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Original Scientific Paper

ULTRASONOGRAPHIC BI-RADS 4 LESIONS RELATED TO BREAST CANCER RISK FACTORS

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SUMMARY – Lifetime risk of developing breast cancer in women is about 12%. This risk is relatively reduced as the time of having no breast cancer is prolonged. In the present study, we aimed to determine the association between BI-RADS 4 lesions detected by breast ultrasound and risk factors for breast cancer. BI-RADS 4 has 3 categories, i.e., BI-RADS A, BI-RADS B and BI-RADS C. Risk factors for breast cancer were defined as follows: age over 40 years, age at menarche 12 years or earlier, no lactation, no delivery, body mass index 30 kg/m^2 or greater, and breast cancer history in a first-degree relative. The relationship between the risk factors and malignancy risk was compared in subjects BI-RADS lesions. One or more risk factors were significant in terms of malignancy when the risk factors were compared with malignancy in BI-RADS 4A, B, C lesions, and the increase in the number of risk factors was significant in terms of malignancy. We think that our study is important for showing the relationship between these risk factors and patients with benign and malignant lesions. However, if patients have one or more of these risk factors, if they are diagnosed with BI-RADS 4 lesion radiologically, it should be kept in mind that the malignancy potential is higher in these patients, and if biopsy results are benign, follow-ups should be done strictly.

Keywords: *Breast cancer; Women; BI-RADS 4; Cancer risk; Ultrasound*

Introduction

Lifetime risk of developing breast cancer in women is about 12%[1,2]. This risk is relatively reduced as the time of having no breast cancer is prolonged. Although many risk factors for breast cancer are tried to be determined, it is difficult to determine cancer risk with those risk factors. The ongoing social awareness studies of breast cancer provide early diagnosis of the disease while reducing mortality and allowing for less invasive methods of treatment. Using high quality radiological methods more effectively, especially ultrasound (US) and mammography, allows for earlier detection of breast lesions. Inflammation is associated with malignant tumors[3].

In the present study, we aimed to determine the association of BI-RADS 4 lesions detected by breast US and risk factors for breast cancer.

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Materials and Methods

Patient selection

Patients with breast lesions that presented to outpatient clinics of our institution between January 2010 and June 2017 were retrospectively analyzed. All patients had undergone surgery at our department. The Breast Imaging Reporting and Data System (BI-RADS) radiological reporting system was used on patient classification[3]. Subjects with breast lesions with radiological classification BI-RADS 4 were included in the study. Women with BI-RADS lesions other than BI-RADS 4 were excluded. BI-RADS 4 has 3 categories, BI-RADS 4A, BI-RADS 4B and BI-RADS 4C. BI-RADS 4A category is used if the lesion is sampled, but with a very low probability of malignancy; BI-RADS 4B includes lesions with an intermediate probability of malignancy; and BI-RADS 4C includes lesions with an intermediate but non-typical risk of malignancy. Postoperative pathological examination results were obtained from patient files and database of our institution. According to histopathological results, the study cohort was divided into two groups of benign or malignant results. Risk factors for breast cancer were defined as follows: age over 40 years, age at menarche 12 years or earlier, no lactation, no delivery, body mass index (BMI) 30 kg/m^2 or greater, and breast cancer history in a first-degree relative. The relationship between the risk factors and malignancy risk was compared in subjects' BI-RADS 4 lesions.

Histopathological verification of BI-RADS 4 lesions was performed by US-guided tru-cut biopsy (in palpable masses), or by US-guided wire marking excisional biopsy (in non-palpable masses). It was found that the wire-marked lesions were removed with at least 1 cm clear surgical margin and borders marked by marking.

Statistical analysis

Data were analyzed by SPSS software (SPSS 15.0 for Windows, IBM Inc., Chicago, IL, USA). Distribution of variables between malignant and benign groups was assessed by Kolmogorov-Smirnov test. Variables that were normally distributed were analyzed by independent samples test. Mann Whitney U test was used on comparison of variables without normal distribution. The χ^2-test was used on comparison of categorical parameters. The level of statistical significance was set at $p<0.05$.

Results

A total of 331 women with BI-RADS 4 lesions were enrolled in the study. US-guided tru-cut biopsy was performed in 302 patients, whereas US-guided wire marking and excisional biopsy were performed in 29 patients in order to obtain histopathological verification. There was no subsequent mortality or morbidity after these procedures. The lesion was in the right breast in 157 and in the left breast in 174 patients. The rate of malignant lesions was not significantly different according to side (p=0.63). Out of 331 patients, 208 were classified as BI-RADS 4A, 42 as BI-RADS 4B, and 81 as BI-RADS 4C. There were 200 (60.4%) patients with benign and 131 (39.6%) patients with malignant lesions. Of the lesions, 46 (22.1%) were malignant in BI-RADS 4A group, 23 (54.8%) were malignant in BI-RADS 4B group, and 62 (76.5%) were malignant in BI-RADS 4C group. The rate of lesion malignancy was statistically significant (p=0.000) when BI-RADS 4 advanced from A to C.

Histopathological results were as follows: fibroadenoma (46.5%), intraductal papilloma (2.1%), granulomatous mastitis (5.1%), epithelial hyperplasia (6.6%), ductal carcinoma *in situ* (1.5%), phyllodes tumor (0.6%), invasive lobular carcinoma (2.7%), and invasive ductal carcinoma (34.7%). When we compared risk factors for malignant outcome in BI-RADS 4A lesions, age older than 40 years (p=0.01) and early menarche (p=0.01) were significantly more common in malignant lesions compared to benign 4A lesions; however, number of deliveries (p=0.41), BMI (p=0.79) and number of risk factors (p=0.57) were not different between benign and malignant 4A lesions (Table 1). Risk factors were also compared between malignant and benign BI-RADS 4B lesions. The number of risk factors (p=0.02) and early menarche (p=0.01) were significantly different between malignant and benign lesions. However, the number of deliveries (p=0.39), age (p=0.28), and BMI (p=0.06) were found to be statistically nonsignificant in patients with benign or malignant lesions (Table 2). In patients

Table 1. Comparison of risk factors between benign and malignant groups in BI-RADS 4A

BI-RADS 4A	Benign/malignant	n	Mean	Standard deviation	p
Age (years)	Benign	162	42.49	11.951	0.01
	Malignant	46	49.02	10.303	
Menarche age (years)	Benign	162	13.26	0.889	0.01
	Malignant	46	12.63	1.554	
Number of deliveries	Benign	162	2.72	1.297	0.41
	Malignant	46	1.74	0.953	
Body mass index (kg/m^2)	Benign	162	25.78	2.604	0.79
	Malignant	46	25.33	2.781	
Number of risk factors	Benign	162	1.3642	0.79405	0.57
	Malignant	46	1.8913	0.92444	

RI-RADS = Breast Imaging Reporting and Data System

Table 2. Comparison of risk factors between benign and malignant groups in BI-RADS 4B

BI-RADS 4B	Benign/malignant	n	Mean	Standard deviation	p
Age (years)	Benign	19	50.53	14.657	0.28
	Malignant	23	52.30	11.664	
Menarche age (years)	Benign	19	13.79	0.419	0.01
	Malignant	23	12.13	1.486	
Number of deliveries	Benign	19	2.79	1.134	0.39
	Malignant	23	2.65	1.695	
Body mass index (kg/m^2)	Benign	19	25.05	2.818	0.12
	Malignant	23	26.39	3.056	
Number of risk factors	Benign	19	1.2105	0.78733	0.02
	Malignant	23	2.2609	1.32175	

RI-RADS = Breast Imaging Reporting and Data System

Table 3. Comparison of risk factors between benign and malignant groups in BI-RADS 4C

BI-RADS 4C	Benign/malignant	n	Mean	Standard deviation	p
Age (years)	Benign	19	49.00	11.377	0.89
	Malignant	62	54.37	11.922	
Menarche age (years)	Benign	19	13.89	0.459	0.01
	Malignant	62	12.50	1.906	
Number of deliveries	Benign	19	3.00	1.414	0.03
	Malignant	62	1.23	0.857	
Body mass index (kg/m^2)	Benign	19	25.68	3.198	0.84
	Malignant	62	25.98	3.134	
Number of risk factors	Benign	19	1.3158	0.58239	0.04
	Malignant	62	2.1774	1.01665	

RI-RADS = Breast Imaging Reporting and Data System

Table 4. Comparison of risk factors between benign and malignant groups in BI-RADS 4

BI-RADS 4	Benign/malignant	n	Mean	Standard deviation	p
Age (years)	Benign	200	43.88	12.449	0.59
	Malignant	131	52.13	11.501	
Menarche age (years)	Benign	200	13.37	0.852	0.01
	Malignant	131	12.48	1.716	
Number of deliveries	Benign	200	2.75	1.291	0.09
	Malignant	131	1.66	1.188	
Body mass index (kg/m^2)	Benign	200	25.70	2.679	0.04
	Malignant	131	25.82	3.004	
Number of risk factors	Benign	200	1.3450	0.77393	0.01
	Malignant	131	2.0916	1.04844	

RI-RADS = Breast Imaging Reporting and Data System

with BI-RADS 4C lesions, the number of deliveries (p=0.03), early menarche (p=0.01) and number of risk factors (p=0.02) were significantly different between the study groups. On the other hand, age (p=0.89) and BMI (p=0.84) were not statistically different between benign and malignant cases (Table 3). The number of risk factors was significantly different between malignant and benign groups (p=0.01). Similarly, age at menarche (p=0.01) and BMI (p=0.04) were also statistically different between the study groups (Table 4).

Discussion

In the development stage of cancer in the breast, age, family history, lactation status, hormonal status, obesity, age at menarche, radiation, and many other risk factors are involved. A combination of these risk factors has been used to identify risk situations. Although these studies were carried out to estimate the risk of breast cancer risk, real breast cancer continues to increase day by day. Breast cancer is the most important concern among women and is considered a major social problem worldwide. Despite increased social awareness, new cases every year keep doctors busy trying to solve problems related to breast cancer. In Turkey, the number of women with breast cancer in 1999 was 8,879, whereas in 2003 it rose to 12,772. It is also stated that breast cancer constitutes about 28% of all cancers in the world[4]. All these data show that early detection of breast cancer, and even detection of mammary lesions in stages prior to conversion to cancer, lead to better use of developing technological devices. While mammography is safely used in breast cancer screening in general population, the usefulness and easiness of US in patients under 40 years of age becomes ever more important every day. Classification of lesions detected by US has made it easier to follow up patients. In BI-RADS categorization, each category becomes a separate feature, and in BI-RADS 4, things become more serious and more complex because after this stage, lesions can change from suspicious to malignant.

Theoretically, BI-RADS 4 lesions are indeterminate and malignancy rates range from 2% to 95%[5,6]. It seems that this broad spectrum of BI-RADS 4 lesions actually shows that we are faced with bad surprises at some unexpected moments and we should not be following a careful path. Elverici *et al.* examined 186 BI-RADS 4 lesions and 73 (39%) of them were histologically proven as malignant. The rates in subcategories 4A, 4B and 4C were 19.5%, 41.5% and 74.3%, respectively[3]. In addition, Yoon *et al.* found 18.6% of cancers in biopsies performed on BI-RADS 4 lesions in a study of 2,430 cases[7]. In our study, 39.6% of the BI-RADS 4 lesions were found to be malignant. Malignant were 22.1% of lesions with BI-RADS 4A, 54.8% of BI-RADS 4B and 76.5% of BI-RADS 4C.

The rate of malignancy development from BI-RADS 4 A to C was statistically significant. In this case, there is a question of whether there is a link with the risk factor of BI-RADS 4 lesions.

One of the first of these risk factors is age. While the risk of breast cancer in a 20-year-old woman is 0.05%, this ratio increases to 1.49% in a 40-year-old woman, and 3.45% in a 60-year-old woman[7-9]. In our study, the relation between malignancy and age was significant in lesions with BI-RADS 4A.

It is well established that breastfeeding reduces the risk of breast cancer[10]. It is also known that breast cancer risk is high in women who do not breastfeed during studies[11-13]. In a study that included 110,604 women over 20 years of age, Lee *et al*. found that 51.9% of them were breastfeeding their children[11]. In Germany, Brinton *et al*. found that breast cancer risk was lower in women who started breastfeeding under the age of 22[13,14]. In the study of the relationship of breastfeeding and breast cancer in Mexican women, Romieu *et al*. found that breast cancer risk decreased in women offering suckling to their babies between 12 and 24 months[15]. In our study, the association between malignancy and lack of lactation in patients with BI-RADS 4C lesion was statistically significant.

Breast cancer is a family story, i.e., if first-degree relatives (mother, sister, daughter) are affected, the risk of breast cancer is increased 2-3 times[6]. In our study, the relationship between malignancy and family history was significant in patients with BI-RADS.

There is a close relationship between age at menarche and regular ovarian cycle and breast cancer. In case-control studies, the risk of breast cancer is reduced by 20% *per* year for each year that menarche is delayed[16]. In our study, the relationship between malignancy and early menarche was significant in all patients with BI-RADS 4A, B and C.

Early breastfeeding is one of the most important factors to reduce the risk of breast cancer[9]. Having never given birth is one of the risky conditions in terms of breast cancer. In our study, the relationship between malignancy and no delivery in patients with BI-RADS 4C was significant.

In our society, the incidence of obesity is increasing day by day, and this situation has started to take place on the agenda that it may be a risk factor for breast cancer. Obesity, especially in postmenopausal women, increases the risk of breast cancer by a factor of two, whereas in premenopausal women the incidence is low in obese subjects[16,17]. In our study, there was no statistical significance in the association of malignancy and obesity in BI-RADS 4A, B and C groups.

In the literature, risk factors for breast cancer are older age, obesity, hormone therapy, early menarche, late menopause, no lactation, and family history[17,18]. Although we do not see generalization for factors such as age, obesity, hormone use, early menarche, late menopause, family history, and lack of lactation, studies always show that cancer is related to these risk factors.

In conclusion, we think that our study is important for showing the relationship between these risk factors and patients with benign and malignant lesions. However, if patients have one or more of these risk factors and if they are diagnosed with BI-RADS 4 lesion radiologically, it should be kept in mind that the malignancy potential will be higher in these patients, and if biopsy results are benign, follow-ups should be done strictly.

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Sažetak

ODNOS ULTRASONOGRAFSKIH LEZIJA BI-RADS 4 I RIZIČNIH ČIMBENIKA ZA RAK DOJKE

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Rizik da će za života razviti rak dojke u žena iznosi oko 12%. Taj se rizik relativno snižava tijekom života ako žena ne dobije rak dojke. Cilj ovog istraživanja bio je utvrditi povezanost lezija BI-RADS 4 otkrivenima ultrazvukom dojke i rizičnih čimbenika za rak dojke. BI-RADS 4 ima tri kategorije, BI-RADS A, BI-RADS B i BI-RADS C. Definirani su sljedeći čimbenici rizika za rak dojke: dob iznad 40 godina, dob početka menstruacije 12 godina ili ranije, bez laktacije, bez porođaja, indeks tjelesne mase 30 kg/m^2 ili veći te povijest raka dojke u srodnica prvog stupnja. Odnos rizičnih čimbenika i rizika od zloćudnih promjena uspoređen je u osoba s lezijama BI-RADS. Jedan ili više rizičnih čimbenika pokazalo se značajnima za zloćudne promjene kad su čimbenici rizika uspoređeni sa zloćudnim lezijama BI-RADS 4A, B, C, a porast broja rizičnih čimbenika bio je značajan za malignitet. Smatramo da je ovo istraživanje važno zato što ukazuje na odnos ovih čimbenika rizika i bolesnica s dobroćudnim i zloćudnim promjenama. Međutim, ako bolesnice imaju jedan ili više ovih rizičnih čimbenika te ako imaju radiološku dijagnozu lezija BI-RADS 4, treba voditi računa o tome da je kod ovih bolesnica zloćudni potencijal veći, a ako su razultati biopsije dobroćudni treba provoditi strogo praćenje.

Ključne riječi: *Rak dojke; Žene; BI-RADS 4; Rizik za rak; Sonografija*