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Association of mammographic breast density with breast cancer and its common risk factors in Afghan women referring to French Medical Institute for Mothers and Children: A case-control study.

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Abstract

Aim: To identify the association of mammographic breast density with breast cancer and its common risk factors in the context of Afghanistan.

Methods: A case-control study enrolled Afghan women, age 35-years and above who were referred to the Radiology Department of French Medical Institute for Mothers and Children. Of all participants (n=270), 71 had pathology proven breast malignancy labelled as cases and rest with normal/abnormal Mammograms but negative pathology report for malignancy were labelled as controls.

Results: Mammographic Breast Density (MBD) type B, C and D had greater likelihood to be diagnosed with breast cancer compared to MBD type A and this difference was statistically significant, P=0.025. The odds ratio of 10.057 suggests that participants with MBD type B, C and D were 10.057 times more likely to have a breast cancer diagnosis compared to MBD type A with 95% CI of (1.337-75.660). The association between MBD and age, parity, breast-feeding history, breast feeding number, menopausal status, passive smoking, and Body Mass Index (BMI) were statistically significant with the p value less than 0.05, whereas no statistically significant association was found between MBD and family history of breast cancer, active smoking, physical activity, Oral Contraceptive Pill (OCP) and Hormone Replacement Therapy (HRT) usage.

Conclusion: Afghan women with higher types of MBD (B, C and D) are 10 times more likely to be diagnosed with breast cancer compared to Afghan women with type A MBD. Age, BMI, parity, breast feeding history and number, menopausal status and passive smoking are associated with MBD.

Keywords: Breast cancer, Mammographic breast density, Risk factor.

Abbreviations: CC: Cranio-Caudal; CI: Confidence Interval; MLO: Medio Lateral Oblique; MoPH: Ministry of Public Health; BI-RADS: Breast Imaging-Reporting and Data System; MBD: Mammographic Breast Density; BMI: Body Mass Index; OCP: Oral Contraceptive Pills; OR: Odds Ratio; HRT: Hormonal Replacement Therapy; UK: United Kingdom; ANOVA: Analysis of Variance; FMIC: French Medical Institute for Mothers and Children; FNAC: Fine Needle Aspiration Cytology.

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Introduction

In 2020, there were 2.3 million women diagnosed with breast cancer and 685 000 deaths Globally [1]. In Asian countries breast cancer mortality has increased over time [2]. The United Nations allocates these countries into different sub-regions that include Eastern, Southern, South-Eastern, Central, Western, and South-Central Asia. In Southern Asia, there are nine countries: Afghanistan, Bangladesh, Bhutan, India, Iran (the Islamic Republic of), Maldives, Nepal, Pakistan, and Sri Lanka [2,3]. Nepal is in the South-central Asia according to UN Regions in Global Cancer Observatory Survey (GLOBOCAN) [3].

In Afghanistan in March 2020 a study was conducted in Jumhoryat hospital which is the only public hospital for diagnosis and treatment of cancer. This study revealed that among women, the highest common cancers were breast cancer (45.8%) followed by esophagus (12.5%), colorectal (4.8%), sarcoma (4.7%), Non-Hodgkin Lymphoma (4.7%), ovary (3.8%), both stomach and liver (2.6%) and cervix uteri (1.9%) [4]. Another study aimed to find out age distribution and common breast pathology through Fine Needle Aspiration Cytology (FNAC) in Afghan women was conducted in the Pathology Department of French Medical Institute for Mothers and Children (FMIC). It concluded that the most prevalent diagnosis among samples was cancer, which constituted 24% of all diagnosed cases [5].

Screening methods such as Mammography, Breast Ultrasound and clinical breast examination play significant role in early detection and management of breast cancer [6]. Radiographic appearance of a mammogram is determined by the relative amount of fat (which is radiolucent) and epithelial/fibrous tissue (which is radiodense). Mammographic density is a measure of the radiodense area on the mammogram [7]. The degree of density is a consequence of the hormonal, environmental and underlying genetics regulating the epithelial proliferation [8]. Numerous density assessment methods have been proposed and developed over the past four decades that measure various aspects of fibro-glandular tissue [9]. These methods can broadly be classified by: (a) Their mode of assessment (visual, semi-automated, fully automated), (b) whether they are measured area-based or volumetric parameters and (c) whether they are qualitative or quantitative in nature [9]. A commonly accepted and easy way of determining Mammographic Breast Density (MBD) is by BI-RADS (Breast Imaging-Reporting and Data System) which is a risk assessment and quality assurance tool developed by American College of Radiology. This tool provides a widely accepted lexicon and reporting schema for imaging of the breast. Regardless of the method used to classify breast density, it is an independent predictor of breast cancer risk, increasing with increasing density [7].

Materials and Methods

Case-control study was designed to find out the association of MBD with breast cancer and its common risk factors in the context of Afghanistan where lifestyle of people is different from those living in American and European countries. This study was conducted from November 1, 2020, to October 30, 2021. Participants were Afghan women having mammograms done at FMIC using a full-field digital Mammography machine. Histopathologic work up of participants were done either at FMIC or any well-known pathology lab outside FMIC. During the study period, 520 women had their Mammographic examination done at FMIC and each of them were approached to participate in this study. Among these, 52 women aged under 35 years, therefore they were not included in the study. 56 women did not consent to undergoing contralateral breast imaging (CC view) for determination of MBD in case dense lesion was detected in one breast. 51 women did not respond to the call for participation in the research, 35 participants after their mammographic examination did not get their recommended histopathological workup done. The primary investigator due to being off duty or on leaves could not connect with 38 women while they had their Mammographic examination done. 12 women were not familiar with the national spoken languages of Afghanistan and English hence were unable to answer the questionnaire, 6 women were foreigners and were excluded from participation in the study. Thus, from the remaining 270 women, 71 had pathologically proven malignancy, classified as cases and remaining 199 had normal or benign breast pathologies classified as controls.

Case

Afghan, non-pregnant women, 35 years or above who were referred to Radiology Department of FMIC for Mammography whose breasts were categorized as BI-RAD 4 and 5, proved as malignant lesion through histopathologic workup. In addition, women whose breasts were classified as BI-RAD 6 were also eligible in cases as they were known cases of breast malignancy.

Control

Afghan women 35 years or above whose breasts were categorized as BI-RAD 1, 2, 3 or 4 (normal, benign, most likely benign finding or probably benign with negative histopathology report for breast malignancy) were included in the control group.

Participants' details were included in the data collection. Dependent variable was breast cancer in women. The independent variables were MBD, age, Body Mass Index (BMI), marital status, socio-economic status, breast feeding history, parity, menopausal state, Hormone Replacement Therapy (HRT), Oral Contraceptive Pill (OCP), family history of breast cancer, and smoking. MBD of participants were classified using 5th Edition of BI-RADs. Entirely fatty breasts were classified as type A, breasts with scattered areas of fibro-glandular density were categorized as type B, heterogeneously dense breasts were classified as type C and extremely dense breasts were classified as type D.

Results

Of total number of participants in the study (271), 71 had proven breast malignancy labelled as cases and remaining 199 had normal, benign or suspicious mammographic findings excluding malignancy in their pathological reports hence assigned in control group. In case group, 1 had MBD type A, 30 had MBD type B, 36 had MBD type C and 4 had MBD type D. In control group 25 had MBD type A, 94 had MBD type B, 59 had MBD type C and 21 had MBD type D as seen in Table 1 and Figure 1.

Mean age of participants in case group was 49.25 and in

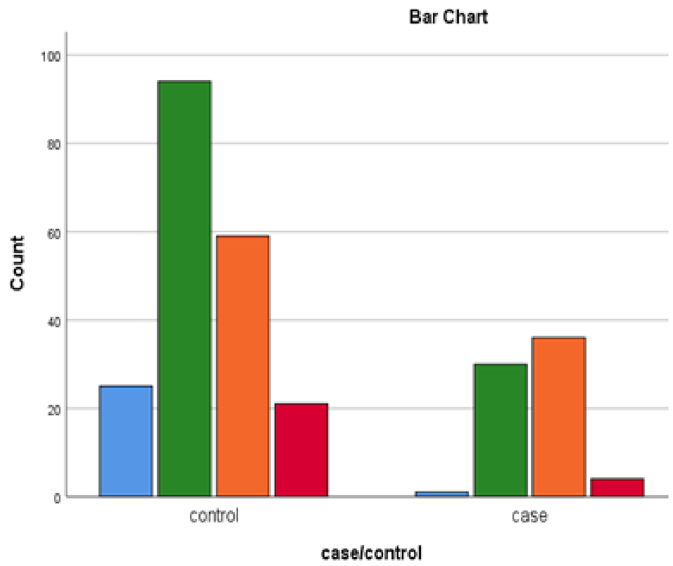

Figure 1. *Mammographic Breast Density (MBD) categories in case and control.* ***Note:*** *( ) The breast almost entirely fatty; ( ) Scattered areas of fibro-glandular tissue; ( ) Heterogeneously dense; ( ) Extremely dense.*

Table 1. *Mammographic breast density categories in case verses control.*

Case/Control-Mammographic Breast Density Crosstabulation						
Count						
		Mammographic Breast Density				Total
		The breast almost entirely fatty (a)	Scattered areas of fibro-glandular tissue (b)	Heterogeneously dense (c)	extremely dense (d)	
case/control	control	25	94	59	21	199
	case	1	30	36	4	71
Total		26	124	95	25	270

control group it was 43.22. This finding was statistically significant, P-value=0.00, 95% CI (3.9-8.1).

The result of chi-square test suggests that significant association exists between MBD and breast cancer, x2(3, N=270)=15.005a, P=0.002. Logistic regression analysis used to find out strength of association between MBD and breast cancer suggests that women with MBD type B, C and D cumulatively have greater likelihood to be diagnosed with breast cancer compared to MBD type A, P-value=0.025. The odds ratio of 10.057 suggests that participants with MBD type B, C, and D were 10.057 times more likely to have breast cancer diagnosis compared to MBD type A with 95% CI of (1.337-75.660) as seen in Table 2. According to Table 3, multinomial regression analysis shows that MBD type B had 7.979 times more odds of being diagnosed with breast cancer compared to MBD type A, P=0.046, 95% CI (1.037-61.398). MBD type C had 15.254 times greater odds of being diagnosed with breast cancer relative to MBD type A, P=0.009, 95% CI (1.981-117.468). The odds ratio of breast cancer in MBD type D over MBD type A was calculated as 4.768 with P=0.177, 95% CI (0.494-45.945) which was not statistically significant.

The association between MBD and breast feeding history, menopausal status, passive smoking, and BMI categories were determined using chi-square test, showing statistically significant association with the P value less than 0.05. There was no statistically significant association found out between MBD and family history of breast cancer, active smoking, physical activity, OCP and HRT usage, using chi-square test as seen in Table 4. The ANOVA test results as shown in Table 5 suggest that mean of age of participants significantly differ across different levels of MBD which was statistically significant (F=9.718, P=0.00). Mean of parity also differed across different types of MBD with statistically significant values (F=4.859, P=0.03). Moreover, mean of BMI differed in each level of MBD with F=7.887, P=0.00, which is also statistically significant. There was also found to be a negative linear association between MBD and BMI. Finally, mean of breast-feeding number also differed in different types of MBD, showing statistically significant P value, F=2.772, P=0.042.

Table 2. *Logistic regression analysis result.*

Variables in the Equation									
		B	S.E.	Wald	df	Sig.	Exp(B)	95% C.I.for EXP(B)	
								Lower	Upper
Step 1[a]	mammographic breast density 1(1)	2.308	1.03	5.027	1	0.025	10.057	1.337	75.66
	Constant	-3.219	1.02	9.963	1	0.002	0.04		
Note: [a]Variable(s) entered on step 1: Mammographic breast density 1.									

Table 3. *Multinominal regression analysis results.*

Parameter Estimates									
Mammographic Breast Density[a]		B	Std. Error	Wald	df	Sig.	Exp(B)	95% Confidence Interval for Exp(B)	
								Lower Bound	Upper Bound
Scattered areas of fibro-glandular tissue	Intercept	1.324	0.225	34.64	1	0			
	case/control	2.077	1.041	3.979	1	0.046	7.979	1.037	61.398
Heterogeneously dense	Intercept	0.859	0.239	12.947	1	0			
	case/control	2.725	1.042	6.845	1	0.009	15.254	1.981	117.468
extremely dense	Intercept	-0.174	0.296	0.347	1	0.556			
	case/control	1.561	1.157	1.821	1	0.177	4.762	0.494	45.945
Note: [a]The reference category is: The breast almost entirely fatty.									

Table 4. *Chi-square test results run between MBD and categorical variables.*

Cat Variables	Pearson Chi-Square Value	Degree of Freedom	Asymptomatic Significance (2sided)
Family history of BC	0.437	3	0.932
Menopausal status	15.472	3	0.001
Breast feeding history	10.238	3	0.017
Active smoking	1.937	3	0.586
Passive smoking	8.084	3	0.044
Physical activity	3.73	3	1
0.292	1	1	1
Economic status	8.565	6	0.2
Body mass index categories	25.791	9	0.002
HRT	8.345	6	0.214
OCP usage	8.716	6	0.19
Note: Cat: Categorical; BC: Breast Cancer; HRT: Hormonal replacement Therapy; OCP: Oral Contraceptive Pills			

Table 5. *ANOVA run between numerical variables and different classes of MBD.*

		Sum of Squares	df	Mean Square	F	Sig.
Age of subjects in years	Between groups	1795.789	3	598.596	9.718	0
	Within groups	16384.196	266	61.595		
	Total	18179.985	269			
Parity	Between groups	101.401	3	33.8	4.859	0.003
	Within groups	1850.362	266	6.956		
	Total	1951.763	269			
Body mass index	Between groups	579.636	3	193.212	7.887	0
	Within groups	6516.731	266	24.499		
	Total	7096.367	269			
Breast feeding number	Between groups	60.379	3	20.126	2.772	0.042
	Within groups	1931.384	266	7.261		
	Total	1991.763	269			

Discussion

This study contributes to the growing literature that MBD is an important risk factor for breast cancer [10-14]. Our results indicate strong association between breast cancer and MBD which was visually assessed using BI-RADS fifth edition. This study suggests that women with greater breast densities (B, C, D) are 10 times more likely to be diagnosed with breast cancer compared to women with breast MDB type A. Breast density as a risk factor is because it refers to the amount of epithelial and stromal elements of the breast, and breast cancer arises in epithelial cells hence greater amount of epithelial tissue in the breast indicates a greater chance of malignancy [15,16]. MBD type B had 7.979 times more odds of being diagnosed with breast cancer compared to MBD type A, P=0.046, 95% CI (1.037-61.398). MBD type C had 15.254 times greater odds of being diagnosed as breast cancer relative to MBD type A, P=0.009, 95% CI (1.981-117.468). The odds ratio of breast cancer in MBD type D over MBD type A was calculated as 4.768 with P=0.177, 95% CI (0.494-45.945) which was not statistically significant. A case-control study, conducted by Vachon *et al*., concluded that breast density is strongly associated with breast cancer risk [15]. In the above mentioned study increasing number of breast cancer was associated with increasing quartiles of percentage density and dense area, irrespective of the side of cancer (ipsilateral or contralateral) or view (CC or MLO). For the CC contralateral side, the estimated ORs were 3.1 [95% confidence interval (95% CI), 1.7-5.8], 4.8 (95% CI, 2.5-9.1), and 11.3 (95% CI, 5.0-25.9) for women with 10-24%, 25-49%, and 50%+ density, respectively, compared with women with <10% [1.00 (ref)] [15].

The study did not find statistically significant association between MBD type D and breast cancer keeping in view the fact that MBD type D is the highest degree of density. This could be justified by the masking effect of extreme density on underlying cancer [16,17]. It is a well-established hypothesis that mammographic sensitivity decreases with increasing density as a function of the superimposition of overlapping radiopaque dense breast tissue on an underlying cancer [18].

This study failed to find out significant association between MBD and family history of breast cancer, P=0.93, opposing many other studies that found a significant association between MBD and family history of breast cancer in first degree relatives. A study conducted by Ziv *et al*., aiming to explore the association between mammographic breast density and a history of breast cancer among first-degree relatives found out interesting statistics [10]. This study included women who had mammography between January 1997 and July 2001 done in the National Institutes of Health-funded San Francisco Mammography Registry. During study period 6146 women met the inclusion criteria of the study and demographic information and a breast health history were obtained. This study concluded that compared to women with BI-RADS 1 readings, women with higher breast densities were more likely to have first-degree relatives with breast cancer (BI-RADS 2, Odds Ratio [OR]=1.37, 95% Confidence Interval [CI]=0.96 to 1.89; BI-RADS 3, OR=1.70, 95% CI=1.19 to 2.40; BI-RADS 4, OR=1.70, 95% CI=1.05 to 2.71). Thus, the genetic factors that determine breast density may also determine breast cancer risk [10]. The reason this study couldn't find association between MBD and breast cancer risk could be due to lower number of cases (71). It may also be a result of lack of awareness of Afghans regarding the actual diagnosis of cancer in women as there is only one public cancer diagnosis and treatment center in Afghanistan and not all patients with breast cancer end up diagnosed accurately before they pass away. Social dilemma and embarrassment of people regarding sharing past medical or family history especially malignancy may also hinder gathering accurate data and subsequent analysis.

Mean age of participants in this study differed across different levels of MBD which was statistically significant (F=9.718, P=0.00), suggesting an inverse relationship between MBD and age. Premenopausal women are expected to have dense breasts compared to postmenopausal women due to postmenopausal alteration of glandular breast tissue. However, the overall decrease in breast density with age and clear increase in breast cancer incidence with age seems contradictory. A retrospective descriptive study on women undergoing screening mammography performed at the New York University (NYU) Langone Medical Center's Breast Imaging Center Checka *et al*., [19] concluded that although there is an inverse linear relationship between age and mammographic breast density, a meaningful population of outliers at both extremes of age exist with reference to the incidence of heterogeneously dense or extremely dense tissue in older women and entirely fatty breasts in younger populations [19].

Statistically significant association was found out between MBD and BMI P=0.002. Accordingly, negative linear association between MBD and BMI was found out in which women with dense breasts were more likely to have lower BMI compared to women with entirely fatty breasts. This can be justified by different literature findings supporting an inverse relationship between MBD and BMI. However, considering the inverse association between BMI and MBD and the positive association between MBD and breast cancer risk, the positive association between BMI and breast cancer risk remains unexplained. A study conducted by Tran *et al*., aimed to explore association of the interaction of mammographic breast density and BMI with breast cancer risks among premenopausal and postmenopausal women [20]. The study found out an association between BMI and the risk of breast cancer only in the postmenopausal women in all breast density categories. The study also concluded that elevated breast density and obesity are independently associated with an increased risk of breast cancer and interact synergistically to augment breast cancer risk for both premenopausal and postmenopausal women [20].

Passive smoking was found to affect MBD, P=0.04. Cigarrete smoke has multiple carcinogenic substances that may also alter breast tissue. Several studies have been conducted to investigate the dominant effect of cigarrete smoking on MBD. A cross sectional study by Pepłońska *et al*., [21] found out that former smokers had a significantly lower volumetric mammographic density compared to the non-smokers in the crude analysis (P=0.022). The analyses adjusted for important confounders revealed an inverse statistically significant association between the number of pack-years and volumetric mammographic density among the current smokers (P=0.048).

According to our study, reproductive factors related to childbearing (parity and breast feeding numbers) were statistically significant with MBD P=0.00 and P=0.042, however both did not show ascending or descending pattern of association and further studies focusing on the topic is recommended. While several studies have been conducted focusing in relation of childbearing on MBD and its interaction with breast cancer risk factors, concluding younger age at first child's birth, multiparity and breast feeding as favorable breast density patterns with subsequent breast cancer risk reduction [22,23], this might not be the case with Afghan women as majority included in our study were married, having at least 4 children.

Contradictory to the growing literature HRT usage had no statistically significant association with MBD, (P=0.19). A case control study conducted by Vachon *et al*., found out significant positive association between MBD and HRT [24]. Unadjusted for other risk factors, women who experienced a mammographic increase in density with HRT had 2.3 greater odds of having taken estrogen-progestin combined therapy and 1.6 greater odds of having taken progestin alone, compared with controls [24]. The reason why we could not find association between HRT and MBD might be the fact that majority of participants in our study had no information regarding HRT and as almost all of them were old age (postmenopausal) using different types of medications for comorbidities, that were unable to remember exactly and minority who knew about the usage of HRT had no idea regarding its type. Chi square test run to find out the association between OCP and MDB shows no significant P value, (P=0.21). A study by Yaghjyan *et al*., explored the association of MBD with OCP in premenopausal women [25]. According to this study total duration of OCP use, time since last use, age at first use, and age at last use were not associated with percent density, absolute dense and non-dense areas in participant's mammogram. This finding is supporting our finding but, in our study we could not obtain information regarding their OCP status (former vas current), age at first or last use and duration of usage.

Conclusion

Afghan women with higher types of MBD (B, C and D) are 10 times more likely to be diagnosed with breast cancer compared to Afghan women with type A MBD. No increased likelihood of breast cancer was found out in women with MBD type D, despite being the highest degree of density. This may be due to masking effect of density on underlying breast lesions and hiding actual pathology. Among common risk factors of breast cancer, age, menopausal status, passive smoking, parity, breast feeding history, breast feeding number and BMI were found to be associated with MBD in Afghan women.

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Competing Interests

The authors have no relevant financial or non-financial interests to disclose.

Data Availability

The datasets generated analyzed during the current study are not publicly available due to [this was first author's thesis data and not in public domain] but are available from the corresponding author on reasonable request.

Ethics Approval

This study was performed in line with the principles of the Declaration of Helsinki. Approval was granted by the Ethics Committee of at FMIC (November 17, 2020/ref.# 94-FMIC-ER-20.) The Ministry of Public Health (MoPH), Afghanistan has also approved the study.

Consent to Participate

Informed consent was obtained from all individual participants included in the study.

Consent to Publish

The authors affirm that human research participants provided informed consent for publication of the findings of this research.

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