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ORIGINAL ARTICLE

# Genetic Polymorphisms Associated With Breast Cancer in Malaysian Cohort

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**Abstract** Genome-wide association studies have discovered multiple single nucleotide polymorphisms (SNPs) associated with the risk of common diseases. The objective of this study was to demonstrate the replication of previously published SNPs that showed statistical significance for breast cancer in the Malaysian population. In this case–control study, 80 subjects for each group were recruited from various hospitals in Malaysia. A total of 768 SNPs were genotyped and analyzed to distinguish risk and protective alleles. A total of three SNPs were found to be associated with increased risk of breast cancer while six SNPs showed protective effect. All nine were statistically significant SNPs ($p \leq 0.01$), five SNPs from previous studies were successfully replicated in our study. Significant modifiable (diet) and non-modifiable (family history of breast cancer in first degree relative) risk factors were also observed. We identified nine SNPs from this study to be either conferring susceptibility or protection to breast cancer which may serve as potential markers in risk prediction.

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**Keywords** Breast cancer · SNP · Association · Risk prediction model · Case–control study

**Abbreviations**

| | |
|---|---|
| CI | Confidence interval |
| HWE | Hardy–Weinberg equilibrium |
| OR | Odds ratio |
| SNPs | Single nucleotide polymorphisms |

## Background

Cancer is not a contagious disease; however, the burden of cancer continues to rise largely due to a prolonged life expectancy, the increase in the world population, a change in lifestyle, and exposure to environmental factors [1]. Clinico-pathologically, breast cancer is a cancer that starts in the tissues of the breast. Damaged DNA triggers uncontrolled cell division which leads to lump formation. The breast is made up of ducts and lobes which are surrounded by supporting stroma and adipose tissues. Thus, based on morphological features, ductal carcinoma is the cancer that originates from mammary ducts, while lobular carcinoma is that of milk producing glands [2]. Invasive ductal carcinoma, the most common type of breast cancer, arises when malignant cells start proliferating, detaching from the basement membrane and invading the stroma [3]. Breast cancers have also been classified based on the presence or absence of receptors, i.e. estrogen receptor (ER), progesterone receptor (PR) and human epidermal growth factor receptor (HER2) [4].

Collectively, cancer is the third most common cause of death in Malaysia after heart diseases and septicemia [5]. Being the leading cause of cancer death in females

worldwide, breast cancer accounted for 23 % (1.38 million) of the total new cancer cases and 14 % (458,400) of the total cancer deaths in 2008 [1]. The American Cancer Society estimates that in the United States, about 232,340 new cases of invasive breast cancer will be diagnosed in women, about 64,640 new cases of carcinoma in situ (CIS) will be diagnosed (CIS is non-invasive and is the earliest form of breast cancer) and about 39,620 women will die from breast cancer in 2013 [http://www.cancer.org/cancer/breastcancer/detailedguide/breast-cancer-key-statistics].

Breast cancer has been reported as the most frequent cancers in females, in Peninsular Malaysia, with current incidence rate of 31.3 % and continues to rise [2, 6]. This is followed by the cancers of the cervix uteri (10.6 %), large bowel (9.9 %), ovary (4.3 %), leukemia (3.7 %) and lung (3.6 %) [6].

The etiology of sporadic and familial breast cancer is complex and its susceptibility is largely polygenic, i.e. contributed by a number of loci, each with its own effect on breast cancer risk [7]. High-penetrance susceptibility genes such as BRCA1 and BRCA2 contribute to only a fraction of all breast cancer cases [8]. Besides genetic factors, there are several other known risk factors such as hormonal and reproductive risk factors, mammographic density, family history of breast cancer, as well as lifestyle factors associated with the development of breast cancer [9]. Dietary factors such as canned food have been associated with breast cancer. Leaching of Bisphenol A (BPA), a synthetic estrogen found in the lining of most food cans, is toxic and may increase breast cancer risk. A number of risk-assessment models have been proposed in breast cancer research [8–10]. The risk factors excluding genetic factors are components of Gail's Model, a breast cancer risk assessment tool for White women [11, 12]. This model was further modified to provide assessment for Black women by the National Surgical Adjuvant Breast and Bowel Project (NSABP) statisticians [13]. The other risk assessment models include Claus model that estimates risk using family history, and the BRCAPRO model that incorporates BRCA1 and BRCA2 mutations [9].

Breast cancer screening and diagnosis may involve some invasive measures. Currently available methods include clinical breast examination ranging from needle biopsy to mammogram, as well as lab tests of tumor markers e.g. Cancer antigen (CA15-3/CA27.29), Carcinoembryonic antigen (CEA) and hormone receptor status (HER2, ER/PR), alongside commercial molecular tests on the tumor tissues. Awareness, early detection through mammography, and increased treatment options have shown to reduce cancer death rates in developed countries; but this approach is cost prohibitive and not feasible in many developing countries [1].

Given that known high-penetrance genetic mutations only account for a small proportion of all breast cancer cases, emphasis should also be given to identifying new and common genetic variants. Therefore, we aimed to study the association of a group of 768 previously published SNPs with breast cancer cases in Malaysia, and the suitability of using these SNPs in predicting risk predisposition for breast cancer.

## Materials and Methods

### Study Subjects

A total of 160 unrelated female subjects, between the ages of 25–65 were included in this case–control study. The 80 cancer subjects were women who were diagnosed with breast cancer histopathologically. Breast cancer included malignant neoplasm of breast in any of the subcategories of code C50 of International Classification of Diseases (ICD), 10th Revision. The recruited cancer subjects were either undergoing chemotherapy or follow-up treatments at Hospital Kuala Lumpur (HKL), Hospital Putrajaya (HPJ), Beacon International Medical Centre (BIMC) (formerly Wijaya International Medical Centre), or Hospital Sultan Ismail (HSI) between 2010 and 2011. The 80 control female subjects from the same age range as the cancer subjects were concurrently recruited from these 4 participating centers.

Subjects were required to give an informed consent to be included in this study. A standardized questionnaire was used to collect information on demography and socioeconomic characteristics, obstetrics and gynecology history as well as family history of cancer. Risk factors of Gail's Model were also included in the questionnaire [13]. This study protocol was approved by Ministry of Health's (MOH) Medical Research Ethics Committee (MREC) (Project: NMRR-10-652-6473). Sample size approximations was done using an online calculator. (http://www.stat.ubc.ca/~rollin/stats/ssize/caco.html).

The number of 80 samples each in cancer cases and controls gives this study a power of 80 %, accepting an $\alpha$-error of 0.05.

### Genotyping

Genomic DNA from all subjects was extracted from a total of 200 µL of whole blood each, using QIAamp DNA Mini Kit (Qiagen, Gmbh, Hilden,Germany). Qualitative and quantitative estimations were carried out on the DNA samples. All DNA samples were normalized to 50 ng/µl prior to genotyping. For long-term storage, blood and DNA samples were stored at −80 and −20 °C, respectively.

SNPs published in literature were data-mined, and probes were designed for Illumina®'s GoldenGate® Genotyping (GGGT) Assay. The average genotype call rate

**Table 1** Significant risk SNPs associated to breast cancer in a case–control study of Malaysian population

| SNP (gene) | Genotype | Case (*n*) | Control (*n*) | OR (95 % CI) | *p* value | HWE | Effect |
|---|---|---|---|---|---|---|---|
| rs17576 (MMP9) | AA | 4 | 15 | – | – | 0.06 | |
| | AG | 26 | 29 | 3.14 (0.92–10.74) | 0.061 | | |
| | GG | 50 | 37 | 4.73 (1.44–15.54) | 0.006 | | **Risk** |
| rs2250889 (MMP9) | CC | 1 | 8 | – | – | 0.21 | |
| | CG | 18 | 27 | 5.33 (0.61–46.37) | 0.098 | | |
| | **GG** | **61** | **45** | **10.84 (1.31–89.83)** | **0.007** | | **Risk** |
| rs2857653 (CCL2) | GG | 58 | 71 | – | – | 0.19 | |
| | GA | 21 | 8 | 3.21 (1.33–7.79) | 0.008 | | **Risk** |
| | AA | 1 | 1 | 1.22 (0.07–20.00) | 0.887 | | |
| rs10434 (VEGFA) | GG | 44 | 29 | – | – | 0.09 | |
| | AG | 27 | 44 | 0.40 (0.21–0.79) | 0.008 | | **Protective** |
| | AA | 9 | 7 | 0.85 (0.28–2.53) | 0.766 | | |
| rs10917589 (DDR2) | GG | 61 | 45 | – | – | 0.35 | |
| | AG | 17 | 32 | 0.39 (0.19–0.79) | 0.008 | | **Protective** |
| | AA | 2 | 3 | 0.49 (0.08–3.07) | 0.439 | | |
| rs2228000 (XPC) | GG | 72 | 67 | – | – | 0.59 | |
| | AG | 2 | 12 | 0.16 (0.03–0.72) | 0.007 | | **Protective** |
| | AA | 6 | 1 | 5.58 (0.65–47.6) | 0.079 | | |
| rs9975588 (MCM3AP) | GG | 58 | 41 | – | – | 0.06 | |
| | AG | 20 | 37 | 0.38 (0.19–0.75) | 0.005 | | **Protective** |
| | AA | 2 | 2 | 0.71 (0.10–5.23) | 0.733 | | |
| rs13181 (ERCC2) | AA | 66 | 53 | – | – | 0.26 | |
| | AC | 9 | 26 | 0.28 (0.12–0.64) | 0.002 | | **Protective** |
| | CC | 5 | 1 | 4.02 (0.46–35.42) | 0.179 | | |
| rs11556218 (IL16) | AA | 68 | 53 | – | – | 0.89 | |
| | **AC** | **11** | **24** | **0.36 (0.16–0.79)** | **0.010** | | **Protective** |
| | CC | 1 | 3 | 0.26 (0.03–2.57) | 0.217 | | |

Data in boldface indicated significant after controlling for red meat intake, fruits and vegetables intake and family history

*n* number, *OR* odds ratio, *HWE* Hardy–Weinberg equilibrium

was 98.9 % on Illumina®'s Bead Array Reader. All SNPs that deviated from Hardy–Weinberg equilibrium (HWE) in the control group were excluded from analysis. Haplotype Map (HAPMAP) was referenced for genotype comparisons in HCB (HapMap's Han Chinese of Beijing) population.

### Statistical Analysis

Allele and genotype frequencies in cancer subjects and controls were compared using a logistic regression model treating SNPs as co-variates. Deviation from the HWE was examined using the Michael H. Court's (2005–2008) online calculator Excel-based HWE Test (http://www.tufts.edu/~mcourt01/Documents/Court%20lab%20%20HW%20calculator.xls). Odds ratios (ORs) and 95 % confidence intervals (95 % CIs) were computed using a MS-Excel add-in, called SNP_tools developed by Chen et al. [14].

## Results

### SNP Analysis

A total of 768 SNPs were initially genotyped. The output was filtered for failed SNPs and SNPs with monoallelic genotype. SNPs that deviated from Hardy–Weinberg equilibrium ($P_{HWE} < 0.05$) and SNPs with a less than 95 % call rate were excluded. Analysis was continued with 633 remaining SNPs. Among these 633 SNPs, 9 SNPs were found to be significantly associated with breast cancer risk in our population (Table 1). According to previously published literature, only five out of these 9 SNPs were reported in other breast cancer association studies in Asian and non-Asian populations. Therefore, we identified 4 breast cancer-associated SNPs that were not previously reported in Asia.

**Table 2** Baseline characteristics of breast cancer cases and controls based on components outlined in Gail's model

| Variable | Controls (mean ± SD) | Breast cancer cases (mean ± SD) |
|---|---|---|
| Age (years) | 46.5 ± 9.81 | 48.5 ± 7.14 |
| Age at menarche (years) | 13.1 ± 1.32 | 13.2 ± 1.61 |
| Age at first live birth (years) | 25.7 ± 4.98 | 24.5 ± 4.13 |
| Age at menopause (years) | 51.1 ± 3.58 | 47.2 ± 5.39 |
| First degree relatives with breast cancer (*n*) | | |
| Yes | 0 | 11 |
| No | 80 | 69 |

$p > 0.05$ for all age groups signifying that the differences are not significant

*SD* standard deviation, *n* number

Out of the 9 SNPs, 3 SNPs conferred risk (rs17576, rs2250889, rs2857653) while 6 SNPs were protective (rs10434, rs10917589, rs2228000, rs9975588, rs13181, rs11556218). Based on the analyzed data, rs2250889-GG is the risk SNP with the highest OR of 10.84 ($p$ value = 0.007; 95 % CI 1.31–89.83), while protective SNPs rs2228000-AG have the lowest OR of 0.16 ($p$ value = 0.007; 95 % CI 0.03–0.72). These SNPs are located in genes functioning in different pathways (Supplementary Table 1).

### Non-Genetic Risk Factor Analysis

In the present study, the mean age of the cancer study subjects was 48.5 (±SD 7.14) (Table 2). Out of the 80 breast cancer subjects, 79 % were diagnosed with invasive ductal carcinoma. These are consistent with observations made in another Asian study, and it was reported that approximately 50 % of Asian women were diagnosed before the age of 50 years. The effects of non-modifiable and modifiable factors on breast cancer were analyzed in this study. The factors studied include non-modifiable risk factors such as ages at menarche, first pregnancy, menopause, nulliparity, and family history of breast cancer in first degree relatives, as well as modifiable factors such as body mass index (BMI), exercise and diet. All subjects were non-smokers and had no history of alcohol consumption.

It was observed that only the association of family history and dietary factors were statistically significant in our study (Table 3). Family history showed significant OR of 26.6 ($p$ value = 0.00059; 95 % CI 1.54–460.35). As for the modifiable factors, only the intake of fruits and vegetables and red-meat actually showed a significant correlation with OR of 0.26 ($p$ value = 0.0032; 95 % CI 0.11–0.67) and 3.23 ($p$ value = 0.02; 95 % CI 1.10–9.45) respectively (Table 3).

## Discussion

Breast cancer is the most prevalent cancer in Malaysian women, commonly occurring in younger women aged between 40 and 49 years. However, the study of genetic predisposition to breast cancer, as well as that of other non-genetic risk factors in Malaysian women is still lacking. In this study, we identified 9 SNPs associated with breast cancer in Malaysian population. This represents the first of its kind association study done on a Malaysian cohort, and 4 SNPs that were not previously reported to be associated with breast cancer were identified.

In the present study, out of the nine identified SNPs, five have been previously reported in other breast cancer studies (rs17576 [15], rs2250889 [16], rs10434 [16], rs2228000 [17] and rs13181 [18–20] and the association patterns were replicated here.

The SNP rs13181 of the *ERCC2* gene has been associated with decreased risk breast cancer risk (OR = 0.56; $p$ value = 0.002; 95 % CI 0.39–0.81) [20], consistent with our finding of the AC genotype (OR = 0.28; $p$ value = 0.002; 95 % CI 0.12–0.64) significantly associated with reduced risk of breast cancer.

These 9 SNPs are involved in various pathways that lead to carcinogenesis including apoptosis, cell growth, DNA repair, inflammation, steroid response, and others (Supplementary Table 1). These biological pathways play a central role since they are reported to interact with different proteins and activate downstream cascades to confer susceptibility to the development of breast cancer [21]. Based on the statistical significance observed from our data, it is established that these 9 SNPs could serve as biomarkers for breast cancer prediction.

In addition to genetic factors, sporadic breast cancer risk could also be contributed by lifestyle factors. Data analysis of this study also showed that intake of fruit and vegetable rich diet protects against breast cancer (OR = 0.26; $p$ value = 0.0032; 95 % CI 0.11–0.67), consistent with previous findings [22]. Consumption of red meat have been highly associated with breast cancer (OR = 4.30; 95 % CI 1.74–10.67; $p$ for trend = 0.00) partly due to possible risks from meat-derived dietary iron and meat mutagens such as heterocyclic amines (HCAs) [23, 24]. The association of the other known risk factors of breast cancer, such as the lack of physical exercise, obesity, early age of menarche, and late age of first pregnancy are not statistically significant (Table 3).

An individual risk allele may confer a weak association but their combined effect is expected to be useful for risk prediction [25]. Breast cancer in a first degree relative increases a woman's risk in developing breast cancer by 2-fold or more [26]. We observed an OR of 26.6 ($p$ value = 0.00059; 95 % CI 1.542–460.346) for this risk

**Table 3** Odds ratio (OR) of known risk factors in the development of breast cancer

| | Criteria | Case (*n*) | Control (*n*) | OR (95 % CI) | *p* value |
|---|---|---|---|---|---|
| Non-modifiable risk factors | | | | | |
| Age | >50 | 34 | 30 | 1.26 (0.67–2.38) | 0.48 |
| | ≤50 | 45 | 50 | | |
| Age of menarche | <12 | 8 | 8 | 1.03 (0.37–2.91) | 0.95 |
| | ≥12 | 65 | 67 | | |
| First pregnancy | <30 | 55 | 57 | 0.92 (0.44–1.90) | 0.82 |
| | ≥30 | 20 | 19 | | |
| Age of menopause | ≥45 | 31 | 22 | **0.14 (0.012–1.18)** | **0.04** |
| | <45 | 10 | 1 | | |
| Family history and age of menopause (logistic regression) | – | – | – | 0.22 (0.03–1.96) | 0.11 |
| | – | – | – | | |
| Family history of breast cancer in first degree relative(s) | Yes | 11 | 0 | **26.6 (1.54–460.35)** | **0.0006** |
| | No | 69 | 80 | | |
| Modifiable risk factors | | | | | |
| Body mass index (BMI) | ≥25 | 20 | 17 | 1.01 (0.41–2.49) | 0.98 |
| | <25 | 21 | 18 | | |
| Exercise | Yes | 42 | 41 | 1.08 (0.58–2.01) | 0.06 |
| | No | 37 | 39 | | |
| Canned food | Yes | 3 | 1 | 3.03 (0.31–29.87) | 0.31 |
| | No | 76 | 77 | | |
| Fruits and vegetables | ≥50 % | 58 | 73 | **0.26 (0.11–0.67)** | **0.0032** |
| | <50 % | 21 | 7 | | |
| Red meat | ≥50 % | 14 | 5 | **3.23 (1.104–9.454)** | **0.02** |
| | <50 % | 65 | 75 | | |

Data in boldface indicates significant ($p < 0.05$)

factor supporting the notion that a family history of breast cancer in the first degree relatives is associated with the risk of developing breast cancer [27]. The behavior of some polymorphisms in this study that deviated from previous findings may suggest diversity in the genetic make-up of the Malaysian population. The significance of these associated variants could be confirmed by functional studies in future.

## Conclusion

In summary, this study established for the first time, the association of nine polymorphisms with breast cancer risk in the Malaysian population. Together with the assessment of clinical risk factors, the utilization of these statistically significant genetic markers in MMP9, CCL2, VEGFA, DDR2, XPC, MCM3AP, ERCC2, and IL16 genes may bear clinical importance in the assessment of cancer risk. This study will facilitate the understanding of genetic markers in breast cancer susceptibility to certain extent and the management of breast cancer predisposition in the clinical settings in Malaysia.

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**Conflict of Interest** The authors declare that they have no competing interest.

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