

Montgomery-Asberg Depression Rating Scale (MADRS) in Healthy Study Subjects, in Patients with Breast Disease and Breast Cancer: A Prospective Case-Control Study

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Abstract. *Background:* In 1979, Montgomery and Asberg introduced an inventory for screening of depression. To our knowledge, the associations between the MADRS 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 (BDI, Forsen, Spielberger), and all study variables were obtained before any diagnostic procedures were carried out. 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). There was a trend for the women of the HSS group to have less apparent sadness (MADRS mean score, 1.14) than these of the BC (MADRS mean score, 1.47) and BBD groups (MADRS mean score, 1.66). The HSS group tended to have less inner tension and less lassitude (MADRS mean score, 0.93 and 0.50) than the patients in the BC group (MADRS mean score, 1.24 and 1.18) and in the BBD group (MADRS mean score, 1.13 and 1.28). The HSS group also reported less inability to feel (MADRS mean score, 1.14) than the patients in the BC group (MADRS mean score, 1.41) and the patients in the BBD group (MADRS mean score, 1.28). The mean sum of the scores of MADRS variables were significantly lower in the HSS group (MADRS mean score, 8.43) than in the BC (MADRS mean score, 11.35) and BBD groups (MADRS mean score, 10.68). *Conclusion:* The results of this study do not support a specific link between MADRS and breast cancer risk. However, patients with BC or BBD tended to have an increased risk for experiencing depressive symptoms.

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When depressed, women are not prone to seek doctor's consultation or breast cancer (BC) screening when breast symptoms or a breast lump appears. A poor cultural or social environment can also be a cause of depression and delay in the diagnosis of breast disease (1). Moreover, among the population with breast disease, depressive symptoms can be associated with low income, ethnic minority and health-related quality of life (1). 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 of breast cancer. 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 (2). In addition, life-style 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 (2-8). Psychological factors, such as stressful and adverse life events, are widely thought to play a role in the etiology of BC (9-24). In 1979, Montgomery and Asberg introduced an Inventory (MADRS) for screening of depression (25). To our knowledge, the associations between the MADRS and the risk of BC are rarely considered together, and therefore this was a prospective study to examine the role of MADRS in women with breast symptoms referred by physicians to the Kuopio University Hospital (Finland).

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

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.

on Cancer (IARC). 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 consent. Women with breast symptoms or a suspicious 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 (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, 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 (15). 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. 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 (15). The defences used were also assessed on a 5-point scale (15). The 'Working through and actively confronting the stressful event' variable was also rated on a 5-point scale (15).

The rated case record included the loss events from childhood (under 3 years of age and 4-12 years of age), adolescence (13-23 years of age), adulthood and in particular the 10 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.

Forsen inventory (FI). The women completed the Forsen inventory (33) with 11 variables. The investigator used the FI divided into three grades: grade 0, no psychiatric symptoms; grade 1, moderate psychiatric symptoms; grade 2, severe psychiatric symptoms.

Spielberger trait inventory. All study participants completed the Spielberger trait inventory (34). 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-Asberg Depression Rating Scale (MADRS). The MADRS with ten variables (scores from zero to six) was used to evaluate the depression of the study participants (25), 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., 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 and 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 completed primary school education, 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 figure for the patients with BBD was 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 psychiatric symptoms by MADRS. The psychiatric symptoms by MADRS are shown in Table II. There was a trend for the women with HSS to have less apparent sadness (MADRS mean score, 1.14) than those of the BC (MADRS mean score, 1.47) and BBD groups (MADRS mean score, 1.66). The HSS group tended to have less inner tension (MADRS mean score, 0.93) than the patients in the BC group (MADRS mean score, 1.24) and in the BBD group (MADRS mean score, 1.13). The HSS group also slept more (MADRS mean score, 1.21) than did the patients in the BC group (MADRS mean score, 1.36) and the patients in the BBD group (MADRS mean score, 1.41). There was a trend for the women with HSS to have less lassitude (MADRS mean score, 0.50) than those of the BC (MADRS mean score, 1.18) and BBD groups (MADRS mean score, 0.94). The HSS group also reported less inability to feel (MADRS mean score, 1.14) than the patients in the BC group (MADRS mean score, 1.41) and the patients in the BBD

Table II. *The MADRS scores in healthy study participants (HSS), patients with benign breast disease (BBD) and in patients with breast cancer (BC).*

Variable	HSS (n=28)		BBD (n=53)		BC (n=34)		p -Value
	Mean	(SD)	Mean	(SD)	Mean	(SD)	
Apparent sadness	1.14	(1.58)	1.66	(1.60)	1.47	(1.50)	0.37
Reported sadness	0.86	(1.58)	1.09	(1.33)	1.12	(1.41)	0.73
Inner tension	0.93	(1.27)	1.13	(1.14)	1.24	(1.21)	0.60
Reduced sleep	1.21	(1.57)	1.36	(1.56)	1.41	(1.74)	0.89
Reduced appetite	0.21	(0.63)	0.23	(0.64)	0.29	(0.87)	0.88
Poor concentration	1.00	(1.28)	0.98	(1.28)	1.47	(1.50)	0.22
Lassitude	0.50	(1.17)	0.94	(1.28)	1.18	(1.49)	0.13
Inability to feel	1.14	(1.67)	1.28	(1.41)	1.41	(1.44)	0.78
Pessimism, guilt	1.00	(1.28)	1.58	(1.54)	1.41	(1.26)	0.21
Suicidal thoughts	0.36	(1.10)	0.38	(0.79)	0.35	(0.77)	0.99

Scoring: 0=no symptoms, 6=severe symptoms.

group (MADRS mean score, 1.28). The HSS group tended to have less pessimism and guilt (MADRS mean score, 1.00) than the patients in the BC group (MADRS mean score, 1.41) and in the BBD group (MADRS mean score, 1.58). The mean sum of the scores of MADRS variables were significantly lower in the HSS group (MADRS mean score (SD), 8.43 (9.7)) than in the BC (MADRS mean score (SD), 11.35 (9.2)) and BBD groups (MADRS mean score (SD), 10.68 (9.2)). However, the distribution of the mean sum of the MADRS scores for HSS, BBD and BC groups differed only slightly when the scores were grouped into four separate categories (Figure 1).

Discussion

There was a trend for the women with HSS to have less apparent and reported sadness and less inner tension and reduced sleep and lassitude than these of the BC and BBD groups. The HSS group also reported less inability to feel and less pessimism and guilt than the patients in the BC group and the patients in the BBD group. The mean sum of the scores for the MADRS variables were significantly higher in the BC and BBD groups than in the HSS group. However, our study does not provide support for the hypothesis that depression in MADRS is associated with BC risk.

Excess of moderate or severe depression among patients with BBD has not been found before probably due to different sampling of the study participants. Most of the previous clinical trials were carried out on individuals who had already attended a breast clinic and been advised to have breast biopsy (35). This sampling method of study subjects excludes many women with minor breast pathology not considered to need breast biopsy and means that assessment of psychological factors takes place after

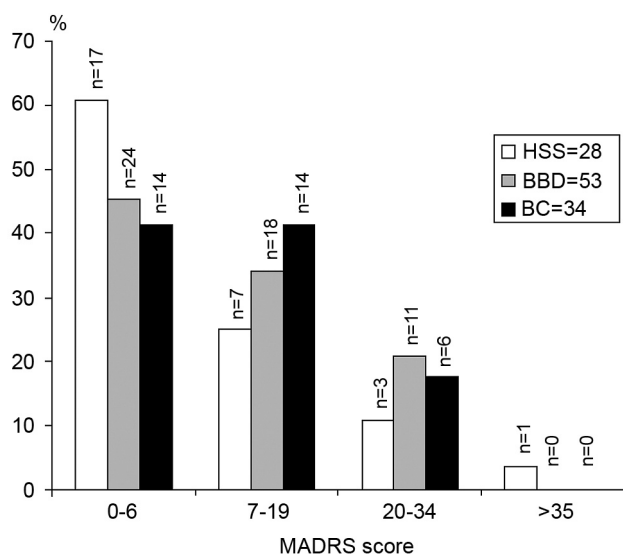


Figure 1. The distribution of the mean sum of the MADRS scores for HSS, BBD and BC groups are shown in four separate categories.

the study subjects have been examined by their doctors and hence they had probably already gained an impression as to whether the breast problem was malignant or BBD. Therefore, we designed our study to reduce this recall bias; the reports on psychological factors were obtained from the study subjects who had breast symptoms but had not yet been given a definitive diagnosis. After the breast biopsy and the confirmation of diagnosis in histology, the study subjects were divided into the three groups of BC, HSS and BBD. 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 (27).

Excess of apparent and reported sadness, inner tension, reduced sleep, lassitude, inability to feel, pessimism and guilt in patients with BBD has not been found previously either (24). BBD can develop or regress rapidly in response to hormonal changes, whereas the BC is usually a more slow-developing condition. If psychological factors and depression play any role in the aetiology of breast disease, they would logically be expected to operate over a few weeks or months for BBD but over years for BC. There is possible mechanism through which depression and BBD might be linked. A link of this kind would fit the observed sequence of events, depression, then breast symptoms, but a link in the opposite

direction is also possible; a pre-existing sex hormone imbalance could cause BBD and depression. However, the popular belief that sex hormone imbalance may cause depression in women is not supported by any firm evidence. The BBD category in our study is a heterogeneous group of breast diseases with different histological entities (benign fibrocystic disease, $n=37$; fibroadenoma, $n=5$; adenoma, $n=3$; papillomatosis, $n=2$; other BBD, $n=6$). Patients with nonproliferative lesions (benign fibrocystic disease, $n=37$) have no or only slightly increased risk for BC. Women whose breast biopsies showed epithelial hyperplasia have about a 2- to 4-fold increased risk of developing BC.

From the widely held belief that psychological factors have a significant role in carcinogenesis of the breast, it follows that study subjects with breast tumour may be more prone than healthy subjects to report prior stress and other psychological problems in an effort to explain their breast disease. This could lead either to a false-positive association between psychological factors and BC risk or to overestimation of true-positive associations (36). One potential bias arises from age being a confounding factor, and some of the earlier studies have been criticized on such methodological grounds as have limited controlling for age (37). 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 ($p=0.12$).

In summary, the results of this study do not support a specific link between MADRS and BC risk. However, the patients with BC and BBD tended to have an increased risk for depressive symptoms.

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