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ORIGINAL ARTICLE

Stressful life events and breast cancer risk: a hospital-based case-control study

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Summary

Purpose: *Elucidation of the factors contributing to the incidence of breast cancer is of crucial importance for the development of preventive or therapeutic strategies targeting the disease. Research on stress and breast cancer has been documented by various studies published over the years. In view of breast cancer importance as the most commonly occurring malignancy in females in Serbia, this study was undertaken to examine the association between stressful life events and breast cancer risk.*

Methods: *The present hospital-based case-control study comprised 120 new breast cancer cases and 120 hospital controls matched with respect to age (± 2 years). This study used the Paykel Life Events Scale to obtain information about stressful life events in the years before diagnosis. The SPSS statistical package was used and odds ratios (OR) and 95% confidence intervals (95% CI) were calculated from multivariate conditional logistic regression model.*

Results: *Multiple conditional logistic regression analysis revealed six independent predictors of breast cancer risk: experience of severe and moderate threats (first 25 life events from the scale) (OR=3.15, 95% CI=2.01-4.93), son's military service (OR=6.09, 95% CI=4.17-12.37), death of close family member (OR=7.98, 95% CI=2.18-9.14), moderate financial difficulties (OR=3.26, 95%CI=1.24-8.56), maternal death in childhood (OR=3.46, 95% CI=1.21-9.92) and serious financial difficulties (OR=3.55, 95% CI=1.20-10.52).*

Conclusion: *Stress exposure has been proposed to contribute to the etiology of breast cancer. There is a need for understanding the differing physiological effects of types or times of stress exposure.*

Key words: *breast cancer, epidemiology, risk factors, stressful life events*

Introduction

Elucidation of the factors contributing to the incidence of breast cancer is of crucial importance for the development of preventive or therapeutic strategies targeting the disease. In addition to well-established risk factors for breast cancer, i.e., having a first-degree relative with breast cancer, early menarche, late menopause, nulliparity or bearing of first child at a later age, certain types of benign breast diseases, etc, [1], other contributors, whose effects have been more difficult to evaluate, include smoking, certain aspects of nutrition, physical activity, and psychological stress [2,3].

The possible contribution of psychological stress to breast cancer development has been extensively studied within different disciplines, i.e. epidemiology, physiology, and molecular biology. Epidemiologic studies, which look at the stress–breast cancer association in human populations, provide inconsistent findings regarding relative contribution of stress to breast cancer risk, probably due to the use of different measures of stress and other study methods.

In view of breast cancer importance as the most commonly occurring malignancy in females

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in Serbia [4], this study was undertaken to examine the association between stressful life events and breast cancer risk.

Methods

One hundred and twenty new breast cancer cases (within two years from diagnosis) and 120 hospital controls (patients from the Clinic of Physical Medicine and Orthopedic Clinic, with non-occupational accidental injuries and no breast cancer and benign breast disease) matched by age (± 2 years) were interviewed by a single interviewer. This study used the Paykel Life Events Scale [5], with 65 event items ranging from most to least upsetting, to obtain information about stressful life events in the years before diagnosis.

Statistics

The SPSS statistical package (SPSS Inc, Chicago, Ill) was used and variables were considered to be significant when p<0.05. OR and 95% CI were calculated from multivariate conditional logistic regression models.

According to McNemar's and t-test 19 variables were selected and considered for further analyses. These variables were: death of close family member, unfaithful husband, serious financial difficulties, time period of exposure to serious financial difficulties prior to diagnosis, being fired, getting divorced, serious illness of family member, time period between serious illness of family member and diagnosis, beginning of extramarital affair, child married without approval, increased arguments with husband, son's military service, increased arguments with family member, moderate financial difficulties, decrease in working time, new person in the family, experience of life events, experience of severe life events (first 5 life events from the scale), and experience of severe and moderate threats (first 25 life events from the scale).

Table 1. Selected characteristics of the study population

Characteristics	*Patients (%)*	*Controls (%)*	*p-value*†
Age (years)			
30-39	8.3	12.5	
40-49	40.8	33.3	
50-59	30.8	35.0	matched
60-69	20.0	19.2	
Mean age, years (±SD)	50.8 (8.9)	50.8 (8.7)	0.55
Marital status			
Never married	2.5	4.2	
Married	79.2	81.7	1*
Widowed	10.0	10.0	
Divorced	8.3	4.2	0.27
Education			
No formal	8.3	3.3	
Primary school	37.5	38.3	
Secondary school	25.8	26.0	1*
College	2.5	24.0	
University	5.8	8.3	0.57
Occupation			
Working	68.3	73.3	
Housewife	30.8	26.7	
Retired	0.8	0.0	0.25
Place of residence			
Rural	37.5	43.3	1*
Urban	62.5	56.7	0.20
Menopausal status			
Premenopausal	80.8	80.0	1*
Postmenopausal	19.2	20.0	0.55

†p-value by matched t-test, *risk ratio=1 in baseline category, SD: standard deviation

Results

Table 1 summarizes selected characteristics of the study population.

Patients and controls were similar in terms of age, marital status, education, occupation, place of residence and menopausal status.

Both groups of respondents consisted of female patients with median age 50.8 years (range 30-69). Most of them were married (79.2 vs 81.7%), working (68.3 vs 73.3%), premenopausal (80.8 vs 80.0%), urban dwellers (62.5 vs 56.7%), with primary (37.5 vs 38.7%) and secondary education (25.8 vs 26.0%).

Patients were statistically more likely to have a stressful life event in the years prior to diagnosis, severe life events (first 5 from the scale) and severe and moderate life events (first 25 from the scale), compared to controls (Table 2).

Multiple conditional logistic regression analysis revealed six independent predictors of breast cancer risk: experience of severe and moderate threats (first 25 from the scale) (OR=3.15,95% CI=2.01-4.93), son's military service (OR=6.09,95% CI=4.17-12.37), death of close family member (OR=7.98, 95% CI=2.18-9.14), moderate financial difficulties (OR=3.26, 95% CI=1.24-8.56), maternal death in childhood (OR=3.46, 95% CI=1.21-9.92) and serious financial difficulties (OR=3.55, 95% CI=1.20-10.52) (Table 3).

The time lapse between the date of the life event and the date of diagnosis was not associated with increased risk for breast cancer.

Table 2. Experience of stressful life events

Variable	*Mean*	*SD*	*p-value*†
Experience of stressful life events			
Cases	11.13	2.66	
Controls	8.79	2.14	0.0000
Experience of severe life events (first 5 from the scale)			
Cases	1.33	0.429	
Controls	1.00	0.000	0.0390
Experience of severe and moderate life events (first 25 from the scale)			
Cases	2.81	1.29	
Controls	1.54	0.67	0.000

†p-value by matched t-test, SD: standard deviation

Discussion

The plausibility of a stress–breast cancer association stems from two important physiological roles of the stress hormone cortisol. Cortisol plays an essential part in mammary gland development and function, which may sensitize mammary tissues to modulations in cortisol signaling in the presence of stress. It also has an impact on certain aspects of estrogen activity in the mammary gland, which may initiate protumorigenic changes during periods of stress [6,7].

In our study, patients were statistically more likely to have stressful life events in the years prior to diagnosis, severe life events and severe and moderate life events, compared to controls. Also, this study found that experience of severe and moderate threats (first 25 life events from the scale), death of close family member and son's military service increase the risk for breast cancer development. The stress most strongly associated with increased breast cancer risk appears to be stress induced by major life events [8], whereas findings regarding work-related, caregiving, or everyday stress vary considerably [9-11]. A meta-analytical review of epidemiologic studies in the area of stress and breast cancer incidence, between 1966 and 1997 was carried out by Petticrew and colleagues, with specific testing for an association between bereavement and breast cancer and other life events (including total number of life events, major life changes, separation, war experiences, serious illness, financial problems, and work problems) and breast cancer [12]. The analysis was limited to case–control and limited prospective designs: 11 studies for bereavement and breast cancer (six case–control studies and five limited prospective studies); 15 studies for other life events and breast cancer (eight case–control studies and seven limited prospective studies). This meta-analysis demonstrated no association between bereavement and breast cancer (OR=1.06, 95% CI=0.95-1.18), but a more than twofold increase in breast cancer risk was associated with other life events (OR=2.63, 95% CI=2.34-2.96).

A more recent meta-analysis was performed by Duijts and colleagues [13]. Twenty-seven studies published between 1966 and December 2002 examining the relationship between stressful life events and breast cancer risk were analyzed. The studies encompassed a wider variety of research designs and included ten retrospective case–control studies, four prospective case–control studies, nine limited prospective cohort studies, and four prospective cohort studies. The findings concluded that variables significantly associated with breast cancer risk are stressful life events (OR=1.77, 95% CI=1.31-2.40), death of a spouse (OR=1.37, 95% CI=1.10-1.71), and death of a relative or friend (OR=1.35, 95% CI=1.09-1.68). A disparity in results was found on the basis of study design. Prospective studies showed a higher summary OR associated with stressful life events than retrospective design studies (OR=2.46, 95% CI=0.98-6.18 and OR=1.93, 95% CI=1.13-3.31, respectively). This was attributed to the possible presence of recall bias in retrospective studies. Studies that took into account well-established breast cancer risk factors showed a statistically significant association with stress (for example, OR=2.22, 95% CI=1.39-3.56 for stressful life events), whereas studies that did not control for such factors did not report an association when pooled (for example, OR=1.04, 95% CI=0.90-1.20 for stressful life events).

In our study, women diagnosed with breast cancer were found to be significantly more likely to have undergone stress due to maternal death in childhood. There is a possibility that exposure to stress at certain periods of development may have a stronger impact on breast physiology. For example, women diagnosed with breast cancer were found to be significantly more likely to have undergone stress due to losses or social deficits in childhood and adolescence [14]. Death of a mother during a girl's childhood was found to be significantly associated with increased breast cancer risk in a prospective cohort in the Baltimore Epidemiologic Catchment Area Study [15]. Jacobs and

Table 3. Significant predictors of breast cancer

Variable	*OR**	*95% CI*[§]	*p-value*[†]
Experience of severe and moderate life events	3.15	2.01-4.93	0.0000
Son's military service	6.09	4.17-12.37	0.0011
Death of close family member	7.98	2.18-9.14	0.0017
Moderate financial difficulties	3.26	1.24-8.56	0.0162
Maternal death in childhood	3.46	1.21-9.92	0.0209
Serious financial difficulties	3.55	1.20-10.52	0.0221

*odds ratio, [§]95% confidence interval and [†]p-value estimated by multivariate conditional logistic regression analysis

Bovasso [15] speculated that increasing vulnerability to breast cancer is most likely attributed to the depression and trauma due to the loss of the mother, which last for several years and are a well-documented research finding.

The latency period between stress exposure and breast cancer initiation is unknown. In general, the process of breast cancer development is estimated to occur over 10 to 20 years [16,17]. In agreement with this, a study by Lillberg and colleagues found that breast cancer risk is most strongly correlated with life events that have occurred within 11 years prior to diagnosis [18]. Since the time periods of exposure examined in different studies vary widely, some of the assessed exposures may fall outside the biologically relevant time, thus leading to different study results. According to our study, the time lapse between the date of the life event and the date of diagnosis was not associated with an increased risk for breast cancer.

Our study supported the possibility that financial difficulties might be associated with an increased risk of breast cancer. At this point in time, it is unclear whether stress acts as a mediating factor between socioeconomic status and breast cancer, or whether socioeconomic status and stress are independently correlated with breast cancer risk. Evidence has been presented for both possibilities [19,20]. The analysis of stress–breast cancer associations should therefore be carried out in both the presence and the absence of socioeconomic status in order to rule out a confounding effect.

Stress induced by life events shows a more consistent association with breast cancer risk in prospective studies [18,21,22]. The European Prospective Investigation into Cancer – Norfolk study, however, found no association for life events within the 5 years previous to study baseline [23], demonstrating that factors other than the type of stress also contribute to study discrepancy.

Conclusion

Stress exposure has been proposed to contribute to the etiology of breast cancer. Epidemiologic evidence has been difficult to interpret due to use of different measures of stress and other study methods that lead to inconsistent findings. There is a need for understanding the differing physiological effects of types or times of stress exposure.

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