Anxiety, Depression, and the History of Psychiatric Symptoms in Patients with Breast Disease: A Prospective Case-control Study in Kuopio, Finland

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Abstract. *Background: Many case-control studies have investigated the association between anxiety, depression, the history of psychiatric symptoms and risk of breast cancer. However, findings are inconsistent, and 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. These subjects were interviewed and all study variables were obtained before any diagnostic procedures were carried out, 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 semistructured in-depth interview method. The Montgomery-Asberg Depression rating scale (MADRS) was used to evaluate the depression of the study subjects. All study subjects were also asked to complete standardised questionnaires (Beck Depression Inventory and Spielberger Trait Inventory). The Forsen Inventory was used to evaluate the history of psychiatric symptoms of the subjects in the six years prior to admission. Results: Clinical examination and biopsy showed breast cancer (BC) in 34 patients, benign breast disease (BBD) in 53 patients, while 28 study subjects were healthy (HSS). The mean "Forsen-score 2-6 yrs" of the BC group was lower (9.8) than the scores of the BBD group (11.8) and the HSS group (12.5) (p=0.4). The investigator-*

characterized variables, "MADRS"- and "depression"-variables correlated significantly (p-value under 0.001) with those variables reported by the study subjects, "BDI", "A-trait" and "Forsen-score". The "anxiety"-variables characterized by the investigator correlated to the "A-trait"-variable and "Forsen-score"-variable reported by the study subjects (p-value under 0.05). Conclusion: Our results do not support an overall association between anxiety, depression, history of psychiatric symptoms and increased breast cancer risk. However, the exact effects of psychological factors on the various hormones relevant to the development of breast cancer are at present poorly defined.

Epidemiological studies have identified a number of endogeneous and exogenous risk factors for breast cancer. 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 (1-5). 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 attracted a considerable amount of attention in the field of psychosocial investigation (6-11) and our results from the Kuopio Breast Cancer Study have recently been reported (12). As in the case of stress, the relationship between anxiety, depression, a history of psychiatric symptoms and the risk of breast cancer has been investigated in many case-control studies. The dominant finding in these earlier studies was the increased risk of breast cancer in relation to suppression of emotions in general, and anger in particular (13-18). However, the field of psychosocial cancer research is often problematic, and findings have been contradictory. The two largest case-control studies published recently found no evidence of an association between various personality characteristics, anxiety, depression and risk of breast cancer (19, 20).

We carried out a prospective study to examine the role of anxiety, depression and the history of psychiatric symptoms

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Table I. *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 I 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 oral contraceptives	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.

as a risk factor for breast cancer in women with breast symptoms referred by physicians to the Kuopio University Hospital (Finland).

Materials and Methods

This case-control study is an extension of the Kuopio Breast Cancer Study (21-22). 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 (P.O.) 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. 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 P.O. asked the patient to draw positive life experiences ("the good times") with lines pointing upwards and negative life experiences ("the hard times") with lines pointing downwards. Adverse and stressful life events were evaluated from the whole lifespan, 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 P.O. 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 non-threatful event and grade V (5 points) severely threatful event. The defences used were also assessed on a five-point scale: grade I (one point) indicating very defensive, denying and grade V (5 points) non-defensive. "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 (5 points) fully resolved. These measurements were put together in the final statement, 1 to 2 points in the scale meaning little or mild loss or stress and 5 meaning very hard loss or stress.

The rated case record includes the loss events from childhood (under 3 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 P.O. used the modified Haan coping and defence inventory (23). This inventory is divided into 10 scales, and each scale has subscales from grade 0 to grade 3. Zero means no definition, 1=coping, 2=defending and 3=fragmentation. In addition, the researcher estimated the patients' ability to cope (scale of 1 to 5), the amount of defensiveness (scale of 1 to 5) and fragmentation (scale of 1 to 5).

Beck Depression Inventory (BDI). The women completed the Beck Depression Inventory (BDI) (24, 25) with 21 variables. The investigator used the modified inventory divided in three grades; grade I (0-13), no depression; grade II (14-24), moderate depression; grade III (over 24), severe depression.

Spielberger Trait Inventory. All study subjects completed the Spielberger Trait Inventory (26). Trait anxiety was assessed using the subscale from the Inventory, and the 10 items refer to how a

Table II. *The severity of depression in the BC, BBD and HSS groups in the Beck Depression Inventory (BDI).*

Severity of depression	BC		BBD		HSS		*p*-value
	No.	%	No.	%	No.	%	(overall)
	34	100.0	53	100	28	100	
Gr I (no depression)	27	79.4	39	73.6	25	89.3	0.5
Gr II (mild/moderate)	7	20.6	11	20.8	2	7.1	
Gr III (severe)	--	--	3	5.7	1	3.6	

Table III. *The severity of depression in the BC, BBD and HSS groups in the MADRS Inventory.*

Severity of depression	BC		BBD		HSS		*p*-value
	No.	%	No.	%	No.	%	(overall)
	34	100.0	53	100	28	100	
Gr I (no depression)	14	41.2	24	45.3	17	60.7	0.23
Gr II (mild)	14	41.2	18	34.0	6	21.4	
Gr III (moderate)	6	17.6	11	20.8	3	10.7	
Gr IV (severe)	--	--	--	--	1	3.6	

person generally feels, with a higher total score reflecting higher trait anxiety (20-80 range). The investigator rated the test as follows: grade I (20-29), seldom anxious; grade II (30-49), sometimes anxious; grade III (50-69), often anxious; grade IV (70-80), always anxious.

Montgomery Asberg Depression Rating Scale (MADRS). The Montgomery Asberg Depression Rating Scale (MADRS) with 10 variables (scores from 0 to six) was used to evaluate the depression of the study subjects (27), and the test was rated as follows: grade I (0-6 scores), no depression; grade II (7-19), mild depression; grade III (20-34), moderate depression; and grade IV (35-60), severe depression.

History of psychiatric symptoms in the past 2 years (0-2 yrs) and in the 2- to 6-year period (2-6 yrs) before admission. In order to evaluate the history of psychiatric symptoms of the subjects in the 6 years before admission, the P.O. used the Alf Forsen classification, the Forsen Inventory (FI) (28). The P.O. completed the FI comprised of 11 variables divided into three grades: grade I (0 points), no psychiatric symptoms, grade II (1 point), moderate psychiatric symptoms and grade III (2 points), severe psychiatric symptoms.

The history of psychiatric symptoms was assessed for two time-periods: A. the 2 years, prior to admission (0-2 yrs) and B, the 2- to 6-year period prior to admission (2-6 yrs). The 11 items refer to how a person feels generally, with a higher score (Forsen-score) reflecting more psychiatric symptoms.

Statistical analysis. The significance of the results was calculated with the SPSS/PC statistical package (SPSS Inc., Chicago, IL, USA). Correlations and differences between the study groups (BC group, BBD group and HSS group) were measured with the 2-sided Chi-square test and non-parametric Kruskal-Wallis variance analyses. Results were considered statistically significant at *p*-value<0.05. Associations between the major study variables and breast cancer risk were analysed by the unconditional logistic regression to estimate odds ratios (ORs) and 95% confidence intervals (CI).

Results

The mean (SD, range) age of the breast cancer (BC) patients was 51.5 (11.1, 32-74) years. The corresponding

Table IV. *The severity of the A-trait anxiety (Spielberger trait) in the BC, BBD and HSS groups.*

Severity of A-trait anxiety	BC		BBD		Healthy		*p*-value
	No.	%	No.	%	No.	%	(overall)
	34	100.0	53	100	28	100	
Gr I (seldom)	3	8.8	2	3.8	1	3.6	0.18
Gr II (sometimes)	27	79.4	44	82.3	26	92.9	
Gr III (often)	4	11.8	7	13.2	1	3.6	
Gr IV (always)	--	--	--	--	--	--	

figures 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 those in the BBD or HSS groups, the age difference was not statistically significant (*p*=0.12). The majority of 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%), 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 and for the HSS group 24,521 € 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 regarding the reproductive life of the women (Table I).

Table V. *Correlation and significance of personality variables characterized by the investigator (P.O.) and by the study subjects.*

Variables characterized by the P.O.	Variables characterized by the study subject			
	BDI	A-trait	Forsen-score 0-2 years	Forsen-score 2-6 years
	Correlation coefficient (r)	Correlation coefficient (r)	Correlation coefficient (r)	Correlation coefficient (r)
MADRS	0.82***	0.55***	0.81***	0.56***
Depression	0.74***	0.60***	0.72***	0.49***
Anxiety	0.52(ns)	0.59*	0.43*	0.29(ns)

p=significance of correlation; ns=non-significant, *=*p*-value under 0.05, ***=*p*-value under 0.001.

Psychological self-report questionnaires (BDI and Spielberger Trait) and MADRS. The mean BDI score (SD) of the BC group was 8.4 (6.9), and 8.8 (7.4) and 7.1 (7.3) (*p*=ns) for the BBD and HSS groups, respectively. The mean MADRS score (SD) of the BC group was slightly higher 11.4 (9.2) than that 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 between the BC, 40.1 (8.6), the BBD, 41.5 (7.2) and the HSS, 39.1 (6.4) (*p*=ns) groups.

Characteristics of depression in the Beck Depression Inventory (BDI). The characteristics and severity of depression in the BDI were categorized as follows: severe (grade III), mild or moderate (grade II) and no depression (grade I). The characteristics of depression in the study subjects according to the BDI are given in Table II. One-fifth (20.6%, 7/34) of the BC group reported mild or moderate depression, whereas over a quarter (26.5% , 14/53) of the BBD group and only two patients (7.1%, 2/28) of the HSS group displayed mild or moderate depression.

Characteristics of depression in the MADRS Inventory. The characteristics of depression in the study subjects according to the MADRS Inventory are provided in Table III. The characteristics and severity of depression in the MADRS were assigned as follows: severe (grade IV), moderate (grade III), mild (grade II) and no depression (grade I). The patients with breast cancer had slightly more mild or moderate depression (20/34 patients, 58.8%) than the patients with BBD (mild or moderate depression in 29/53 patients, 54.8%) or the healthy study subjects (mild or moderate depression in 9/28 patients, 32.1%) (*p*=0.23).

Characteristics of the A-trait anxiety (Spielberger trait). The characteristics of the A-trait anxiety in the study subjects are given in Table IV. The characteristics and severity of the A-

Table VI. *Study variables and breast cancer risk ratio (RR) with 95% confidence interval (CI) and p-value of significance.*

Study variable	RR	CI	*p*-value
Anxiety	1.1	(0.74-1.56)	0.71
Spielberger (A-trait)	1.0	(0.95-1.11)	0.49
Depression	1.1	(0.77-1.65)	0.51
MADRS	1.0	(0.95-1.11)	0.37
Beck (BDI)	1.0	(0.92-1.11)	0.86
Forsen-score 0-2 yrs	1.0	(0.96-1.04)	0.92
Forsen-score 2-6 yrs	1.0	(0.96-1.09)	0.21

trait anxiety were assigned as follows: always anxious (grade IV), often anxious (grade III), sometimes anxious (grade II) and seldom anxious (grade I). The groups differed only slightly from each other with regard to this parameter (Table IV).

History of the psychiatric symptoms in the 2 years and in the 2- to 6-year period prior to admission. The history of the subjects psychiatric symptoms was subdivided into: A, psychiatric symptoms occurring in the 2 years prior to admission (0-2 yrs) and B, those psychiatric symptoms occurring in the 2- to 6-year periods prior to admission (2-6 yrs). The mean "Forsen-score 0-2 yrs" of the BC group was 14.1, and the corresponding figures for the BBD and HSS groups were 14.2 and 14.3 (*p*=ns), respectively. The mean "Forsen-score 2-6 yrs" of the BC group was lower (9.8) than that the BBD, (11.8) and HSS, (12.5) (*p*=0.4) groups.

The correlation and significance of the study variables characterized by the investigator (P.O.) and by the study subjects. The correlation and significance of the study variables characterized by the P.O. and the study subjects are given in Table V. The variables characterized by the investigator, the "MADRS"- and "depression"-variables, correlated with high significance (*p*-value under 0.001) to those reported by the study subjects, "BDI", "A-trait", "Forsen-score 0-2 yrs" and "Forsen-score 2-6 yrs". The "anxiety"-variable characterized by the P.O. correlated to the "A-trait" and "Forsen-score 0-2 yrs"-variable reported by the study subjects (*p*-value under 0.05).

The variables in this study and breast cancer risk ratio (RR) with 95% confidence interval (CI). The variables in this study and breast cancer risk ratio (RR) with 95% confidence interval (CI) and *p*-value of significance are shown in Table VI. The variables of this study correlated only slightly with increased breast cancer risk (Table VI). The "anxiety"-variable and "depression"-variable characterized by the P.O. correlated slightly with increased breast cancer risk (RR=1.1).

Discussion

Breast cancer is the most common cancer in women in North America and in Western and Northern Europe (1). In Finland, 3,471 new cases of female breast cancer were diagnosed in 1999, accounting for 32% of all cancer in women (29). The overall 5-year survival rate of breast cancer patients is close to 80% in Finland, despite 844 breast cancer deaths documented in 1999 in Finland (29).

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 in 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 and Switzerland (30). The participants of the Kuopio Breast Cancer Study 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 was 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 (31). We maintain that our study sample can be considered clinically representative for this type of prospective case-control study design.

Epidemiological (32), case-control (13-20, 33-36), cohort (37, 38) and record-linkage studies (39, 40) have been conducted to assess the relationship between anxiety, depression, history of psychiatric symptoms, personality and breast cancer risk. Epidemiological research on these variables and breast cancer risk has been motivated by theories of a so-called "cancer-prone personality" (32).

Case-control and cohort studies take into account anxiety, depression, history of psychiatric symptoms, personality and confounding factors at the individual level. Epidemiological studies of these factors and breast cancer risk are more common, because they are easier, quicker and cheaper to carry out than the case-control and cohort studies.

The important bias related to case-control studies is recall bias, which occurs, for example, if cases report their life experiences differently from controls. This may happen because subjects have often thought about their previous experience in order to find causes for their breast cancer. To avoid 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 have been criticized on such methodological grounds as limited controlling for age (41). 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 ($p=0.12$).

The study sample can be considered clinically representative of this type of prospective case-control study design if the variables characterized by the investigator and the variables characterized by the subjects correlate. In our study, the variables reported by the investigator, the "MADRS"- and "depression"-variables, correlated with high significance (p-value under 0.001) to those variables reported by the study subjects, "BDI", "A-trait", "Forsen-score 0-2 yrs" and "Forsen-score 2-6 yrs". The "anxiety"-variable characterized by the investigator correlated to the "A-trait" and "Forsen-score 0-2 yrs"-variable reported by the study subjects (p-value under 0.05).

The findings of earlier case-control studies, on the anxiety, depression, history of psychiatric symptoms and personality characteristics, vary from no association to strong association. In three studies, BC patients were significantly more often depressed than control subjects (15, 33, 34), whereas other studies indicated no association (17, 35, 36). The most powerful positive association was reported in an Italian study (34) using self-reports on the Minnesota Multiphasic Personality Inventory, a diagnostic interview with DSM-III-R criteria and a psychological test. In a well-conducted Australian study (20), in which assessed with the Hospital Anxiety and Depression scale, no relationship between depression and breast cancer risk was reported. In our study, the BC patients had slightly more mild or moderate depression (20/34 patients, 58.8%) than those with BBD (mild or moderate depression in 29/53 patients, 54.8%) or than healthy study subjects (mild or moderate depression in 9/28 patients, 32.1%) ($p=0.23$), according to the MADRS Inventory. In addition, the mean MADRS score (SD) of the BC group was slightly higher 11.4 (9.2) than those of the BBD, 10.7 (9.2) and HSS, 8.4 (9.7) groups. The groups differed only slightly from each other as to the characteristics of depression in BDI.

The P.O. used the Forsen Inventory to evaluate the subjects history of psychiatric symptoms in the 2 years prior to and in the 2- to 6-year period prior to admission. BC, BBD and HSS groups differed only slightly from each other in the 2 years prior to admission (0-2 yrs). However, the groups differed from each other as to the characteristics of the history of psychiatric symptoms in the 2- to 6-year period to admission (2-6 yrs). The mean "Forsen-score 2-6 yrs" of the BC group (9.8) was lower than that of the BBD

(11.8), and HSS 12.5 (*p*=0.4) groups. The BC, BBD and HSS groups differed only slightly from each other as to the characteristics of A-trait anxiety. The variables of this study correlated only slightly to increased breast cancer risk (risk ratio with 95% confidence interval). The "anxiety"-and "depression"-variables, characterized by the investigator, correlated to slightly increased breast cancer risk (RR=1.1). Our findings of a lack of relationship between depression, anxiety, history of psychiatric symptoms and risk of breast cancer are in line with the findings of the two other prospective case-control studies, recently investigating anxiety, depression, history of psychiatric symptoms, personality and breast cancer risk (19, 20).

Conclusion

Our results do not support an overall association between anxiety, depression, history of psychiatric symptoms and increased breast cancer risk. However, the exact effects of psychological factors on the various hormones relevant to the development of breast cancer are at present poorly defined. The relationship between psychological factors and increased risk of breast cancer might be attributed to a third factor, perhaps genetic, that predisposes to both conditions (38, 42).

Acknowledgements

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