

# Forsen Psychological Risk Inventory for Breast Cancer Patients: A Prospective Case–Control Study with Special Reference to the Use of Psychiatric Medications

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**Abstract.** *Background:* In 1989, Forsen introduced an inventory for psychological identification of breast cancer (BC) patients before biopsy. The associations between the Forsen inventory (FI) and the risk of 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 and asked to complete standardised questionnaires (Beck, Forsen and Spielberger) 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 more severe anxiety during a two-year prodromal period (4/34 patients, 11.8%) than the BBD (3/53 patients, 5.7%) and HSS groups (1/28 patients, 3.6%). The mean sum of the scores of the FI variables during a six-year prodromal period were significantly lower in the BC group (9.8) than in the BBD (11.8) and HSS groups (12.5). In addition, the women in the BC group tended to use more psychiatric medication during a six-year prodromal period (7/34 patients, 20.6%) than the patients in the BBD (7/53, 13.2%) and HSS groups (3/28, 10.7%). *Conclusion:* The results of this study support a very weak association between the FI and BC risk. However, the number of cases with psychiatric medications was insufficient to support statistically a specific link between psychiatric medications and increased BC risk.

The first description of psychiatric symptoms in breast cancer (BC) occurred when Galen (130-200 AD) noticed that women with a melancholic mood due to increased rate of black bile were prone to develop BC (1). Several meta-analysis studies have attempted to find a correlation between psychiatric symptoms and BC. One such study, performed by McKenna *et al.* (2), assessed 46 studies, providing overall support for a modest association between specific psychosocial factors (coping, separation and loss) and BC risk. Because BC is a hormonally responsive neoplasm and one with great psychological impact, it has been the most extensively investigated tumour for possible psychological variables associated with risk and survival. 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 BC (3). In addition, lifestyle factors, such as obesity, smoking, alcohol consumption and lack of physical activity, appear to contribute to an 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 (10-22). In 1989, Alf Forsen introduced an inventory for psychological identification of BC patients before biopsy (23, 24). The associations between the Forsen inventory (FI) and the risk of BC are rarely considered together and, therefore, this prospective study examined the role of the FI in women with BC symptoms.

## 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 the Kuopio University Hospital (North-Savo Health Care District) for a breast examination between April 1990 and December 1995. The Kuopio Breast Cancer Study followed the protocol of the International Collaborative Study of Breast and Colorectal Cancer coordinated by

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*Key Words:* Breast disease, psychosocial factors, psychiatric drugs.

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

the European Institute of Oncology in Milan, and was initiated as a SEARCH programme of the International Agency for Research on Cancer (25). The collaborative study was based on the assumption that BC and colorectal cancer may have common risk factors. Study centres for the BC study were situated in Canada, Finland, Greece, Ireland, Italy, Russia, Slovakia, Spain and Switzerland. The participants of the Kuopio Breast Cancer 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 and the indications for referral in this study were in line with those of a previous study in a Breast Cancer Diagnostic Unit in Finland (26).

The present case-control study is an extension of the Kuopio Breast Cancer Study (27, 28). 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 BC symptoms or a suspect breast lump had been referred by physicians to the Kuopio University Hospital 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 to determine the level of emotional depression. As a result, 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 and benign breast disease (BBD) in 53 (46.1%) patients, while 28 (23.4%) patients had healthy breasts (HSS) (Table I).

*Assessment of life events and stress.* The research method was a semi-structured in-depth interview (16). 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' part, 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 ten years prior to 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 the psychiatrist (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 with grade I (one point) indicating a non-threatening event and grade V (five points) indicating a severely threatening event. The defence mechanisms used were also assessed on a five-point scale with grade I (one point) indicating very defensive, in denial and grade V (five points) indicating non-defensive. The 'working through and actively confronting the stressful event' variable was also rated on a five-point scale with grade I (one point) indicating unresolved and grade V (five points) indicating fully resolved. These measurements were put together in the final statement, where one to two points on the scale corresponded to little or mild loss or stress, and five corresponded to 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 admission.

*Coping and defence strategies.* A modified Haan coping and defence inventory (29) was used. This inventory is divided into ten scales, and each scale has subscales from grade 0 to grade III with the following meaning: grade 0, no definition; grade I, coping; grade II, defending and grade III, fragmentation.

*Beck depression inventory (BDI).* The patients completed the BDI (30, 31) with 21 variables. The investigator used the modified inventory divided into three grades with the following meaning: grade I (score 0-13), no depression; grade II (score 14-24), moderate depression and grade III (score over 24), severe depression.

Table II. The main symptoms in the FI are shown during the two- and six-year prodromal periods in the healthy study participants (HSS), patients with breast disease (BBD) and patients with breast cancer (BC). The main variables in the FI were divided into three grades with the following meaning: grade 0, no psychiatric symptoms; grade 1, moderate psychiatric symptoms; and grade 2, severe psychiatric symptoms.

Variable	HSS (n=28) %			BBD (n=53) %			BC (n=34) %			p-Value
	0	1	2	0	1	2	0	1	2	
Insomnia										
0-2 years	57	21	21	58	32	9	62	18	21	0.35
2-6 years	71	18	71	64	28	8	68	24	9	0.88
Anxiety										
0-2 years	57	39	4	58	36	6	59	29	12	0.7
2-6 years	57	25	18	55	38	8	74	21	6	0.18
Tension										
0-2 years	32	61	7	45	49	6	41	56	3	0.77
2-6 years	39	50	11	36	55	9	50	50	-	0.34
Fear										
0-2 years	64	36	-	66	32	2	68	29	3	0.91
2-6 years	61	36	4	72	25	4	79	18	3	0.59
Depression										
0-2 years	64	21	14	42	34	25	62	12	26	0.17
2-6 years	64	11	25	47	26	26	65	12	24	0.27
Guilt										
0-2 years	68	29	4	62	21	17	76	18	6	0.23
2-6 years	68	21	11	64	25	11	74	24	3	0.70
Headache										
0-2 years	36	54	11	32	60	8	41	41	18	0.43
2-6 years	50	39	11	42	51	8	53	26	6	0.76
Other pain disorder										
0-2 years	8	57	36	26	51	23	21	53	24	0.31
2-6 years	18	57	25	40	43	17	32	38	26	0.29
Lowered concentration										
0-2 years	57	32	11	60	34	6	57	32	11	0.86
2-6 years	71	18	11	83	15	2	71	18	11	0.14
Tiredness										
0-2 years	36	39	25	30	45	25	41	29	29	0.69
2-6 years	68	21	11	55	34	11	65	21	15	0.61
Discomfort										
0-2 years	57	32	11	55	36	9	53	38	9	0.99
2-6 years	68	21	11	62	34	4	68	32	-	0.26

FI. The patients completed the FI (23, 24) with 11 variables. The investigator used the FI divided into three grades with the following meaning: grade 0, no psychiatric symptoms; grade 1, moderate psychiatric symptoms and grade 2, severe psychiatric symptoms.

*Spielberger trait inventory.* All study participants completed the Spielberger trait inventory (32). Trait anxiety was assessed using a ten-item subscale from the inventory. The ten items referred 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 (score range: 0 to 6) was used to evaluate the depression of the study participants (33), 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 version 4 (SPSS Inc., Chicago, 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 and BBD patients and the HSS group was 51.5, 47.5 and 45.7 years, respectively. 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 in a steady relationship. Almost half of the patients (41.7%) had graduated from primary school

Table III. The mean scores for the FI for the healthy study participants (HSS), patients with breast disease (BBD) and patients with breast cancer (BC).

Variable	HSS (n=28) Mean (SD)	BBD (n=53) Mean (SD)	BC (n=34) Mean (SD)	p-Value
Forsen score				
0-2 yrs	14.3 (9.8)	14.2 (8.7)	14.1 (11.0)	0.99
2-6 yrs	12.5 (11.0)	11.8 (7.9)	9.8 (7.2)	0.43

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%), while approximately 23.5% were retired. The mean gross annual family income of the BC and BBD patients was 36,100 and 27,714 €, respectively. The BC patients were significantly ( $p=0.03$ ) wealthier than the BBD patients and the HSS group, as estimated by their gross annual family income. The groups differed only slightly from each other with regard to the factors of the reproductive life of the women (Table I).

*The psychiatric symptoms in FI.* The psychiatric symptoms in FI during the two- and six-year prodromal periods in the HSS, BBD and BC groups are shown in Table II. There was a trend for the women with BC to have more severe anxiety during the two-year prodromal period (4/34 patients, 11.8%) than those of the BBD (3/53 patients, 5.7%) and HSS groups (1/28 patients, 3.6%). The BC group tended to have more severe headaches during the two-year prodromal period (6/34 patients, 17.6%) than the women in the BBD (4/53 patients, 7.5%) and HSS groups (3/28 patients, 10.7%). The BC group also had more severe tiredness during the six-year prodromal period (5/34 patients, 15.7%) than the women in the BBD (6/53 patients, 11.3%) and HSS groups (3/28 patients, 10.7%). The mean sum of the scores of the FI variables during the six-year prodromal period were significantly lower in the BC group (9.8) than in the BBD (11.8) or HSS groups (12.5). However, the mean scores for the FI for the HSS, BBD and BC groups differed only slightly when the FI variables were considered separately (Table III).

*The use of psychiatric medications.* The use of psychiatric medications during the two- and six-year prodromal periods in the HSS, BBD and BC groups is shown in Table IV. The patients in the BC group tended to use more psychiatric medications during the six-year prodromal period (7/34 patients, 20.6%) than the patients in the BBD (7/53, 13.2%) and the HSS groups (3/28 patients, 10.7%).

Table IV. The use of psychiatric medications during a two-year and six-year prodromal period in the healthy study participants (HSS), patients with benign breast disease (BBD) and patients with breast cancer (BC).

Variable	HSS	BBD	BC
	n=28 (%)	n=53 (%)	n=34 (%)
No medications			
0-2 years	23 (82)	41 (77)	27 (79)
2-6 years	24 (86)	44 (83)	27 (79)
Irregular medication			
0-2 years	2 (7)	7 (13)	4 (12)
2-6 years	1 (4)	4 (8)	5 (15)
Regular medication			
0-2 years	3 (11)	4 (7)	3 (9)
2-6 years	2 (7)	3 (6)	2 (6)
Medication (irreg/reg)			
0-2 years	5 (18)	11 (21)	7 (21)
2-6 years	3 (11)	7 (13)	7 (21)

## Discussion

In 1893, Herbert Snow published the first scientifically designed study considering women with a depressive state at high risk of developing breast cancer. He investigated 250 female cancer patients at the London Hospital and found that 156 of them had experienced ‘immediately antecedent trouble’, loss of close relative, deprivation and problems in work-life and possible somatic trauma (34). The present study used the FI to evaluate the participants’ history of psychiatric symptoms during the two- and six-year prodromal periods. The BC group tended to have more severe anxiety and more severe headache during the two-year prodromal period. The patients in the BC group also had more severe tiredness during the six-year prodromal period than the women in the BBD and HSS groups. The mean sum of the scores of the FI variables were significantly higher in the BC group than in the BBD or HSS groups.

Starting from the popular belief that psychological factors have a significant role in the carcinogenesis of the breast, it follows that women with BC may be more prone than healthy women to report prior stress and other psychological problems in an effort to explain their BC. This may lead either to a false-positive association between psychological factors and BC risk, or to the overestimation of true-positive associations. Therefore, the present study was designed to reduce the recall bias; the reports on psychological factors were obtained from the study participants who had BC symptoms but had not yet been given a definitive diagnosis. After the breast biopsy and the confirmation of diagnosis in histology, the study participants were divided into three groups (BC, BBD and HSS).



One potential bias may have arisen from age being a confounding factor and some of the earlier studies have been criticised on such methodological grounds as having provided limited control for age (35). In the present study, the women in the BC group were 4.0 and 5.9 years older than those in the BBD and HSS groups, respectively. However, no statistically significant age difference between these groups was found ( $p=0.12$ ).

The participants of this 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. There had been no pre-selection and the indications for referral in this study were in line with previous results in a Breast Cancer Diagnostic Unit in Finland (26). The study sample may be considered clinically representative for this type of prospective case-control study design. It should be noted that the control group (healthy individuals) in this study was not representative of the whole population, since it consisted of women who presented primarily with BC symptoms.

One should consider if there is a possible link between the use of psychiatric medications and the later development of BC. So far, epidemiological data have shown conflicting and inconsistent results for any association between the use of psychiatric medication and BC risk (36-38). In the present study, the patients in the BC group tended to use more psychiatric medication during the six-year prodromal period (20.6%) than the women in the BBD (13.2%) and HSS groups (10.7%). However, the number of cases with psychiatric medication in the study is insufficient to support statistically a specific link between psychiatric medications and increased breast cancer risk.

In summary, the present findings of a weak relationship between the FI and breast cancer risk are in line with the finding of Forsen (23, 24), who specifically investigated the psychological identification of BC patients before biopsy.

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