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RESEARCH ARTICLE

The Role of Stressful Life Events in Breast Cancer Etiology

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SUMMARY

INTRODUCTION: *This study aimed to investigate the relationship between stressful life events experienced in the last year and breast cancer.*
METHODS: *Measurements were made with the Life Experiences Survey developed by Sarason. The sum of the scores perceived as negative was calculated separately as the negative life experiences score (NegLES), and the sum of the scores reported as positive was calculated separately as the positive life experiences score (PosLES). The sum of the two scores was evaluated as the total life experience score (TotLES).*
RESULTS: *A total of 278 participants, 139 patients with breast cancer and 139 diagnosed with breast fibrocystic disease (control), were included in this study. The median age of all participants was 48 (range:21-75). The median age of the cancer group was 49 years (range: 26-75) and the median age of the control group was 48 years (range 21-71)(p=0.118). The mean of NegLES was -7.0±6.5 in cancer patients and 4.6±5.7 in control group and the mean TotLES was -5.9±6.6 in cancer patients and -3.5±6.3 in control group (for both, p=0.001). PosLES was similar for both groups (p=0.697). Compared to the control group, absolute low NegLES (OR: 0.938 95% CI 0.900-0.977, p=0.002) and absolute low TotLES (OR: 0.942 95% CI 0.906-0.979, p=0.002) were associated with decreased breast cancer. PosLES did not predict breast cancer (OR: 0.988 95% CI 0.891-1.095, p=0.813).*
DISCUSSION AND CONCLUSION: *It was concluded that the negative life events experienced by women in the last year contributed to the risk of breast cancer.*

Keywords: *Breast cancer, Sarason, Stressful Life Events*
İngilizce Kısa Başlık: Stressful Life Events and Breast Cancer

Stresli Yaşam Olaylarının Meme Kanseri Gelişimdeki Rolü

ÖZET

GİRİŞ ve AMAÇ: *Son bir yıl içerisinde yaşanılan stresli yaşam olayları ile meme kanseri arasındaki ilişkiyi araştırmak.*
YÖNTEM ve GEREÇLER: *Ölçümler Sarason tarafından geliştirilen Yaşam Deneyimleri Ölçeği ile gerçekleştirildi. Olumsuz olarak algılanan yaşam olaylarının puanlarının toplamı negatif yaşam deneyimleri skoru(NegLES), olumlu olarak bildirilen ise pozitif yaşam deneyimleri skoru(PosLES) olarak ayrı ayrı hesaplandı. Toplanması ile de toplam yaşam deneyimleri puanı(TotLES) elde edildi.*
BULGULAR: *Bu çalışmaya, 139 meme kanseri hastası ile birlikte 139 meme fibrokistik hastalık tanısı olan toplamda 278 gönüllü dahil edildi. Tüm katılımcıların medyan yaşı 48'di (min: 21 maks: 75). Kanser grubunun medyan yaşı 49(min: 26-maks: 75) ve fibrokistik grup ise medyan yaşı 48(min: 21 maks: 71) olarak saptandı(p=0.118). NegLES kanser hastalarında ortalama -7.0±6.5, fobrikist hastalarında ortalama 4.6±5.7 ve TotLES kanser hastalarında ortalama -5.9±6.6, fibrokistik hastalarında ortalama -3.5±6.3 olarak saptandı (her ikisi için, p=0.001). PosLES her iki grup için benzerdi (p=0.697). Kontrol grubuna göre kanser olanlar logistik regresyon ile değerlendirildi. Buna göre NegLES azalması (OR: 0.938 95% CI 0.900-0.977, p=0.002) ve TotLES azalması (OR: 0.942 95% CI 0.906-0.979, p=0.002) meme kanseri riskini azaltıyordu. PosLES meme kanseri gelişimini tahmin etmiyordu (OR: 0.988 95% CI 0.891-1.095, p=0.813).*
TARTIŞMA ve SONUÇ: *Bu çalışma ile, kadınların son bir yıl içerisinde yaşadıkları olumsuz yaşam olaylarının, meme kanseri gelişimine katkı sağladığı sonucuna ulaşıldı.*

Anahtar Kelimeler: *Meme kanseri, Sarason, Stresli yaşam olayları*
Türkçe Kısa Başlık: Stresli Yaşam Olayları ve Meme Kanseri

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1. INTRODUCTION

Breast cancer is the most common type of cancer in women and is the cause of approximately 15.5% of cancer-related deaths in women. Approximately 2.3 million new breast cancer diagnoses are expected in 2020. This value represents approximately 11.7% of all cancers[1].

Physiological risk factors for breast cancer, such as high body mass index, height, dense breast tissue, history of radiation exposure, and the presence of the first pregnancy at an advanced age, have been defined[2-9]. In addition, genetic facilitating factors that are effective in the development of breast cancer continue to be investigated [10]. The breast cancer risks for BRCA1 carriers to age 70 to be between 57% and 66%, and between 45 and 61% in BRCA2 carriers[11]. Breast cancer risk factors have not been sufficiently revealed yet, and identifying treatable or modifiable factors may contribute to the development of prevention strategies that reduce the incidence of breast cancer.

Stressful life events are associated with worse survival and higher mortality in cancer patients, and it is still controversial whether they increase the incidence of cancer[12] Most patients diagnosed with breast cancer believe that the stress they have experienced in the past contributes to their cancer development[13]. However, despite many studies, the relationship between stressful life events in the past and breast carcinogenesis has not been clearly demonstrated. Some epidemiological studies have found that life experiences increase breast cancer risk [14-16]. However, other studies did not support these results[17]. Differences in the scales used in the studies, not evaluating the positive or negative effects of events from the perspective of the patients, and researching different time periods in the past may cause different results. Divorces in troubled marriages may have negative psychological effects in some individuals, while it may cause positive effects in others.

In this case-control study, we aimed to reveal the life events of the last year from the patient's perspective and investigate their contribution to the risk of developing breast cancer.

2. MATERIALS AND METHOD

2.1. Participants

Breast cancer patients who applied to university hospital outpatient oncology clinic between January 1, 2021 and November 01, 2021, and patients who applied with breast cancer screening (control group) were included in this study. Inclusion criteria were determined as being over 18 years old and being diagnosed with breast cancer in the last one year or having fibrocystic disease confirmed with tru-cut biopsy in the last three months. Patients with BRCA1-2 positive breast cancer and those with a family history of breast cancer were excluded from the study.

This study was conducted by the provisions of the 1995 Declaration of Helsinki, and an informed consent form was signed by all participants. Approval was obtained by the local ethics committee. (protocol no: 2020.229.09.16).

2.2. Measurements and procedures

Measurements were made with the "Life Experiences Survey" developed by Sarason[18]. The Turkish validity and adaptation study of the survey, which has 47 questions in its generic version, was published by Aytar and Erkman, and it was formed as a total of 57 questions by adding 10 events that are frequently encountered in the Turkish population[19].

The questionnaire was filled with face-to-face interviews. Participants were asked about life events with sentences starting with "in the last year" and were asked to report the events if any. Then, they were asked to score the impact of the events on their lives as negative (-3 points), neutral (0 points), or positive (+3 points). The sum of the scores perceived as negative was calculated separately as the negative life experiences score (NegLES), and the positive ones as the positive life experiences score (PosLES). By the sum of two scores, it was evaluated as the Total Life experiences score (TotLES).

2.3. Statistical analysis

Participants were divided into 2 as cancer group and control group, and categorical variables such as marital status, number of children, occupation, education, and total monthly income were compared with the Pearson's chi-squared test. The normal distributions of age and life experience scores, which are continuous variables, were tested with Kolmogorov-Smirnov. Independent sample t-test was used for the age variable, and the Mann-Whitney u test was used for other parameters. A logistic regression model analysed whether the variables predicted breast cancer or not. SPSS Statistic software version 24 (SPSS Inc., Chicago, III) was used for all statistical analyses and a p-value <0.05 was considered significant.

3. RESULTS

A total of 278 patients, 139 of whom were diagnosed with breast cancer and 139 were diagnosed with breast fibrocystic disease (control), were included in this study. The median age of all participants was 48 (range:21-75). The median age of the cancer group was 49 (range:26-75) and the median age of the control group was 48 (range: 21-71). There was no difference between the two groups age (p=0.118), marital status (p=0.430), number of children (p=0.348), occupation (p=0.637), education (p=0.419), and monthly income (p=0.618). (Table 1)

NegLES was found to be mean -7.0±6.5 in cancer patients, mean -4.6±5.7 in control group, and TotLES as mean -5.9±6.6 in cancer patients and mean -3.5±6.3 in control group. (for both p=0.001). PosLES was similar for both groups (p=0.697).

Cancer patients compared to the control group were evaluated by logistic regression. Absolute low NegLES (OR: 0.938 95% CI 0.900-0.977, p=0.002) and absolute low TotLES (OR: 0.942 95% CI 0.906-0.979, p=0.002) were associated with decreased breast cancer. PosLES did not predict breast cancer (OR: 0.988 95% CI 0.891-1.095, p=0.813).

In the subgroup analysis, the mean of NegLES was -6.8±6.5 in hormone receptor (HR) (+) HER2(-) patients, 7.4±7.1 in HER2(+) HR (any) patients, and -6.9±5.5 in triple-negative patients. Both NegLES and TotLES scores were lower in HR(+) HER2(-) patients compared to control group. (respectively, p=0.002, p=0.002) (Table 3)

4. DISCUSSION

The role of stressful life events in the development of breast cancer is discussed with different hypotheses. In the study conducted by Priestman et al. in the British population, it was concluded that stressful life events in the last 3 years did not increase the risk of breast cancer compared to normal individuals[17]. However, in the analyses of Lillberg et al. in Fin population, it was determined that the negative life events of divorce/separation, death of a spouse, with an effect accumulated over years, increased the breast cancer risk of patients between 1.35 and 2.26 fold[12]. In another study, the relationship between breast cancer and life events could not be shown [20]. In our study, life events which are common in societies were examined from the perspective of individuals instead of "the number of events", and the effects of the events on individuals were investigated as positive or negative. The absolute value of NegLES was higher in breast cancer patients than in the control group (mean -7.0 vs -4.6, p=0.001). The two groups were similar in score of positive life events calculated with the survey (mean 1.1 vs 1.1 p=0.697). When the total life experiences score was evaluated, it was seen that cancer patients were under more psychological stress than the control group in the last 1 year (mean -5.9±6.6 vs -3.5±6.3, 0.001). When examined by regression analysis, a decrease in negative life events also reduces the risk of cancer. No relationship could be established between positive life events and breast cancer risk (OR: 0.988 95% CI 0.891-1.095, p=0.813)

Exposure to high levels of estrogen throughout life is an important risk factor for breast cancers[21]. As a result of early menarche and late menopause, women are exposed to estrogen for a longer period of time and are at risk for breast cancer[22]. In the study of Ursin

et al., reproductive factors affecting lifetime estrogen exposure only create a risk for HR (+) breast cancer, but do not increase the risk of HR (-) breast cancer. Ma et al. showed the relationship between hormone exposure and HR (+) breast cancer[23]. In animal experiments, it was revealed that catecholamines increased due to stress caused an increase in estrogen and that spatial memory regions in the brain played a role in this increase [24 25]. In the subgroup analyses of our study, NegLES was found to be higher in women with HR+ breast cancer compared to those without breast cancer (mean -6.8 vs -4.6 p=0.002). However, negative life events were found to be similar in both HER2 (+) and triple-negative breast cancer patients compared to the control group (respectively, p=0.070, p=0.133).

The small number of patients compared to other cohort studies was a limitation of our study[14, 26]. To the best of our knowledge, the sample size was not planned before the study, since there was no study with a similar design. Finally, data on early-late menopause were not collected in our study. What made our study stronger than other studies was that it measured the impact of these life events on individuals, not the number of life events. To our knowledge, it was the first study to investigate the relationship between breast cancer subtypes and life events.

As a result, we concluded that patients with hormone receptor-positive breast cancer have more negative life experiences in the last year than individuals without cancer, and this may have a role in the development of cancer. In future studies, the pathophysiology of negative life events in the development of breast cancer should be investigated

Acknowledgment

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Conflicts of Interest

None

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Ethical Approval

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TABLES

Table 1. Characteristics of the participants

		Cancer (%) n=139	Control (%) n=139	p
Age	Mean(±sd)	49.6±10.2	47.6±11.1	0.118
	Median(range)	49(26-75)	48(21-71)	
Marital status	Married	114 (82.0%)	113 (81.3%)	0.430
	Single	3 (2.2%)	8 (5.8%)	
	Divorced	12 (8.6%)	9 (6.5%)	
	Widow	10 (7.2%)	9 (6.5%)	
Number of children	No	4 (2.9%)	9 (6.5%)	0.348
	1-2	107 (77.0%)	101 (72.7%)	
	3 and above	28 (20.1%)	29 (20.9%)	
Occupation	Never worked	89 (64.0%)	82 (59.0%)	0.637
	Retired	9 (6.5%)	12 (8.6%)	
	Employee	41 (29.5%)	45 (32.4%)	
Education	Primary education	87 (62.6%)	78 (56.1%)	0.419
	High school	35 (25.2%)	37 (26.6%)	
	University and above	17 (12.2%)	24 (17.3%)	
Monthly income (TL)	Under 2500	38 (27.3%)	31 (22.3%)	0.618
	2500-5000	66 (47.5%)	67 (48.2%)	
	5000-10.000	29 (20.9%)	31 (22.3%)	
	10,000 and above	6 (4.3%)	10 (7.2%)	
TL: Turkish lira, SD: standard deviation				

Table 2. Evaluation of the effects of variables on breast cancer development by univariate logistic regression analysis according to the control group

Variable	Category	OR (95% CI)	p^*
Age	Continuous	1.018 (0.995-1.041)	0.118
Number of children	0/1-2/>3	1.030 (0.783-1.355)	0.834
Education	Categorical	0.808 (0.586-1.114)	0.194
Monthly income	Categorical	0.836 (0.628-1.113)	0.220
NegLES	Continuous	0.938 (0.900-0.977)	**0.002**
PosLES	Continuous	0.988 (0.891-1.095)	0.813
TotLES	Continuous	0.942 (0.906-0.979)	**0.002**
**Statistically significant values are marked in bold.*			

Table 3. Comparison of life change scores of breast cancer subgroups with the control group

		Cancer (n=139)	Control (n=139)	p*
Negative life experiment score	• HR (+) HER2 (-)	• -6.8±6.4	-4.6±5.7	**0.001**
	• HER2 (+) HR (any)	• -7.4±7.1	-4.6±5.7	0.066
	• Triple Negative	• -6.5±5.5	-4.6±5.7	0.126
Positive life experiment score	• HR (+) Her (2-)	• 1.1±2.1	1.1±2.4	0.968
	• HER2 (+) HR (any)	• 1.2±2.5	1.1±2.4	0.961
	• Triple Negative	• 0.4±1.3	1.1±2.4	0.165
Total life experiment score	• HR (+) Her (2-)	• -5.7±6.3	-3.5±6.3	**0.001**
	• HER2 (+) HR (any)	• -6.2±7.4	-3.5±6.3	0.094
	• Triple Negative	• -6.1±5.8	-3.5±6.3	0.074
HR: Hormone receptor, HER2: Human Epidermal growth factor receptor-2. *Statistically significant values are marked in bold.				

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