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

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Abstract. *Background: To our knowledge, the associations between the life stress due to losses and deficit at childhood and adolescence and the risk of breast cancer are rarely considered together in a prospective study. Materials and Methods: This study is an extension of the Kuopio Breast Cancer Study. Women with breast symptoms were referred by physicians to the Kuopio University Hospital (Finland) and were asked to participate in this study. These women (n=115) were interviewed, and all study variables were obtained before any diagnostic procedures were carried out, so neither the investigator nor the participants knew the final diagnosis of breast symptoms at the time of the interview. The research method used was the semistructured in-depth interview method. The investigator used the Montgomery-Åsberg depression rating scale (MADRS) to evaluate the depression of the study participants. All participants were also asked to complete standardized questionnaires (Beck depression inventory and Spielberger trait inventory). Results: The clinical examination and biopsy showed breast cancer in 34 patients, benign breast disease in 53 patients, and 28 individuals were shown to be healthy. The BC group had significantly higher mean score for the deficit in childhood than the BBD and HSS groups (p<0.05). The women in the BC group had almost significantly higher mean scores for the loss of social status in childhood than the women in the BBD and HSS groups (p=0.05). The BC group had also significantly more severe deficit in childhood than the BBD and HSS groups (p=0.02). The results indicated that breast cancer patients tended to have more life stress due to losses and deficit in childhood and adolescence than BBD and HSS groups. Conclusion: The results of this study support a weak association between life stress due to losses and deficit in childhood and adolescence and breast cancer risk. However, the biological explanation for such an association is unclear and it might be that stress due to losses and deficit 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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According to McEwen's allostasis theory (1, 2), early stressful live 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 etiology of BC (10-17). Some studies have found associations between early stressful life events and the risk of breast cancer. Maternal death in childhood (18, 19) and negative childhood experiences of World War II (18) tended to be more prevalent among women with BC than among controls. In addition, Grassi and Molinari (20) reported that patients with BC tended to describe their childhood experiences and relationship with their mothers as being less close than did the controls.

To our knowledge, the associations between the life time stress due to losses and deficit in childhood and adolescence and risk of breast cancer are rarely considered together, and therefore we carried out a prospective study to examine the role of losses and deficit in childhood and adolescence as breast cancer risk factors in women with breast symptoms referred by physicians to the Kuopio University Hospital (Finland).

Table I. *Characteristics of the study participants. Results are shown for the patients with breast cancer (BC), for those with benign breast disease (BBD) and for the healthy study participants (HSS).*

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.

Patients and Methods

The Kuopio Breast Cancer Study is 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 centers for the breast cancer study are situated in Canada, Finland, Greece, Ireland, Italy, Russia, Slovakia, Spain and Switzerland (21). 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 detected during outpatient consultations for women referred to the Surgical Outpatient Department at the Kuopio University Hospital, Finland. There had been no pre-selection of the study participants and the indications for referral in this study are in line with our previous results in a Breast Cancer Diagnostic Unit in Finland (22). We maintain that our study sample can be considered clinically representative this type of prospective case–control study design.

This case–control study is an extension of Kuopio Breast Cancer Study (23, 24). The study was approved by the Joint Committee of the University of Kuopio and Kuopio University Hospital. Participation was based on written 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 interviewed by a psychiatrist (P.O.) before any diagnostic procedures (clinical examination and biopsy), so neither the interviewer nor the patient knew the diagnosis at the time of the interview. The interviews were tape recorded (P.O.), and the ratings were completed before the final diagnosis. The clinical examination, mammography and biopsy showed BC in 34 (29.6%) patients, benign breast disease (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 semistructured in-depth interview (25). 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 10 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 5-point scale, grade I (1 point) indicating non-threatening event and grade V (5 points) a severely threatening event. The defences used were also assessed on a 5-point scale: grade I (one point) indicating very defensive, in denial and grade V (5 points) non-defensive. The 'Working through and actively confronting the stressful event' variable was also rated on a 5-point scale: grade I (one point) indicating not resolved and grade V (5 points) fully resolved. These measurements were put together in the final statement, 1 to 2 points on the scale means little or mild loss or stress, and 5 means 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 10 years prior to the investigation.

Table II. *The mean (SD) scores for the losses and deficit in childhood and adolescence 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
A Losses in childhood	4.00 (0.00)	4.36 (0.67)	4.4 (0.84)	0.29
B Loss of social status in childhood	2.67 (1.15)	3.2 (0.45)	4.0 (0.00)	0.07
C Deficit in childhood	3.15 (0.55)	3.46 (0.72)	3.94 (0.83)	0.05
D Loss of health in childhood	2.00 (0.00)	2.86 (0.9)	3.00 (1.73)	0.08
E Loss of health in adolescence	3.00 (0.53)	3.00 (0.71)	3.56 (0.73)	0.11
F Deficit in adolescence	3.36 (0.50)	3.36 (0.63)	3.75 (0.58)	0.22

Coping and defence strategies. A modified Haan coping and defence inventory (26) was used. This inventory is divided into ten scales, and each scale has subscales from grade 0 to grade 3: with 0 meaning no definition, 1=coping, 2=defending and 3=fragmentation.

Beck depression inventory (BDI). The women completed the BDI (27, 28) 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 (29). 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 0 to 6) was used to evaluate the depression of the study participants (30), 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 women (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% 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).

Table III. *The severity of deficit at childhood for the healthy study participants (HSS), for the patients with benign breast disease (BBD) and for the patients with breast cancer (BC).*

	Study group (n, %)						
	HSS		BBD		BC		*P*-Value
Severity of deficit	n	%	n	%	n	%	(overall)
None (I)	15	54	29	55	17	50	0.02
Little (II)	1	4	2	4	1	3	
Some (III)	9	32	10	19	3	9	
Clear (IV)	3	11	11	21	9	26	
Strong (V)	0	0	1	2	4	12	
Total	28	100	53	100	34	100	

The losses and deficit in childhoods. The patients in the BC group had significantly more losses at childhood (10/34 patients, 29.4%) than the patients in the BBD group (losses in childhood in 11/53 patients, 20.7%) and the patients in HSS group (losses in childhood in 3/28 patients, 10.7%). There was a trend for the women with BC to have more

severe losses in childhood than these of the BBD and HSS groups (Table II). The BBD group tended to have more losses of health in childhood (7/53 patients, 13.2%) than the patients in the BC group (losses of health in childhood in 3/34 patients, 8.8%) and in the HSS group (losses of health in childhood in 2/28 patients, 7.1%). However, the BC group had more severe losses of health than did the patients with BBD and the HSS group (Table II). The patients with BC had more severe deficit (grade IV-V deficit) in childhood (13/34 patients, 38.2%) than the patients in the BBD group (severe deficit in childhood in 12/53, 22.6%) and the patients in HSS group (severe deficit at childhood in 3/28, 10.7%) (p=0.02, Table III). There was also a trend for the women with BC to have higher mean score of deficit in childhood than those in the BBD and HSS groups (Table II). The BC group had also higher mean score of loss of social status in childhood than the patients with BBD and HSS group (Table II).

The losses and deficit in adolescence. The patients with BC (losses in adolescence in 9/34 patients, 26.5%) and the HSS group (losses in adolescence in 8/28 patients, 28.6%) had significantly more losses in adolescence than did the patients in the BBD group (losses in adolescence in 5/53 patients, 9.4%). The patients in the BC group had more deficit in adolescence (in 16/34 patients, 47.1%) than did the patients in the BBD group (deficit in adolescence in 14/53, 26.4%) and the HSS group (deficit in adolescence in 11/28 patients, 39.3%). The BC group also had a higher mean score of deficit in adolescence than did the patients with BBD and the HSS group (Table II).

Discussion

In 1914, Cannon described the well-known fight or flight response: the discharge of the noradrenergic nervous system induced by an upsetting life situation (31). Four decades later, Selye defined stress as the non-specific response of the body to any demand made upon it (32) and two decades later Lazarus (33) stated that stress occurs where there are demands on the person which tax or exceed his adjustive resources. The definitions of stress of Selye and Lazarus are widely known and used today, but no definitive consensus exists on the concept of stress.

The most commonly used hypothesis of the relationship between stress and breast cancer in previous epidemiological studies is that the risk of breast cancer 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 for the assessment of stress have been i) a checklist of life events, ii) a semi-structured interview and iii) use of register data. In the checklist study, the study subjects are asked to indicate which major life events on a given list have occurred over a specific period. A semi-structured interview method 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 semi-structured interview method 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 (previous 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 critized on such methodological grounds as limited controlling for age (34). In our 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 in our study (p=0.12).

The allostasis theory postulates that stress causes the body to activate human physiologic systems in order to maintain stability. Our aim in this study was to examine the relationship between stress due to losses and deficit in childhood and adolescence and breast cancer risk. Breast cancer is a slow-growing tumor with a long subclinical phase that may extend 18 years and even more (35). Through allostasis, various physiologic 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. Experience of chronic stress may result in increased allostatic load with repeated or in the 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 association between the allostatic load due to stress and the risk of breast cancer is, however, a complex study issue. According to Nielsen *et al*. (37) the persistent activation of the HPA axis and the sympathetic nervous system may protect from breast cancer through the suppression of estrogen secretion. However, the study by Sephton *et al*. (38) of diurnal cortisol rhytm as a predictor of breast cancer survival showed that an abnormal diurnal pattern of cortisol predicts earlier mortality in breast cancer and these findings contradicts those of the study by Nielsen *et al*. (37).

The participants of our 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 our previous results in a Breast Cancer Diagnostic Unit in Finland (22). We maintain that our 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) of our study is not representative of the whole population, since it consists of women who presented primarily with breast symptoms.

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

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