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

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UNIVERSITI SAINS MALAYSIA
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By

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DECLARATION

I certify that this thesis does not incorporate without acknowledgement any material previously submitted for a master, degree or diploma in any university; and that to the best of my knowledge and belief it does not contain any material previously published or written by another person except where due reference is made in the text. This is to certify that the dissertation entitled **"A Preliminary Study of Risk Factors of Breast Cancer and the Usefulness of MRI as an Addition to Mammography in detecting Breast Cancer in High Risk Women"** is the bona fide record of research work done by Nur Hashamimi Binti Hashim, Matric Number P-IPM0022/15 during the period of February 2015 until January 2016. This dissertation is submitted in partial fulfilment for the degree of Master of Science (Medical Research). Research work and collection of data belong to Universiti Sains Malaysia.

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LIST OF ABBREVIATIONS

1. AMDI	=	Advanced Medical and Dental Institute
2. BI-RADS	=	Breast Imaging Reporting and Data System
3. BMI	=	Body Mass Index
4. BRCA	=	Breast Cancer gene
5. CI	=	Confidence Interval
6. HBM	=	Health Believe Model
7. HER2	=	Human Epidermal Growth Factor Receptor 2
8. HPE	=	Histopathological Examination
9. HRT	=	Hormone Replacement Therapy
10. MARIBS	=	Magnetic Resonance Imaging in Breast Screening
11. MRI	=	Magnetic Resonance Imaging
12. OR	=	Odds ratio
13. p53	=	Tumour protein p53
14. SD	=	Standard Deviation
15. USM	=	Universiti Sains Malaysia
16. WHO	=	World Health Organization

LIST OF APPENDICES

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

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. 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. Therefore, the aim of this study was to identify the significant risk factor(s) 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 since 2007 until present. Data were taken from those who undergone mammography for screening or diagnostic purposes and diagnosed with breast cancer in Advanced Medical and Dental Institute, Universiti Sains Malaysia. Data from 289 subjects were successfully retrieved and analysed based on their risk factors of breast cancer. Meanwhile, data from 120 subjects who have undergone both mammography and breast MRI were also analysed. The final results showed that there were significant risk factors of breast cancer among the study population; family history of breast cancer (p=0.04), HER2 gene mutation (p= 0.006) and previous history of breast or ovarian cancer (p=<0.001). Breast MRI showed high sensitivity (90%) while mammography showed high specificity (80%) in detection of breast cancer. 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 >0.05). In conclusion, this study showed that there were significant risk factors of breast cancer seen among women and

there was no statistically significant usefulness of breast MRI as an addition imaging modality to mammography in detection of breast cancer in high risk women.

KAJIAN AWAL MENGENAI FAKTOR RISIKO KANSER PAYUDARA DAN PENGGUNAAN MRI PAYUDARA SEBAGAI MODALITI TAMBAHAN KEPADA MAMOGRAFI DALAM PENGESANAN KANSER PAYUDARA DALAM KALANGAN WANITA YANG MEMPUNYAI FAKTOR RISIKO TINGGI

ABSTRAK

Faktor risiko kanser payudara dalam kalangan wanita seperti factor genetik, sejarah keluarga dan factor gaya hidup seharian, boleh diklasifikasikan sebagai tinggi, pertengahan dan biasa. 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 mengenal pasti factor 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. Reka bentuk kajian retrospektif kohort ini menggunakan data pesakit sejak dari tahun 2007 sehingga sekarang. Data diambil daripada subjek yang menjalankan mamografi dengan tujuan penyaringan atau diagnostik dan didiagnosa dengan kanser payudara di Institut Perubatan dan Pergigian Termaju, Universiti Sains Malaysia. Sejumlah 289 data subjek telah berjaya diperoleh berdasarkan kepada faktor risiko kanser payudara yang terdapat pada setiap subjek. Sementara itu, data daripada 120 subjek yang menjalankan kedua-dua pengimejan mamografi dan MRI payudara juga dianalisa. Hasil akhir yang diperoleh menunjukkan bahawa terdapat faktor risiko kanser payudara dalam kalangan wanita yang mempunyai sejarah kanser payudara dalam keluarga ($p=0.04$), mutasi gen HER2 ($p= 0.006$) dan juga sejarah kanser payudara atau ovari ($p<0.001$). Sementara itu, MRI payudara menunjukkan sensitiviti yang tinggi iaitu 90%, manakala mamografi menunjukkan

spesifisiti yang tinggi iaitu 80% dalam mengesan kanser payudara. Walau bagaimanapun, 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 ($p > 0.05$). Oleh itu, kajian ini menunjukkan bahawa terdapat beberapa faktor risiko yang signifikan untuk kanser payudara dalam kalangan wanita dan penggunaan MRI payudara didapati tidak menunjukkan sebarang statistik yang signifikan sebagai modaliti pengimejan tambahan kepada mamografi untuk mengenalpasti kanser payudara dalam kalangan wanita yang mempunyai faktor risiko yang tinggi.

CHAPTER 1

INTRODUCTION

1.1 Background of the Study

Approximately 1.4 million women were diagnosed with breast cancer worldwide, and nearly 450,000 deaths were recorded in year 2008 (Youlden *et al*., 2012). Ultimately, it is the second most common cancer overall and the leading cause of cancer mortality among women with estimated 1.67 million new cases diagnosed in 2012 (Ferlay *et al*., 2012). Obviously, these data show the climbing pattern of the incidence rate of breast cancer worldwide.

Most health professionals believe that early detection of breast cancer through screening save thousands of life each year (American Cancer Society, 2015). Recommended screening guideline should be considered for early breast cancer detection as most women are asymptomatic when the tumour is small and is easily cured at the early stage (Altery *et al*., 2013). In United States, it is estimated that in 2015, almost 231,840 incidence of invasive breast cancer and 60,290 incidence of carcinoma in situ will be diagnosed. Of these, 40,290 women will be dying from breast cancer (American Cancer Society, 2015).

Meanwhile in Malaysia, breast cancer was reported to be the most common cancer in females and also the most common cancer among population despite of sex with 3242 female breast cancer cases diagnosed in 2007(Malaysian Cancer Statistics, 2007). Additionally, breast cancer is the most frequent cancer among Malaysians (18.0 %), followed by large bowel cancer (11.9%) and lung cancer (7.4%) (Chye *et al*., 2008).

In 2002, there was decrease in breast cancer incidence seen in United States, occurring after the highly publicised series by Women's Health Initiative. This was in contrast with the incidence rate among Asian countries which increasingly occur (Pathy *et al.*, 2011), proved by the audit done by University Malaya Medical Centre which demonstrated the rise in the incidence of breast cancer with 83 cases in 1995, followed by 154 cases in 2000 and 340 cases in 2005 (Nur Aisyah Taib *et al.*, 2007). The proposed factors for this trend include alteration in reproductive factors, environmental exposure, and lifestyle such as dietary intake and physical activity (Pathy *et al.*, 2011).

1.2 Problem Statement

Every disease has their own features and risk factors. There is high tendency for an individual to get the disease if there is high risk factor seen. Same goes to the risk factors of breast cancer which are highly responsible for the increase in the incidence rate of breast cancer in women. Yip *et al*. in 2006 demonstrated that the incidence rate of breast cancer in Malaysia, differs among three major races; 1 in 16 Chinese, 1 in 16 Indian and 1 in 28 women having breast cancer at certain stage in their lifetime which were highly related to the lifestyle and reproductive factor (Yip *et al*., 2006).

In Western populations, risk factors of breast cancer have been widely investigated. Lifestyle-associated and reproductive factors were found to be highly correlated with breast cancer (Norsaadah *et al.*, 2005). 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 (Li, *et al.*, 2003). The survival rate for late stage detection of breast cancer was found to be worse in Malays followed by Chinese and Indians (Yip *et al*., 2006).

Early detection of breast cancer can be overcome by identifying the risk factors and selection of the appropriate screening tool. However, there is less information available relating to the risk factors of breast cancer among Asian women (Norsaadah *et al.,* 2005). Early detection of breast cancer plays a vital role in improving the survival rate among breast cancer in women, and identifying related factors having high tendency in getting breast cancer at some stage of their lifetime is essential. Over the past few decades, mammography and clinical breast examination were the gold standard for screening test for early detection of breast cancer as suggested by American Cancer Society. Nowadays, for those women with high risk for breast cancer due to certain factor, they are recommended to undergo breast magnetic resonance imaging (MRI) which is highly sensitive in detecting breast cancer (American Cancer Society, 2015).

Ministry of Health in Malaysia plays a major role in health screening program and promoting early breast cancer detection among women by breast self examination, clinical breast examination and mammography (Yip *et al.,* 2006) especially for those with high risks. This is important for early diagnosis and treatment of breast cancer and subsequently for better quality of life.

As well as the appropriate screening tool, Western countries are widely investigating the effectiveness of breast MRI in detection of breast cancer in women with high risk. By far, breast MRI appears to be more sensitive than mammography in detecting breast cancer among women with high risk (Kriege *et al.,* 2004). However in Malaysia, no studies have been done in looking at the effectiveness of breast MRI as adjunct tool to mammography in detection of breast cancer. To date, this is the first study to be conducted in northern Malaysia to identify the risk factors of breast cancer

and also the efficacy of breast MRI as an addition to mammography in detecting the breast cancer in high risk women.

1.3 Research objectives

1.3.1 General Objective

To study the risk factors of breast cancer and the usefulness of breast MRI as an addition to mammography in detecting breast cancer in high risk women.

1.3.2 Specific Objectives

(a) To identify the significant risk factor of breast cancer in women

(b) To determine the usefulness of breast MRI as an addition to mammography in detecting breast cancer in high risk women

1.4 Research Questions

(a) What is the significant risk factor of breast cancer in women?

(b) Is there any role of breast MRI as an addition to mammography in detecting breast cancer in high risk women?

1.5 Research Hypothesis

(a) Null hypothesis, $H_{\circ}$: There is no significant association between risk factors and breast cancer

Alternative hypothesis, H_A: There is significant association between risk factors and breast cancer.

(b) Null hypothesis, $H_{\circ}$: Breast MRI is not useful imaging modality as an addition tool to mammography in detecting breast cancer in high risk women.

Alternative hypothesis, H_A: Breast MRI is useful imaging modality as an addition tool to mammography in detecting breast cancer in high risk women.

1.6 Significance of the Study

In Malaysia, risk factors of breast cancer among women are not widely investigated yet. There is lack of information regarding which risk factor is significant for Malaysian women in developing this disease. Even though the risk factors of breast cancer in Western countries have been well investigated, there should be differences seen in Malaysian women as there are differences in lifestyle habit, socioeconomic status and dietary habit.

In fact, the incidence report of newly diagnosed breast cancer in Western countries is decreasing due to continuous health awareness programme held. In contrast, in Asian countries, the incidence report of newly diagnosed breast cancer is increasing, suggesting the lack of knowledge and information, accessibility of the facilities of screening program as well as inadequate health awareness programme in our population. Therefore, this study is important to identify significant risk factors of breast cancer among women in Malaysia, in particular the northern Malaysia. New information gained will be beneficial and can be implemented effectively in health screening and health awareness programmes in promoting early breast cancer detection

In addition, appropriate screening tool plays a vital role especially in detecting high risk of breast cancer among women. Studies showed that mammography is the first line screening tool besides breast self examination and clinical breast examination. However, mammography alone is inadequate in diagnosing breast cancer. Therefore, breast MRI is found to be a sensitivity imaging tool towards detection of breast cancer in the images produced. Breast MRI was suggested in women with high risk of breast cancer after screening by mammography. Therefore, the aim of this study is to

determine the usefulness of breast MRI as an addition to mammography in high risk women in detecting breast cancer.

CHAPTER 2

LITERATURE REVIEW

2.1 Introduction

Cancer is mutated cells in the body which can grow and form a tumour, named after the part of the body where it originates (Altery *et al.*, 2013). Breast cancer is a type of cancer that forms from breast tissues, potentially to be malignant and can invade the surrounding cells and metastasise to distant organs (American Cancer Society, 2015).

Basically, breast cancer has five stages; Stage 0 (carcinoma in situ which does not spread to other tissues beside breast), stage 1 (subdivided into stage 1A and 1B based on the size of the tumour - less than 2cm with no lymph node involvement), stage II (subdivided into stage IIA and IIB based on the size of the tumour - 2cm to 5cm and with/without lymph nodes involvement), stage III (subdivided into IIIA, IIIB and IIIC based on the size of the tumour - more than 5cm and spreads to axillary lymph nodes, overlying skin or chest wall) and stage IV (cancer spreads to other organs e.g. lungs, liver or brain) (National Cancer Institute, 2015).

However, all of these stages of breast cancer can be determine by screening through appropriate screening tool and need to be investigated thoroughly by health professionals. In addition, early detection as well as early treatment of breast cancer can be implemented by identifying the risk factors that are related to breast cancer which can help in preventing late stage detection of breast cancer. The survival rate for late stage detection is worse than early detection (Yip *et al.*, 2006).

2.1.1 Risk factors of Breast Cancer

According to the American College of Radiology, women with high risk of breast cancer have 20% or greater risk in getting breast cancer in their lifetime, whereas those with intermediate risk have 15% to 20% lifetime risk of breast cancer and of those with average risk, less than 15% lifetime risk of breast cancer (Maineiro *et al.,* 2013). There are several risk factors of breast cancer which can be classified into genetic, family history and lifestyle factors (Tyrer *et al.,* 2004). Genetic factors include mutation of breast cancer gene (BRCA 1 and BRCA 2) (Martin and Weber, 2000), Human Epidermal Growth Factor Receptor 2 (HER2) mutation (Yang *et al.,* 2007) and Tumour protein p53 (p53) mutation (Miler *et al.,* 2005). Meanwhile, family history can be subdivided into family history of breast cancer (Colditz *et al.,* 1996) and family history of ovarian cancer (Mcpherson *et al.,* 2000). Personal history or lifestyle factors include previous history of breast cancer, previous history of atypia on breast biopsy (Singletary, 2003), current treatment with hormone replacement therapy (HRT), previous radiation therapy to chest or breast area, nulliparity, delivery at age more than 30 years, first menarche before the age of 12 years, body mass index (BMI) more than 30 and smoking (Mcpherson *et al.,* 2000).

Recently, two known genes with high susceptibility in developing breast cancer have been widely investigated. These genes of BRCA1 and BRCA2 have been identified as having a germ line mutation accountable for between 5% and 10% of all breast cancer (Martin and Weber, 2000). Some women that carry these mutations underwent mastectomy or oophorectomy as the cancer risk was very high (Antoniou *et al.,* 2003). Predictive testing have been widely done for screening mutation in these genes and more than 750 protein truncating mutation within these genes have been identified. Additionally, somatic mutation has been identified at the p53 genes which

give a high percentage of susceptibility to get breast cancer (Sirandsky *et al.,* 1992). Although the frequency of genetic mutation at the p53 genes is lower than others solid tumour, molecular pathological study of the structure and expression of the p53 pathway are able to generate value in diagnosis, prognosis and treatment of breast cancer (Gasco *et al.*, 2002). Besides that, it has been estimated that 1 in 5 patients with breast cancer has numerous HER2 receptor on the surface of the cells which are also known as growth promoting protein leading to aggressive spread of the cancer disease (American Cancer Society, 2015)

Family history of breast cancer is an established risk factor for breast cancer among women (Colditz *et al.,* 1996). In Malaysia, study in Kelantan showed that nulliparity and family history were well established risk factors of breast cancer among women whereas the correlation of oral contraceptive and obesity with breast cancer was still unclear (Yip *et al.,* 2006). Meanwhile, Martin and Weber demonstrated that estrogen exposure was directly associated with risk factor of breast cancer and related to age of menarche, nulliparity and late onset of menopause (Martin and Weber, 2000). In addition, risk factors of breast cancer such as age and postmenopausal hormone usage differed according to Estrogen Receptor status and at the same time, reproductive history and BMI after menopause differed according to Progesterone Receptor status (Colditz *et al.,* 2004). In fact, study done by Yip *et al.,* in 2006 showed that almost 55.7% of all studied cases were found to be Estrogen Receptor positive (Yip *et al.,* 2006). These data demonstrated that the incidence of breast cancer is highly related to estrogen level among women. Additionally, it was proven by the studies shown that repeated estrogen exposure would lead to development of breast cancer (Martin and Weber, 2000). Differences in exercise and dietary intake of certain nutrients may also influence exposure to estrogen (Clemons *et al.,* 2001). Several studies also showed that

nulliparity, late age at first birth, as well as obesity among postmenopausal women were strongly linked to estrogen and progesterone receptor positive and prone to cause breast cancer (Yang *et al.,* 2007).

2.1.2 Screening tools of Breast Cancer

Screening of breast cancer can be done before the symptoms or after the symptoms have developed such as breast lump (Altery *et al.,* 2013). Mammography screening is the gold standard as first line screening and diagnostic tool for breast cancer. Recently, breast MRI has been widely investigated, demonstrating high sensitivity in early detection of breast cancer. There was recommendation for breast self examination, clinical breast examination and mammography in those with high risk of breast cancer in early detection of the disease (Coldit *et al.,* 1996). Compared to mammography or even combination of mammography with high frequency ultrasound, breast MRI did not demonstrate essential role in early diagnosis of familial breast cancer (Kuhl *et al.,* 2005). Generally, women with breast cancer are asymptomatic and thus, it is vital for women to follow recommended screening guidelines for the detection of breast cancer at an early stage (Altery *et al.,* 2013). Despite that, women with genetically inherited breast cancer often developed the disease at young age and the dense breast tissues reduced the sensitivity of mammography in detecting lesions (Magnetic Resonance Imaging in Breast Screening (MARIBS), 2005). Therefore, there was strong evidence that breast MRI should be included in breast cancer screening programs for young high risk women in detection of breast cancer compared to conventional screening strategies (Lord *et al.,* 2007).

According to American College of Radiology, mammography screening can be done as early age of 25 to 30 years old or 10 years before age of first-degree relative

with breast cancer or 8 years after radiation therapy and both mammography and breast MRI are complementary examinations that should be performed (Maineiro *et al.*, 2012). Additionally, screening breast MRI was recommended for women with an approximately 20 to 25% or greater lifetime risk to get breast cancer including women with a strong family history of breast or ovarian cancer and women who were treated for Hodgkin disease (Kuhl *et al.*, 2005). It was suggested that more frequent screening should be needed for women with genetic mutation of BRCA 1, BRCA2, phosphatase and tensin homolog, and p53 as larger tumours more than 2cm were found more often in these women (Kriege *et al.*, 2004). Besides that, MRI was found to be significantly high in sensitivity in detecting intraductal and invasive familial or hereditary breast cancer (Kuhl *et al.*, 2005).

However, the cost in performing breast MRI is more as compared to mammography. Mammography is fairly cheap and widely available. However, breast MRI was found to be potentially cost-effective for screening women younger than 50years with high risk of breast cancer (Lord *et al.*, 2007). Contrast enhancement MRI was found to be the new screening tool that gave more benefits in carriers of BRCA1 germ line mutations (MARIBS, 2005).

There is limitation in detecting breast cancer in younger women with high risk of breast cancer due to their dense breasts. Therefore, breast MRI is the appropriate screening tools and as reported, breast MRI was able to detect mammographically occult breast cancer in women at high risk (Lehman *et al.*, 2005).

In conclusion, several studies suggested that breast MRI can help in detection of breast cancer in high risk women and help in early detection of breast cancer. However, there is still a need in investigating the usefulness of breast MRI as an addition to

mammography in high risk women. Furthermore in Malaysia, there are limited studies available related to this research which can potentially give a lot of benefits to public health as well as improvement to quality of care.

2.2 Theoretical Framework

The Health Belief Model (HBM) is a psychological model that attempts to explain and predict health behaviours. This is done by focusing on the attitudes and beliefs of individuals. The HBM was first developed in the 1950s by social psychologists Hochbaum, Rosenstock and Kegels working in the United States of America Public Health Services (Janzand Becker, 1984). The HBM suggests that a person's belief in a personal threat of an illness or disease together with a person's belief in the effectiveness of the recommended health behaviour or action will predict the likelihood the person will adapt to the behaviour. Based on this study, this model helps in explaining the seeking behaviour to get medical attention as well as initiative to do screening and diagnostic test for early detection of breast cancer. In HBM, it predicts that women will likely to adhere to screening mammography recommendations if they feel susceptible to breast cancer, think breast cancer is a severe disease, perceived barriers to screening as lower than perceived benefits, have higher self-efficacy for obtaining mammograms and receive cue to action (Fulton *et al.*, 1991). Figure 2.1 shows basic element of HBM. Meanwhile Table 2.1 shows modified from Key concepts and definition of health belief models.

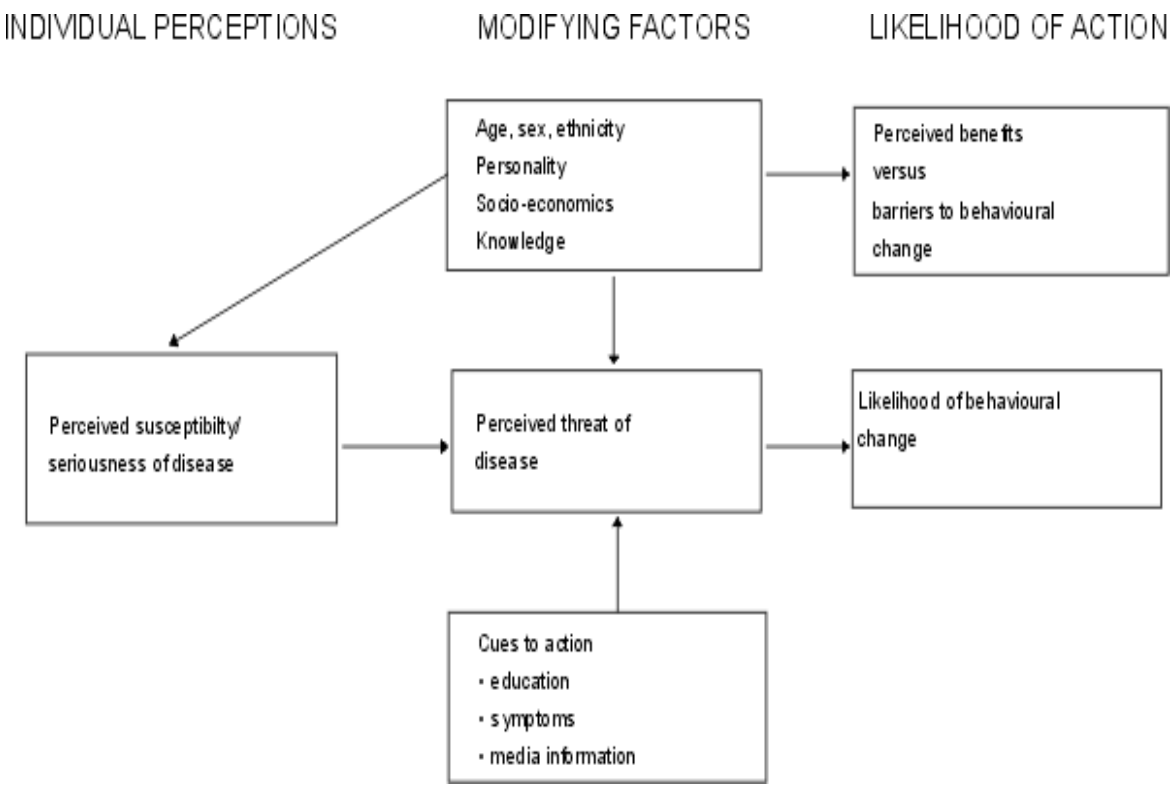

Figure 2.1: Basic elements of health believe models (Janz and Becker, 1984, The Health Believe Model: A Decade Later)

Table 2.1: Modified from Key concepts and definition of health belief models (Fulton *et al.*, 1991, "A study guided by the Health Belief Model of the predictors of breast cancer screening of women ages 40 and older").

Concept	Definition	Application
Perceived Susceptibility	Belief about the chances of experiencing a risk or getting a condition or disease	Women with either risk factors of family history of breast or ovarian cancer; gene mutation; previous history of atypia; previous history of breast or ovarian cancer; hormone replacement therapy; nulliparity; radiation; menarche at age less than 12 years old or BMI<30 believe about the chances to have breast cancer
Perceived Severity	Belief about how serious a condition and its sequelae are	Have chances to get breast cancer in whatever stages in lifetime
Perceived Benefits	Belief in efficacy of the advised action to reduce risk or seriousness of impact	Undergone screening or diagnostic test such as mammogram and/or MRI breast for early detection of breast cancer
Perceived Barriers	Belief about the tangible and psychological costs of the advised action	The test suggested is depend on the degree of the seriousness of the illness according to the physician
Cues to Action	Strategies to activate "readiness"	Frequently do breast self examination and yearly mammogram screening test to alert any abnormalities
Self-Efficacy	Confidence in one's ability to take action	Moral support and encouragement from family members is needed to take the action.

CHAPTER 3

RESEARCH METHODOLOGY

3.1 Research Design

This study was conducted using quantitative, retrospective and cohort study design in order to identify the significant risk factor of breast cancer among women, as well as to determine the usefulness of using breast MRI in high risk women as an addition to mammography. The study was conducted over a period of eight months starting from April 2015 until November 2015.

3.2 Population and Setting

The study was conducted at Advanced Medical and Dental Institute (AMDI), UniversitiSains Malaysia (USM). The study populations were women who came to AMDI for screening or diagnostic mammography since August 2007 until present.

3.3 Sampling plan

3.3.1 Sample

3.3.1.1 Inclusion Criteria

1. Female age > 25 years old
2. Women with either high, intermediate or average risk of breast cancer.
3. Women who had undergone mammography alone or mammography and breast MRI.
4. Available histopathological examination (HPE) results for women who were diagnosed with benign breast lesion or breast cancer.

3.3.1.2 Exclusion Criteria

1. Women who have psychological disorder.

3.3.2 SamplingMethod

Probability sampling method i.e. simple random sampling was used in this study. All selected women were classified as high, intermediate or average risk for breast cancer and undergone mammography or breast MRI and mammography examinations.

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3.3.3 Sample Size

The calculation of sampling size was done by using Raosoft method. The margin error used in this calculation is 5%. The margin of error is the amount of error which can be tolerated. Lower margin of error requires a larger sample size. In addition, 95% of confident interval (CI) level used in this calculation.

Higher confidence level requires a larger sample size. Response distribution used was 50%. From calculation of the sample size, the population size used in this study was 289 respondents.

Calculation method:

$$x = Z(c/100)^2 r(100-r)$$

$$n = Nx / ((N-1)E^2 + x)$$

$$E = \text{Sqrt}[(N-n)x / n(N-1)]$$

Where,

n = the sample size

E= margin of error

N= the population size,

r = Fraction of responses of interest

Z(c/100) = Critical value for the confidence level c.

3.4 Variable

3.4.1 Variable measurement

The independent variable in this study was the risk factors of breast cancer which include family history of breast cancer, family history of ovarian cancer, HER2 mutation, p53 mutation, previous history of atypia on breast biopsy, previous history of breast cancer or ovarian cancer, currently on HRT, previous radiation therapy (breast or chest area), nulliparous, first menarche before the age of 12 and BMI of more than 30. Meanwhile, the dependent variable was the detection of breast lesion whether it was benign or malignant.

Besides that, the usefulness of breast MRI was determined by using specificity and sensitivity method calculation in contingency table.

3.5 Instrumentation

Using quantitative, retrospective and cohort study design, all data kept since August 2007 were collected from the Imaging Unit, as well as Data and Records Unit of AMDI. All women who came to AMDI were firstly classified into which risk factors they have based on the checklist provided by Imaging Unit, AMDI. The mammography examination form comprised of selected demographic data, clinical history, hormonal status, clinical signs, physical examination findings, radiographer's finding and radiologist's report.

3.6 Ethical Considerations

Ethical aspect for research study is important and acts as a baseline for research to be conducted in the right way. For this study, the ethical consideration includes the approval from the Human Research Ethics Committee USM. The letter of requesting permission was sent to them prior to the conduct of the study and started only after receiving the written approval. In addition, the data obtained from those who were included in this study would be confidential and strictly used for the purpose of this study only.

3.7 Data Collection Methods

The data was collected from the AMDI mammography audit system that was kept since August 2007 until present. The data collection was conducted a month after the approval from Human Research Ethics Committee USM.

3.7.1 Flow chart of Data Collection

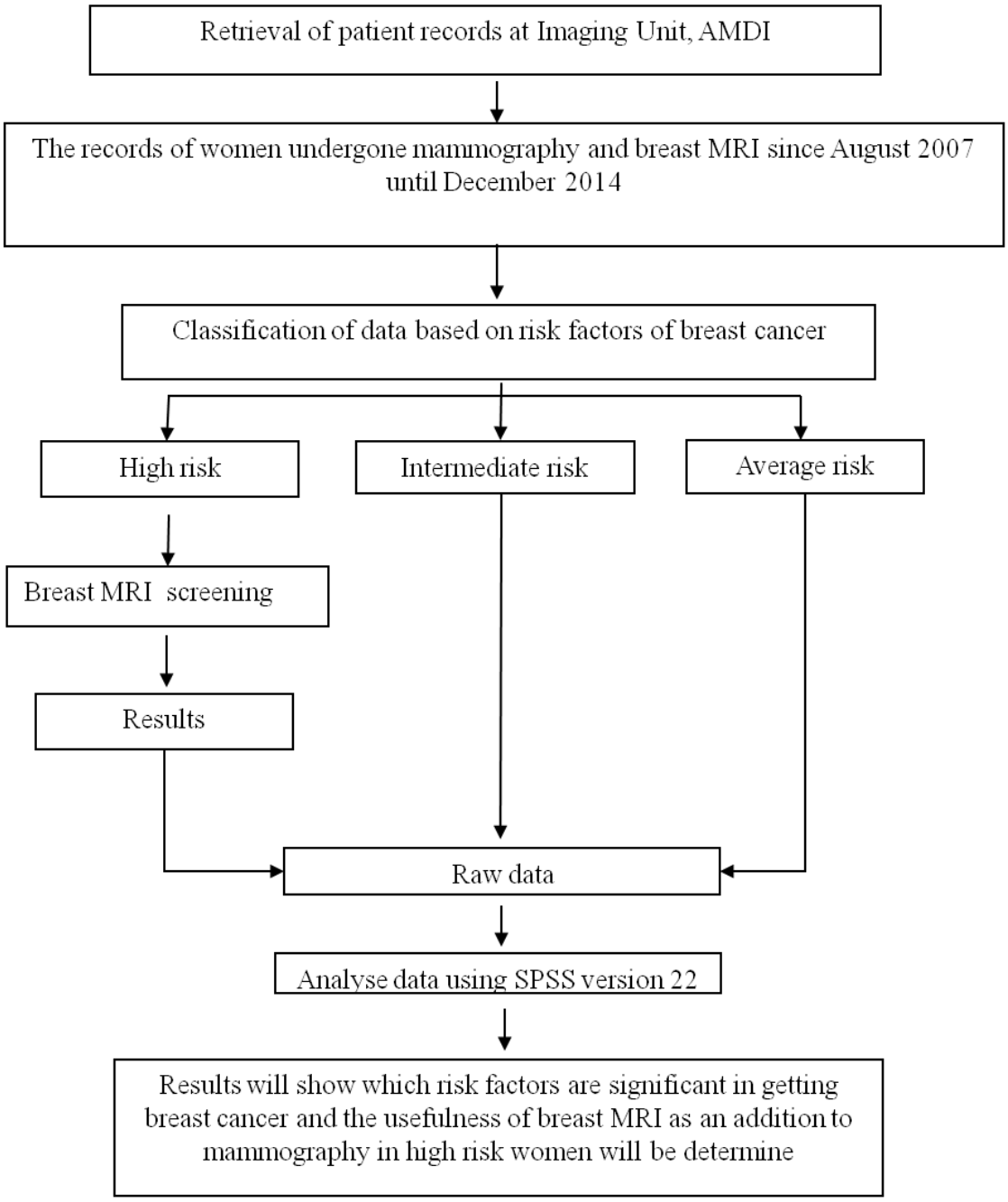

Figure 3.1: Flow Chart of Data Collection

3.8 Data 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. Besides that, the logistic regression analysis was used to determine the significant risk factors (independent) of breast cancer (dependent). Meanwhile, 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 determine by contingency table and Pearson Chi Square test.

A 5% error in rejecting null hypothesis with 95% CI was used. Significant level was defined as $p < 0.05$.

3.9 Definition of Operational Term

3.9.1 Independent Variables (Risk Factors)

Risk factor is any attribute, characteristics or exposure of an individual that increases the likelihood of developing a disease or injury [World Health Organisation (WHO), 2015]. There is also an aspect of personal behaviour or lifestyle, an environmental exposure, or an inborn or inherited characteristic associated with an increase likelihood of disease or other health-related event or condition, a variable that affects the probability of a specified adverse event (Segen's Medical Dictionary, 2011). Risk factors for breast cancer can be classified into three major part; high risk of breast cancer (women had 20% or greater in their lifetime risk to get the breast cancer), intermediate risk (women had 15% to 20% lifetime risk of breast cancer) and average risk (women had less than 15% lifetime risk of breast cancer) (Maineiro *et al.,* 2013).

Below are the risk factors that were included in this study:

1. Family history of breast cancer
   a) Mother, sisters or daughters even had breast cancer before the age of 50 years
   b) Two or more maternal or paternal relatives ever had breast cancer (grandmother, aunt, niece)
2. Family history of ovarian cancer
   a) Mother, sisters or daughters even had ovarian cancer before the age of 50 years
   b) Two or more maternal or paternal relatives ever had ovarian cancer (grandmother, aunt, 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. Previos history of breast cancer or ovarian cancer
6. Currently on hormone replacement therapy
7. Previous 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 of more than 30

3.9.2 Dependent Variables

1. Mammography result

Mammography is the radiographic examination soft tissue of the breast. It is used to identify various benign and malignant neoplastic processes (Mosby's Medical Dictionary, 2008). Annual screening for mammography is recommended at the age of 40 years old for general population, at age 25 to 30 years old for BRCA 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 (Maineiro *et al.*, 2013). In this study, mammography result was classified into Breast Imaging Reporting and Data System (BI-RADS) category, negative and positive finding. The BI-RADS category was the standard measurement of imaging modalities. Meanwhile, negative and positive finding were the results of cancer detection based on HPE finding.

2. Breast MRI result

MRI is a non-invasive diagnostic technique that uses nuclear magnetic resonance to produce cross-sectional images organ and other internal body structures. Several studies showed that breast MRI was recommended for women with high risk of developing breast cancer due to its higher sensitivity than mammography (Maineiro *et al.*, 2013). In this study, breast MRI results were also classified into BI-RADS category, negative and positive findings. The BI-RADS category was the standard measurement of imaging modalities. Meanwhile, negative and positive findings were the results of breast cancer detection based on HPE finding.

3. Breast lesion detection (benign or malignant)

Benign cells are non-cancerous cells that do not invade other cells while malignant cells are cancer cells that are made up of cells that grow out of control. Breast cancer is caused by the development of malignant cells in the breast (Breastcancer.org., 2015). The malignant cells originate in the lining of the milk glands or ducts of the breast (ductal epithelium), defining this malignancy as a cancer. Cancer cells are characterised by uncontrolled division leading to abnormal growth and the potential of these cells to intrude into normal tissue locally or to spread throughout the body which is also known as metastasis (Gale Encyclopedia of Medicine, 2008).

CHAPTER 4

RESULTS

4.1 Sociodemographic Data

Data was collected from 289 female subjects (representing 100% of total sample size) who underwent screening or diagnostic mammography and diagnosed with breast cancer in AMDI. The average age ± standard deviation (SD) was 54.77 ± 11.26 years (age range, 31 to 92 years). Of the 289 subjects included, 278 (96.2%) were married or divorce and majority was Malay (50.9%), followed by Chinese (36.7%) and Indian (12.5%) following the normal race distribution in this country. The baseline demographic data in the study population is shown in Table 4.1.

Table 4.1: 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/divorce		278	96.2
Race			
Malay		147	50.9
Chinese		106	36.7
Indian		36	12.5