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The frequency of autoimmune disease in the first degree and other relatives of the breast cancer patients

Meme kanserli hastaların birinci derece ve diğer yakınlarındaki otoimmün hastalık sıklığı

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Abstract

Objective: Autoimmune diseases (ADs) are observed more frequently in patients with breast cancer (BC) compared to healthy population. However, the frequency of ADs in their relatives has not been studied. In the present study, we aimed to compare the frequency of ADs among the first-degree and other relatives of patients with BC with healthy controls.

Methods: We included 100 women aged 18 years and older who were followed up with the diagnosis of BC in our oncology clinic, and randomly selected female employees aged 18 and over in our hospital as the control group. The frequencies of ADs among relatives of the two groups were investigated using a detailed questionnaire.

Results: Frequency of having at least one relative with AD was 76% in the BC group and 36% in the control group (p<0.001). The frequency of ADs in the relatives of the BC group was 5.5 times higher than in the relatives of the control group. In detailed analyzes, when the degree of kinship was considered, it was found that the risk increased to 11.5 times in the first-degree relatives of BC patients; however, no increased risk was found among more distant relatives.

Conclusion: In our study, we found more ADs among the first-degree relatives of patients with BC compared to the control group. This result suggests that common genetic factors may be playing roles in the pathogenesis of BC and ADs.

Keywords: Breast cancer, autoimmune diseases, genetic predisposition

Öz

Amaç: Otoimmün hastalıklar (OİH), meme kanseri (MK) hastalarında sağlıklı popülasyona göre daha sık görülmektedir. Ancak hasta yakınlarında OİH sıklığı çalışılmamıştır. Bu çalışmada, MK'li hastaların birinci derece ve diğer akrabalarında OİH sıklığını sağlıklı kontrollerle karşılaştırmayı amaçladık.

Yöntem: Onkoloji kliniğimizde MK tanısı ile izlenen 18 yaş ve üstü ardışık 100 kadını ve kontrol grubu olarak hastanemizin rastgele seçilmiş 18 yaş ve üzeri kadın çalışanlarını dahil ettik. İki grubun akrabaları arasındaki OİH sıklıkları ayrıntılı bir anket kullanılarak araştırıldı.

Bulgular: Çalışma gruplarının akrabaları arasında en az bir OİH varlığı, MK grubunun akrabalarında %76 iken, kontrol grubunun akrabalarında %36 idi (p<0,001). MK grubu akrabalarındaki OİH sıklığı, kontrol grubu akrabalarına kıyasla 5,5 kat daha fazlaydı. Akrabalık derecesi dikkate alınarak yapılan detaylı analizlerde, MK hastalarının birinci derece akrabalarında riskin 11,5 kat arttığını; ancak, daha uzak akrabalar arasında risk artışı olmadığı tespit edildi.

Sonuç: Çalışmamızda, MK hastalarının birinci akrabaları arasında, kontrol grubuna kıyasla daha fazla OİH saptadık. Bu sonuç, MK ile OİH'nin patogenezinde ortak genetik faktörlerin rol oynayabileceğini düşündürmektedir.

Anahtar Kelimeler: Meme kanseri, otoimmün hastalıklar, genetik yatkınlık

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Introduction

Autoimmune diseases (ADs) are a frequent cause of morbidity, affecting about 7-10% of individuals living in Western countries.[1] Malignant disorders may contribute to the risk of ADs by leading to a predisposition to the development of autoantibodies.[2] The previous studies demonstrated a positive epidemiological correlation between breast cancer (BC) and ulcerative colitis, psoriasis, Graves' disease, and multiple sclerosis. [3-6]

ADs are observed more frequently among patients with cancer than in the healthy population.[7] Environmental factors, occupational status, drug exposures and genetic predisposition could be involved in the pathogenesis of both cancers and AD. However, the frequency of ADs among the first-degree relatives of cancer patients has not been studied. If found to increase, this might suggest the possibility of common genetic predisposition of these two conditions. Thus, we aimed to compare the frequency of ADs in first-degree and other relatives of BC patients with that of healthy controls.

Materials and Methods

We included 100 consecutive female patients; aged 18 years and over; who were followed up with the diagnosis of BC in the oncology clinic in our hospital in March 2017. The control group comprises 100 randomly selected women aged 18 years and over from our hospital's staff. After the patient and control groups were informed about the study and their consent was obtained, data were collected with a questionnaire, through face-to-face interviews.

First, we collected data, including past medical history, age at diagnosis, smoking status, and presence of ADs in first-degree and other relatives of patients in the BC group and individuals in the control group. We specifically questioned the presence of type 1 diabetes mellitus (DM), Hashimoto's thyroiditis, Graves' disease, rheumatoid arthritis (RA), systemic lupus erythematosus (SLE), autoimmune hepatitis, myasthenia gravis (MG), primary biliary cirrhosis (PBS), autoimmune hemolytic anemia, connective tissue disorders, Sjögren's syndrome, and scleroderma. Data on other parameters, such as pathological diagnosis, hormone receptor test results, and body mass index (BMI), were obtained from medical records.

Statistical Analysis

While categorical variables are shown as frequencies and percentages, we reported continuous variables as means and standard deviations. Regarding statistical analysis, we compared the continuous variables between the groups using an Independent Samples t-test. For categorical variables, on the other hand, we utilized a chi-square test when the number of observations less than 5 was less than 25% and Exact and Likelihood Ratio tests when it was more than 25%. Then, we compared the ratios for the values with a significant association. Finally, we calculated odds ratios (ORs) with confidence intervals (CIs) using logistic regression analysis to determine how many times more type 1 DM, Hashimoto's thyroiditis, Graves' disease, and RA were encountered in first-degree and other relatives in the patient group compared to the control group. The One-Way ANOVA method was used to simultaneously compare the means of three or more independent conditions. SPSS 21 was used for statistical analyses (IBM Corp. Released 2012. IBM SPSS Statistics for Windows, Version 21.0. Armonk, NY: IBM Corp.).

Ethical Considerations

The Research Ethics Committee of Gazi University granted ethical approval to our study (no: 2017-114 dated: 03.07.2017).

Results

The median [interquartile range (IQR)] ages of the BC and control groups were 54 (32-76) years and 36 (20-55) years, respectively ($p<0.00001$). The med (IQR) BMIs of the study groups were 27.9 (17.9-46.5) in the patient group and 24.3 (16.4-34.6) in the control group ($p<0.001$). There was no significant difference between the groups by smoking status ($p=1.00$). The pathological diagnosis, stage of disease at the time of diagnosis, and hormone receptor test results in patients with BC are given in Table 1.

We found a significant difference in the presence of at least one AD between the relatives of BC patients and the relatives of those in the control group (76% vs. 36%, $p<0.001$). This difference was more marked when only the first-degree relatives were analyzed (65% vs. 14%, $p<0.00001$). The incidence of ADs in the relatives of the BC patients was higher than in the relatives of the control group (OR: 5.5). In detailed analyses, when the degree of kinship was considered, it was found that the risk increased more in the first-degree relatives of BC patients (OR: 11.5); however, no increased risk was found among distant relatives. The distribution of ADs among the first-degree and other relatives of the groups is shown in Table 2.

Regarding ADs, type 1 DM was detected in 16% of the first-degree relatives of the patient group, 5% of the first-degree relatives of the control group; 8% of the other relatives of the patient group, and 9% of the other relatives of the control group. Graves' disease was detected in 20%

of the first-degree relatives of the patient group, 1% of the first-degree relatives of the control group; 4% of the other relatives of the patient group, and 3% of the other relatives of the control group. Hashimoto's thyroiditis was detected in 33% of the first-degree relatives of the patient group, 8% of the first-degree relatives of the control group; 7% of the other relatives of the patient group, and 5% of the other relatives of the control group. While 29% of the first-degree relatives and 10% of the other relatives of the BC patients had RA, this was 5% and 12% in the control

Table 1. Patient distribution by pathological diagnosis, disease stage at the time of diagnosis, and hormone receptor test results

		Frequency (n=100)
Pathological diagnosis, n (%)	Invasive ductal carcinoma	86 (86)
	Invasive lobular carcinoma	6 (6)
	Mixed tumor	7 (7)
	Medullary carcinoma	1 (1)
Diagnostic stage, n (%)	Early stage	47 (47)
	Locally advanced	44 (44)
	Metastatic	9 (9)
Hormone receptor test results, n (%)	ER +	9 (9)
	PR +	2 (2)
	ER +, PR +	50 (50)
	c-ERB B2	9 (9)
	ER +, PR +, c-ERB B2 +	19 (19)
	ER -, PR -, c- ERB B2 -	8 (8)
	ER +, c-ERB B2 +	2 (2)
	PR +, c- ERB B2 +	1 (1)

Results are expressed as frequency (%). ER: Estragen receptor, PR: Progesterone receptor

Table 2. Autoimmune diseases distribution among the relatives of the groups

		Patient (n=100)	Control (n=100)	p1	OR (95% CI)	p2
Autoimmune disorders, n (%)	Yes	76 (76)	36 (36)	<0.001	5.54 (2.96-10.25)	<0.001
	No	24 (24)	64 (64)			
Type 1 diabetes mellitus, n (%)	Yes	24 (24)	14 (14)	0.071	-	-
	No	76 (76)	86 (86)			
Graves' disease, n (%)	Yes	24 (24)	4 (4)	<0.001	7.58 (2.52-22.78)	<0.001
	No	76 (76)	96 (96)			
Hashimoto's thyroiditis, n (%)	Yes	40 (40)	13 (13)	<0.001	4.46 (2.20-9.05)	<0.001
	No	60 (60)	87 (87)			
Rheumatoid arthritis, n (%)	Yes	39 (39)	17 (17)	<0.001	3.12 (1.62-6.3)	<0.001
	No	61 (61)	83 (83)			

Results are expressed as frequency (%). CI: Confidence interval, OR: Odds ratio, p1: Chi-square test, p2: Logistic regression

Table 3. Autoimmune diseases distribution among the first-degree relatives of the groups

		Patient (n=100)	Control (n=100)	p1	OR (95% CI)	p2
Autoimmune disorders, n (%)	Yes	67 (67)	15 (15)	<0.001	11.51 (5.78-22.92)	<0.001
	No	33 (33)	85 (85)			
Type 1 diabetes mellitus, n (%)	Yes	16 (16)	5 (5)	0.011	3.62 (1.27-10.30)	0.016
	No	84 (84)	95 (95)			
Graves' disease, n (%)	Yes	20 (20)	1 (1)	<0.001	24.75 (3.25-188.42)	0.002
	No	80 (80)	99 (99)			
Hashimoto's thyroiditis, n (%)	Yes	33 (33)	8 (8)	<0.001	5.66 (2.46-13.04)	<0.001
	No	67 (67)	92 (92)			
Rheumatoid arthritis, n (%)	Yes	29 (29)	5 (5)	<0.001	7.61 (2.86-21.05)	<0.001
	No	71 (71)	95 (95)			

Results are expressed as frequency (%). CI: Confidence interval, OR: Odds ratio, p1: Chi-square test, p2: Logistic regression

Table 4. Autoimmune diseases distribution among the other relatives of the groups

		Patient (n=100)	Control (n=100)	p1	OR (95% CI)	p2
Autoimmune disorders, n (%)	Yes	25 (25)	33 (33)	0.741	-	-
	No	75 (75)	67 (67)			
Type 1 diabetes mellitus, n (%)	Yes	8 (8)	9 (9)	0.800	-	-
	No	92 (92)	91 (91)			
Graves' disease, n (%)	Yes	4 (4)	3 (3)	0.552	-	-
	No	96 (96)	97 (97)			
Hashimoto's thyroiditis, n (%)	Yes	7 (7)	5 (5)	0.700	-	-
	No	93 (93)	95 (95)			
Rheumatoid arthritis, n (%)	Yes	10 (10)	12 (12)	0.651	-	-
	No	90 (90)	88 (88)			

Results are expressed as frequency (%). CI: Confidence interval, OR: Odds ratio, p1: Chi-square test, p2: Logistic regression

Table 5. Hormone receptor distribution in first-degree relatives have any autoimmune disease of patients with breast cancer

Hormone receptor status	Patient (n=100)	First-degree relatives with the autoimmune disease in the patient group (n=65)	First-degree relatives without the autoimmune disease in the patient group (n=35)	p1 value
ER+, n (%)	9 (9)	7 (11)	2 (6)	0.399
PR+, n (%)	2 (2)	2 (3)	0 (0)	-
ER+/PR +, n (%)	50 (50)	33 (51)	17 (49)	0.833
c-ERB B2 +, n (%)	9 (9)	5 (8)	4 (11)	0.533
ER+/PR+/c-ERB B2 +, n (%)	19 (19)	13 (20)	6 (17)	0.728
ER-/PR-/c-ERB B2 -, n (%)	8 (8)	4 (6)	4 (11)	0.353
ER+/PR-/c-ERB B2+, n (%)	2 (2)	0 (0)	2 (6)	-
ER-/PR+/c- ERB B2+, n (%)	1 (1)	1 (1)	0 (0)	-
p2 value		0.763	0.00001	

Results are expressed as frequency (%).ER: Estragen receptor, PR: Progesterone receptor, p1: Chi-square test, p2: One-Way ANOVA analysis

group, respectively. Accordingly, we concluded that type 1 DM (OR: 3.6), Graves' disease (OR: 24.7), Hashimoto's thyroiditis (OR: 5.7), and RA (OR: 7.6) were more common in the first-degree relatives of the patient group compared to the first-degree relatives of the control group (Table 3). The findings revealed that the groups did not significantly differ by the presence of at least one AD among their other relatives (Table 4).

In the groups, only one relative had autoimmune hepatitis, MG, or autoimmune hemolytic anemia, while none of the relatives of the study populations had SLE, PBS, connective tissue disorder, Sjögren's disease, or scleroderma.

The comparison of hormone receptor test results with the frequency of at least one AD in first-degree relatives was evaluated in Table 5, and no statistical difference was found between the groups (p=0.763). On the contrary, comparing the hormone receptor test results of patients whose first-degree relatives did not have AD, a statistically significant difference was detected between the patient group with estrogen and progesterone receptor positivity and with estrogen-only or c-ERB B2 or triple-negative or both estrogen and c-ERB B2 positivity ($p<0.05$). No statistically significant difference was detected when the hormone receptor test results were compared individually between groups with and without first-degree relatives with any AD.

Discussion

We found a significantly increased frequency of ADs among the first-degree relatives of the patients with BC, but not among distant relatives compared to the control group. The disease stage at the time of diagnosis and pathological diagnosis were evaluated. We found that 47% of the patients were early stage, 44% were locally advanced, and 9% were metastatic. Yet, the literature does not offer sufficient findings pertinent to the disease stage at diagnosis. In this study, we could not conclude a significant difference between ADs between the groups' relatives by the disease stage at the time of diagnosis and pathological diagnosis.

In a previous study, it was reported that autoimmune thyroiditis is more common in patients with estrogen-positive compared to other thyroid diseases.[8] However, relationship between hormone receptor test results and other ADs has not been studied previously. In our study, we did not find a significant difference between the hormone receptor test

results of patients with BC and the frequency of ADs in their first-degree relatives. However, more comprehensive studies are needed to evaluate the relationships between hormone receptors status and ADs.

We found that the frequency of ADs in the first-degree relatives of the patient group was significantly higher than in the first-degree relatives of the control group and that there was no significant difference in other relatives, supporting the hypothesis of the role of common genetic pathogenesis. However, it should be noted that the low rate of ADs in other relatives could also be attributed to the patients' lack of knowledge about their relatives' medical history. In addition, the prevalence of SLE, autoimmune hepatitis, MG, PBS, autoimmune hemolytic anemia, connective tissue disease, Sjögren's syndrome, and scleroderma are less than the prevalence of type 1 DM, Hashimoto's disease, Graves' disease, and RA was low due to our study groups scale remained relatively small. Therefore, we could not analyze the less common diseases due to insufficient data to evaluate the relationship between the study groups. Consequently, we think the results might differ in more extensive multicenter studies.

Study Limitations

Our study had several limitations. First of all, data were obtained through verbal questionnaires. Therefore, there is a risk of missing data in this study. Our study was designed to have a relatively small sample size at a single center, and the number of children of individuals in the study population was not recorded at the time of data collection. However, we still think detecting a significant difference in OR is valuable. Another weakness is the differences between the BC and the control groups. BC group was older than the control group. Since the frequency of AD diseases increases with age,[9] the finding of more common ADs in the first-degree relatives of the BC group compared to the control group, could partly be attributed to the difference in the mean age between the groups; however, it is unlikely to be the sole reason. In addition, our study did not include data regarding the age of relatives, which could affect differences in the frequency of ADs. The mean BMI of the patient group was also significantly higher than that of the control group. However, this is compatible with the previous research that demonstrated obesity to be associated with an increased incidence of BC[10-20] and unlikely to have any influence on the results of the study. Our study was planned to investigate the frequency of ADs in the relatives of the patient and control groups, and a possible limitation was that we did not record the presence of ADs in the patient and control groups, which could potentially impact the results.

The prevalence of ADs in the relatives of patients with BC has not been previously studied in detail; therefore, our study might shed light on this association and might guide future studies to elucidate this issue.

Conclusion

Our results suggest that the first-degree relatives of BC patients could be at increased risk of developing ADs, and common genetic factors might play roles in the pathogenesis of these two different categories of diseases.

Ethics

Ethics Committee Approval: The Research Ethics Committee of Gazi University granted ethical approval to our study (no: 2017-114 dated: 03.07.2017).

Informed Consent: Written informed consent form was obtained from each patient.

Authorship Contributions

Concept: A.A., B.G., M.A.Ö., A.T., Ş.H., H.B., A.Ö., A.Ü., N.G., G.T., Design: A.A., B.G., M.A.Ö., A.T., Ş.H., H.B., A.Ö., A.Ü., N.G., G.T., Data Collection or Processing: A.A., G.T., Analysis or Interpretation: A.A., B.G., Literature Search: A.A., Writing: A.A., B.G.

Conflict of Interest: No conflict of interest was declared by the author.

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