

RESEARCH ARTICLE

Mammographic Appearances in Mongolia: Causal Factors for Varying Densities

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Abstract

Objective: Mammographic density (MD) is a significant risk factor for breast cancer and an important determinant for establishing efficiency of any screening program. Currently, the distribution and influential factors of MD is unknown among Mongolian women. This work aims to characterize MD of Mongolian women. **Methods:** The ethical approval was obtained from Research Ethics Board of the University of Sydney (2014/973) and National Ethic Committee from Ministry of Mongolia (2015/04). We recruited 1985 women aged 16-83 from the National Cancer Center in Mongolia for whom MD and age of each woman was known. From this total group, 983 women also had additional available details on height, weight, body mass index (BMI) and area of residency. We investigated the association of each of these variables with breast density, which was assessed by using the Breast Imaging Reporting and Data System (BIRADS) lexicon. Univariate and multivariate regression analyses were conducted to explore the importance of these variables as predictors of MD. **Results:** Category B (33%) was the most common type of MD, whereas 25%, 18% and 24% of women belonged to the category A, C and D respectively. The univariate analysis demonstrated that, younger women had more dense breasts than their older counterparts (OR=6.8). Also, increased MD was significantly ($p<0.05$) associated with decreased weight (OR=4.5), increased height (OR=0.4) and lower BMI (OR=13.2). Urban women had significantly higher MD compared with rural counterparts (OR=2.2). In the multivariate analysis, 75% of variation in MD was explained by age (OR=4.5) and BMI (OR=7.3). **Conclusion:** A high proportion of Mongolian women have very high density breasts and age and body size are key factors determining MD among these women.

Keywords: Breast cancer- mammographic density- Mongolia

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Introduction

Among women in the world, breast cancer remains the most commonly diagnosed cancer. The breast cancer incidence (age standardized rate, ASR) was reported in Mongolia as 6.0 per 100,000 women in 2013 (Breast cancer statistics 2009-2013, NCC, Mongolia). This measure, whilst relatively low compared with other countries, has been rapidly increasing on an annual basis (Troisi et al., 2012) and between 2009 and 2013, the number of new cases of breast cancer more than doubled. In addition, approximately 90% of breast cancer patients in Mongolia are diagnosed at a relatively late stage, resulting in a high mortality rate.

Many risk factors have been reported to be associated with breast cancer in the westernized world and these include family history, lifestyle activity and hormonal factors. However, in recent years, it is increasingly recognized that mammographic density (MD) is a critically important determinant. Previous authors have linked high density with up to 6 times higher risk of

breast cancer resulting in a plethora of research around causal factors of, or associations with MD (McCormack and Silva, 2006; Boyd et al., 2007). Researchers have also linked increased breast density to the aggressiveness of tumors particularly for younger women (Bertrand et al., 2013). Despite all this increasing evidence around density, in Mongolia we know little about MD. It is not known for example what is the distribution of density within Mongolian women, we have no data associated to risk factors and we do not understand the influence of age and body size measures. Without this information, it is difficult to optimize preventative strategies for breast cancer in Mongolia.

It has also been argued that increased MD can hinder the visualization of breast cancer by obscuring underlying abnormalities, which contributes to reduction in the sensitivity of screening mammography and therefore affect optimum imaging protocols (Freer, 2015). Currently, routine screening mammography is not established in Mongolia. The breast screening guidelines in Mongolia have to date not included details on modality

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choice, instead focusing on breast self-assessment and clinical breast examination. These guidelines however are of limited value since only one in three women undergo breast self-assessment and only 3.2% have experienced clinical breast examination as reported in a recent WHO review (WHO, 2013). Whilst mammographic screening reduces mortality by 15% to 32 % in western countries (AIHW, 2014; Pace and Keating, 2014) there is no evidence that systems used elsewhere would be effective in Mongolia. There is urgency therefore, to identify density distributions among Mongolian women so that more sophisticated and relevant screening approach are employed, facilitating early detection and intervention in the disease.

Breast density can be assessed by various qualitative and quantitative methods, involving mostly mammography. To date, there is no standard for density assessment however, the Breast Imaging-Reporting and Data System (BIRADS) is the most common method in clinical practice (Sickles et al., 2013), and the only method in Mongolia used to report breast density. The objectives of the current study are therefore to identify the density distribution among Mongolian women using BIRADS density categories to establish the relationship between density and women's age and body size and to explore differences in MD between urban and rural areas of Mongolia.

Materials and Methods

The ethical approval was obtained from Research Ethics Board of the University of Sydney (2014/973) and National Ethic Committee from Ministry of Mongolia (2015/04).

Sample size

This cross-sectional study was based on digital mammograms from 1985 women aged 16-83, who underwent mostly diagnostic mammography at the National Cancer Center (NCC) in Mongolia between September 2014 and September 2015. We randomly collected all available images for which two standard views were accessible. Otherwise, no selection criteria were applied for data collection.

From the total group, 983 women also had available details on height, weight and body mass index (BMI)

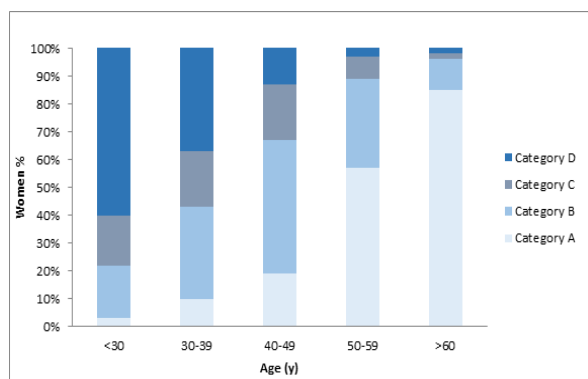


Figure 1. Frequency of Women Allocated to One of the Four Breast Density Grouping According to Age Group (n=1985).

which were obtained from the hospital registry. The area of residency was also recorded for these women and women are allocated to the following grouping: Ulaanbaatar-UB (urban, capital city) and non-UB (rural) groupings.

Breast density by Radiologists

The evaluation of breast density was determined by an experienced breast radiologist and validated with density reading from three breast radiologists who independently examined a random sample of 400 of the total number of cases. Absolute agreement was used as a measure of overall agreement between radiologists and a high inter rater reliability was found between the three radiologists.

Each mammogram was evaluated according to BIRADS density categories A-D (Sickles EA et al., 2013): Category a – almost entirely fatty; Category b- scattered areas of fibroglanduar density; Category c- heterogeneously density; Category d- extremely dense.

Statistical analysis

Logistic regression analysis was used to explore univariate and multivariate associations between dichotomized MD (categories a and b as low vs c and d as high densities) and independent variables age, weight, height, BMI and geographical location. Odds ratio (ORs) and confidence intervals (95% CIs) were estimated. All analyses were performed using SPSS software (version 22.0). A p value of less than 0.05 was considered as significant.

Results

The mean age of the 1985 Mongolian women examined was 40.55 (± 11.8) years with a range of 16-83 years. Whilst category B (33% of women) was the most common type of MD, 25%, 18% and 24% of women belonged to the category A, C and D respectively.

The investigated variables were available for 983 women and table 1 demonstrates the summary characteristics of the study sample on all parameters

Table 1. The Baseline Characteristics of the Study Population (n=983)

Variables	BIRADS ^a density			
	Category A	Category B	Category C	Category D
	Mean \pm SD	Mean \pm SD	Mean \pm SD	Mean \pm SD
Age (years)				
Mean \pm SD	52 \pm 10.5	41.6 \pm 9.0	37.4 \pm 8.8	32 \pm 7.5
Weight (kg)				
Mean \pm SD	71.8 \pm 14.2	66.0 \pm 10.7	62.3 \pm 9.2	56.8 \pm 8.4
Height (m)				
Mean \pm SD	1.57 \pm 0.06	1.59 \pm 0.06	1.61 \pm 0.07	1.6 \pm 0.05
BMI ^b (kg/m ²)				
Mean \pm SD	35.9 \pm 6.4	31.3 \pm 4.9	28.9 \pm 4.4	26.3 \pm 3.9
Area of residency (N%)				
Urban	197 (82)	289 (90)	146 (92)	250 (94)
Rural	44 (18)	30 (10)	12 (8)	15 (6)

^a, BIRADS: Breast Imaging and reporting system, 2013; ^b, BMI: Body mass index

Table 2. The Association between MD and the Factors

Variables	Univariate OR 95%CI	Multivariate OR 95%CI
Age (n=1985)		
<40	6.8 (5.5-8.3)*	
>40	1	
Age (n=983)		
<40	7.3 (5.4-9.8)*	4.5 (3.4-6.2)*
>40	1	1
Weight (kg)		
<64	4.5 (3.4-6.0)*	
>64	1	
Height (m)		
<1.6	0.43 (0.3-0.6)*	
>1.6	1	
BMI ^a (kg/m ²)		
Normal	13.2 (8.6-20.0)*	7.3 (4.6-11.5)*
Overweight	5.1 (3.8-7.0)*	3.6 (2.6-5.0)*
Obese	1	1
Area of residency		
Urban (UB)	2.2 (1.4-3.5)*	1.5 (0.9-2.5) ^a
Rural (non-UB)	1	

^a, Body mass index; *p<0.05; ^ap, 0.12

examined.

Univariate analysis

Age

The overall age distribution of MD was examined for 1985 women. Figure 1 demonstrates the age distribution of four categories of BIRADS according to five age

Table 3. Age and BMI Distribution by Area of Residency

Variables	Area of residency	
	Urban N (%)	Rural N (%)
Age (years)	<40	484 (55)
	>40	37 (37)
Mean ± SD	398 (45)	64 (63)
BMI ^a (kg/m ²)	Normal	40.0 (11.4)
	Overweight	45.0 (12.5)
	Obese	156 (18)
Mean ± SD	327 (37)	23 (23)
	399 (45)	65 (64)
	30.3 (6.0)	32.3 (6.0)

^a, Body mass index

groups. The frequency of extremely dense breast (category D) was the largest (60%) among the youngest age group, consistently declining as age increases and reaching its lowest point (2%) among women in the oldest age groups. The two oldest age groups contained the highest number of women with fatty breasts (Figure 1).

The association between MD and age was explored for all 1985 women along with a separate estimation for 983 women. Since only a small number of women belonged to the high density categories among older ages, women were then grouped into two groups (below and above 40 years old) to identify the relationship between age and dichotomized MD. Table 2 shows the univariate and multivariate associations between MD and all the factors examined. Age was shown to be an important predictor for MD; a significantly increased risk of having higher dense breasts noted for women aged below 40 years old, compared with women aged above 40 years old.

Table 4. Distribution and Association of MD and Investigated Factors

Variables	Age < 40 (N%)			Age > 40 (N%)		
	Low density	High density	OR (95% CI)	Low density	High density	OR (95% CI)
Weight (kg)						
>64	95 (60)	63 (40)	1	234 (86)	39 (14)	1
<64	93 (26)	270 (74)	4.3	137 (73)	51 (27)	2.2
Height (m)						
>1.6	92 (33)	185 (97)	1	127 (75)	43 (25)	1
<1.6	96 (40)	148 (60)	0.7	245 (84)	47 (16)	0.5
			(0.5, 1.0)			(0.3, 0.9)*
BMI ^a (kg/m ²)						
Obese	88 (65)	48 (35)	1	265 (88)	35 (12)	1
Overweight	64 (30)	147 (70)	4.2	88 (72)	35 (28)	3
			(2.6, 6.6)*			(1.7, 5.1)*
Normal	36 (21)	138 (79)	7	16 (47)	18 (53)	8.5
			(4.2, 11.6)*			(3.9, 18.2)*
Area of residency						
Rural (non-UB)	18 (47)	20 (53)	1	57 (88)	8 (12)	1
Urban (UB)	170 (35)	313 (65)	0.6	315 (79)	82 (21)	0.5
			(0.3, 1.2) ¹			(0.2, 1.1) ²

^a Body mass index; *p<0.05; ¹ p, 0.14; ² p, 0.12

Weight, height and BMI

Body size data were available for 983 women. The mean weight was 57.0 kg (± 8.4) and 72.0 kg (± 14.2) for extremely dense and almost fatty categories respectively (Table 1). The mean height was 1.59 m (± 0.06) and was similar across four density groupings. Majority of women (83%) were classified in the overweight and obese groupings whereas 17% of women grouped in normal BMI category.

Associations were found between MD and body size measurements (Table 2). Increased risk of having high MD was significantly ($p < 0.05$) associated with decreased weight (OR=4.5, 95% CI: 3.4, 6.0), increased height (OR=0.43, 95% CI: 0.3, 0.6) and decreased BMI (OR=13.2, 95% CI: 8.6, 20.0).

Area of residency

Table 3 demonstrates the age and BMI distribution by area of residency. In total 882 and 101 women were allocated to UB and non-UB groupings respectively with UB residents having significantly (OR=2.2, 95% CI: 1.4, 3.5 $p < 0.05$) higher density breasts than non-UB residents, however, the association was not significant after controlling for age and BMI (Table 2). Since the Non-UB women came from across the country, these were then further classified by geographical locations, but no statistical differences were noted between north vs south ($p = 0.56$) nor east vs west ($p = 0.92$) regions of Mongolia.

Distribution and determinant of MD within women of different age categories

To identify the differences in determinant factors of MD, women over ($n = 462$) and under 40 ($n = 522$) years old were compared (Table 4). For the young women, the magnitude of odd ratios for some factors were different for the two groups of women. This is summarized in table 4.

Multivariate analysis

Multivariate logistic regression model was built to explore the relative importance of the dichotomous variables of age, area of residency and BMI as predictors of MD, dichotomized into high and low density.

In the full model, 76% of variation in MD was explained by the measured risk factors. After entering age, BMI and area of residency into a regression model, age (OR=4.5, 95% CI: 3.4-6.2), BMI (OR=7.3, 95% CI: 4.6-11.5) were the significant predictors for MD whilst area of residency did not contribute to the model (Table 2).

Discussion

The current study was carried out to explore variations of mammographic density (MD) among Mongolian women using the fifth edition of BI-RADS lexicon. The results demonstrated interesting patterns of MD and statistically significant relationships between MD and age, body size and area of residency.

Although density values were almost equally distributed between low and high density groupings, we expected to observe predominantly low density mammographic appearance since the majority of women

in our study have much greater BMI compared with those described by the previous studies (Dai et al., 2014). However, a large proportion (24%) of women in our study was classified as having an extremely dense pattern (BI-RADS category D) compared with 7.4% and 8.6% in USA and China respectively (Dai et al., 2014; Sprague et al., 2014) which could be linked to our age profile (see below). In general, Asian women have consistently been reported to have higher density than other ethnic populations (del Carmen et al., 2007; Mariapun et al., 2015) yet, the amount of women within the highest density category was unusually higher than that described for these other countries. Conversely, the overall proportion of high density (BI-RADS categories C and D) within the age groups was lower than those reported in other ethnic populations (Kim et al., 2000; Sprague et al., 2014), suggesting a paucity of category C women. In particular, high density (C and D) was described for 31% of women in our study between the ages of 40 to 49 years old whilst this value was approximately 74% in USA and 80% in Korea for the same age category (Checka et al., 2012; Youn et al., 2016). The variation may be due to differences in the studies samples however the influence of geographical location cannot be ruled out.

We examined age and body size, as two main determinants of MD. In agreement with other studies (McCormack and Silva, 2006; Checka et al., 2012), an overall inverse association between age and MD was identified, however age-density relationship was very clear in our study with under 40 year olds having 6 times higher density than over 40 year olds. It should be acknowledged that the mean age for women in our study is younger than that generally examined elsewhere in previous Western and Asian studies (Ellison-Loschmann et al., 2013; Youn et al., 2016). For example, the magnitude of our finding was greater than the odds ratio of 2 described in a recent Japanese study (Kawahara et al., 2013), however this latter comparison was for women under compared with over 45 year olds. Nonetheless, other causal factors for this large age-dependent change need to be considered. Firstly, the statistical method we employed could be a factor: unlike some of the previous work in our study, age was treated as a categorical variable which tends to provide systematically higher odds ratio (Lovasi et al., 2012) and although, odd ratios do not accurately characterize individuals' risk (Pepe et al., 2004), as a method to identify the population risks, our approach is valid and has been used in numerous studies elsewhere. Secondly, this finding may actually be unique for Mongolian women. To our knowledge, this preliminary work is the first study regarding breast density in a large sample of Mongolian women, however, important factors of breast density peculiar to Mongolia such as lifestyle and reproductive factors (which were not available to us) need to be explored if we are to better understand causal agents for specific temporal and spatial density patterns and distributions.

A greater weight and BMI were associated with lower MDs in our study which aligns well with the existing evidence across many populations (Boyd et al., 2006; Sung et al., 2010). However, consistent with some but

not all previous studies (Sellers et al., 2007; Boyd et al., 2009; Dorgan et al., 2012), height showed a weak but significant association with MD. Whilst less is known regarding the relationship between this latter measure and breast density, some authors have investigated possible associations and a direct relationship between the height in childhood and young adulthood and density has been previously shown (Dorgan et al., 2012; Andersen et al., 2014). Specifically, two studies (Boyd et al., 2009; Dorgan et al., 2012) focusing on young women (15 to 30 years old), demonstrated a significant height density association which aligns reasonably well to the current paper particularly since the majority of women in our study were below 40 years old. The physiological mechanism underlying this association is unclear, however factors associated with breast development in early life such as increased growth hormone may mediate this association (Dorgan et al., 2012). The interaction between height of older adults and MD has not been previously investigated. We also compared women over and below 40 years old to identify any differences in determinant factors of MD and some subtle differences were noted, particularly related to patient weight.

Geographical location appears to be an important indicator of variation in breast density. The present study provides evidence that women living in urban areas (Ulaanbaatar-UB) have higher MD than rural (non UB) women, although no differences was found within rural parts of Mongolia. This aligns with several studies which found positive associations between urbanization and breast density (Viel and Rymzhanova, 2012; Emaus et al., 2014; van der Waal et al., 2015), the authors of which suggested that exposure to increased socio-economic status (SES) was at least in part responsible. Similarly, our data suggest that SES is an important causal agent since UB women tend to be more educated and more willing to adopt westernized culture than their rural counterparts (Dickson, 2012). In addition, as shown elsewhere, reproductive factors are probably contributing to this location discrepancy, since urban mothers are two times less likely to breastfeed for longer than 6 months compared to rural mothers in Mongolia (Dickson, 2012). However, the location density association shown in the univariate analysis was not significant after controlling for age and body size. We should acknowledge that our study participants consisted mainly of urban women (90%) which may have impacted on the results.

The main limitation of this study was the unavailability of information on important determinants of MD. For example, we were unable to collect comprehensive data on reproductive and lifestyle factors, all of which would have provided more thorough understanding of breast density risk factors. It could also be argued that BIRADS density assessment is an imperfect method since high rates of inter radiologist variability have been previously reported, however, this measure is the most widely used and accepted method in clinical practices and the only method to assess density used in Mongolia. Furthermore, we successfully validated our BIRADS scores in a subset of 400 women with three breast radiologists demonstrating high inter-rater reliability. On a positive note, this study has

for the first time systematically examined mammographic density patterns among Mongolian women and since our study population was gathered from the National Cancer Center, the only cancer center in Mongolia, we can be fairly sure that most types of Mongolian women have been reasonably represented.

In conclusion, this work has shown that age, body size and geographical location are key determinants of breast density among Mongolian women. The data from the work should be valuable to those health strategists exploring effective screening programs, however the link between breast density and breast cancer risk amongst this population of women needs first to be established and quantified.

Conflict of interest

The authors declare no potential conflicts of interest.

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