore the molecular profiling of the germline of patients with BC in order to identify known and potential high, moderate, and low-risk susceptibility loci. The association
of germline mutations with BC can be employed for clinical risk assessment, diagnosis, and treatment planning.

The translational utility of genetic screening is promising, but more research and findings are needed for patients to fully benefit from it. Even the empirical evidence for risk stratification based on genetic predisposition is still lacking, but combining multiple common susceptibility variants may be beneficial to identify Malaysian women at different levels of BC risk. Subsequently, this could be used for improving guidelines for screening, prevention, diagnosis, and treatment. This review reports available information regarding genetic susceptibility to BC in the Malaysian population. Information from the review is now available to both researchers and physicians which may enhance and promote the utility of genetic services for personalized screening and prevention of BC in Malaysia.

Learning points
Out of thirteen high and moderated penetrance pathogenic mutations for BC, only five, being **BRCA1**, **BRCA2**, **PALB2**, **APOBEC3B**, and **P53**, have been linked to BC susceptibility in Malaysian BC patients. According to the lowest survival rates and early onset of BC in Malaysian BC patients, there is an urgent need to conduct more comprehensive studies to detect the genetic profile of BC in Malaysia.

List of Abbreviation
**APOBEC**-3B: apolipoprotein B mRNA editing enzyme catalytic subunit 3B; **ATM**: ATM serine/threonine kinase; **BARD1**: BRCA1 associated RING domain 1; **BRCA1**: breast cancer 1; **BRCA2**: breast cancer 2; **BRIP1**: BRCA1 interacting protein C-terminal helicase 1; **CCL2**: C-C motif chemokine ligand 2; **CDH1**: cadherin 1; **CHEK2**: checkpoint kinase 2; **CYP2D6**: cytochrome P450 family 2 subfamily D member 6; **CYP2E1**: cytochrome P450 family 2 subfamily E member 1; **DDR2**: discoidin domain receptor tyrosine kinase 2; **ERCC2**: ERCC excision repair 2, TFIIH core complex helicase subunit; **IL16**: interleukin 16; **MCM3AP**: minichromosome maintenance complex component 3 associated protein; **MMP9**: matrix metalloproteinase 9; **MRE11A**: MRE11A homolog A, double strand break repair nuclease; **NBN**: nibrin; **NF1**: neurofibromin 1; **PALB2**: partner and localizer of BRCA2; **PSEN**: phosphatase and tensin homolog; **RAD50**: RAD50 double strand break repair protein; **STK11**: serine/threonine kinase 11; **STK15**: serine/threonine kinase 15; **TP53**: tumor protein p53; **VEGFA**: vascular endothelial growth factor A; **XPC**: complex subunit, DNA damage recognition and repair factor, **XRCC1**: X-ray repair cross complementing 1

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Competing interests
The authors declared that they have no competing interests.

References


**Supplementary Table 1:** Scoring of selected studies based on 5 questions for assessment

<table>
<thead>
<tr>
<th>Study</th>
<th>Did the study mention about genes related to BC?</th>
<th>Did the study reported the SNP of breast cancer?</th>
<th>Did the study is lab-based experiment?</th>
<th>Was the proper statistical analysis employed?</th>
<th>Was the study conducted in Malaysia?</th>
<th>Total score</th>
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