ANTICANCER RESEARCH *25*: 531-536 (2005)

Stressful and Adverse Life Experiences in Patients with Breast Symptoms; a Prospective Case-control Study in Kuopio, Finland

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Abstract. *Background: Psychosocial stress is widely thought to play a role in the aetiology of cancer in general and breast cancer in particular. Many studies have investigated the association between stressful life events and risk of breast cancer. However, the field of psychosocial cancer research is often problematic and findings have been contradictory, varying from no association to strong association. This inconsistency in results may be explained by the fact that most of the epidemiological data available come from retrospective case-control studies. We have conducted this case-control study with a so called "limited prospective study design"to reduce the potential for recall bias. 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. The women were interviewed and reports on adverse and stressful life events were obtained before any diagnostic procedures were done, so neither the investigator nor the subject knew the final diagnosis of breast symptoms at the time of the interview.The research method used was the semi-structured in-depth interview method. All study subjects were also asked to complete standardised questionnaires (Beck Depression Inventory, Spielberger Trait Inventory). Results:The clinical examination and biopsy showed breast cancer (BC) in 34 patients, benign breast disease (BBD) in 53 patients, while 28 study subjects showed to be healthy (HSS). The results indicated that BC patients had had significantly ($p=0.02$) more very severe (Gr IV) and severe (Gr III) stress in the previous 10 years preceding the investigation than the BBD and HSS groups.The BC group also reported significantly more moderate or severe losses than the BBD or the HSS groups ($p=0.0009$). Conclusion: The results of this study support an overall association between stressful life events and breast cancer risk. The biological explanation of the overall association might be that stress disturbs various areas of the immune systems predisposing to neoplasia.*

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Key Words: Breast symptoms, psychosocial stress.

Breast cancer is the most common cancer in the western world and the leading cause of death of all neoplasms in women in Finland (1). In Finland, 3471 new cases of female breast cancer were diagnosed in 1999 and the incidence is increasing (1). The overall five-year survival rate of breast cancer in Finland was 80% and 844 breast cancer deaths were documented in 1999(1). Although a number of breast cancer risk factors have been identified, substantial gaps remain in current knowledge on the aetiology of the disease. Many risk factors are related to a woman's reproductive life and thus to female hormones. Life-style factors, such as obesity and alcohol consumption, also seem to be relevant (2-6).

Psychological factors, such as stressful life events, are widely thought to play a role in the aetiology of cancer in general and breast cancer in particular. Whether emotional stress causes breast cancer has received a considerable amount of attention in the field of psychosocial investigation (7-12). However, the field of psychosocial cancer research is problematic and findings have been contradictory, with many studies prone to recall bias or errors of measurements (12). This was partly the reason why we carried out a prospective study to examine the role of stressful life events as a risk factor for breast cancer.

Materials and Methods

This case-control study was an extension of the Kuopio Breast Cancer Study (13,14). The study was approved by the Joint Committee of the University of Kuopio and Kuopio University Hospital, Finland. Participation was based on a written consent. Women with breast symptoms or a suspect breast lump had been

referred by a physician 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 and the ratings were completed before the final diagnosis. The clinical examination, mammography and biopsy showed breast cancer in 34(29.6%) patients (BC), 53 (46.1%) patients with benign breast disease (BBD) and 28 (24.3%) patients with healthy breasts (HSS) (Table I).

Assessment of life events and stress. The research method was a semi-structured in-depth interview. 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 investigator (P.O.) asked the patient to draw positive life experiences ("the good times") with lines indicating upwards and negative life experiences ("the hard times") with lines indicating downwards. Adverse and stressful life events were evaluated from the whole life-span, with particular reference to the previous 10 years before the admission. The adverse or stressful life events and the context surrounding them was marked on the "life line paper" during the interview. After the interview, the investigator then rated the life events according to the degree of threat or stress they were likely to pose to a particular study subject and each adverse or stressful life event was graded on a five-point scale, grade I (one point) indicating a non-threatful event and grade V (5 points) a severely threatful event. The used defences were assessed on a five-point scale, grade I (one point) indicating very defensive and grade V (5 points) non-defensive. "Working through and actively confronting the stressful event"-variable was rated on a five-point scale, grade I (one point) indicating non-worked through and grade V (5 points) fully worked out. These measurements were put together in the final statement, where 1 to 2 points in the scale means little or mild loss or stress and 5 means very severe 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 10 years prior to the investigation.

Coping strategies. The investigator used the modified coping and defence inventory made by Haan (15). This inventory is divided into ten scales, each scale having subscales from grade 0 to grade 3. Zero means no definition, 1=coping, 2=defending and 3=fragmentation. In addition to this, the researcher estimated the patients' ability to cope (scale 1 to 5), the amount of defensiveness (scale 1 to 5) and fragmentation (scale 1 to 5).

Other psychosocial variables. The women completed psychological self-report questionnaires which were the Beck Depression Inventory (BDI) (16, 17) and the Spielberger Trait Inventory (18). The investigator used the Montgomery Asberg Depression Rating Scale (MADRS) to evaluate the depression of the study subjects (19).

Statistical analysis. The significance of the results were calculated with the SPSS/PC statistical package (SPSS Inc., Chicago, Illinois, USA). Correlations and differences between the study groups (BC group, BBD group and HSS group) were counted by using the 2-sided Chi-square test and non-parametric Kruskal-Wallis variance analyses. Results were considered statistically significant at p-value<0.05.

Table I. *The final diagnostic categories of the study subjects.*

Diagnostic categories	Number of patients	%
Healthy	28	24.3
Carcinoma	33	28.7
Carcinoma *in situ*	1	0.9
Benign fibrocystic disease	37	32.2
Fibroadenoma	5	4.3
Adenoma	3	2.6
Papillomatosis	2	1.7
Other BBD	6	5.2
	115	**100**

Results

The mean (SD, range) age of the breast cancer (BC) patients was 51.5 (11.1, 32-74) years. The corresponding figure for the patients with benign breast disease (BBD) was 47.5 (10.9, 25-75) years and for the healthy study subjects (HSS) 45.7 (13.2, 20-70) years. Although the patients in the BC group were older than in the BBD group or HSS group, 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 one in four 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%), while almost one-fourth (23.5%) were retired. The combined mean gross income of both spouses in the patients with BC was 36100 € per year. The corresponding figure for the patients with BBD was 27714 € per year and for the HSS group 24521 € 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 both spouses.

The groups differed only slightly from each other as to the factors relating to the woman's reproductive life (Table II).

Psychological self-report questionnaires (BDI and Spielberger Trait) and MADRS. The mean (SD) BDI score of the BC group was 8.4(6.9) and the corresponding figures for the BBD and HSS groups were 8.8(7.4) and 7.1(7.3) (p=ns). The mean (SD) MADRS score of the BC group was slightly higher at 11.4 (9.2) than the score of the BBD group, 10.7(9.2) and the HSS group, 8.4(9.7) (p=ns). The mean (SD) Spielberger Trait Inventory differed only slightly

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

Variable	BC (n=34)	BBD (n=53)	HSS (n=28)	Statistics
Age (mean, yrs)	51.6	47.6	45.7	*p*=ns
Height (mean, cm)	164.4	162.3	160.8	*p*=ns
Body weight (mean, kg)	72.5	67.8	68.3	*p*=ns
Age at menarche (mean, yrs)	13.4	13.4	13.4	*p*=ns
Age at birth of first child (mean, yrs)	25.2	25.0	25.0	*p*=ns
Age at menopause (mean, yrs)	47.9	48.9	50.0	*p*=ns
No. of children (mean)	2.6	2.4	2.5	*p*=ns
Parity	31/34 (91%)	44/53 (83%)	23/28 (82%)	*p*=ns
Breast feeding (mean, months)	3.6	3.4	3.9	*p*=ns
Using of pills	13/34 (38%)	25/53 (47%)	18/28 (64%)	*p*=ns
HRT*	27/34 (79%)	36/53 (68%)	14/28 (50%)	*p*=ns
Premenopausal	13/34 (38%)	28/53 (53%)	18/28 (64%)	*p*=ns
Postmenopausal	21/34 (62%)	25/53 (47%)	10/28 (36%)	*p*=ns
History of previous BBD	18/34 (53%)	22/53 (42%)	10/28 (36%)	*p*=ns
Family history of BC	1/34 (3%)	5/53 (9%)	5/28 (18%)	*p*=ns
Use of alcohol	21/34 (62%)	31/53 (58%)	13/28 (46%)	*p*=ns
Smoking	15/34 (44%)	21/53 (40%)	10/28 (40%)	*p*=ns

*HRT=use of hormonal replacement therapy.

between the BC group, at 40.1(8.6) and the BBD group, 41.5(7.2) and the HSS group, 39.1(6.4) (*p*=ns).

Stressful life experiences in the past 6-10 years before admission. The characteristics and severity of the stressful life experiences were divided into four grades; very severe (grade IV), severe (grade III), moderate (grade II) and mild (grade I). Table III shows the characteristics of the stressful life experiences of the study subjects in the previous 6-10 years before admission. Nearly half (44.3%) of all the study subjects (n=115) had had stressful life experiences. The patients with breast cancer reported significantly more severe stressful life experiences than the other study subjects. Over two-thirds (69.2%, 9/13) of the BC group reported severe or very severe stress, whereas one-fourth (23.8% , 5/21) of the BBD group and nearly one-third (29.4%, 5/17) of the HSS group had had severe or very severe stress in the previous 6-10 years before admission.

Stressful life experiences in the previous 2-6 years before admission. Table IV shows the characteristics of the stressful life experiences of the study subjects in the previous 2-6 years before admission. The patients with breast cancer had had significantly more severe stressful life experiences (severe or very severe stress in 9/17 patients, 52.9%) than the patients with BBD (severe or very severe stress in 6/28 patients, 21.4%) and healthy study subjects (severe or very severe stress in 5/16 patients, 31.2%).

Table III. *The characteristics of the stressful life experiences in the previous 6-10 years before admission.*

Severity of stress	BC		BBD		Healthy		*p*-value
	N	%	N	%	N	%	(overall)
	34	100	53	100	28	100	
Gr IV (very severe)	3	8.8	-	-	-	-	0.02*
Gr III (severe)	6	17.6	5	9.4	5	17.9	
Gr II (moderate)	3	8.8	10	18.9	9	32.1	
Gr I (mild)	1	2.9	6	11.3	3	10.7	
Total #	13	38.2	21	39.6	17	60.7	

Total number of the study subjects (% of group) reporting stressful life experiences in the previous 6-10 years before admission.

Stressful life experiences in the previous two years before admission. Table V shows the characteristics of the stressful life experiences of the study subjects in the previous two years before admission. Fourteen (41.2%) patients with BC, 30 (56.6%) patients with BBD and 16 (57.1%) healthy study subjects reported stressful life experiences. The breast cancer group reported significantly more severe and very severe stress than the BBD group and the HSS group. About two-thirds of (9/14, 64.3%) patients in the BC group,

Table IV. *The characteristics of the stressful life experiences in the previous 2-6 years before admission.*

Severity of stress	BC		BBD		Healthy		*p*-value
	N	%	N	%	N	%	(overall)
	34	100	53	100	28	100	
Gr IV (very severe)	2	5.8	-	-	-	-	0.04*
Gr III (severe)	7	20.6	6	11.3	5	17.9	
Gr II (moderate)	8	23.5	16	30.2	9	32.1	
Gr I (mild)	-	-	6	11.3	2	7.1	
Total #	17	50.0	28	52.8	16	57.1	

Total number of the study subjects (% of group) reporting stressful life experiences in the previous 2-6 years before admission.

Table V. *The characteristics of the stressful life experiences in the previous two years before admission.*

Severity of stress	BC		BBD		Healthy		*p*-value
	N	%	N	%	N	%	(overall)
	34	100	53	100	28	100	
Gr IV (very severe)	3	8.8	-	-	1	3.6	0.02*
Gr III (severe)	6	17.6	6	11.3	3	10.7	
Gr II (moderate)	3	8.8	12	22.6	8	28.6	
Gr I (mild)	2	5.8	12	22.6	4	14.3	
Total #	14	41.2	30	56.6	16	57.1	

Total number of the study subjects (% of group) reporting stressful life experiences in the previous two years before admission.

6/28 (21.4%) patients in the BBD group and 4/16 (25%) in the HSS group had had severe or very severe stress in the previous two years.

Losses of the study subjects in adulthood. Table VI shows the characteristics of losses of the study subjects in adulthood. Fifteen (15/34, 44%) patients in the BC group, 27/53 (51%) patients in the BBD group and 13/28 (46%) patients in the HSS group reported losses in adulthood. The BC group had significantly more moderate or severe losses than the BBD or the HSS groups. Thirteen (13/15, 87%) patients of the BC group, 5 (5/27, 19%) patients of the BBD group and 8 (8/13, 62%) patients in the HSS group had had moderate or severe losses in adulthood.

Table VI. *The characteristics of losses in adulthood.*

Severity of stress	BC		BBD		Healthy		*p*-value
	N	%	N	%	N	%	(overall)
	34	100	53	100	28	100	
Gr IV (very severe)	1	2.9	-	-	1	3.6	0.0009*
Gr III (severe)	1	2.9	1	1.9	2	7.1	
Gr II (moderate)	11	32.4	4	7.5	5	17.9	
Gr I (mild)	2	5.8	22	41.5	5	17.9	
Total #	15	44.0	27	50.9	13	46.4	

Total number of the study subjects (% of group) reporting losses in adulthood.

Discussion

Our study group consisted of subjects 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, referred to the Surgical Outpatient Department at the Kuopio University Hospital, Finland. There had been no pre-selection of the study subjects and the indications for referral in this study are in line with our previous results in a Breast Cancer Diagnostic Unit in Finland (20). We feel that our study sample can be considered clinically representative for this type of prospective case-control study design.

McKenna *et al.* (9) considered, in a recent meta-analysis, that about 50% of all breast cancer cases can be attributed to the most important risk factors including family history of breast cancer, parity, early menarche, late menopause, the use of oral contraceptives and age. Breast cancer risk might also be related to stressful life events or emotional factors. Many studies have investigated the associations between stressful life events and risk of breast cancer. However, these studies have produced conflicting results, varying from no association (8, 10, 11) up to a strong association (7, 12). This inconsistency in results may be explained by the fact that most of the epidemiological data available come from retrospective case-control studies. In a recent meta-analysis, 10 retrospective case-control studies, 9 limited prospective cohort studies, 4 prospective cohort studies and only 4 prospective case-control studies were identified (11). The previous studies in this meta-analysis differed in populations (from which study subjects were selected). Study subjects were selected from a suspicion cohort (9 studies), from a screening cohort (3 studies), from

hospitals (7 studies) and from a general population (8 studies). The same classification was used in the selection of controls, in case-control studies and in cohort studies. Seven studies selected their controls from the general population and in 7 studies from hospitals. In 3 cohort studies, the study base was selected from the general population, in 7 studies from a suspicion cohort and in one study from a screening cohort. Four studies used interviewing techniques to assess the effect of stressful life events, whereas 20 studies used questionnaires. Three studies were population-based linkage studies (12).

A typical case-control study comparing women with and without breast cancer in terms of their reports of past (or present) psychological factors inevitably raises concern about the possibility of selective memory and reporting due to the diagnosis. In questionnaire surveys in Western countries, it is estimated that 40% of the general public and more than 20% of clinicians believe that stress contributes to the risk of breast cancer (21, 22) and, therefore, women with breast cancer may be more prone than healthy subjects to report prior stress in an effort to explain their illness.

In an attempt to avoid the recall bias, we conducted this case-control study with a so-called "limited prospective study design"; women were asked to participate in the study and were interviewed and reports on psychological factors were obtained before any diagnostic procedures, so neither the investigator nor the subject knew the diagnosis at the time of interview.

One potential bias comes from age being a confounding factor and some studies has been criticized on such methodological grounds as limited controlling for age (23). In our study, the BC group was 4.0 years and 5.9 years older than than the BBD group and the HSS group, respectively. However, no statistically significant age difference between these groups was found ($p=0.12$). The subjects in the BC group were significantly wealthier than the subjects in the BBD and HSS groups, as estimated by the combined gross income of both spouses. This finding has implications for health-care practioners to ask women's socioeconomic status in Breast Cancer Diagnostic Units.

The reader may find that the BBC category (n=53) in our study is a heterogeneous group of breast diseases with different histological entities. Study subjects with non-proliferative lesions (benign fibrocystic disease, n=37) have no or only a slightly increased risk of breast cancer. Women whose breast biopsies showed epithelial hyperplasia have about 2 to 4-fold increased risk of developing breast cancer.

The two most often used methods for assessment of stressful life events are a semi-structured interview and a interview which is administered by using a checklist of stressful life events. In the semi-structured interview approach, the interviewer collects detailed information on the occurrence of stressful life events and the context surrounding them. The researcher then objectively rates the life events according to the degree of threat they are likely to pose to a particular subject. A semi-structured interview approach developed by Brown and Harris (The Life Events and Difficulties Schedule)(7) has been used in three recent case-control studies (7, 10, 11). In the study by Chen (7), women with suspicion of a breast lump were referred for breast biopsy and they were interviewed about the prior stress before their biopsy outcome. The patients with BC were much more likely to have stressful life events than the women with BBD. However, the two recent studies using a similar study design reported no association between stressful life events and breast cancer (10, 11).

In conclusion, our results support an overall association between adverse and stressful life experiences and increased breast cancer risk. The biological explanation of the overall association might be that stress disturbs various areas of neuroimmunological systems and possibly the functions of the neuroendocrine axes, which can lead to changes in blood concentrations of various hormones including oestrogens, progesterone, FSH, prolactin and melatonin (6, 24). However, the exact effects of psychological stress on the various hormones relevant to the development of breast cancer are, at present, poorly defined.

Acknowledgements

We thank Ms A.K. Lyytinen, R.N., for help in data collection. The support from the Academy of Finland, the Paavo Koistinen Foundation and EVO funds from Kuopio University Hospital, Finland, are gratefully acknowledged.

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Received August 23, 2004
Accepted December 16, 2004