ASM Sc. J., 13, Special Issue 6, 2020 for InCOMR2019, 46-52

# Correlation Between Three Factors Contributing to Breast Cancer Risk in Klang Valley, Malaysia: Breast Density, BMI and Family History of Breast Cancer

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There are few contributing factors that can be related to breast cancer. The purpose of this research was to study the correlation between breast density, Body Mass Index (BMI) and family's history of breast cancer. The research was carried out at the Women Cancer Detection and Breast Clinic, National Cancer Society, Kuala Lumpur. Two hundred Malaysian women aged between 40 and 60 years volunteered to become subjects in this research. The modality used in this research was mammography. Each subject was given a brief explanation of the research to be carried out and a letter of consent had to be signed before she could participate in this research. Subjects later being asked to answer a questionnaire before their BMI was collected. Subjects were identified via their mammography number. All images were stored in data storage for further analysis. BI-RADS classification was carried out by four experienced radiologists to prevent bias during reporting. BI-RADS breast density classification is divided into four classes: BI-RADS I, BI-RADS II, BI-RADS III and BI-RADS IV. Majority of the subjects have breast density of class BIRADS III (74 subjects), followed by BI-RADS II (60 subjects), BI-RADS IV (34 subjects) and finally BI-RADS I (32 subjects). Overall, majority of subjects have normal BMI class (97 subjects), followed by overweight (59 subjects), obese (42 subjects) and finally underweight (two subjects). BMI are inversely correlated with breast density where ($r_s$=-0.245, $\rho$<0.01). Only 18 subjects have family history of breast cancer with ($r_s$=0.237, $\rho$>0.01) and about half of them had lesser dense breast (BI-RADS I=four subjects and BI-RADS II=five subjects, I-RADS III=nine subjects and BI-RADS IV=none). In conclusion, these results did not represent total population as it only include one centre. However, it is suggested for women to go for their mammogram check-up for early detection of breast cancer as every woman are at risk due to overlapping contributing factors related to breast cancer.

**Keywords:** breast density; body mass index; BI-RADS; Breast cancer risk; mammography; family's history of breast cancer

## I. INTRODUCTION

Breast screening using mammography helps many women to have their early detection of breast cancer and majority of them have their lives saved by it. Early detection helps the medical professional to plan and suggest the better choice of medical procedure and lifestyle change to their patient to help them minimize the risks of developing breast cancer. However, the radiologist still encounter difficulty in reading the images from mammogram as women breast density can mask the breast lesion or mass that may develop to cancer if not detected earlier. There were researched done that indicated that breast cancer is the second deadliest cancer in worldwide including in Malaysia. Due to the lack of

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involvement in breast cancer screening (Akhtari-Zavare *et al.*, 2016), the costs incurred for screening and mere negligence of important in breast screening among Malaysian women are the main contributing factors for late detection of breast cancer (Mahmud and Aljunid, 2018). This might give an impact on survival rate among of women at risk. Majority of Asian women especially Malaysian have dense breasts (Zulfiqar *et al.*, 2012) especially Chinese women (Mariapun *et al.*, 2015). Breast density can be defined as the amount of fibro glandular tissue that appears radiopaque with the background of radiolucent structure like fat tissue in mammography image. Studies carried out in the previous three decades showed that the breast density is directly linked with breast cancer risk (Bleyer and Welch, 2012). It substantially increased the risk of developing breast cancer compared to women with fatty breast as the pathological change in the breast had being masked by dense tissue. The same researcher also has noted that even though women were in the same age group, one with extremely dense breast has a likelihood of developing breast cancer four times more compared to their companion with fatty breast. The main reason for this linkage is the fact that the dense structure in the breast can mask the growth in the breast which leads to false-negative findings by the radiologists.

The breast density in mammography can be classified using Breast Imaging Reporting and Data Systems or BI-RADS for breast density classification. This classification can be done by visual estimation alone by a radiologist or with the aid of Computer-Aided Diagnosis or CAD software. Breast density was classified according to BI-RADS Breast Density Classification which is BI-RADS I for fatty breast, BI-RADS II for fibro glandular, BI-RADS III for dense and BI-RADS IV for extremely dense breast. For this study, the radiologist evaluates the sample of image using an eye balling technique or visual estimation alone without using any software.

Body Mass Index or BMI is also an important factor that might contribute to breast cancer risk. Body Mass Index or BMI contributed a significant increase risk of breast cancer (Neuhouser *et al.*, 2015). Some researcher conducted a life time study to find the effect of BMI towards cancer risk (Taghizadeh *et al.*, 2015). BMI becomes the focus of the research due to the prevalence of obesity in Malaysia because there an increase of percentage of overweight (29.1%) and obese (14.0%) from total population (Ghee, 2016). Moreover, obese women have a tendency to have higher mortality rate from breast cancer compared to those who have a normal weight, due to poor prognosis and false-positive result (Protani *et al.*, 2010). The main reason for this was majority of obese women had larger breast compared to leaner women (Sung *et al.*, 2010). This is because radiologist might overlook the breast mass due to overlapping breast structure in the larger breast and obese women also were more likely to delay or avoid breast screening compared to leaner women. However obese women tended to have low density breast which sometimes helped the radiologist to detect the dense mass easier compared to women with leaner body majority of whom had higher breast density. This finding was supported by the finding where these researchers found that women's BMI is inversely correlated with breast density (Hart *et al.*, 2015). The research done on mix racial subjects stated that the inverse correlation between BMI and breast density was possibly due to common genetic influence that led to those opposite effect (Sung *et al.*, 2010). Although increasing number of studies used self-reported BMI for their research, it is inevitable that this can lead to an under or overestimated report by the subject. This can be prevented by measuring the subject weight and height at the researcher's site by the research assistant. Subject's BMI Class were determined by using this criteria (underweight: $<18.50 kg/m^2$, normal: $18.50\text{-}24.99 kg/m^2$, overweight: $\geq 25.00 kg/m^2\text{-}29.kg/m^2$, obesity class I: $30\text{-}34.99 kg/m^2$, obesity class II: $35\text{-}39.99 kg/m^2$ and obesity class III: $\geq 40.00 kg/m^2$).

Family history of breast cancer is a well-known risk of breast cancer. Almost all previous researchers agreed with this fact. It is believed that there are genes responsible for breast cancer (*BRCA1* and *BRCA2)*, thus there is possibility for the genes to be inherited in the family (Wen *et al.*, 2018). Research done on family tree found that women with first or second degree family history of breast cancer are prone to develop breast cancer once in their life time (Nindrea *et al.*, 2017) and regardless of their races (Kwong *et al.*, 2016) . This factor commonly left undetected due to lack of

awareness among the public about the importance of gene screening and at the same time the gene screening is not approachable because of the cost (Kuchenbaecker *et al.*, 2017).

Unlike BMI, family history of breast cancer is the factor that cannot be modified since women carried the gene toward their lifetime. Most of researcher included this family' s history as one of their main concern as women' breast density also depended on their gene before other factor such as BMI taken place (Stone, 2018). Some researcher suggested woman with family's history of breast cancer should when for breast cancer screening as early as 40 years as this women had 20% risk of developing breast cancer once in their life time (Monticciolo *et al.*, 2018). Women with family's history of breast cancer and have a dense breast often recalled for an extra view using mammogram and other modalities like ultrasound and MRI (Duffy *et al.*, 2018) which subsequently affect the women physiologically and economically.

Some researcher suggest woman with family's history of breast cancer undergoes genetic screening to ensure the type of gene they carry whether it is *BRCA1* or *BRCA2*. This is because both gene give different effect of breast cancer development as *BRCA1* prone to induce breast cancer at premenopausal stage meanwhile *BRCA2* more likely to effect women whom at postmenopausal stage. However, the research done by Kucheacker *et al.* (2017) stated that not only the main concern as the gene also can induce ovarian cancer. As the gene screening need a specialized modality thus the prevalence of subject's in this research of whether they are the carriers or otherwise were not investigated further in this research. The researcher in this study only included whether the subject do have family's history of breast cancer and the relationship of subject with the family whom having the breast cancer. As women whom had family history of breast cancer and first degree relative whom had breast cancer, had 1.75 fold risk of developing breast cancer compare to women who did not have both factors (Sun *et al.*, 2017).

## II. MATERIALS AND METHOD

The research was carried out at Women Cancer Detection and Breast Clinic at National Cancer Society in Kuala Lumpur. Two hundred Malaysian women aged between 40-60 years old who have had a normal mammography report thus involving no pathological condition, no mastectomy or any breast surgery or breast implant done and not subjected to Hormone Replacement Therapy (HRT) were invited to become a subject voluntarily. These criteria were adhered to ensure the subjects were free from factors that can influence the density change in breast.

### *A. Data Collection for Body Mass Index (BMI) and Family's History of Breast Cancer*

Subject's height and weight was collected before their mammographic examination. This data collection was done with the help of a research assistant. The scale was calibrated every morning to ensure the accuracy of the reading obtained. Meanwhile, a questionnaire question was given to subject to help them providing further information about their background including their family history of breast cancer. Guidance was given to the subject during the answering process to ensure the validity of the data collected.

### *B. Data Collection for Mammogram*

All subjects were identified via their patient number. All subjects' mammography images were taken in two standard views, CC or Craniocaudal and MLO or Mediolateraloblique. CC view was taken from the upper (head) to bottom (leg) of patient by placing the image detector 90 degree above an X-ray tube. Meanwhile for the MLO, image was taken when the image detector was tilted from 40 to 60 degree depending to the body curvature of the subjects. The MLO produced the image of side way of the breast. Both images were essential in viewing the breast density scoring to ensure an optimum visualization of glandular tissue of the breast (Mohamed *et al.*, 2018). The subjects' mammogram was viewed by a four-qualified radiologist by visual estimation and experience. The images were edited so that no subjects' identity was revealed to the radiologist. One radiologist gives the scoring

at the site and three others at Serdang Hospital. The scored were determined by the majority of the class decided by the radiologist. If result could be classified into more than one class, the highest class was chosen. All images were stored for further analysis.

Assessing from three variables involve in this research i.e correlation between the qualitative variable (BI-RADS Breast Density Classification), family history of breast cancer and the quantitative variable (subject's BMI), the researcher was more inclined to use Spearman's Rho correlation to analyse the results (George, 2011). Researcher use software SPSS version 15.0 for the analysis.

## III. RESULT AND DISCUSSION

The mean age for subject is 48 years old. Majority of the subjects have breast density of class BIRADS III (74 subjects or 37%), followed by BI-RADS II (60 subjects or 30%), BI-RADS IV (34 subjects or 17%) and finally BI-RADS I (32 subjects or 16%). The distribution of subjects according to BI-RADS breast classification can be viewed in Table 1.

Table 1. Subject's distribution according to BI-RADS breast classification

| BI-RADS Class | Number of Subject | Percentage (%) |
|---|---|---|
| I | 32 | 16 |
| II | 60 | 30 |
| III | 74 | 37 |
| IV | 34 | 17 |

### *A. Correlation Between BI-RADS and BMI*

Subjects were divided their BMI classes. The distribution of subjects and their percentage according to their BMI class can be viewed in Table 2.

Table 2. Distribution of subject's according to BMI class

| BI-RADS Class | Number of Subject | Percentage (%) |
|---|---|---|
| Underweight | 2 | 1 |
| Normal | 97 | 48.5 |
| Overweight | 59 | 29.5 |
| Obese | 42 | 21 |

Overall, majority of subjects have normal BMI class (97 subjects or 48.5%), followed by overweight (59 subjects or 29.5%), obese (42 subjects or 21%) and finally underweight (two subjects or 1%). No subject fall under obese type II and III. Spearman Rho's correlation was done to find the correlation between breast density and BMI. Table 3 shows the correlation between the two variables.

Table 3. Spearman's Rho correlation between BI-RADS and classification for BMI class

| Spearman's Rho | | BI-RADS | Classification for BMI Class Correlation Coefficient |
|---|---|---|---|
| | BI-RADS Correlation Coefficient | 1.00 | -.245** |
| | Classification for BMI Class Correlation Coefficient | -.245** | 1.00 |

This led to inverse correlation between BI-RADS class and BMI class. ($r_s$=-0.245, $\rho$<0.01). The previous reseacher, where they also found that Asian women especially Japanese and Chinese possessed leaner body (lower BMI class) and denser breast or higher BI-RADS class (Zakariyah *et al.*, 2016; Mariapun *et al.*, 2015). Since all subjects selected were Asian and most of them were Chinese, this might be the contributing factor for the negative significant correlation observed between both factors. Even though the sampling for subject in these researches was the same as previous researcher which were Malaysian Women, however there was different component in selection of the subject. Both Mariapun *et al.* (2015) and Zakariyah *et al.* (2016) include women with background of breast cancer history, taken hormone replacement therapy and have undergone breast surgery. All these factors might affect the evaluation and estimation of breast density and BMI. This is because any external factor given had being proven to masking breast density estimation (Kerlikowske *et al.*, 2010). To prevent such risk to happen, the researcher in this study exclude the subject which have any factors that might affect their breast density. Mariapun *et al.* (2015) using the software to aid their radiologist in reporting the breast density of their sample. This can, therefore, help to reduce any overestimation from the visual estimation alone.

Some researcher found that the menopausal statues did contributed to the BMI of women since the reaction of hormonal toward menopausal cycle will contribute to woman increase of BMI especially post menopaused woman since imbalanced of oestrogen and progesterone did lead to

fat deposition in waist of post menopaused woman (Kyrou *et al.*, 2018; Neuhouser *et al.*, 2015). Nevertheless, other researcher did found out that increase in BMI during female growth did contribute to premenopausal breast cancer especially for woman that having BMI>30.0 (Schoemaker *et al.*, 2018). But Schoemaker *et al.* (2018) using data from self-reported BMI value and this can lead to under or overestimation of the finding. Thus, to maximize the validity of the data for this study, the researcher did measure subject's BMI on site. However, these researches did not specially divide the subject according to their menopausal statues. As such, this factor can be further investigated in the future.

### *B. Correlation between BI-RADS and Family History of Breast Cancer*

In this research, from 200 subjects, only 18 subjects had family history of breast cancer. Thirteen of subjects had first degree family relative (their mother and sister) and another five had second degree family relative (aunty and cousin) who contracted breast cancer. About 72% of the subjects who had family history of breast cancer had first degree relative diagnosed with breast cancer.

Spearman's rho correlation analysis performed to find the correlation between family history of breast cancer and BI-RADS breast density, it was discovered that there no correlation between both variables ($r_s$=0.237, ρ>0.01). Spearman's Rho correlation between BI-RADS breast density classification a family history of breast cancer can be viewed in Table 4.

Table 4. Spearman's Rho correlation between BI-RADS and Family's history of Breast Cancer

| Spearman's Rho | | BI-RADS | Family's history of Breast Cancer Correlation Coefficient |
|---|---|---|---|
| | BI-RADS Correlation Coefficient | 1.00 | .237 |
| | Family's History of Breast Cancer Correlation Coefficient | .237 | 1.00 |

This researcher using questionnaire as a tool to gather data about subject's family history. The subject also being assisted on how to answer the questionnaire to ensure the validity of the data. Some previous researcher only relied on their subjects' self-reporting about their family history. This can lead to under or overestimation of the data provided by the subject.

Breast density for this research was done via visual estimation regardless of subject's family history of breast cancer. Duffy *et al.* (2018) suggested mammographic images of women with family history of breast cancer need to be viewed using both visual estimation and CAD to validate their breast density. This to ensure the overlaying pathology if existed can be detected earlier. To overcome this situation, the researcher involves four experience radiologists to evaluate the image and if the BI-RADS class for subject's disputed in to group equally for four radiologists, the highest classification of BI-RADS was taken as a result.

Subjects in this research was not tested further whether they are the carrier for *BRCA1* and *BRCA2* since this research only involve the data from questionnaires and mammographic images. Even though gene testing help to design women's breast cancer screening, yet one must not neglect the fact that women with no family history of breast cancer also at risk at developing breast cancer as other factors too might play the role to induce the cancer such as BMI and lifestyle. Afterall, gene screening is expensive and not widely available for women from rural area. Thus, the researcher found that majority of women who came for mammography screening had benefited from awareness campaign by local government especially the mammograph subsidy for women who had low family income. However, the subject must acknowledge the fact that having relative whether first degree or second degree will in increase the possibility developing breast cancer.

## IV. CONCLUSION

There was inversely correlated between BI-RADS Breast Density Classification and BMI where ($r_s$=-0.245, ρ<0.01) and family history of breast cancer did not of significant relationship with breast density ($r_s$=0.237, ρ>0.01). This might due to limitation in terms of coverage of sampling area which involves only one centre compare to others researcher with most of them gaining their sample via

database. One must note that this finding did not represent Malaysian's total population as it only covered urban area in Kuala Lumpur.

## V. ACKNOWLEDGEMENT

The authors would like to thank Dr Sulaiman Tamanang, Consulting Radiologist, Mdm Umi Kalsum, Mammographer and the staff of National Cancer Society. Also, to UiTM Negeri Sembilan's Management by allowing us do this research.

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