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Mammographic Findings in Women attending Menopause Clinic at King Chulalongkorn Memerial Hospital

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ABSTRACT

Objectives To determine the prevalence of high risk mammographic pattern, according to Wolfe's classification and to assess the association of these findings with some clinical and hormonal characteristics of the women who had been using HRT.

Design A retrospective descriptive study.

Setting Menopause Clinic, Chulalongkorn Hospital.

Material and methods High resolution mammography was performed in 165 women. Wolfe's mammographic parenchymal classification was used with the knowledge that women with dense patterns have a higher risk of developing breast cancer. Four types of mammographic parenchymal density were classified. The N1and P1 were categorized in "low risk mammographic pattern" where as the P2 and DY were categorized in "high risk mammographic pattern". We ran the regression of mammographic risk pattern against age, body mass index, age at menarche, menopausal status, type of menopause, parity and the use of HRT.

Results Of the 165 women in this study, 21 (12.7%) were premenopausal and 144 (87.3%) were postmenopausal. The mean age of these women was 52.34 ± 5.66 years old. BMI of these woman range from 18 to 34 and the mean BMI was 23.89 ± 3.00 kg/m^2. One hundred and thirty six (82.4%) women were married and 29 (17.6%) women were unmarried. Of the 144 postmenopausal women, 104 (72.2%) women were natural menopause, 37 (25.7%) women were surgical menopause and 3 (2.1%) women were premature menopause. The prevalence of the high risk and the low risk mammographic pattern in this study was 73.9 percent and 26.1 percent, respectively. Only the age of the patients and the use of HRT are significantly associated with high risk mammographic parenchymal pattern.

Conclusion We found high prevalence of high risk mammographic pattern in pre- and postmenopausal women. Age and the use of HRT are found to be associated with high risk mammographic pattern.

Key words : Mammographic pattern, wolfe's classification, menopause, HRT2

Nowadays, the number of women in climacteric period has been increasing. Estrogen and progestrogen are commonly prescribed worldwide for a relief of menopausal symptoms and prevention of osteoporosis. However, there are some reported adverse effects which are associated with hormonal replacement therapy, for example, prolonged use of unopposed estrogen is proved to increase the risk of endometrial cancer.[1] Recently the largest meta-analysis published in the Lancet in the year 1997 revealed a slight increase in risk of breast cancer in those who used estrogen for longer than 5 years[2] The risk seemed to be higher according years of estrogen use.

At present, mammography is a useful method for screening of breast cancer. Mammography can detect early breast lesions that might be undetected by manual breast examination for instance, clusters of abnormal microcalcification or small masses. Moreover, mammography is reported to reduce the mortality rate of breast cancer. Breast cancer mortality in women older than 35 years decreases by 50 percent with annual mammographic screening.[3] Mammographic screening for breast cancer has been advocated in "asymptomatic woman" to diagnose early malignant lesions so that the treatment of breast cancer will become more effective.

Several previous studies on mammographic risks of breast cancer interestingly showed that the odds of breast cancer increased steadily with increasing breast density.[4-7] Therefore, we conducted a descriptive study to determine the prevalence of high risk mammographic pattern, according to Wolfe's classification and to assess the association of these findings with some clinical and hormonal characteristics of the women who had been using HRT.

Material and methods

One hundred and sixty five women who attended the menopause clinic at Chulalongkorn hospital between December 1999 and December 2000 were recruited. All women were older than 35 years of age and had at least one screening mammography. All these women did not have any breast surgery such as mammoplasty or mastectomy. The interested variable are of the followings: age, body mass index (BMI), parity, menopausal status, the usage and duration of hormonal replacement therapy.

High resolution mammography was performed, using Senograph 2000D, full field digital, CE medical system. All mammograms were reviewed by the author and an expertised radiologist. We looked for Wolfe's mammographic parenchyma pattern of the breast with the knowledge that women with dense patterns have a higher risk of developing breast cancer. According to Wolfe's classification, four types of mammographic parenchymal density were classified.[8] The N1 pattern is the mammogram that the parenchyma composed primarily of fat and no duct is visible. The P1 pattern is the mammogram that the parenchyma was chiefly fat with prominent ducts less than 25% of the breast volume. The P2 pattern is the mammogram that the ductal prominent component is occupying more than 25% of the breast volume. The DY pattern is the mammogram that the parenchyma is severely involved with dysplasia which often obscured the underlying prominent ductal pattern. The N1 and P1 are categorized as "low risk" mammographic pattern where-as the P2 and DY are categorized in "high risk" mammographic pattern.[4]

The menopausal status was classified into 2 categories, pre and postmenopause. Menopause is the point of time when permanent cessation of menstruation occurs following the loss of ovarian activity.[9] Premenopause is defined as the entire reproductive period up to the final menstrual period. Postmenopause is dated from the final menstrual period, regardless of whether the menopause was induced or spontaneous.[10]

Three types of menopause were defined as follow[10]: natural menopause ie., the permanent cessation of menstruation resulting from the loss of ovarian follicular activity. Natural menopause is recognized to have occur after 12 consecutive months of amenorrhea, for which there is no other obvious pathological or physiological cause. Menopause

occurs with the final menstrual period which is known with certainty only in retrospective a year or more after the final period. Premature menopause ie., permanent cessation of menstruation due to loss of ovarian function before the age of 40. Surgical menopause ie., the cessation of menstruation which follows surgical removal of both ovaries.

We also classified HRT in 4 categories (1) estrogen regimen (2) continuous combined estrogen & progestogen regimen (3) cyclic estrogen & progestogen regimen and (4) other regimens such as tibolone, selective estrogen receptor modulators (SERMs).

The sample size of this study was calculated by the formula of descriptive study ($N = Z_{\alpha/2}^2 P(1-P)/\delta^2$). A pilot study was done in 30 women to look at the proportion of high risk mammographic patterns accordings to Wolfe's classification. There were 21 women who had high risk pattern so that the proportion of the event was 0.7. With 95 percent confident interval and 10 percent of acceptable error, the sample size was calculated to be 165. This study was approved by the Ethical committee of the Faculty of Medicine, Chulalongkorn university.

SPSS 10.0 program for windows was use for data analysis. Menopausal status is one of the most important factors we interested. Chi-Square test was used to evaluate the association between menopausal status and mammographic pattern. Because several factors can have effects on mammographic pattern. We opted for the multiple logistic model to analyze the data. By SPSS, we ran the regression of mammographic risk against age, BMI, age at menarche, type of menopause, parity and the use of HRT

Results

Of all 165 women in this study, 21 (12.7%) women were premenopausal and 144 (87.3%) women were postmenopausal. The mean age of these women was 52.34 ± 5.66 years old. BMI of these women ranged from 18 to 34 kg/m^2 and the mean BMI was 23.89 ± 3.00 kg/m^2. One hundred and thirty six (82.4%) women were married and 29 (17.6%) women were unmarried. Of the 144 postmenopausal women, 104 (72.2%) were natural menopause, 37 (25.7%) were surgical menopause and 3 (2.1%) were premature menopause. The demographic data is shown in table1-4.

Table 1. The demographic data

	Minimum	Mean ± SD.	Maximum
Age (years)	36	52.34 ± 5.66	74
BMI (kg/m2)	18	23.89 ± 3.00	34
Menarche (years)	12	13.41 ± 0.79	15
Age at menopause (years)	36	47.64 ± 4.24	56
Parity	0	1.75 ± 1.62	9

BMI = body mass index, SD.= standard deviation

Table 2. Menopausal status

	Number of patients	Percentage (%)
Premenopause	21	12.7
Postmenopause	144	87.3
Total	165	100.0

Table 3. Types of menopause

	Number of patients	Percentage (%)
Premature menopause	3	2.1
Natural menopause	104	72.2
Surgical menopause	37	25.7
Total	144	100.0

Table 4. Number of HRT users & nonusers

Estrogen regimen	30 (18.2%)
Continuous combined regimen	40 (24.2%)
Cyclic combined regimen	24 (14.5%)
Others	9 (5.5%)
Nonuser	62 (37.6%)

In a view of the mammographic findings of the studied population, there were 19.6% of microcalcification, 14.9% of macrocalcification, 4.2% of benign masses and 4.8% of cysts. Breast sonography was done in all women which revealed 18.4% of cysts, 4.8% of fibroadenomas and 3.0% of benign masses.

According to Wolfe's classification, 3 (1.8%) women were in the N1 pattern and 40 (24.2%) women were in the P2 pattern. These two pattern were categorized in "low risk mammographic pattern". Another two patterns, P2 and DY patterns, had 113 (68.5%) women and 9 (5.5%) women respectively and these two patterns were categorized in "high risk mammographic pattern".

Table 5. Mammographic findings according to Wolfe's classification

Wolf'e's classification	Number of patients	Percentage (%)
N1	3	1.8
P1	40	24.2
P2	113	68.5
DY	9	5.5
Total	165	100.0

The prevalence of the high risk and the low risk mammographic pattern in this study was 74 percent and 26 percent, respectively.

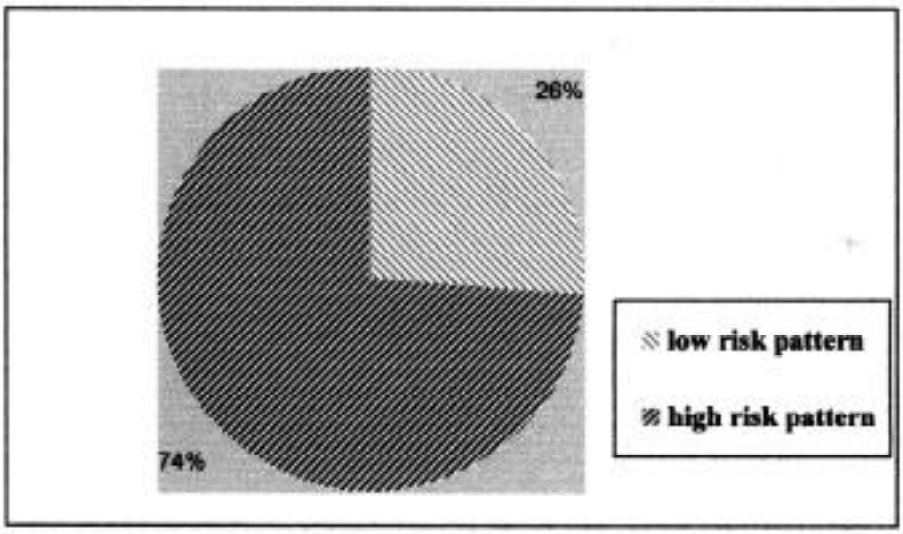

Fig. 1. The prevalence of high risk mammographic pattern.

Table 6 compares the demographic data of the low risk and the high risk groups. We found that age is the only variable that was statistically different. The mean age of the low risk group was significantly higher than that of the high risk group (P=0.00.)

Table 6. The demographic data between high risk and low risk group of mammographic pattern

	Low risk group	High risk group	Unpaired t-test
Age (years)	55.26 ± 5.89	51.31 ± 5.23	P=0.00
BMI (kg/m^2)	24.2 ± 2.89	23.70 ± 3.03	P=0.17
Menarche (years)	13.37 ± 0.79	13.43 ± 0.74	P=0.70
Parity	2.16 ± 1.73	1.61 ± 1.57	P=0.07

BMI = body mass index

Table 7 compares the demographic data of patients in the pre- and postmenopausal groups. Only the age was statistically significant different between the two groups.

Table 7. The demographic data between different menopausal status

	Premenopause	Postmenopause	Unpaired T-test
Age (years)	47.57 ± 4.93	53.03 ± 5.44	P=0.00
BMI (kg/m^2)	23.14 ± 3.14	24.00 ± 2.98	P=0.25
Menarche (years)	13.38 ± 0.80	13.42 ± 0.79	P=0.85
Parity	2.29 ± 2.08	1.67 ± 1.54	P=0.21

BMI = body mass index

Seventeen (81.0 percent) women in the premenopausal group and 105 (72.9 percent) women in the postmenopausal group have high risk mammographic pattern. There was no significant association between the menopausal status and mammographic parenchymal pattern (table 8.)

Table 8. The association of menopausal status and mammographic pattern

	Mammographic pattern		
	Low risk	**High risk**	**Total**
Premenopause	4	17	21
Postmenopause	39	105	144
Total	43	122	165

χ^2 , P=0.433

As we use the multiple logistic model to analyze the data. The result shows that only the age of the patients and the use of HRT are significantly associated with high risk mammographic pattern. There was negative correlation between age and percentage of high risk pattern (table 9.)

Table 9. Logistic regression analysis to assess the risk factors for high risk mammographic pattern

	B	**S.E.**	**df**	**Sig.**
Age	-.154	.048	1	.001
BMI	-.129	.072	1	.074
Menarche	.265	.281	1	.346
Type(0)			2	.081
Type(1)	-2.838	1.520	1	.062
Type(2)	-1.041	.590	1	.077
Parity	-.107	.149	1	.472
Use of HRT	1.064	.503	1	.035
Constant	9.632	5.120	1	.060

BMI: body mass index (kg/m^2), Type: type of menopause,
Type (0): surgical menopause, Type(1): premature menopause,
Type(2): natural menopause.
B: partial regression coefficient, S.E.: estimation of standard deviation of regression
df: degree of freedom, sig.: significant.

As we concern the duration of HRT in these studied population. Of 103 women who used HRT, 60 women used HRT less than 5 years, 34 women used HRT for 5 to 9 years and only 9 women used HRT for 10 years or more (table 10.) All patient who used HRT for 10 years or more had high risk mammographic pattern.

Table 10. The number of the HRT user according to duration of use

Mammographic pattern	< 5 years	5 - 9 years	≥ 10 years
Low risk pattern	19	12	0
High risk pattern	41	22	9*

* All patients have the DY pattern.

Discussion

Density of the breast parenchyma is important in evaluation of a mammogram. Density of breast may change with increasing age. The changes with aging from dense breast parenchyma in younger women toward lesser density of breast parenchyma in older women is observed. This is because normally, fat tissue replaces breast parenchyma in older women.[11] Wolfe described his mammographic classifications based on the ratio of fat density in breast parenchyma.[4] He found a progressive increase in breast cancer prevalence according to the progression of breast density from N1 to DY. The association between breast density and malignancy is probably due to[1] the increased density on a mammogram may obscure a non-calcified malignant mass that does not cause appreciable distortion of the surrounding tissue[2] the increased density or a new density over time per se can be signs of malignancy.

According to our study we found that 74.0 percent of our studied population have high risk mammographic pattern. This prevalence is much higher than those reported previous studies. In the study of Norwegian,[12] only 20 percent of perimenopausal women showed high risk pattern. The difference of the studies is probably due to the difference in studied population. We studied hospital-based population which is a more selective and higher risk women compared to those in the Norwegian study which is a community-based population that is more random and low risk group.

In this study we use high resolution sonography as an adjunct to mammography in all women and especially in women with dense breast to detect a significant number of lesion that can't be detected by mammography. Although most incidental findings on screening sonography are benign, the biopsy rate can be held within acceptable limits by using sonographic characteristics of low malignancy risk to allow imaging follow up rather than biopsy.[13]

The mean age of the high risk group is lesser than the low risk group. That corresponds to the theory that breast tissue of the young is denser than the elder's. There is substantial evidence that endogenous estradiol (E2) levels may play an important role. Estrogen promote growth of the ducts by causing proliferation and differentiation of mammary duct epithelium. The connective tissue surrounding the duct is very sensitive to the action of estrogen. Progesterone acts in synergism with estrogen on the distal portion of the ducts and promotes growth of lobuloalveolar structures. However, progesterone also acts as an antagonist to estrogen. It converts the proliferative effect of estrogen on the ductal cell into cellular differentiation.[14] In the year 1996, Erel et. al. found that endogenous E2 level affect the increase in breast density. The women with increase density on theirs mammograms had significantly higher initial E2 levels than those who had not.[11]

Using the multiple logistic regression for data analysis, we found two interesting factors showing significant association. These are age and the use of HRT. We noticed that all of women who used HRT for 10 years or more had high risk mammographic pattern (the DY pattern.) In 1995 Bartow et. al. studied factors that associated with radiographic parenchymal pattern (accordings to Wolfe's classification) and found that advancing age and postmenopausal status

were the strongest predictors of low risk parenchymal pattern. Obesity, defined as a quetelet index (weight (kg)/height $(m)^2$) of > 25 kg/m^2 and large breast size were also significant factors in predicting the mammographic pattern. Parity was not found to be a significant predictor of breast parenchymal pattern.[15]

Our results support the notion that age and usage of HRT are involved in determining the mammographic parenchymal pattern among pre- and postmenopausal women. The negative correlation of age and high risk mammographic pattern is probably due to the fact that the fat content of breast increases with aging which reduces the breast density when compared to young age group and may be explained by the higher level of endogenous E2 in the young. The result confirms previous studies that HRT could increase breast density and consequently increased the prevalence of high risk mammographic pattern. In addition, the increased density may obscure some significant breast lesion that need further investigation. Another possibility is that breast tenderness, linked with HRT exposure, might make adequate compression of the breast difficult and lead to a reduced quality of the mammogram. Therefore, regular mammography is recommended for women during HRT. We consider it important to use HRT regimens that achieve the treatment goal of adequately controlling the endometrium and that affect the density of breast tissue as little as possible. This may involve the use of low-potency progestins or reduction of the dosage, particularly in continuously combined regimens. Effect of such modification of treatment practices, including temporary discontinuation of HRT a few weekly before mammography, need to be studied.

It is interesting that how HRT affect the breast, on mammographic parenchymal pattern and which type of HRT has its most effect. This study can be used as a baseline data for further study since, to the best of our knowledge, there is no published report of descriptive data on Thai women's breast parenchymal pattern.

The limitation of this retrospective study was that some informations were obtained by patient's recall such as age at menarche, age at menopause which might cause information inaccuracy. Moreover, the sample size is relatively small when compared to other studies most of which were multicenters.

From our study, we found high prevalence of high risk mammographic pattern in pre- and postmenopausal women attended at Chulalongkorn hospital. We should aware of this finding because it could obscure the significant lesion that may cause difficulty in detecting any abnormality in screening mammography.

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