toma of the sternum: surgical resection with long-term follow-up. *Ann Thorac Surg* 1989, **48**, 859–862.
8. Colak A, Cataltepe O, Ozgen T, Erbengi A. Spinal cord compression caused by plasmocytomas. A retrospective review of 14 cases. *Neurosurg Rev* 1989, **12**, 305–308.
9. Löfvenberg R, Löfvenberg EB, Ahlgren O. A case of occipitocervical fusion in myeloma. *Acta Orthop Scand* 1990, **61**, 81–83.
10. Goodman MA. Plasma cell tumours. *Clin Orthop* 1986, **204**, 86–92.
11. Greenberg P, Parker RG, Fu YS, Abemayor E. The treatment of solitary plasmacytoma of bone and extramedullary plasmacytoma. *Am J Clin Oncol* 1987, **10**, 199–204.
12. Alexanian R. Localized and indolent myeloma. *Blood* 1980, **56**, 521–525.
13. Mayr NA, Wen BC, Hussey DH, *et al.* The role of radiation therapy in the treatment of solitary plasmacytomas. *Radiother Oncol* 1990, **17**, 293–303.
14. Sinoff CL, Blumsohn A. Spinal cord compression in myelomatosis: response to chemotherapy alone. *Eur J Cancer Clin Oncol* 1989, **25**, 197–200.
15. Colyer RA. Surgical stabilization of pathological neoplastic fractures. *Curr Probl Cancer* 1986, **10**, 117–168.

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Screening for Psychiatric Disorders in a Lymphoma Out-patient Population

Darius Razavi, Nicole Delvaux, Anne Bredart, Marianne Paesmans, Louisette Debusscher, Dominique Bron and Pierre Stryckmans

The Hospital Anxiety and Depression Scale (HADS), a four-point, 14-item self-assessment questionnaire, was tested as a screening method for psychiatric disorders in a sample of 117 Hodgkin's lymphoma and non-Hodgkin lymphoma consecutives out-patients. A receiver operating characteristic (ROC) analysis was performed, giving the relationship between the true positive rate (sensitivity) and the false positive rate (1 – specificity). This makes it possible to choose an optimal cut-off score that takes into account the costs and benefits of treatment of psychiatric disorders (mainly adjustment, depressive and anxiety disorders) in a lymphoma out-patient population. A cut-off point of 10 gave 84% sensitivity and 66% specificity. HADS appears in this study to be a well accepted, simple, sensitive and specific tool.
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INTRODUCTION

LYMPHOMAS REPRESENT a relatively common form of malignancy. Radiotherapy and especially chemotherapy may be given over long periods of time. Patients under treatment, in remission or cured, require frequent follow-up in a specialised treatment centre. A substantial mortality rate reduction has been obtained for Hodgkin's and non-Hodgkin lymphoma in the last few years, giving a higher recovery frequency and a significant lengthening of life. Nevertheless, patients may still suffer from psychological distress since treatments are unfortunately often accompanied by side-effects and long-term sequelae.

The prevalence and specificity of psychological distress in a lymphoma population has been retrospectively studied on a 90-patient sample at a mean of 32 months after diagnosis [1]. Although most patients were free of disease and not receiving treatment at follow-up, some still suffered from a lack of energy (31 patients), loss of libido (19), irritability (22) and tiredness (19); 30 patients complained of continued impairment of thinking or disturbance of short-term memory. After diagnosis, 21 (23.3%) patients had suffered from an anxiety state or depressive illness, or both, while 27 (30%) had experienced borderline anxiety or depression. These results have been confirmed in a prospective study [2].

The psychological problems that develop in long-term survivors of Hodgkin's disease were examined in a cross-sectional survey of 403 patients [3]. Energy had not returned to patients' satisfaction in 37% of the cases. Patients with self-reported energy loss were more likely to be depressed. 18% of the 403 patients had scores consistent with clinical levels of depression; this rate of depression is comparable to a general community sample. However, 29% of the 62 patients who were below 3 years from the diagnosis had elevated depression scores that were significantly higher than the standard community sample and the 333 patients with longer follow-up.

Although high prevalence rate of psychiatric diagnosis has been reported, no studies have investigated screening procedures in out-patient settings for site-specific malignancies. Early detection of psychological and psychiatric morbidity is therefore needed in these ambulatory settings in order to facilitate identification of patients who may be helped by specific rehabilitation or psychosocial interventions.

The Hospital Anxiety and Depression Scale (HADS), a short self-assessment instrument developed by Zigmond and Snaith [4] has been found to be useful in screening adjustment disorders and major disorders in an in-patient cancer population [5] with sufficiently enough sensitivity (75%) and specificity (75%), regarding the prevalence of these conditions, for a cut-off score of 13.

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As the prevalence of psychiatric disorders on one hand and the feasibility of screening procedures on the other hand may be different across settings (in- and out-patient) and site of malignancies, it was decided to investigate the validity of the Hospital Anxiety and Depression Scale as a method of screening for psychiatric morbidity in a lymphoma out-patient population.

PATIENTS AND METHODS

Sampling and testing

Between December 1989 and December 1990, 138 consecutive Hodgkin's and non-Hodgkin's lymphoma out-patients were met at a follow-up medical visit of the Jules Bordet Institute. Among them, 117 were interviewed and tested by a clinical psychologist (A.B.). 21 were not eligible for the study: 7 patients refused to participate, 11 patients did not have a sufficient knowledge of French, 2 patients did not have a confirmed diagnosis of lymphoma and 1 patient had a DSM-III-R diagnosis of psychotic disorder. For all patients, medical data (type of lymphoma, phase of illness, extent of the disease, type of treatment. . .), socio-demographic data (age, sex, race, marital status, educational background, professional status. . .), and psychological data (psychiatric status and history) were collected. Clinical data included also the assessment of performance status [Eastern Collaborative Oncology Group (ECOG)] [6] and treatment toxicity (WHO) [7].

The clinical interview yielding DSM-III-R diagnoses was adapted from the Diagnostic Interview Schedule [8] and the Clinical Interview using DSM-III-R [9]. Patients were invited just before their scheduled oncological follow-up visit to participate in the study. Interviews lasted at least 30 min and focused on the physical and emotional state experienced during the previous week.

The interviews were conducted by one psychologist (A.B.) who had received further clinical training in a comprehensive cancer centre in order to be able to use DSM-III-R. Moreover, all the diagnostic problems met with during the study were reviewed and discussed by the investigators.

The psychological distress was tested by inviting the eligible subjects to fulfil at the end of the interview the HADS scale, a four-point, 14-item self-assessment scale which was translated into French by Zigmond and Snaith (1983). The French version of HADS has been validated in a general medical population [10] and in a sample of cancer in-patients [11].

Patients

The usefulness of HADS as a screening procedure for psychological distress was tested on a sample of 117 Hodgkin's or non-Hodgkin's lymphoma out-patients. The mean age of the study population was 46.8 years (S.D. = 15.8; 15–85 range) and 54.7% of the subjects were male and 45.3% were female. A Hodgkin's lymphoma was diagnosed for 41% of the subjects and a non-Hodgkin's lymphoma for 59% (14.5% stage I, 23.1% stage II, 21.4% stage III, 31.6% stage IV, 9.4% of the subjects could not be precisely assigned to this staging). 29.1% of the patients were assessed during a treatment period. At the time of assessment, the mean number of months elapsed since diagnosis was, for the total sample, 74.9 (S.D. = 88.0; 1–420 range). For the 70.9% which had been assessed after treatment, the mean number of months elapsed since the end of treatment was 42.4 (S.D. = 67.7; 0–336 range). 19.7% of the patients were in their initial treatment phase, 4.3% were in the second (or more) treatment phase. 6.0% had a first relapse, 3.4% had a second (or more) relapse, 36.8% were in their first remission period, 23.9% in their second (or more) remission period, 6.0% could not be assigned to any one of these phases.

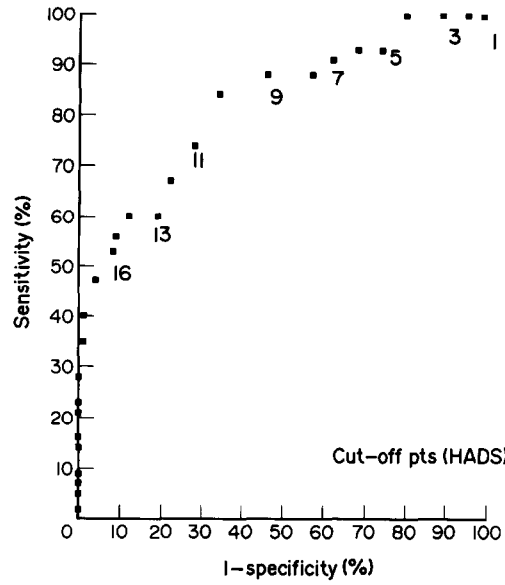

Fig. 1. ROC curve for screening for psychiatric disorder using the HADS.

Analysis

In order to test the specificity and the sensitivity of the HADS, receiver operating characteristic (ROC) analysis was performed. The specificity and sensitivity of HADS was tested for assessing its validity as a method for screening for adjustment disorders and major depressive or anxiety disorders taken together.

Representing ROC analysis on a curve is a way of expressing the relationship between the true positive rate (sensitivity) and the false positive rate (1−specificity). The curve is a representation of the ability of the screening instrument to discriminate between 'cases' and 'non-cases'. The desired cut-off point is generally chosen in order to minimise the sum of false positive and false negative test results [12]. ROC analysis has been chosen because of its usefulness in decision making related to screening methods [13–17].

Positive predictive value (PPV) was calculated for each cut-off score. This value gives the probability of being a case at a precise cut-off point.

RESULTS

The sample was divided in two groups: a group of 74 (63.2%) patients without psychological distress (no distress or adjustment effort) and a group of 43 (36.8%) patients with adjustment disorders (30%), major depressive or anxiety disorders (6.8%). In our study population, 47.1% on-treatment patients and 32.5% off-treatment patients had psychiatric conditions meeting DSM III-R diagnosis.

Socio-demographic (age, sex, Hollingshead index) [18], and medical data (diagnosis, phase of illness, stage of illness, number of months since diagnosis and number of months since the end of treatment) showed no difference between the group of patients with no psychiatric disorder and the group of patients with psychiatric disorder (χ^2-tests or Student's t-tests, not significant, i.e. $P > 0.05$). No significant differences were found between on-treatment and off-treatment patients for HADS mean scores and the frequency of psychiatric disorders.

The ROC curve (Fig. 1) expresses the relationship between

Table 1. PPVs at each HADS score

HADS score	PPV (%)
1	37
2	37
3	38
4	39
5	42
6	42
7	44
8	46
9	48
10	53
11	59
12	60
13	64
14	65
15	74
16	77
17	79
18	87
>19	100

PPV = Positive predictive value.

the true positive rate and the false positive rate for each of the HADS score. The optimal cut-off point for screening of psychological distress (both adjustment disorders and major depressive or anxiety disorders) seems to be 10. This cut-off score is associated with 84% sensitivity and 66% specificity. The probability of a high HADS score (15) being associated with a case (the positive predictive value, PVV) is 77.4% and the PPV of a low score (4) is 42.2%. Table 1 shows the PPVs computed for each cut-off point.

DISCUSSION

Adjustment disorders, major depressive and anxiety disorders were diagnosed using criteria of the DSM-III-R. The first category definition does not refer to a clear and specific profile of signs and symptoms [19]. The stress imposed by the illness on lymphoma patients constantly challenges their coping abilities. The high prevalence of psychological distress found in this study emphasises the need for organising services in order to provide specific interventions to help them.

The false positive rate (34%) found in this study is possibly related to the frequency of acute stress reactions. A follow-up medical visit may have heightened the level of HADS scores of patients who usually would show no adjustment problems. On the other hand, one must consider that self-reported distress is not always correlated with the presence of a given disorder. False negative rates could be related to social desirability which led patients to under-report, on self-reported measures, their psychological distress.

Optimal cut-off points on the ROC curve for this out-patient lymphoma population are lower to those recommended in our previous study of a cancer in-patient population [5]. This can be explained certainly by acute stress reactions which are less frequent in an out-patient population. This difference emphasised the need to further assess screening instruments across settings (in- and out-patients, cancer centres, general hospitals, general practice).

The optimal cut-off point on the ROC curve should be determined also by a cost–benefit analysis. The benefit and cost should be objective. One must take into account the medical costs implicated in the decision to screen for psychological distress and the benefits in terms of quality of life. The medical costs include the expenses related to the screening procedure and to the optimal treatment of the disorder detected. The benefits stem from the improvement of quality of life for patients and their families. This issue is closely related to the effectiveness of the interventions designed for the treatment of adjustment disorders and other psychiatric disorders met within a lymphoma out-patient population.

The ROC curve reported in this study gives the optimal cut-off point in screening for psychiatric disorders in a lymphoma out-patient population. Knowing this cut-off point will make possible not only screening for psychological distress, but also the design and assessment of specific and effective interventions for the rehabilitation of lymphoma out-patients.

The ideal threshold for a test can be influenced by the prevalence of the disorder. The high prevalence found in this study justifies the choice of cut-off point associated with a high sensitivity. Positive predictive values (PPVs) reported above could be used to estimate the prevalence of psychiatric diagnosis at all cut-off points.

In this study, HADS seems to be a specific, simple, inexpensive tool which can be used for screening procedures in a lymphoma out-patient population. Moreover, in our study most of the patients accepted to participate in the study underlying the fact that screening in an out-patient setting is well accepted. The ROC curves provide a way of expressing sensitivity and specificity for a given cut-off point determined by a cost–benefit analysis. This analysis measures the benefit in terms of quality of life against the medical costs incurred in the screening procedures, and subsequently in the treatment of the disorders detected.

Future research must seek to look for the feasibility and validity of screening procedures in other site-specific malignancies along with the development of more simple, sensitive and specific methods of detection.

1. Devlen J, Maguire P, Phillips P, Crowther D, Chambers H. Psychological problems associated with diagnosis and treatment of lymphomas. I. Retrospective study. *Br Med J* 1987, **295**, 953–954.
2. Devlen J, Maguire P, Phillips P, Crowther D. Psychological problems associated with diagnosis and treatment of lymphomas. II. Prospective study. *Br Med J* 1987, **295**, 955–957.
3. Fobair P, Hoppe RT, Bloom J, Cox R, Varghese A, Spiegel D. Psychological problems among survivors of Hodgkin's disease. *J Clin Oncol* 1986, **4**, 805–814.
4. Zigmond AS, Snaith RP. The Hospital Anxiety and Depression Scale. *Acta Psychiat Scand* 1983, **67**, 361–370.
5. Razavi D, Delvaux N, Farvacques C, Robaye E. Screening for adjustment disorders and major depressive disorders in cancer in-patients. *Br J Psychiat* 1990, **156**, 79–83.
6. Zubrod CG, Schneiderman M, Frei E, *et al.* Appraisal of methods for the study of chemotherapy of cancer in man: comparative therapeutic trial of nitrogen mustard and triethylene thiophosphoramide. *J Chron Dis* 1960, **11**, 7–33.
7. World Health Organization. *WHO Handbook for Reporting Results of Cancer Treatment.* Genève, WHO Offset Publication, 1979.
8. Spitzer RL. *Structured Clinical Interview for DSM-III.* New York, New York State Institute, 1983.
9. Othmer E, Othmer SC. *The Clinical Interview using DSM-III-R.* Washington, American Psychiatric Press, 1989.
10. Lepine JP, Godechau M, Brun P, *et al.* Evaluation de l'anxiété et de la dépression chez des patients hospitalisés dans un service de médecine interne. *Ann Médico-Psychol* 1985, 2, 175–189.
11. Razavi D, Delvaux N, Farvacques C, Robaye E. Validation de

la version française du HADS dans une population de patients cancéreux hospitalisés. *Rev Psychol Appl* 1989, **39**, 295–308.
12. Feinstein AR. Diagnostic and spectral markers. In *Clinical Epidemiology: the Architecture of Clinical Research*. Philadelphia, W.B. Saunders, 1985, 597–631.
13. Metz CE. Basic principles of ROC analysis. *Sem Nucl Med* 1978, **8**, 283–298.
14. Erdreich LS, Lee ET. Use of relative operating characteristic analysis in epidemiology. *Am J Epidem* 1981, **114**, 649–662.
15. Mari JJ, Williams P. A comparison of the validity of two psychiatric screening questionnaires (GHQ-12 and SRQ-20) in Brazil using Relative Operating Characteristic (ROC) analysis. *Psychol Med* 1985, **15**, 651–659.
16. Swets JA. Indices of discrimination or diagnostic accuracy: their ROCS and implied models. *Psychol Bull* 1986, **99**, 100–117.
17. Murphy JM, Berwick DM, Weinstein MC, *et al.* Performance of screening and diagnostic tests: application of receiver operating characteristic analysis. *Arch Gen Psychiat* 1987, **44**, 550–555.
18. Hollingshead AB, Redlich FC. *Social Class and Mental Illness*. New York, Wiley, 1958.
19. Fabrega H, Mezzich J. Adjustment disorder and psychiatric practice: cultural and historical aspects. *Psychiatry* 1987, **50**, 31–48.

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High-dose and Low-dose Combined Oral Contraceptives: Protection Against Epithelial Ovarian Cancer and the Length of the Protective Effect

Karin A. Rosenblatt, David B. Thomas, Elizabeth A. Noonan and the WHO Collaborative Study of Neoplasia and Steroid Contraceptives*

The relations between use of high-dose and low-dose combined oral contraceptives and epithelial ovarian cancer were compared in an international hospital-based case–control study. 393 cases from seven countries were compared with 2561 matched controls. The odds ratio (OR) was somewhat lower for women who used high-dose oestrogen oral contraceptives (OR = 0.68) than for women who used low-dose preparations (OR = 0.81) although the difference could have occurred by chance. After controlling for time since last use, risk was slightly lower for long-term users of high-dose preparations than for long-term users of low-dose pills. Both high-dose and low-dose oral contraceptives protect against ovarian cancer, but the degree of protection may be slightly weaker for the newer, low-dose products.
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INTRODUCTION

PREVIOUS FINDINGS from this [1] and other studies [2] have indicated that use of combined oral contraceptives is protective for epithelial ovarian cancer. This study [1] and those of Booth *et al.* [3] and the CASH group [4] have demonstrated that the protective effect conferred by oral contraceptives lasts over 10 to 15 years.

During the past decade, the amounts of oestrogen and progestin in oral contraceptives have decreased in the United States [5] and in many developing countries [6]. The results of most previous studies pertain to high-dose products, and Van Leewen and Rookus [7] have raised the concern that lower dose oral contraceptives may not provide as strong and as long a protective effect against ovarian cancer as high-dose contraceptives. This is a report of results of analyses performed to address this hypothesis using data from a multinational hospital-based case–control study.

PATIENTS AND METHODS

The methods used in this study have been described previously [1]. Incident cases of breast, uterine cervix, uterine corpus, ovarian, and hepatobiliary cancers were identified through records of hospital admissions, outpatient clinics, and pathology departments. Findings from the analysis of data from nine centres in seven countries are included in this report (Australia, Chile, China, Israel, Mexico, the Philippines and Thailand). To be eligible for inclusion in the study, the subjects must have been older than age 15 and been at risk of exposure to steroid contraceptives during their fertile years (born after 1925 or 1930 depending on when steroid contraceptives became available locally). They must also have lived in a defined area served by the hospital of ascertainment for at least 1 year. Dates for recruitment of subjects varied by centre. Ascertainment

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*The data collection centers, and the principal investigator (PI), co-investigator (CI), and pathologist (P) at each participating center in alphabetical order by country are listed in Participants at the end of the paper.
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