Original Article

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Relationship Between Proliferative Breast Lesions and Breast Cancer Risk Factors

Osman Toktaş[1], Sadi Elasan[2], Ümit Haluk İliklerden[1], Remzi Erten[3], Ali Rıza Karayil[1], Abdulselam Özdemir[1], Fırat Aslan[1], Serhat Binici[1], İbrahim Özalp[1], Enes Şentürk[1]

[1]Department of General Surgery, Van Yüzüncü Yıl University Faculty of Medicine, Van, Turkey
[2]Department of Biostatistics, Van Yüzüncü Yıl University Faculty of Medicine, Van, Turkey
[3]Department of Pathology, Van Yüzüncü Yıl University Faculty of Medicine, Van, Turkey

ABSTRACT

Objective: The prognosis of breast cancer (BC) is determined directly based on the stage of disease at the time of diagnosis. Proliferative breast lesions (PBLs) are an important risk factor for BC development. The risk of developing BC varies according to the presence of extent of proliferation in the breast lesions. We aimed to investigate the effect of BC risk factors on the PBLs in this study.

Materials and Methods: Patients who visited the surgical clinic of the university during the past 6 years who presented with PBLs with or without atypia by fine/core needle aspiration biopsy were included in this study. The relationship between PBLs and BC risk factors such as the age, mass size, Body Mass index (BMI), smoking, sports activity, BC family history, the use of hormone replacement therapy, number of pregnancies, and the duration of breastfeeding were compared.

Results: A total of 74 (96.1%) of all patients were women and three were men. The median age of the patients was 38 (range: 19–74) years; the cut-off value of age was 35.5 years. The mean age of patients with PBL-with atypia (PBL-WA) was higher (p=0.005) in the malignant group based on the final pathology and radiological imaging features (for both, p<0.001). The mean size of the mass was large at 2.53±1.33 (1–6) cm; and the cut-off value of the tumor size was 2.5 cm. The mean size was greater in the PBL-WA patients (p=0.171) in the malignant group based on the final pathology and radiological characteristic (respectively, p=0.004 and p=0.016). The mean BMI was 26.8±4.4 kg/m^2 (18.8–35.1) and the cut-off value was 25.4 kg/m^2. BMI was greater in the PBL-WA group and in the malignant group based on the final pathology (respectively, p=0.002 and p=0.001). Smoking was positive in 66.2% (n=51) of the patients, and it was high in the PBL-WA patients (p=0.001). The percentage of patients with no sports activity was 63.6% (n=49), while it was 20.8% (n=16) for those with once a week sports activity and 15.6% (n=12) for those with twice a week activity. There was family history of BC in 16.9% (n=13) of all patients. The number of positive cases of family history of BC was greater in the malignant group (p=0.001). Hormone replacement therapy was recorded in 11.7% (n=9) of the patients. The mean numbers of pregnancies (2.1±2.4) and breastfeeding duration (32.5±37.4 months) were low in the benign groups due to the relatively lower average age of the patients.

Conclusion: Based on our analysis, age is an extremely important aspect for assessing PBLs. The age of the patient was statistically significantly greater in the patients with malignant lesions in all groups. The factors lesion size, BMI, smoking habit, and BC family history were also more frequent in the malignant groups. The rate of sports activity was lower in the malignant groups. Thus, it is necessary to evaluate patients individually when evaluating PBLs. It is recommended to evaluate PBLs together with BC risk factors for the better understanding.

Keywords: Breast cancer, benign breast disease, proliferative breast lesion with atypia or without atypia

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Introduction

Although the relationship between proliferative breast lesions (PBLs) and breast cancer (BC) has been discussed, PBLs are known as an important risk group in BC development. The risk of BC increases according to the type of benign breast lesions. While there is no risk of BC in non-PBLs, this risk doubles on an average for PBL-without atypia (PBL-WOA) patients and increases by 4–6 times in female PBL-with atypia (PBL-WA) patients. Although several studies have been performed on the classification of PBLs, there is only a limited number of studies that have investigated the relationship between PBLs and BC risk factors. Nevertheless, it remains unclear as to which lesions should be completely resected and which should be followed up (1-4). In this study, we aimed to investigate the relationship between the final pathology outcomes of PBLs and other risk factors of BC.

Corresponding Author:
Osman Toktaş; osmantoktas@windowslive.com

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Materials and Methods

Patients who visited the surgical clinic of the university during the past 6 years and who with presented PBLs with or without atypia by fine/core needle aspiration biopsy were included in this study. Patients aged <18 years, whose file information could not be reached, and those without follow-up information were excluded from the study. Fibrocystic disease, fibroadenoma, normal breast tissue, and inflammation were classified as benign, and all cancer types were classified as malignant. We assessed the relationship between PBLs and BC risk factors such as the age, mass size, Body Mass Index (BMI), smoking habit, sports activity, BC family history, use of hormone replacement therapy, the number of pregnancies, and the duration of breastfeeding.

Statistical analysis

The sample size was calculated with Power (least) %80 and Type-1 error 0.05 for all variables. The Kolmogorov-Smirnov (n>50) and Skewness-Kurtosis tests were applied to examine whether the measurements in the study were normally distributed. Accordingly, parametric tests were applied since the measurements were normally distributed. In this study, descriptive statistics for continuous variables were expressed as the mean, standard deviation, and the minimum and maximum values. Categorical variables were described as number (n) and percentage (%). Independent t-test and one-way analysis of variance (ANOVA) tests were performed to compare the group mean values in continuous variables. Following the ANOVA, the Duncan post-hoc test was used to determine the different groups. Pearson's correlation coefficients were calculated to determine the relationship among the variables. The chi-square test was employed to determine the relationship between the groups and among the categorical variables. Statistical significance level was considered as 5% in the calculations, and SPSS (IBM SPSS for Windows, ver.23) statistical package program was used for the calculations.

Results

The medical files of 77 cases were retrospectively reviewed. The descriptive properties are shown in Table 1. The median age of the patients was 38 (range: 19–74) years. The cut-off value of age was 35.5 years. The mean age of the PBL-WA patients was 40.98±12.74 years and that of PBL-WOA patients was 30.75±12.36 years (p=0.005). The mean age as per the final pathology was 33.66±10.17 years for the benign group and 50.33±12.15 years for the malignant group (p<0.001). The mean age as per the radiology features was 35.12±11.6 years for the benign group and 46.19±13.46 years for the malignant group (p<0.001). The mean age of the PBL-WA patients in the benign final pathology group was 34.89±8.84, while it was 51.04±11.90 years for the PBL-WA patients in the malignant final pathology group. In both the groups, the mean age was greater in the malignant group than in the benign groups (Table 2).

Table 1. Descriptive properties of the patients

		n (%)
Sex	M	3 (3.9)
	F	74 (96.1)
Radiological features	Benign	51 (66.2)
	Malignant	26 (33.8)
Side	Right	31 (40.3)
	Left	46 (59.7)
Fine/core needle aspiration biopsy	PBL-WA	61 (79.2)
	PBL-WOA	16 (20.8)
Intervention	Surgery	65 (84.4)
	Follow-up	12 (15.6)
Final pathology	Benign	53 (68.8)
	Malignant	24 (31.2)

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia; M: Male; F: Female; n: Number

The mean size of the mass was 2.53±1.33 (1–6) cm, and the cut-off value of the mass size was 2.5 cm. The mean mass size for the PBL-WA patients was 2.64±1.37 cm, while it was 2.13±1.15 cm for the PBL-WOA patients (p=0.171). The mass size as per the final pathology was 2.25±1.22 cm in the benign group and 3.17±1.37 cm in the malignant group (p=0.004). The mean mass size was greater of the malignant lesions as per the fine/core needle aspiration biopsy, final pathology, and radiological imaging. The mean BMI value was 26.8±4.4 kg/m^2 (range: 18.8–35.1), and the cut-off value was 25.4. The corresponding value was 27.6±4.2 kg/m^2 for the PBL-WA patients and 23.8±3.9 kg/m^2 for the PBL-WOA patients (p=0.002). BMI as per the final pathology was 25.1±3.8 kg/m^2 in the benign group and 30.6±3.0 kg/m^2 in the malignant group (p=0.001). The mean number of children was 3.08±2.1 (0-8) in the PBL-WA group and 2.1±2.4 (0–7) in the PBL-WOA group (p=0.156). The mean overall total duration of breastfeeding was 51.8±41.7 months (0–156), and it was 56.9±41.5 months in the PBL-WA group and 32.5±37.4 months in the PBL-WOA groups (p=0.036). The cause of the lower number of children in the benign group was the lower patient age (Table 2).

Smoking habit was reported in 66.2% (n=51) of the patients. A total of 48 (94.1%) patients were included in the PBL-WA group and 3 (5.9%) patients in the PBL-WOA group (p=0.001). In the PBL-WA group, 68.9% (n=42) of the patients had no history of sports activities, 16.4% (n=10) had a history of sports activities once a week, and 14.8% (n=9) had a history of sports activities twice a week. In the PBL-WOA patients, 43.8% (n=7) of the patients had no history of indulging in sports activities, 37.5% (n=6) of the patients had a history of indulging in sports activities once a week, and 18.8% (n=3) of the patients had a history of indulging in sports activities twice a week (p=0.129). In addition, 83.1% (n=64) of the patients had no BC family history, while 16.9% (n=13) had a BC family history. Moreover, as per the final pathology, there were four (30.7%) patients in the benign group and nine (69.3%) patients in the malignant group (p=0.001). In addition, 88.3% (n=68) of the patients did not use hormone replacement therapy (HRT), while 11.7% (n=9) did (Table 3).

The malignancy rate of the PBL-WA patients was 37.7% (n=23), while it was 6.3% (n=1) in the PBL-WOA patients as per the final pathology (p=0.016). Breast-conserving surgery or mastectomy and sentinel lymph node dissection was performed in 19 (79.1%) patients, axillar lymph node dissection in five (20.9%)patients, and modified radical mastectomy in five (20.9%) patients. The positive predictive value for malignant lesions in the PBLs was 90.2%, negative predictive value was 73%, and accuracy was 84.4% for radiology (p=0.001). Twelve patients (15.6%) did not undergo surgery, and the follow-up time was 4.72±2.49 years. Six of these patients (50%) had PBL-WOA patients and the other six (50%) were PBL-WA patients. The mean age of the

Table 2. Comparison of the results of proliferative breast lesions according to the variables

	Variables	Mean ± SD		p-value
Mean age	Overall mean age	38.86±13.26		
	Cut-off value	35.5 cm		
	Radiological features	Benign	35.12±11.6	<0.001
		Malignant	46.19±13.46	
	Fine/core needle aspiration biopsy	PBL-WOA	30.75±12.36	0.005
		PBL-WA	40.98±12.74	
	Final pathology	Benign	33.66±10.17	<0.001
		Malignant	50.33±12.15	
	PBL-WA	Benign	34.89±8.84	<0.001
		Malignant	51.04±11.90	
	PBL-WOA	Benign	30.53±12.77	0.268
		Malignant	34.00±12.77	
Size of mass	Overall mean size	2.53±1.33		
	Cut-off value	2.5 cm		
	Radiological features	Benign	2.27±1.13	0.016
		Malignant	3.04±1.56	
	Fine/core needle aspiration biopsy	PBL-WOA	2.13±1.15	0.171
		PBL-WA	2.64±1.37	
	Final pathology	Benign	2.25±1.22	0.004
		Malignant	3.17±1.37	
BMI (kg/m^2)	Overall mean BMI	26.8±4.4		
	Cut-off value	25.4		
	Fine/core needle aspiration biopsy	PBL-WOA	23.8±3.9	0.002
		PBL-WA	27.6±4.2	
	Final pathology	Benign	25.1±3.8	0.001
		Malignant	30.6±3	
Number of pregnancies	Mean number pregnancies	3.08±2.1		
	Fine/core needle aspiration biopsy	PBL-WOA	2.1±2.4	0.156
		PBL-WA	3.08±2.1	
Mean breastfeeding time	Overall mean breastfeeding time	51.8±41.7		
	Fine/core needle aspiration biopsy	PBL-WOA	32.5±37.4	0.036
		PBL-WA	56.9±41.5	

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia; BMI: Body Mass Index; SD: Standard deviation

patients was 34.75±10.29 years, and the mean size was 1.67±0.78 cm. Both the mean age and size were lower than the cut-off value. None of them were diagnosed with malignancy during the follow-up time.

Discussion and Conclusion

Benign breast lesion can be classified as non-PBLs, PBL-WOA, and PBL-WA. These lesions were detected more frequently because of the widespread use of mammography, which makes it is important to identify patients at risk for BC. PBLs, especially containing atypia, are the risk factors for both non-invasive and invasive BC. In the PBL-WOA patients (e.g., complex fibroadenoma, moderate or floride hyperplasia, sclerosing adenosis, and intraductal papilloma), there is a slight increased risk for BC [relative risk (RR): 1.3–2]. The risk is greater in PBL-WA patients (such as atypical lobular hyperplasia and atypical ductal hyperplasia; RR: 4–6). When the atypia is multifocal, the risk increases by 10 times (4-6). In our study, the rate of malignancy of PBL-WA patients was greater than that of PBL-WOA patients as per the final pathology.

While the relationship of PBL-WOA and BC does not change with age, it is stronger in postmenopausal patients (6, 7). In our study, however, we observed a significant effect of age on the type of PBLs. The mean age of the PBL-WA patients was 40.98±12.74 years and that

Table 3. Comparison of the results of proliferative breast lesions by risk factors

	Factors	n (%)		p-value
Smoking	Have been smoking	51 (66.2%)		
	Fine/core needle aspiration biopsy	PBL-WOA	18.8%	0.001
		PBL-WA	78.7%	
	Final pathology	Benign	64.2%	0.566
		Malignant	70.8%	
Sports activity	No sports activity	49 (63.6%)		-
	1 day per week	16 (20.8%)		-
	2 days per week	12 (15.6%)		-
Breast cancer family history	Have been family history	13 (16.9%)		-
	Final pathology	Benign	7.5%	0.001
		Malignant	37.5%	
HRT	Positive HRT history	11.7% (9)		

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia; HRT: Hormone replacement therapy; n: Number

of the PBL-WOA patients was 30.75±12.36 years (p=0.005). As per the final pathology, the mean age was 33.66±10.17 years in the benign group and 50.33±12.15 years in the malignant group (p<0.001). As the risk of BC increases with age, age was noted as an important factor in PBLs. Malignant lesions were recorded in the advanced age in both the groups (patients with PBL-WA and patients with malignant pathology result) (Figure 1).

Renshaw et al. (8) reported no correlation between the size of lesion and atypical ductal hyperplasia or ductal carcinoma *in situ*. However, the size of lesions diagnosed as carcinoma was significantly greater than that of lesions diagnosed as PBL-WA (p<0.001). In our study, the mean pathological tumor size was 2.25±1.22 cm in the benign group and 3.17±1.37 cm in the malignant group (p=0.004). The size of the mass was larger in all malignant patients (Figure 2).

Several past epidemiological studies have shown that being overweight and/or obese, indicated by BMI in postmenopausal women, is a risk factor for BC development (9-11). BC is more common in obese women (BMI >30 kg/m^2) (12). When postmenopausal women lose ≥10 kg, they are at a lesser risk than those who do not lose weight (7, 13). In our study, while the BMI was 27.6±4.2 kg/m^2 (n=61) for the PBL-WA patients, it was 23.8±3.9 kg/m^2 (n=16) for the PBL-WOA patients (p=0.002). In addition, as per the final pathology, BMI was 25.1±3.8 kg/m^2 (n=53) for the benign group and 30.6±3.0 kg/m^2 (n=24) for the malignant group (p=0.001) (Figure 3). Several studies have also shown that pregnancy and breastfeeding have a protective

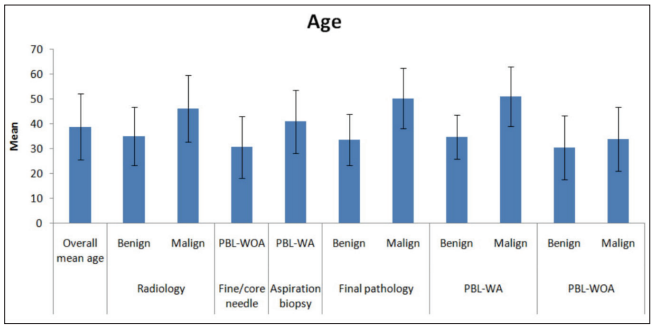

Figure 1. In all groups, the age was greater in patients with malignant lesions

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia

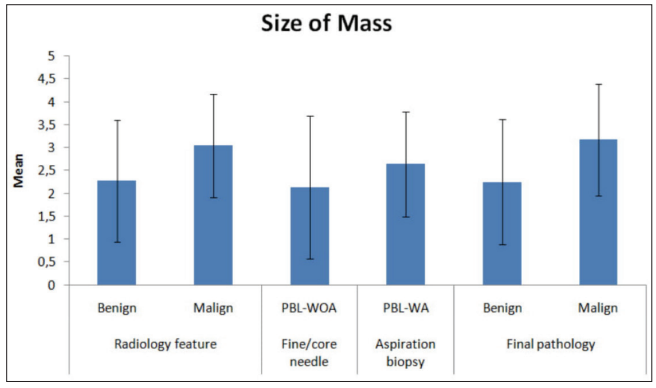

Figure 2. In all groups, the mass size was greater in patients with malignant lesions

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia

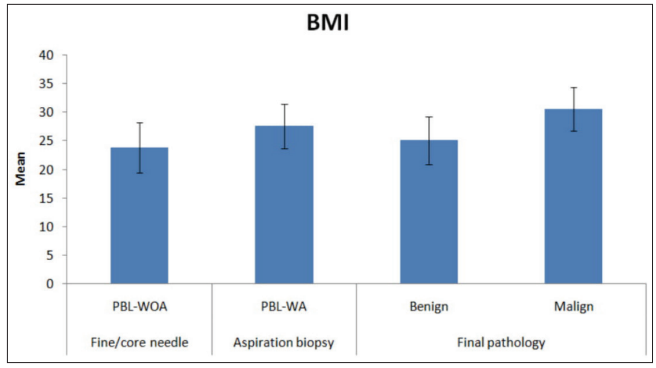

Figure 3. Body mass index was greater in patients with malignant lesions

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia; BMI: Body mass index

effect against BC (14). In our study, the mean number of children and the total duration of breastfeeding were lower in the benign groups due to the young age of the patient. The relationship between smoking and BC is contradictory. Although very different results have been reported in the literature, it is believed to increase the risk associated with some other factors (15, 16). Positive smoking history was 78.7% (n=48) for the PBL-WA patients and 18.8% (n=3) for the PBL-WOA patients (p=0.001) (Figure 4).

Increased physical activity, especially in premenopausal women, is associated with a reduced risk of BC (7). Lynch et al. (17) indicated an average of 25% reduction in BC risk among physically active women when compared with the least active women in a meta-analysis of 73 studies on the relationship between physical activity and BC. In our study, the percentage of patients with no sport activities was more in the malignant group than in the PBL-WA group as per the final pathology.

Patients with a family history showed a higher risk of developing BC, but the effect of PBLs with a family history has been discussed in the literature. The possibility of developing age-related BC in 10 years in women with a family history and proliferative breast disease is one in 2000 at the age of 20 years, one in 256 at 30, one in 67 at 40, one in 39 at 50, and one in 29 at 60 (7, 18, 19). A family history of maternal BC has not been found to be related to the degree of atypia or fibrocystic breast disease in most hospital-population-based studies (20-22). The family history of BC has very little effect on the risk of developing BC in patients with non-PBLs; however, there is an 11-fold increased risk in patients with PBLs presenting with atypia (23). In our study, the percentage of patients with BC family history was greater in the malignant group than in the PBL-WA group, as per the final pathology.

Both the World Health Organization and the One Million Women Study have revealed that women who received HRT had an increased risk of developing BC. however, as per epidemiological studies, no relationship has been established between the use of HRT and the risk of developing BC. Although a relative increase in risk of 1.24 was reported by a few large-scale studies, this relationship has not been revealed in the two recent studies (24-27). In our study, no statistically significant risk was noted between the use of HRT and the development of PBL-WA.

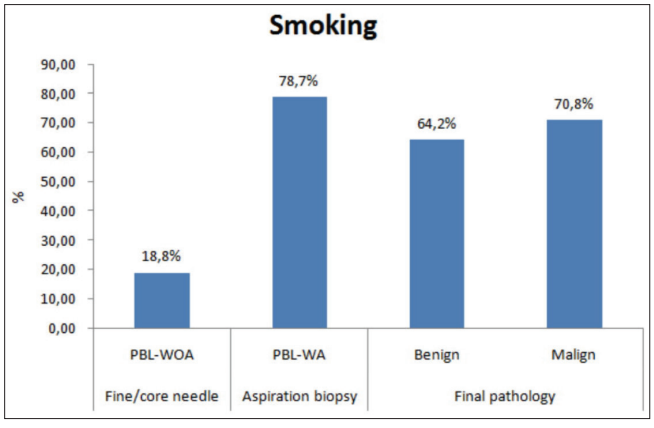

Figure 4. The smoking rate was significantly greater in the PBL-WA patients

PBL-WA: Proliferative breast lesions with atypia; PBL-WOA: Proliferative breast lesions without atypia

The limitation of the present study is that it was a single-center study with a smaller sample size.

In conclusion, our results indicate that age is an extremely important aspect in assessing PBLs. The patient age was statistically significantly greater in those with malignant lesions in all groups, such as the radiological imaging features of the lesions, fine/core needle aspiration biopsy results, and the final pathology. The lesion size, BMI, smoking habit, and family history of BC were also more frequent in the malignant group. The rate of sports activity was lower in the malignant groups. The number of pregnancies and the total breastfeeding time were smaller and lower, respectively, in the benign groups, possibly due to the lower average age of the patients. The use of HRT showed no effect on the benign and malignant lesions. Thus, it seems necessary to evaluate patients individually when evaluating PBLs. It is therefore recommended to evaluate PBLs together with BC risk factors.

Ethics Committee Approval: Ethical approval for this study was obtained with regard to the Ethical Principles for Medical Research Involving Human Subjects (the Helsinki Declaration) from the Local Ethics Committee of Van Yüzüncü Yıl University, Turkey with the registration number of 2019/05-09.

Informed Consent: Written informed consent was not recieved due to the retrospective nature of the study.

Peer-review: Externally-peer reviewed.

Authorship Contributions

Concept: O.T.; Design: O.T., R.E.; Supervision: O.T., S.E., Ü.H.İ.; Resources: A.R.K., A.Ö., F.A., S.B, İ.Ö., E.Ş.; Materials: S.B., İ.Ö., E.Ş.; Data Collection and/or Processing: O.T., S.B., Ü.H.İ., A.R.K., F.A.; Analysis and/or Interpretation: O.T., S.E., Ü.H.İ., A.Ö.; Writing Manuscript: O.T., R.E., S.E.; Critical Review: O.T., S.E.

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