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Life Stress and Losses and Deficit in Adulthood as Breast Cancer Risk Factor: A Prospective Case–Control Study in Kuopio, Finland

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Abstract. *Background: To the Authors' knowledge, the associations between the life stress and losses and deficit in adulthood and the risk of breast cancer (BC) are rarely considered together in a prospective study. Patients and Methods: In an extension of the Kuopio Breast Cancer Study, 115 women with breast symptoms were semi-structurally interviewed in-depth, as well as asked to complete standardised questionnaires, and all study variables were obtained before any diagnostic procedures were carried out. The Montgomery-Åsberg depression rating scale (MADRS) was used to evaluate the depression of the study participants. Results: The clinical examination and biopsy showed BC in 34 patients, benign breast disease (BBD) in 53 patients, and 28 individuals were shown to be healthy (HSS). The BC group had significantly higher mean score for the loss of social status in adulthood than did the BBD and HSS groups ($p<0.05$). In addition, the women in the BC group had significantly higher mean score for stress in adulthood in the previous 6-10 years ($p<0.01$), in the previous 2-6 years ($p<0.05$) and for stress in adulthood in the previous two years ($p<0.05$) than the women in the BBD and HSS groups. The BC group also had significantly more severe losses in adulthood than the BBD and HSS groups ($p<0.01$). The results indicated that breast cancer patients tended to have more life stress and losses in adulthood than did those in the BBD and HSS groups. Conclusion: The results of this study support a weak association between life stress and losses in adulthood and breast cancer risk and it might be that stress and losses impacts indirectly on breast cancer risk, affecting behaviour, or directly on the hypothalamic–pituitary–adrenal axis and autonomic nervous system functioning.*

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Stressful life experiences include physical stressors such as autoimmunity, infections, pathogens, physical trauma and toxins, and psychological stressors such as major life events, abuse, psychological trauma, or factors related to the environment in the home, neighbourhood or workplace. The ability to adjust or habituate to repeated stress is also determined by the way a person perceives a stressful or adverse life situation. According to allostasis theory (1, 2), stressful life events are risk factors for allostatic load later in life, mainly through alteration in the hypothalamic–pituitary–adrenal (HPA) axis and autonomic nervous system functioning. Hormonal factors, such as early age at menarche, later age at menopause, later age at first full-term pregnancy and hormone replacement therapy, are known to be the main risk factors for sporadic breast cancer (BC) (3). In addition, life-style factors, such as obesity, smoking, alcohol consumption and lack of physical activity, appear to contribute to the increased risk for this malignancy, although the results concerning such factors are inconsistent (3-9). Psychological factors, such as stressful and adverse life events, are widely thought to play a role in the aetiology of BC (10-25). Some studies have found associations between stressful life events and the risk of breast cancer. Forsen (24) reported an increased risk of breast cancer in relation to important emotional loss and cumulative amount of life change due to life events during the past six years. Cooper *et al*. (25) observed that BC patients generally perceived life experiences as being more severe than controls, and that a higher proportion of BC patients than controls reported death of a close friend. In addition Chen *et al*. (10) reported that women with BC were much more likely to have life experiences that were rated by the interviewer as severely threatening than the women with benign breast disease (BBD).

To the Authors' knowledge, the associations between life time stress and losses and deficit in adulthood and risk of breast cancer are rarely considered together, and therefore this was a prospective study to examine the role of losses and

deficit in adulthood as breast cancer risk factors in women with breast symptoms referred by physicians to the Kuopio University Hospital (Finland).

Patients and Methods

The Kuopio Breast Cancer Study was a multidisciplinary cooperative project conducted by different departments of the University of Kuopio and Kuopio University Hospital. The participants of the project included all women who were referred to Kuopio University Hospital (North-Savo Health Care District) for breast examination between April 1990 and December 1995. The Kuopio Breast Cancer Study follows the protocol of the International Collaborative Study of Breast and Colorectal Cancer coordinated by the European Institute of Oncology in Milan, and was initiated as a SEARCH program of the International Agency for Research on Cancer. The collaborative study is based on the assumption that breast cancer and colorectal cancer may have common risk factors. Study centres for the breast cancer study are situated in Canada, Finland, Greece, Ireland, Italy, Russia, Slovakia, Spain and Switzerland (26). The participants of the Kuopio Breast Cancer Study consisted of individuals showing breast cancer symptoms (a lump in the breast or in the axilla, pain in the breast, bleeding from the nipple, nipple discharge and skin dimpling), or an abnormality of the breast and the indications for referral in this study are in line with our previous results in a Breast Cancer Diagnostic Unit in Finland (27).

This case–control study is an extension of Kuopio Breast Cancer Study (28, 29). The study was approved by the Joint Committee of the University of Kuopio and Kuopio University Hospital. Participation was based on written informed consent. Women with breast symptoms or a suspect breast lump had been referred by physicians to the Kuopio University Hospital (Finland) during the study period from January 1991 to June 1992. Women were asked to participate in the study and were interviewedy a psychiatrist (P.O.) before any diagnostic procedures (to determine the level of emotional depression), so neither the interviewer nor the patient knew the diagnosis at the time of the interview. The interviews were recorded, and the ratings were completed before the final diagnosis. The clinical examination, mammography and biopsy showed BC in 34 (29.6%) patients, BBD in 53 (46.1%) patients and 28 (23.4) patients with healthy breasts (HSS) (Table I).

Assessment of life events and stress. The research method was a semi-structured in-depth interview (17). At the beginning of the interview, the patients drew their 'life lines' and a line describing being a woman, which supported the interview. In the 'draw a line of your life' the patient was asked to draw positive life experiences ('good times') with lines pointing upwards and negative life experiences ('hard times') with lines pointing downwards. Adverse and stressful life events were evaluated over the whole lifespan, with particular reference to the previous ten years before admission. The adverse or stressful life events and the context surrounding them were marked on the 'life line paper' during the interview. After the interviews, the life events were rated (by P.O.) according to the degree of threat or stress they were likely to pose, and each adverse or stressful life event was graded on a five-point scale, grade I (one point) indicating non-threatening event and grade V (five points) a severely threatening event. The defences used were also assessed on a five-point scale: grade I (one point) indicating very defensive, in denial and grade V (five points) non-defensive. The 'working through and actively confronting the stressful event' variable was also rated on a five-point scale: grade I (one point) indicating not resolved and grade V (five points) fully resolved. These measurements were put together in the final statement, one to two points on the scale meant little or mild loss or stress, and five meant very hard loss or stress.

The rated case record included the loss events from childhood (under three years of age and 4-12 years of age), adolescence (13-23 years of age), adulthood and especially the last ten years prior to the investigation.

Coping and defence strategies. A modified Haan coping and defence inventory (30) was used. This inventory is divided into ten scales, and each scale has subscales from grade 0 to grade III: with 0 meaning no definition, I: coping; II: defending and III: fragmentation.

Beck depression inventory (BDI). The women completed the BDI (31, 32) with 21 variables. The investigator used the modified inventory divided into three grades: grade I (score 0-13), no depression; grade II (score 14-24), moderate depression; grade III (score over 24), severe depression.

Spielberger trait inventory. All study participants completed the Spielberger trait inventory (33). Trait anxiety was assessed using the subscale from the Inventory, and the ten items refer to how a person generally feels, with a higher total score reflecting a higher anxiety trait (20-80 range).

Montgomery Åsberg depression rating scale (MADRS). The MADRS with ten variables (scores from zero to six) was used to evaluate the depression of the study participants (34), and the test was rated as follows: grade I (scores 0-6), no depression; grade II (score 7-19), mild depression; grade III (score 20-34), moderate depression; and grade IV (score 35-60), severe depression.

Statistical analysis. Significance of the results was calculated with the SPSS/PC statistical package (SPSS Inc., Chigaco, IL, USA). Correlations and differences between the study groups (BC, BBD and HSS groups) were measured with the two-sided Chi-square test and non-parametric Kruskal-Wallis variance analyses. Results were considered statistically significant at a p-value <0.05.

Results

The mean age of the BC patients was 51.5 years. The corresponding figure for the patients with BBD was 47.5 years and for the HSS group 45.7 years. Although the patients in the BC group were older than those in the BBD or HSS groups, the age difference was not statistically significant ($p=0.12$). The majority of the patients (85/115, 74%) were married or living in a steady relationship. Almost half of the patients (41.7%) had graduated from primary school, and 25% had a college education. By profession, the patients represented industrial and service employees (25.2%), office employees (10.4%), health care employees (8.7%), and farmers (8.7%), and almost 23.5%

Table I. *Characteristics of the study participants.*

Variable	BC (n=34)	BBD (n=53)	HSS (n=28)	*p*-Value
Age (mean, years)	51.6	47.6	45.7	0.12
Height (mean, cm)	164.4	162.3	160.8	0.75
Body weight (mean, kg)	72.5	67.8	68.3	0.25
Age at menarche (mean, years)	13.4	13.4	13.4	0.99
Age at birth of I child (mean, years)	25.2	25.0	25.0	0.92
Age at menopause (mean, years)	47.9	48.9	50.0	0.53
No. of children (mean)	2.6	2.4	2.5	0.27
Parity	31 (91%)	44 (83%)	23 (82%)	0.50
Breast feeding (mean, months)	3.6	3.4	3.9	0.77
Use of oral contraceptives	13 (38%)	25 (47%)	18 (64%)	0.12
HRT	27 (79%)	36 (68%)	14 (50%)	0.44
Premenopausal	13 (38%)	28 (53%)	18 (64%)	0.10
Postmenopausal	21 (62%)	25 (47%)	10 (36%)	0.12
History of previous BBD	18 (53%)	22 (42%)	10 (36%)	0.37
Family history of BC	1 (3%)	5 (9%)	5 (18%)	0.21
Use of alcohol	21 (62%)	31 (58%)	13 (46%)	0.44
Smoking	15 (44%)	21 (40%)	10 (36%)	0.80

HRT: Use of hormonal replacement therapy; BC: breast cancer; BBD: benign breast disease; HSS: healthy study participants.

Table II. *The severity of losses in adulthood for the healthy study participants (HSS), for the patients with benign breast disease (BBD) and for the patients with breast cancer (BC). The women with BC had significantly more grade III-V losses than the women in the BBD and HSS groups.*

	Study groups (n, %)						
	HSS		BBD		BC		
Severity of losses	n	%	n	%	n	%	*p*-Value (overall)
No losses (I)	15	54	26	49	19	56	0.001
Few losses (II)	5	18	22	42	2	6	
Some losses (III)	5	18	4	8	11	32	
Clear losses (IV)	2	7	1	2	1	3	
Strong losses (V)	1	4	0	0	1	3	
Total	28	100	53	100	34	100	

were retired. The combined mean gross income of both spouses in the patients with BC was 36,100 € per year. The corresponding figures for the patients with BBD were 27,714 € per year. The patients with BC were significantly (p=0.03) wealthier than the patients with BBD and HSS, as estimated by the combined gross income of the both spouses. The groups differed only slightly from each other as to the factors of the reproductive life of the women (Table I).

The losses and deficit in adulthood. The patients in the BBD group had experienced slightly more losses in adulthood (27/53 patients, 51%) than the patients in the BC group (losses in adulthood in 15/34 patients, 44%) and the patients in HSS group (losses in adulthood in 13/28 patients, 46%). However, there was a trend for the women with BC to have more severe losses in adulthood than these of the BBD and HSS groups. In the BC group 21/34 patients (61.8%) had clear/strong losses in adulthood and in the BBD group 1/53 patients (1.9%) and in the HSS group 3/28 patients (10.7%) (Table II, p<0.01).

The BC group tended to have more severe illness of a close relative in adulthood (13/34 patients, 38.2%) than the patients in the BBD group (12/53 patients, 22.6%) and in the HSS group (4/28 patients, 14.3%). However, there was no significant trend for the patients with BC to have higher mean score of severe illness of a close relative than those in the BBD and HSS groups (Table III).

Table III. *The mean (SD) scores for the losses and the deficit and the stress in adulthood for the healthy study participants (HSS), for the patients with benign breast disease (BBD) and for the patients with breast cancer (BC).*

	Mean score (SD)			
	HSS	BBD	BC	*p*-Value
Loss of social status in adulthood	3.25 (0.96)	3.00 (0.82)	4.33 (0.58)	<0.05
Losses in adulthood	2.92 (0.95)	2.22 (0.51)	3.07 (0.70)	ns
Losses in adulthood (previous 6-10 years)	3.33 (1.20)	3.00 (1.21)	3.29 (1.25)	ns
Losses in adulthood (previous 2-6 years)	2.43 (0.53)	2.90 (0.74)	3.17 (0.58)	ns
Losses in adulthood (last 2 years)	2.86 (0.69)	2.75 (0.97)	3.20 (1.10)	ns
Loss of health in adulthood	2.93 (0.96)	2.91 (0.85)	3.18 (0.95)	ns
Severe illness of a close relative	2.75 (0.95)	2.33 (0.65)	2.77 (0.73)	ns
Deficit in adulthood	3.60 (0.77)	3.15 (0.80)	3.50 (0.88)	ns
Stress in adulthood (previous 6-10 years)	3.06 (0.83)	2.90 (0.83)	3.85 (0.90)	<0.01
Stress in adulthood (previous 2-6 years)	3.19 (0.66)	2.96 (0.74)	3.65 (0.70)	<0.05
Stress in adulthood (previous 2 years)	3.06 (0.85)	2.80 (0.76)	3.71 (0.99)	<0.05

ns: Non-significant.

The BC group had higher mean score of loss of social status in adulthood than the patients with BBD and HSS group (Table III). The BC group also had a significantly higher mean score for the stress in adulthood in previous 6-10 years ($p<0.01$) and in adulthood in previous 2-6 years ($p<0.05$) and in adulthood in previous 0-2 years ($p<0.05$) than did the patients with BBD and the HSS group (Table III).

Discussion

The major neural pathways activated by psychological stressors are the HPA axis and the sympathetic nervous system. Neurosensory impulses are processed in the paraventricular nucleus of the hypothalamus and in the locus coeruleus-noradrenergic centre. In response, the hypothalamus secretes corticotrophin-releasing factor (CRF), which activates the HPA axis, leading to release of pituitary peptides, most notably adrenocorticotrophic hormone (ACTH), enkephalins and endorphins. ACTH induces release of glucocorticoids from the adrenal cortex. Activation of the sympathetic nervous system also stimulates the release of CRF in the paraventricular nucleus of the hypothalamus. The stress-response system seems to function as a positive, bi-directional feedback loop and activation of one component of the system stimulates the other components (35).

According to McEwen's allostasis theory, stress causes the body to activate human physiological systems in order to maintain stability and through allostasis, various physiological systems, the HPA axis, the autonomic nervous system and the cardiovascular, metabolic, and the immune systems, react to stress in order to facilitate individual response and adaptation to the stressors (36). Experience of chronic stress may result in increased allostatic load with repeated or prolonged activation of the allostatic systems. It has been suggested that the prolonged activation of the allostatic system may be implicated in the acceleration of disease processes (36).

The most commonly used hypothesis of the relationship between stress and BC in previous epidemiological studies is that the risk of BC increases with (i) major life events (*e.g.* death of a loved one), (ii) cumulative number of major life events, and (iii) amount of self-perceived stress due to major life events.

The main methods used in this study for the assessment of stress were (i) a checklist of life events, (ii) a semi-structured interview and (iii) use of register data. In the checklist study, the study subjects were asked to indicate which major life events on a given list had occurred over a specific period. In only a few studies have subjects also rated the events in terms of self-perceived severity of stress, and one such study is by Holmes and Rahe (37), consisting of 43 common life-time events weighted according to the amount of life change produced by each life-time event. The Life Events and Difficulties Schedule; a semi-structured interview method developed by Brown and Harris, aims at precise definition and objective rating of event severity (10). The investigator collects detailed information on the occurrence of the study subjects past life events and the context surrounding them. The interviewer then objectively rates the life events according to the degree of threat they were likely to pose to a particular individual. The reliability of The Life Events and Difficulties Schedule has been shown by Chen *et al.* (10) in a report on 119 English women referred for biopsy of a breast lump and interviewed about prior stress before learning biopsy outcome. The 41 women diagnosed with BC were much more likely to have prior life events (past five years) that were rated by the investigator as severely threatening than the women with BBD. There was

no such relationship with life events considered to pose little or no threat to the study subjects. One potential bias arises from age being a confounding factor, and the study by Chen *et al*. has been criticised on such methodological grounds as limited controlling for age (38). In the current study, the BC group was 4.0 years and 5.9 years older than the BBD group and the HSS group, respectively. However, no statistically significant age difference between these groups was found (p=0.12). The Life Events and Difficulties Schedule has been used in two recent case–control studies (13, 14), but there was no relationship with life events and breast cancer risk.

The participants of the current study consisted of individuals showing BC symptoms (a lump in the breast or in the axilla, pain in the breast, bleeding from the nipple, nipple discharge and skin dimpling), or an abnormality of the breast detected during outpatient consultations referred to the Surgical Outpatient Department at the Kuopio University Hospital, Finland. There had been no pre-selection and the indications for referral in this study are in line with previous results in a Breast Cancer Diagnostic Unit in Finland (22). The Authors consider that the study sample can be considered clinically representative for this type of prospective case–control study design. It should be noted that the control group (healthy individuals) was not representative of the wider healthy population, since it consists of women who presented primarily with breast symptoms.

The determination of the role of stress in the assessment of risk of cancer has faced many difficulties such as the health behaviours. In addition to the direct effects of psychological stress on physiological function, subjects who are stressed are more likely to have health habits that put them at great risk of cancer; drug abuse, excess use of alcohol, less exercise and worse nutrition.

In summary, the findings of this study suggest a weak relationship between severe losses in adulthood and breast cancer risk are in line with the finding Chen *et al*. (10), who specifically investigated the adverse life events of patients with BC before biopsy.

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