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Psychiatric Disorder in Patients with Advanced Breast Cancer: Prevalence and Associated Factors

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The prevalence of psychiatric disorder and associated factors has been examined in 139 women with advanced breast cancer. Patients completed a self-report assessment of mood, the Hospital Anxiety and Depression Scale (HAD). They were also interviewed to obtain sociodemographic details, UICC performance status and past psychiatric history. Overall, 35 (25%) scored 11 or above (out of a maximum of 21) on either the anxiety or the depression subscales, or both, of the HAD and were therefore probable cases of anxiety and/or depression. These patients are likely to benefit from psychosocial intervention. Clinical anxiety was unrelated to any sociodemographic or disease related factors. Clinical depression was significantly more prevalent amongst patients in the lower socioeconomic classes ($P = 0.01$) and those with poor performance status ($P = 0.007$). Depression can be difficult to detect in patients with advanced breast cancer and these factors may be useful indicators to clinicians of patients at high risk of this disorder.
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INTRODUCTION

THERE IS an increasing clinical concern to improve the quality of life of patients with advanced breast cancer. However, little is known about the prevalence of clinically significant psychological disorder in this population, or its relationship to patient and illness related factors. A better understanding of these issues would provide an indication of the level of need for psychosocial intervention and support, and also help to identify those most likely to benefit from it.

This study aimed to estimate the prevalence of clinically significant anxiety and depression in a sample of women with advanced breast cancer using the Hospital Anxiety and Depression scale (HAD) [1]. This is a self-report mood questionnaire developed specifically for use in patients with physical disease and excludes symptoms that could be due either to physical illness or its treatment. Its use in assessing mood in patients with cancer has been recommended by the MRC Cancer Therapy Committee's working party on quality of life in cancer patients [2]. It has been validated against a psychiatric interview in a population of patients with advanced breast cancer and shown to provide a reasonable estimate of psychiatric disorder [3].

A further aim of the study was to examine the relationship between the psychiatric status of the patients and sociodemographic, personal, and disease and treatment parameters.

PATIENTS AND METHODS

The study sample consisted of 139 women with advanced breast cancer attending a clinical oncology unit. 86 of these formed a consecutive series of inpatient admissions. Patients admitted overnight for chemotherapy were excluded for reasons of convenience. 53 of the women were a series of outpatient clinic attenders who were either receiving endocrine therapy or were being observed without a specific systemic therapy. All patients had a histologically confirmed diagnosis of breast cancer with either inoperable locoregional recurrence or metastatic disease. 34 (24%) of the patients originally presented with locally advanced disease. For the remaining patients, the median time since first recurrence of the disease was 2.3 years (range 0–14 years). It was ensured that the patients had a level of alertness permitting participation in a 20-min interview.

All patients completed the HAD. This questionnaire enquires about symptoms of mood disturbance over the preceding week. It is made up of a seven-item anxiety subscale and a seven-item depression subscale. Each item is rated on a scale of 0–3, ranging from "not at all" to "very much". This gives a maximum subscale score of 21 for both depression and anxiety. The

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generally established threshold score of 11 on both subscales was used to identify patients who were probable cases of anxiety or depression, i.e. those who had anxiety or depression of a severity equivalent to that seen in a psychiatric outpatient clinic. This threshold has been validated on a sample of patients with advanced breast cancer [3].

Patients were also interviewed as part of a standardised psychosocial assessment of patients attending the oncology unit. The following information was obtained at interview:

(1) Sociodemographic details.
(2) Past psychiatric history.
(3) Physical performance status using the UICC scale [4].

Information concerning patients' disease status and treatment was obtained from their medical notes. All data for this study were collected by a nurse specialist in oncology.

Statistical methods

Chi squared tests or Fisher exact tests for 2 × 2 tables were performed to examine the associations between psychiatric disorder and sociodemographic, personal and disease factors. Comparisons of median scores for anxiety and depression between inpatient and outpatient groups were performed using the Mann–Whitney U test. A stepwise logistic regression was performed to ascertain the independence of these associations. The univariate results presented in Table 1 were taken from the logistic regression analysis before the inclusion of any variables to facilitate comparison with the multivariate results given in Table 2. Odds ratios and their confidence limits, where given, were calculated from the multivariate logistic regression after the inclusion of the last significant variable.

RESULTS

All the women who were asked to participate in the study agreed to be interviewed. Their ages ranged from 27 to 90 years with a median of 60.5. 13 out of 139 (9%) patients were in social class 1, with 26 (19%), 54 (39%), 28 (20%) and 17 (12%) in classes 2, 3, 4 and 5, respectively. Socioeconomic class was not recorded for 1 patient. This social class distribution is similar to that of the 1981 Census of the general population of Great Britain [5]. 98 patients (71%) were either married or cohabiting, whilst 8 (6%) were single, 11 (8%) were divorced and 22 (16%) were widowed. 23 patients (17%) had previously been treated by either their GP and/or a psychiatrist for psychological difficulties.

Table 1. Factors associated with psychiatric disorder: univariate analysis

	Probability values		
	Anxiety	Depression	Anxiety and/or depression
Age	0.29	0.37	0.83
Marital status	0.08	0.63	0.27
Social class	0.83	0.002	0.11
Past psychiatric history	0.92	0.61	0.36
UICC performance status	0.12	0.001	0.002
Extent of disease	0.86	0.17	0.74
Lung metastases	0.72	0.82	0.79
Liver metastases	0.52	0.64	0.55
Bone metastases	0.43	0.07	0.09
Brain metastases	0.85	0.35	0.61
Receiving chemotherapy	0.55	0.97	0.85
Receiving radiotherapy	0.09	0.21	0.02
Proximity to death	0.98	0.009	0.18

Table 2. Factors associated with psychiatric disorder: multivariate analysis

	Probability values		
	Anxiety	Depression	Anxiety and/or depression
Age	0.29	0.60	0.85
Marital status	0.08	0.58	0.26
Social class	0.83	0.01	0.19
Past psychiatric history	0.92	0.40	0.18
UICC performance status	0.12	0.007	0.005
Extent of disease	0.86	0.28	0.80
Lung metastases	0.72	0.79	0.88
Liver metastases	0.52	0.60	0.88
Bone metastases	0.43	0.33	0.54
Brain metastases	0.85	0.23	0.41
Receiving chemotherapy	0.55	0.99	0.89
Receiving radiotherapy	0.09	0.89	0.28
Proximity to death	0.98	0.07	0.62

27 patients (19%) had locoregional disease only, 55 (40%) had distant metastases only and 57 (41%) had both local and distant sites of disease. Of the patients with distant sites of metastases, 44% had lung metastases, 25% liver metastases, 57% bone metastases and 4% cerebral metastases. Some patients had more than one site of metastatic disease. 26 (19%) patients were receiving radiotherapy, and 50 (36%) were undergoing chemotherapy. Most patients had a high level of physical function. 55 (40%) patients had a normal performance status (UICC 0) and 58 (42%) had symptoms but were ambulatory (UICC 1). 11 (8%) spent less than half the day in bed (IUCC 2), whilst 13 (9%) spent more than half the day in bed (UICC 3) and 2 (1%) were completely bedridden (UICC 4).

Median scores on the HAD subscales were 7 (range 0–17) for anxiety and 6 (range 0–19) for depression. 27/139 (19%) of patients had scores of 11 or above on the anxiety subscale and were therefore probable cases of anxiety state. 17/139 (12%) were probable cases of depression. Overall, 35/139 (25%) were cases of depression and/or anxiety.

Inpatients had significantly higher median anxiety scores than outpatients (8 vs. 6, $P = 0.02$). Similarly they had higher median depression scores (6.5 vs. 4.0, $P = 0.008$). The proportion of patients with clinical anxiety and/or depression did not, however, differ significantly between inpatients and outpatients (27% vs. 22%).

The relationships between psychiatric disorder and sociodemographic and disease related variables are shown in Tables 1 and 2. Clinical levels of anxiety were not associated with any of the sociodemographic, personal or cancer-related parameters assessed.

Patients in socioeconomic class 5 were significantly more likely to be depressed, and this effect was independent of other factors studied ($P = 0.01$). Proportions of depressed patients were 1/13, 0/26, 8/54, 2/28 and 6/17 for socioeconomic classes 1, 2, 3, 4 and 5, respectively. Patients in social class 5 were 5.1 times more likely to be clinically depressed than those in social classes 1–4 (confidence limits = 1.4–17.6). Marital status and previous psychiatric history were not associated with levels of depression.

Poor performance status was also significantly and independently associated with depressive illness ($P = 0.007$). Proportions of depressed patients were 2/55, 8/58, 2/11, 4/13 and 1/2 for UICC classes 0, 1, 2, 3 and 4, respectively. Patients confined to bed for at least 50% of the day (UICC 3 and 4) had an odds ratio of 9.1 of being clinically depressed compared with those who had no symptoms (confidence limits = 3.4–24.4).

3 patients had poor performance status (UICC 3 or 4) and were in socioeconomic class 5. All 3 of these women were depressed. This was significant in comparison with the remaining 135 patients who had only one or neither of these factors, of whom 14 were depressed ($P = 0.002$). Similarly, 8 of 29 women who had one or both of these risk factors were depressed in comparison with 9 of 109 with neither adverse factor ($P = 0.009$).

The prevalence of depression was similar amongst patients with locoregional recurrence only and those with metastatic disease. There was also no evidence that particular sites of metastases were associated with poor psychological adjustment. No relationship between treatment factors and clinical depression was observed.

The relationship between HAD scores and proximity to death was investigated using a cut-off of 32 days between assessment and death. Patients who died within 1 month of interview had significantly higher levels of depressive illness (5/15) compared with patients with longer survival times (12/112) by univariate analysis. Patients who were close to death were also significantly more likely to have a poor performance status ($\chi^2 = 15.24$, $P = 0.002$). The multivariate analysis showed that proximity to death was not independently associated with depression.

The association between depression and poor performance status was also reflected in overall psychiatric "caseness", i.e. depression and/or anxiety ($P = 0.005$).

DISCUSSION

Studies examining patients with a variety of advanced cancers using standardised psychiatric interviews indicate that between one quarter and one half of such patients have clinically significant anxiety and/or depression [6, 7]. The prevalence of psychiatric disorder in this study is in keeping with these rates as well as with those of other studies using self-report questionnaires in heterogeneous groups of patients with advanced cancer [8, 9] and patients with advanced breast cancer only [10].

The strong association between poor performance status and clinical depression is consistent with the findings of other studies of patients with cancer [7, 10–13]. Poor performance status is usually associated with a greater burden of disease. The depression associated with functional impairment may be in part due to feeling more physically unwell in general and to the experience of pain in particular. In addition, loss of physical function may contribute to depression through loss of independence and ability to perform usual social and professional activities, as well as social isolation. On univariate analysis a strong relationship was observed between proximity to death and performance status. It is, therefore, possible that the implication of functional impairment in terms of the likelihood of imminent death contributes to depression. It is, in turn, possible that the psychomotor retardation and loss of interest associated with severe depressive illness may exacerbate any impairment of function.

Other disease-related variables, including treatment and disease sites, were not related to psychiatric disturbance.

Of the sociodemographic factors measured in this study, only social class was associated with psychiatric disturbance, those in the lower socioeconomic classes being at higher risk. This is similar to the social class distribution for depressive illness in early breast cancer [14] and in the general female population [15]. This association may be due to the increased psychosocial adversity experienced by women in the lower socioeconomic classes. These women are, in particular, more likely to suffer severely stressful life experience [15]. The association may also be a consequence of financial hardship which deprives women of the resources necessary to act as a buffer against the functional and social impact of advanced cancer.

Other psychological and social factors, such as a past history of psychiatric problems and poor social support, which are risk factors for psychiatric disturbance in early breast cancer [14] and non-patient populations [15] seem to be less important in advanced breast cancer. Other studies which have examined psychosocial factors in advanced cancer have also failed to find a relationship between such factors and psychiatric disturbance [7, 12]. It is possible that in advanced cancer these factors are subsumed by deteriorating physical status.

A prospective study is now being undertaken to examine the natural history of clinical anxiety and depression throughout the course of breast cancer. This will enable us to ascertain whether patients with early breast cancer who experience clinically significant anxiety and depression are at high risk of psychiatric disorder following relapse. Such a prospective design will also permit a more rigorous evaluation of the associations described in this cross-sectional study.

It has been shown that clinicians tend to underrate psychiatric disorder, in particular depression, in patients with cancer [16] and other physical illnesses [17]. Clinical depression may be especialy difficult to identify in patients with advanced cancer as the physical signs of depression, such as loss of appetite, fatigue and sleep disturbance are similar to the symptoms of cancer. Low socioeconomic class and poor performance status, which are both easily identifiable, may therefore be useful indicators to clinicians of patients at increased risk of depression. Those patients who are both in socioeconomic class 5 and have UICC scores of 4 or 5 are of particular concern. Improving the detection rate of these patients would facilitate their psychosocial management. Patients with advanced breast cancer who are depressed/and or anxious have been shown to benefit from psychotherapeutic intervention [18–20]. The efficacy of antidepressant drugs in patients with advanced cancer has not been systematically evaluated. A randomised controlled trial is being planned. Ensuring an adequate physical and social environment for patients with advanced breast cancer is, of course, integral to the high quality of their care and the results of this study suggest that attention to these issues may reduce psychiatric disorder. The National Health Service, social services and cancer charities should give priority in terms of resources and effort to these aspects of patient management.

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Decreased Efficacy of Cyclophosphamide, Epirubicin and 5-Fluorouracil in Metastatic Breast Cancer when Reducing Treatment Duration from 18 to 6 months

Bent Ejlertsen, Per Pfeiffer, Dorte Pedersen, Henning T. Mouridsen, Carsten Rose, Marie Overgaard, Erik Sandberg and Bent Kristensen

The impact of treatment duration on survival and progression-free survival is uncertain in metastatic breast cancer. In this trial 359 patients were randomised to receive cyclophosphamide, epirubicin and 5-fluorouracil (CEF) once every 3 weeks for a maximum of 18 months or identical chemotherapy for a maximum of 6 months. Following progressive disease (PD) or severe toxicity CEF was discontinued before the scheduled maximum duration. A second series of CEF continued for a maximum of 12 months was offered to patients with PD more than 3 weeks after completing a maximum of 6 months of CEF. Both groups received tamoxifen (30 mg daily) until PD, and premenopausal patients also received ovarian irradiation. After 6 months 254 evaluable patients were unprogressive. Survival and progression-free survival were significantly longer in 127 patients continuing CEF than in 127 patients interrupting CEF at 6 months (χ^2 = 17.6, P = 0.00003 and χ^2 = 4.7, P = 0.03, respectively). The results of the second series of CEF were discouraging with only one complete response in 44 evaluable patients. In conclusion, prolonged chemotherapy for 18 months is superior to identical chemotherapy for 6 months in the treatment of metastatic breast cancer.
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INTRODUCTION

METASTATIC ADENOCARCINOMA of the breast is associated with a poor prognosis, and only minor therapeutic advances have been made over the past two decades [1]. Definite cure is reported only sporadically [2] and despite the currently used therapy, the median survival from the first metastatic manifestation is between 1 and 2 years [3, 4]. The available cytotoxic and endocrine treatments have been introduced without clinical trials involving comparison with untreated control patients. Thus there is no well defined measure of a possible beneficial effect on survival. A reliable effect of chemotherapy is prolongation of progression-free time and tumour shrinkage [5, 6]. Side-effects may outbalance the palliative benefits of cytotoxic drugs. Reducing the duration of chemotherapy decreases the toxicity, but it is uncertain whether the efficacy is mediated by treatment duration. The present study was initiated to elucidate this question.