Jurnal Teknologi

Full Paper

A PRELIMINARY STUDY OF RISK FACTORS OF BREAST CANCER AND THE USEFULNESS OF BREAST MRI AS AN ADDITION TO MAMMOGRAPHY IN DETECTING BREAST CANCER IN HIGH RISK WOMEN

Article history
Received
13 March 2016
Received in revised form
10 July 2016
Accepted
15 July 2016

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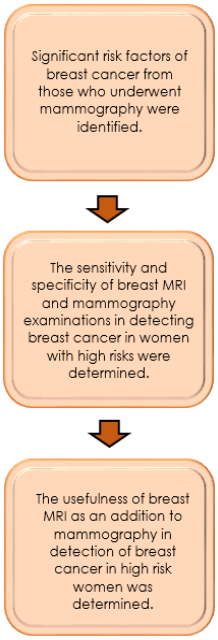
Graphical abstract



Abstract

The risk factors of breast cancer among women, such as genetic, family history and lifestyle factors, can be divided into high-, intermediate- and average-risk. Determining these risk factors may actually help in preventing breast cancer occurrence. Besides that, screening of breast cancer which include mammography, can be done in promoting early breast cancer detection. Breast magnetic resonance imaging (MRI) has been recommended as a supplemental screening tool in high risk women. The aim of this study was to identify the significant risk factor of breast cancer among women and also to determine the usefulness of breast MRI as an addition to mammography in detection of breast cancer in high risk women. This retrospective cohort study design was conducted using patients' data taken from those who underwent mammography for screening or diagnostic purposes in Advanced Medical and Dental Institute, Universiti Sains Malaysia, from 2007 until 2015. Data from 289 subjects were successfully retrieved and analysed based on their risk factors of breast cancer. Meanwhile, data from 120 subjects who had high risks and underwent both mammography and breast MRI were further analysed. There were two significant risk factors of breast cancer seen among the study population: family history of breast cancer (p-value=0.012) and previous history of breast or ovarian cancer (p-value <0.001). Breast MRI demonstrated high sensitivity (90%) while mammography demonstrated high specificity (80%) in detection of breast cancer in all 120 subjects. The number of cases of breast cancer detection using breast MRI [46 (38.3%)] was higher compared to mammography [24 (20.0%)]. However, breast MRI was found to be non-significant as an adjunct tool to mammography in detecting breast cancer in high risk women (p-value=0.189). A comprehensive screening guideline and surveillance of women at high risk is indeed useful and should be implemented to increase cancer detection rate at early stage.

Keywords: Risk factors, breast cancer, mammography, breast MRI, high risk women

Abstrak

Faktor risiko kanser payudara dalam kalangan wanita seperti faktor genetik, sejarah keluarga dan gaya hidup seharian, boleh diklasifikasikan sebagai tinggi, pertengahan dan biasa. Penentuan risiko-risiko ini dapat membantu dalam mencegah berlakunya kanser payudara. Selain itu, penyaringan kanser payudara termasuk mamografi boleh dijalankan untuk pengesanan awal kanser payudara. Pengimejan resonans magnetik (MRI) payudara disyorkan sebagai alat pemeriksaan tambahan dalam kalangan wanita yang berisiko tinggi. Sehubungan itu, tujuan utama kajian ini ialah untuk mengenalpasti faktor risiko yang signifikan terhadap kanser payudara dalam kalangan wanita dan juga untuk merungkai penggunaan MRI payudara sebagai modaliti pengimejan tambahan kepada mamografi untuk pengesanan kanser payudara dalam kalangan wanita yang mempunyai faktor risiko yang tinggi. Kajian retrospektif kohort ini dijalankan menggunakan data yang diambil daripada subjek yang menjalankan mamografi dengan tujuan penyaringan atau diagnostik di Institut Perubatan dan Pergigian Termaju, Universiti Sains Malaysia sejak dari tahun 2007 sehingga sekarang. Data daripada sejumlah 289 subjek telah berjaya diperoleh dan dianalisa berdasarkan kepada faktor risiko kanser payudara yang terdapat pada setiap subjek. Sementara itu, data daripada 120 subjek yang berisiko tinggi dan menjalankan kedua-dua pengimejan mamografi dan MRI payudara juga dianalisa. Terdapat dua faktor risiko kanser payudara dalam kalangan wanita yang signifikan: sejarah kanser payudara dalam keluarga ($p=0.012$) dan sejarah peribadi kanser payudara atau ovari ($p<0.001$). Sementara itu, MRI payudara menunjukkan sensitiviti yang tinggi (90%) manakala mamografi menunjukkan spesifisiti yang tinggi (80%) untuk mengesan kanser payudara dalam 120 subjek yang mempunyai risiko tinggi dan menjalankan kedua-dua pengimejan mamografi dan MRI payudara. Kes pengesanan kanser payudara menggunakan MRI payudara [46 (38.3%)] adalah lebih tinggi berbanding mamografi [24 (20.0%)]. Walaubagaimanapun, kegunaan MRI payudara dapat dilihat tidak memberi statistik yang signifikan sebagai modaliti pengimejan tambahan kepada mamografi untuk pengesanan kanser payudara dalam kalangan wanita yang mempunyai faktor risiko yang tinggi ($p=0.189$). Garis panduan pemeriksaan yang menyeluruh dan penyaringan wanita yang berisiko tinggi adalah amat berguna dan perlu dilaksanakan untuk meningkatkan kadar pengesanan kanser pada peringkat awal.

Kata kunci: Faktor risiko, kanser payudara, mamografi, MRI payudara, wanita berisiko tinggi

1.0 INTRODUCTION

Breast cancer is the second most common cancer overall and the leading cause of cancer mortality among women, with an estimated 1.67 million new cases diagnosed in 2012 [1]. In Malaysia, breast cancer was reported to be the most common cancer in females with 3242 new cases diagnosed in 2007 [2]. Additionally, breast cancer is the most frequent cancer among Malaysians (18.1 %), followed by large bowel cancer (12.3%) and lung cancer (10.2%) [2]. In a 10-year audit conducted by Nur Aishah *et al.*, there was a rise in the number of breast cancer cases seen with 83 cases diagnosed in 1995, followed by 154 cases in 2000 and 340 cases in 2005 [3]. The proposed factors for this trend include alteration in reproductive factors, environmental exposure, and lifestyle changes such as dietary intake and physical activity [4].

There are risk factors that are highly responsible for the increase in the incidence rate of breast cancer identified in women. These risk factors had been extensively investigated and explained in Western populations [5]. However, there is less information available relating to the risk factors of breast cancer among Asian women, particularly in Malaysia [6]. Determining these risk factors may actually help in preventing breast cancer occurrence as some factors could be modified either through environmental or lifestyle changes. Recommended screening guideline should be implemented for those women who are at increased risk of developing breast cancer as most of them are fairly asymptomatic and for early breast cancer detection whereby the tumour is smaller and easily treatable [5]. Breast cancer presentation, stage of disease and survival rates by race and ethnicity were highly influenced by combination of socioeconomic and lifestyle factors, and possible tumour characteristics [7].

In addition, appropriate imaging tool plays a vital role in detecting breast cancer among high risk women. Mammography is a low-dose x-ray examination that allows visualisation of the internal structure of the breast, aids in the early detection and diagnosis of various benign and malignant breast diseases. Mammography is recommended as a first line screening tool besides breast-self and clinical breast examinations [8-9]. Annual screening using mammography is recommended starting at the age of 40 years old for general population, at age 25 to 30 years old for

mutated gene carriers and at age 25 to 30 years or 10 years earlier for women with a first-degree relative having premenopausal breast cancer or for women with a lifetime risk of breast cancer ≥20% on the basis of family history [8-9]. However, mammography alone is inadequate in diagnosing breast cancer especially of those with genetic predispositions to the disease and those with dense breasts. Therefore, supplemental screening tool such as magnetic resonance imaging (MRI) is recommended in selected high-risk populations. Magnetic resonance imaging is a non-invasive diagnostic technique that uses magnetic field and radiofrequency pulses to produce cross-sectional images of the organs and other internal body structures. Breast MRI is found to be a sensitive imaging tool towards detection of cancer and has been suggested in women with high risk of breast cancer after screening by mammography [10-12].

To our knowledge, this is the first study to be conducted in northern Malaysia with the aim of identifying the significant risk factors of breast cancer and also to determine the usefulness of breast MRI as an addition to mammography in high risk women in detecting breast cancer.

2.0 METHODOLOGY

2.1 Study Population

This study was conducted at Advanced Medical and Dental Institute (AMDI), Universiti Sains Malaysia (USM) using quantitative, retrospective study design with ethical approval from the Human Research Ethics Committee USM. A total of 289 women who came to AMDI for screening or diagnostic mammography from August 2007 until December 2015 were studied. Those women included in this study must be of more than 25 years of age, with either high-, intermediate- or average-risk of breast cancer (classification is based on the checklist provided by Imaging Unit, AMDI), and had undergone either mammography alone or combination of mammography and breast MRI. The histopathological examination (HPE) results must be available for women who were diagnosed with breast cancer. Women with psychological disorder were excluded. Simple random sampling was used in this study.

2.2 Independent Variables (Risk Factors)

Independent variables are risk factors that increases the likelihood of developing a disease or injury. These factors include an aspect of personal behaviour or lifestyle, environmental exposure, or an inborn or inherited characteristic associated with an increase likelihood of disease or other health-related event or condition. Risk factors for breast cancer can be classified into three categories: high risk (women with breast cancer gene mutations and their untested first-degree relatives, women with histories of chest irradiation between the ages of 10 and 30 years, and with 20% or greater in their lifetime risk to get the breast cancer), intermediate risk (women with personal histories of breast cancer, lobular neoplasia, atypical ductal hyperplasia, or with 15% to 20% lifetime risk of breast cancer) and average risk (women had less than 15% lifetime risk of breast cancer) [9]. The risk factors that were included in this study are as shown in Table 1.

Table 1 Risk factors of breast cancer

Risk Factor
1. Family history of breast cancer a) Mother, sister or daughter has been diagnosed with breast cancer before the age of 50 years b) Two or more maternal or paternal relatives have been diagnosed with breast cancer (grandmother, aunt or niece)
2. Family history of ovarian cancer a) Mother, sister or daughter has been diagnosed with ovarian cancer before the age of 50 years b) Two or more maternal or paternal relatives have been diagnosed with ovarian cancer (grandmother, aunt or niece)
3. Genetic mutation a) HER2 mutation b) p53 mutation
4. Previous history of atypia on breast biopsy e.g. lobular carcinoma in situ and atypical hyperplasia
5. Previous history of breast cancer or ovarian cancer
6. Previous history of hormone replacement therapy (HRT)
7. Previous history of radiation therapy (to breast/chest area)
8. Nulliparous or deliver after the age of 30
9. First menarche before the age of 12
10. Body mass index (BMI) of more than 30

2.3 Dependent Variable (Outcome)

Dependent variable is the outcome of detecting breast cancer, based on HPE finding.

2.4 Statistical Analysis

The data collected was analysed using Statistical Package for Social Science, SPSS version 22. Descriptive statistic was used to summarise the risk factors of breast cancer mentioned earlier. Multiple logistic regression analysis was used to determine the significant risk factors (independent variables) of breast cancer. The outcome (dependent variable) was breast cancer detection based on HPE finding.

In this study, mammography and breast MRI result was classified based on Breast Imaging Reporting and Data System (BI-RADS) category, along with its negative or positive finding. The BI-RADS category was the standard measurement of imaging modalities. Meanwhile, negative and positive findings were the results of cancer detection based on HPE finding.

The sensitivity and specificity testing was used to determine the efficacy of breast MRI as an addition to mammography in high risk women while the usefulness of breast MRI as an addition to mammography was determined by contingency table and Pearson's Chi-squared test. A 5% error in rejecting null hypothesis with 95% confidence interval (CI) was used. Significant level was defined as p-value <0.05.

3.0 RESULTS AND DISCUSSION

3.1 Sociodemography

Data was collected from 289 female subjects (representing 100% of total sample size) who underwent screening or diagnostic mammography. The average age ± standard deviation (SD) was 54.77 ± 11.26 years (age range, 31 to 92 years). Of the 289 subjects included, majority were either married or divorced (96.2%) and of Malay ethnicity (50.9%), followed by Chinese (36.7%) and Indians (12.5%) (Table 2).

Table 2 Demographic data of study subjects (n=289)

Demographic Data	Mean (SD)	Frequency	Percentage (%)
Age	54.77 (11.26)		
Marital Status			
Single		11	3.8
Married/divorced		278	96.2
Race			
Malay		147	50.9
Chinese		106	36.7
Indian		36	12.5

3.2 Risk factors

Of the 289 subjects, 53 (18.3%) had family history of breast cancer, 9 (3.1%) had family history of ovarian cancer, 139 (48.1%) had HER2 gene mutation, 7 (2.4%) had p53 gene mutation, 25 (8.7%) had previous history of atypia, 24 (8.3%) had previous history of breast or ovarian cancer, 55 (19.0%) had HRT, 48 (16.6%) had exposure to radiation therapy to breast or chest area, 70 (24.2%) were nulliparous, 29 (10.0%) had menarche at age below than 12 years old and 61 (21.1%) had body mass index (BMI) of more than 30 (Table 3).

Table 3 Frequency and percentage of risk factors of breast cancer (n=289)

Risk Factor	Frequency	Percentage (%)
Family history of breast cancer	53	18.3
Family history of ovarian cancer	9	3.1
HER2 gene mutation	139	48.1
p53 gene mutation	7	2.4
Previous history of atypia	25	8.7
Previous history of breast or ovarian cancer	24	8.3
Had HRT	55	19.0
Previous exposure to radiation therapy (to breast or chest area)	48	16.6
Nulliparity	70	24.2
Menarche at age less than 12 years old	29	10.0
BMI more than 30	61	21.1

Simple logistic regression was conducted to the above risk factors. Only variables with p-value <0.25 were considered for further analysis and these include family history of breast cancer, HER2 gene mutation, previous history of breast or ovarian cancer, had HRT and previous exposure to radiation (Table 4).

Variable selection by backward elimination and manual removal of variable showed preliminary main effect model consists of family history of breast cancer and previous history of breast or ovarian cancer. Multicollinearity and interaction were checked between the two variables to obtain preliminary final model. The model goodness of fit was checked by Hosmer-Lemeshow test, classification table and receiver operating characteristic (ROC) curve. Final model was demonstrated in Table 5, confirming the significant of these risk factors.

Table 4 Simple logistic regression for associated factors of breast cancer (n=289)

Variable	Crude OR[a] (95% CI)[b]	p-value
Family history of breast cancer	2.024 (0.180, 1.352)	0.170
HER2 gene mutation	0.173 (0.049, 0.603)	0.173
Previous history of breast or ovarian cancer	18.214 (6.513, 50.941)	<0.001
Had HRT	1.924 (0.704, 5.258)	0.202
Previous exposure to radiation therapy (to breast or chest area)	2.316 (0.842, 6.369)	0.104

a Crude odds ratio (OR)
b 95% confidence interval (CI)

Table 5 Multiple logistic regression for associated factors of breast cancer (n=289)

Risk Factor	β[a]	Adj OR[b] (95% CI)[c]	p-value[d]
Family history of breast cancer	1.587	4.889 (1.421, 16.826)	0.012
Previous history of breast or ovarian cancer	3.378	29.304 (8.891, 95.580)	<0.001

Constant = -3.777

a β Regression coefficient
b Adjusted odds ratio (OR)
c 95% confidence interval (CI)
d p-value multiple logistic regression <0.05 significant interaction checked and not found
Hosmer-Lemeshow test (p=0.879)
Classification table (93.1%)
Area under ROC curve = 80.0%

3.3 Breast Cancer Diagnostic test

120 subjects out of 289 subjects were deemed to be high risks, thus requiring both mammography and breast MRI examinations. The average age (SD) was 49.9 (8.02) years old. Majority were Malays (86.7%), followed by Chinese (9.2%) and Indians (4.2%).

3.4 Sensitivity and Specificity test (Mammography and Breast MRI)

Sensitivity test was carried out on these 120 subjects to identify correctly those patients who had breast cancer and specificity test was carried out to identify correctly who did not have breast cancer. Mammography was shown to have 32% sensitivity in identifying correctly breast cancer and 80% specificity in identifying correctly who did not have breast cancer (with 23% positive predictive value and 86% negative predictive value), whereas breast MRI has shown 90% sensitivity to identify correctly breast cancer and 72% specificity to identify correctly those who did not have breast cancer (with 39% positive predictive value and 97% negative predictive value).

3.5 The usefulness of Breast MRI as an addition to Mammography

The number of cases of breast cancer detection using breast MRI (38.3%) was higher compared to mammography (20%). However, there was no statistical significant value (p-value=0.189) in using breast MRI as an additional imaging modality to mammography in detecting breast cancer (Table 6).

Table 6 Pearson's chi-squared test of Breast MRI and Mammography (n=120)

Variable	n	Positive n (%)	Negative n (%)	X^2 statistic (df)	p-value
Breast MRI	120	46 (38.3)	74 (61.7)	1.727 (1)	0.189
Mammography	120	24 (20.0)	96 (80.0)		

df = degrees of freedom

In this study, among these well-established risk factors of breast cancer, only family history of breast cancer and previous history of breast or ovarian cancer were significantly associated with higher risks of breast cancer. Although several variables such as HER2 gene mutation, had HRT and previous exposure to radiation therapy were significant in simple logistic regression analysis, however they were found to be not significant in multiple logistic regression analysis.

Women with a family history of breast cancer, especially in a first-degree relative (mother, sister, or daughter) who have been diagnosed with breast cancer before the age of 50 years old, are at increased risk of developing breast cancer. The risk is higher if more than one first-degree relative developed breast cancer (1.8 times higher for women with one first-degree female relative who has been diagnosed, nearly 3 times higher for women with two relatives, and nearly 4 times higher for women with three or more relatives) as compared to those without a family history [13,14]. In a recent study conducted in Mexico, hereditary familial history was found to influence the development of breast cancer with OR of 5.182 (95% CI 1694-15855) [15]. Our study also disclosed that those with family history of breast cancer had significant chance of getting breast cancer in their lifetime (p-value=0.012 with adjusted OR of 4.889). Indeed, the degree of breast cancer risk depends on the type of relative affected (first or second degree), age at which the relative developed breast cancer, and the number of relatives affected [16].

Breast cancer survivors are at risk of developing new or recurrent cancer in the conserved and contralateral breast [17]. Those with previous history of ovarian cancer are also at increased risk for developing breast cancer, and the risk is higher if the diagnosis was at a younger age [5,18-20]. This study detected a significant association between previous history of breast or ovarian cancer and breast cancer with p-value <0.001 and adjusted OR of 29.304. Genetic mutation of breast cancer genes should be suspected in individuals with personal breast or ovarian cancer, predisposing them to develop breast cancer [14]. Several other factors which may lead to recurrent of breast cancer include extensive intraductal component, high histological grade, tumour size, nodal status and vascular invasion even after breast conserving therapy and mastectomy [19-21].

There was no significant association between HER2 gene mutation and breast cancer seen in this study, contrary to findings in study conducted by Xie *et al.* [22]. A possible reason for this finding was because HER2 gene amplification, which usually results in overexpression of the encoded transmembrane protein p185, occurs only in about one third of breast cancers [23,24]. Our study also found no significant association between HRT and breast cancer, contrary to study performed by Ross *et al.* [25]. The failure to detect this association may be attributed to the low uptake of HRT among post-menopausal women, as similarly observed in study by Fioretti *et al.* [26]. Women previously treated with radiation therapy to the chest or breast area particularly for those who were first exposed at younger ages are at increased risk of developing breast cancer [5,27]. Breast cancer is one of the most common types of second cancers among childhood cancer survivors. Additionally, secondary breast cancer is strongly associated with high-dose radiation therapy to the chest for women treated between 10 and 30 years of age, such as for Hodgkin lymphoma. Breast cancer risk among women with such exposure starts to rise about 8 years after radiation treatment and continues to be elevated for more than 25 years. However in this study, previous exposure to radiation therapy was found to be not significantly associated with breast cancer. A possible reason for this finding is because of the small sample size of those with previous history of radiation therapy, consisting only 16.6% of the cases. The wide age range and mean age of our sample population may also affect the result obtained.

Furthermore, our study demonstrated no significant association between breast cancer and several other risk factors such as a family history of ovarian cancer, p53 gene mutation, previous history of atypia, nulliparity, menarche at age below than 12 years old and BMI of more than 30, contrary to those in other studies [5,6].

The guidelines for early breast cancer detection vary depending on woman's age and include screening tools of mammography, breast-self and clinical breast examinations, as well as breast MRI for women at high risk. In 2005, Leach *et al.* reported that mammography had high specificity of 93% as compared to breast MRI with specificity of 83% [28]. Similarly, the specificity of mammography in our study was found to be higher than breast MRI. The sensitivity of mammography for breast cancer may be influenced by the density of breast tissue, and vary from 25% to 85% [29], likewise in this study (32%). Moreover, Kriege *et al.* strongly demonstrated that MRI was more sensitive compared to mammography in detecting breast cancer [12], similarly as being observed in our study. Annual MRI screening in addition to mammography is recommended for women at high lifetime risk of breast cancer, beginning at 30 years of age. However in our study, the usefulness of breast MRI as an adjunct tool to mammography did not give statistically significant value with p-value=0.189. In 2007, Lord *et al.* demonstrated that MRI has the capability to detect additional breast cancer only in young high risk women [30]. Again, the age range and mean age of our study population may actually affect this result.

As this study was performed in a single centre setting with small sample size, these findings might not be representative of all women with breast cancer. However, it provides new information that will be beneficial and can be implemented effectively in health screening and health awareness programmes in promoting early breast cancer detection.

4.0 CONCLUSION

As a conclusion, family history of breast cancer and previous history of breast or ovarian cancer are well-established risk factors for breast cancer in this study, although several other risk factors were not significantly associated with it. Breast MRI was found to be sensitive in detecting breast cancer while mammography showed higher specificity in identifying correctly those who did not have breast cancer. It is important to note that surveillance of women at high risk is useful in detecting breast cancer at early stage. However,

breast MRI was found to be not useful as an adjunct imaging modality to mammography in detecting breast cancer in high risk women in our study due to some study limitations.

A comprehensive screening guideline should be implemented especially for those women who are at increased risk of breast cancer although it is challenging and requires dedicated health professionals and adequate imaging modalities. Finally, breast cancer education should be enhanced to increase cancer detection rate at early stage.

Acknowledgement

The authors gratefully thank the staff from Record Unit and Imaging Unit of AMDI, USM and to all those directly or indirectly involved in this study. This study was supported by Student Research Fund of AMDI, USM.

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