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The Effect of Supportive Pamidronate Treatment on Aspects of Quality of Life of Patients with Advanced Breast Cancer

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Selective aspects of quality of life during supportive pamidronate (APD) treatment were assessed in breast cancer patients with osteolytic metastases. 144 patients were randomised to a pamidronate group (n = 76) or a control group (n = 68). A questionnaire measuring mobility impairment, bone pain, fatigue and gastrointestinal toxicity was administered at 3-monthly intervals. The analysis focused on changes in these quality of life domains over time. The median follow-up for both groups was 18 months. Mobility impairment and bone pain were significantly less in the pamidronate group as compared with the control group, due primarily to a rapid improvement shortly after initiation of pamidronate treatment. Thereafter, a gradual increase in these symptoms was noted in both groups. Gastrointestinal complaints and fatigue levels were similar over time in the two groups, suggesting that these symptoms are more dependent on disease-related events and cytotoxic treatment than on pamidronate treatment. The results indicate that reduced skeletal morbidity in breast cancer patients during pamidronate treatment is associated with an improvement in selective aspects of quality of life.
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INTRODUCTION

BREAST CANCER is the predominant malignant tumour in Western European women. In patients with advanced disease, bone metastases are a major cause of morbidity, such as severe bone pain, pathological fractures, hypercalcaemia and spinal cord compression [1–4]. These complications often require palliative treatment. The inhibitory action of bisphosphonates on osteoclastic bone resorption offers new possibilities in the management of metastatic bone disease [5–8]. In breast cancer patients favourable effects of bisphosphonate treatment on morbidity have been reported in some small studies [8, 9]. In 1987, we found that supportive oral pamidronate (APD) resulted in a significant reduction of morbidity related to bone metastases [10].

Any treatment aimed at palliation should be evaluated for its effect on the quality of life of the patient [11–13]. In our prospective trial design a long-term follow-up investigation of selective aspects of quality of life was included. Our hypothesis was that the positive clinical effects observed would also be reflected in the subjective experience of the patients. Specifically, we hypothesised that patients treated with antitumour treatment plus pamidronate would report significantly less mobility impairment, bone pain and fatigue over time than would patients receiving only antitumour treatment. Conversely, it was expected that patients in the pamidronate group would report significantly more gastrointestinal complaints.

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PATIENTS AND METHODS

Details of this multicentre study are described elsewhere [10]. Here we will comment briefly on the trial design and will provide details of the assessment and analysis of selective aspects of quality of life.

Trial design

Breast cancer patients with osteolytic metastases, drawn from 14 centres, were randomly allocated to oral pamidronate treatment or to a control group. Patients with hypercalcaemia, a life expectancy of less than 6 months, creatinine clearance below 30 ml/min, peptic ulcer, malabsorption or pregnancy were excluded from the trial.

Morbidity due to bone metastases was evaluated at 3-monthly intervals. The following events were recorded: hypercalcaemia, pathological or imminent fractures, severe bone pain requiring radiotherapy or surgery, and changes in cytotoxic treatment regimens (hormonal therapy or chemotherapy) due to progression of osteolytic metastases.

At the time of this interim evaluation, May 1989, 167 unselected patients with predominantly osteolytic metastases of a histologically or cytologically confirmed breast cancer had been randomised to either the pamidronate treatment group (n = 86) or the control group (n = 81). The median clinical follow-up for both groups was 15 months. The characteristics of the

Table 1. Characteristics of the patient sample

	Pamidronate	Control
No. of patients	86	81
Age (yr) mean (range)	62 (40–84)	60 (38–78)
ER status		
Positive	57	52
Negative	6	9
Unknown	23	20
Extra-osseous metastases	55	55
Previous skeletal complications*	21	16
Systemic pretreatment†	54	56
Actual therapy‡		
Hormonal	58	57
Chemotherapy	21	20
None	7	4

ER = oestrogen receptor.
*Hypercalcaemia or pathological fracture prior to trial entry.
†At least one systemic treatment modality which was initiated more than 1 month before entrance into the trial.
‡Systemic treatment at the time of accrual onto the trial.

patients at the time of accrual onto the trial were comparable (Table 1).

Pamidronate treatment

Pamidronate was given in a dose of 150 mg twice a day as an enteric coated tablet to be taken 30 min before breakfast and supper. This treatment was intended to be given life-long as a supportive treatment added to optimal, variable and unrestricted concomitant cytotoxic treatment.

The control group did not receive a placebo treatment since it was considered unethical to treat control patients for an undetermined period, possibly lasting some years, with a placebo drug. Trial participation ended with death, severe pamidronate toxicity or withdrawal on patient request.

The main side-effects of oral pamidronate therapy are dose-related nausea, vomiting and occasionally gastritis. These side-effects become particularly relevant at doses exceeding 300 mg daily [7, 10].

Assessment of quality of life

The assessment of selective aspects of quality of life was carried out at 3-monthly intervals using a questionnaire designed specifically for this trial (Table 2). The first questionnaire was completed by the patient with the help of the physician. Subsequent questionnaires were sent by mail to the home address and returned by the patient to our trial management office. If no reply was received within one month, a reminder was sent to the patient. The questionnaire consisted of 17 items, grouped into 4 scales: mobility impairment (6 items), bone pain (3 items), gastrointestinal toxicity (4 items) and fatigue (4 items). Patients scored each item on a 4-point ordinal scale ranging from 0 to 3; 0 = none, 1 = mild, 2 = moderate, 3 = severe.

Quality control

The questionnaires were subjected to a retrospective quality control by a data manager, a statistician and the trial coordinator. Those cases where 2 or more item responses on the pain, toxicity or fatigue scale or 3 or more item responses on the mobility impairment scale were missing, were excluded from the analysis of the corresponding scale.

Statistical analysis

At each point in time the item scores for every patient were averaged per scale. Factor analysis was employed to assess the dimensionality of the constructed scales, i.e. whether the mean of a scale summarised satisfactorily the information contained in all of the item responses of that scale. The reliability of the scales (i.e. the internal consistency) was estimated with Cronbach's alpha coefficient [14].

The group comparisons focused on scale score changes over time. Trends over time for each scale within each group were estimated using a multivariate repeated measurements MANOVA model [15]. These estimated time trends were then tested for differences between the two treatment groups. It should be stressed that mortality, censoring and dropping out because of treatment toxicity or patient request do not violate the assumptions underlying the statistical analysis. When time trends are estimated individually, the number of time points on which the trends are estimated are less important.

An alternative approach might have been the definition of an "event" on the basis of the quality of life measurements for use in an event-free survival analysis. This latter approach was not taken due to the difficulty in defining such an "event".

A detailed description of the statistical analytical method is presented in the Appendix.

RESULTS

Sample accrual

144 patients were evaluable: 76 pamidronate patients and 68 control patients. This reduction in sample size is due to the refusal of one of the participating centres with 14 patients entered, and by 9 patients from other centres to carry out the quality of life assessments. Results were not evaluated beyond 36 months per patient. The median follow-up period was 18

Table 2. Domains and item content of the quality of life questionnaire

1. Mobility impairment: Did you experience difficulties with
   - Walking indoors
   - Walking outdoors
   - Climbing some stairs
   - Standing up, stooping or bending
   - Washing or dressing
   - Your household activities or job?
2. Gastrointestinal toxicity
   - Did you have pain in the stomach?
   - Did you experience a feeling of fullness?
   - Were you nauseated?
   - Did you lack appetite?
3. Bone pain
   - Did you have bone or back pain?
   - Did the pain increase with activity?
   - Did you have sleeping problems due to the pain?
4. Fatigue
   - Were you tired?
   - Did you feel listless?
   - Did you feel ill?
   - Did you need to rest?

Items were scored on a 4-point ordinal scale (0 = none, 1 = mild, 2 = moderate, 3 = severe) based on the situation of the past week.

Table 3. Number of patients at risk at each time interval

Months	No. of patients*	Deaths	Pamidronate toxicity	Other*
0	76 (68)	2 (2)	3	2 (1)
3	69 (65)	2 (6)	1	0 (1)
6	66 (58)	6 (3)	5	2 (0)
9	53 (55)	2 (3)	1	0 (1)
12	50 (51)	0 (5)	4	1 (0)
15	45 (46)	1 (4)	2	2 (1)
18	40 (41)	1 (4)	2	2 (2)
21	35 (37)	3 (3)	0	4 (1)
24	28 (33)	1 (4)	1	2 (0)
27	24 (29)	2 (3)	0	3 (4)
30	19 (22)	1 (1)	1	1 (1)
33	16 (20)	2 (3)	0	2 (2)
36	12 (15)	0 (2)	0	0 (0)

Numbers of control patients are given in parentheses.
*Censored, including lost to follow-up.

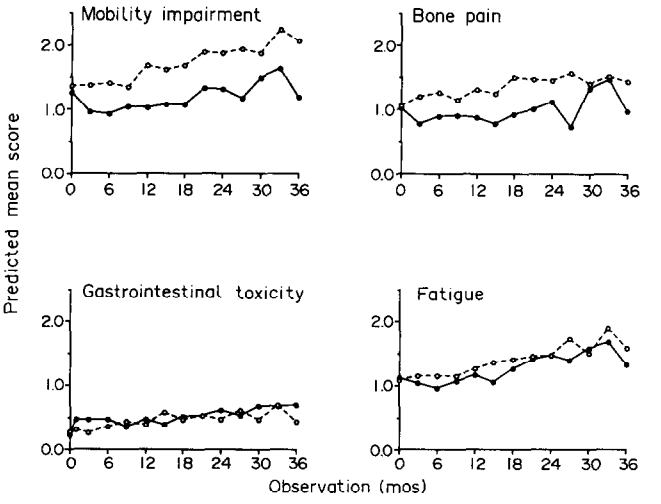

Fig. 1. Predicted mean scores for each of the four scales over time. —•— = Pamidronate patients, ---○--- = control patients.

months for the pamidronate group and 21 months for the control group.

Of the mailed questionnaires, 1132/1179 (96%) were returned to the trial office. In both groups, 80% of the scales was evaluable. There were no differences between the four scales in terms of evaluability.

For every observation period the number of evaluable at risk patients in each group was roughly comparable (Table 3). The reported number of deaths was higher in the control group (n = 43) than in the pamidronate group (n = 23). Conversely, a substantial number of patients in the pamidronate group (n = 20) went off study due to reported gastrointestinal toxicity of pamidronate.

Psychometric properties of the questionnaire

The reliability at the first observation point of the mobility impairment, bone pain, gastrointestinal toxicity and fatigue scales, was 0.94, 0.76, 0.51 and 0.88, respectively. The relatively low reliability of the toxicity scale at the first observation point reflects both the heterogeneity of the items comprising the scale and the limited variability in responses to these items at this first measurement. Item analysis indicated that the second question (feeling of fullness) was particularly responsible for the low reliability. Deletion of this item slightly increased the reliability to 0.58.

Factor analysis indicated unidimensionality for at least three of the four scales. The first common factor explained 72%, 60%, 44% and 71% of the common variance in the mobility impairment, bone pain, gastrointestinal toxicity and fatigue scale at the first observation point, respectively. The reliability and dimensionality of the mobility impairment, bone pain and fatigue scales did not change notably over time. The psychometric properties of the toxicity scale, however, showed a marked improvement over time: 0.72 and 60% at three months, 0.77 and 62% at 24 months, respectively.

Treatment results

The analysis yielded for each of the scales and for each of the two treatment groups a predicted mean at each observation point. Figure 1 gives the time trends for these predicted means.

The group mean values for each of the four scales did not differ significantly at baseline (Table 4). During pamidronate treatment the mean mobility impairment score was significantly higher in the control group than in the pamidronate group (P = 0.03). There was a rapid improvement of mobility in the pamidronate group within the first 3 months (P = 0.002). Thereafter, the difference in mobility between groups was maintained despite a gradual increase in impairment for both groups over time (P = 0.0001). Bone pain scores were significantly higher in the control group (P = 0.007), reflecting an early reduction of bone pain in the pamidronate group in the first three months (P = 0.006). In both groups, however, bone pain then increased significantly over time (P = 0.005), although more rapidly in the control group than in the pamidronate group (P = 0.02).

With respect to fatigue and, surprisingly, gastrointestinal toxicity no significant differences were found between the two groups. For both scales a significant increase of the scores over time was found (P = 0.01 and P = 0.001, respectively).

The lack of differences between the two groups in gastrointestinal symptoms based on patients' self reports can be contrasted with the ratings of pamidronate-induced gastrointestinal toxicity reported by the clinicians which resulted in discontinuation of treatment in 20 cases. To clarify this discrepancy, a subset analysis was performed which made use of an additional evaluation point one month after trial entrance. This analysis was not carried out beyond 24 months follow-up because the number of

Table 4. Group comparison of the mean values for the four scales at the first evaluation point

	Pamidronate (n = 76)	Control (n = 68)	P*
Mobility impairment	1.27 (0.93)	1.23 (0.96)	0.78
Bone pain	1.07 (0.77)	0.99 (0.88)	0.62
Toxicity	0.47 (0.58)	0.32 (0.44)	0.11
Fatigue	1.16 (0.85)	1.06 (0.87)	0.50

Mean (S.D.).
*t test.

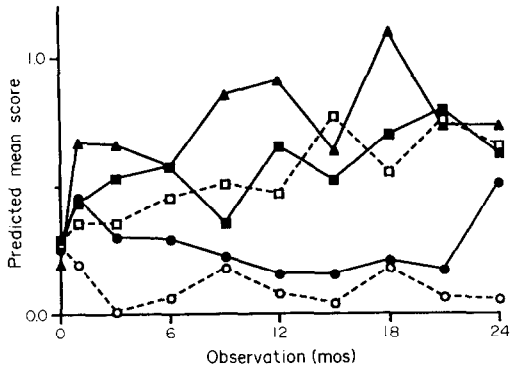

Fig. 2. Subset analysis of gastrointestinal toxicity scores in patients classified as non-dropout pamidronate (—•—, n = 25) and control patients (---○---, n = 15), or as dropout pamidronate gastrointestinal toxicity (—▲—, n = 17), pamidronate non-toxicity (—■—, n = 34) and control patients (—□—, n = 53).

patients in the subsets after this time was too small for comparison. Based on clinical data, both groups were divided into dropout and non-dropout subsets. The dropout subsets contained all patients who went off study because of death, unacceptable pamidronate toxicity, own request or who were lost to follow-up. Censored patients were included in the non-dropout subsets. Pamidronate patients with dropout due to gastrointestinal toxicity were entered into a separate dropout subset. The predicted model means of the gastrointestinal toxicity scores over time of the several subsets of patients are given in Fig. 2.

The toxicity scores did not differ between the pamidronate group (n = 25) and the control group (n = 15) patients composing the non-dropout subset. Both groups within this subset of patients scored low for gastrointestinal toxicity and this remained fairly constant over time. For those patients in the dropout subsets, no significant differences in gastrointestinal scores were detected between the two pamidronate subgroups (non-toxicity dropouts, n = 34, gastrointestinal dropouts, n = 17) or between the total group of pamidronate dropouts (n = 51) and the control group (n = 53). For the entire dropout subset, however, the toxicity scores increased over time (P = 0.0001), and the degree of change over time of toxicity differed significantly between the dropout and the non-dropout subsets (P = 0.0007).

DISCUSSION

Pamidronate treatment is not expected to have a general antitumour effect but rather to protect against malignant osteolytic destruction [16]. Our previously reported clinical evaluation [10] indicated that pamidronate reduces significantly the morbidity associated with such osteolytic metastases. The current study was undertaken to determine the extent to which these clinical effects impact upon selective aspects of the quality of life of patients, as reported by the patients themselves. The investigation was limited to those aspects of quality of life that were expected to be affected by pamidronate treatment; namely mobility impairment, bone pain (skeletal morbidity) and fatigue. Additionally, gastrointestinal toxicity was assessed as this is a known relevant side-effect of the treatment. The results indicate that reduced skeletal morbidity in patients treated with pamidronate [10] is indeed associated with a measurable improvement in the impairment and symptom levels. For mobility impairment and bone pain the scores of the pamidronate group were significantly better due to a rapid improvement in these quality of life domains shortly after initiation of treatment. The gradual increase of bone pain and of mobility impairment over time in both groups supports the earlier finding [10] that pamidronate does not provide complete protection against skeletal morbidity.

Due to the palliative nature of the pamidronate treatment, special attention was directed to potential toxic effects. A substantial number of patients was reported by the clinicians to suffer from intolerable gastrointestinal side-effects of pamidronate. In contrast, the current analysis does not find a significant difference in the self-reported gastrointestinal symptoms between pamidronate and control patients. A more detailed subset analysis indicated that gastrointestinal toxicity scores increased significantly over time in a similar fashion only among dropout patients in both groups, irrespective of the stated reason for dropout from the study. In view of the variability of the cytotoxic treatment regimens allowed throughout the trial, it is difficult to assess exactly the gastrointestinal toxicity of pamidronate. However, the similarity of the toxicity scores in comparable subsets of patients suggests that gastrointestinal symptoms in both pamidronate and control patients associate more with disease-related events, side-effects of cytotoxic treatment or prognosis than with pamidronate treatment.

Similarly, the failure to detect significant group differences in fatigue scores, but rather a significant increase in fatigue over time for all patients, irrespective of treatment, might be attributed to the progressive nature of the disease itself.

The difference between the two groups in the reported number of deaths may be an artefact of differential dropout rates. Dropout attributed to pamidronate side-effects appeared to be a preterminal event in about half of the pamidronate patients (7 of the 16 patients from whom such information was available). Among these patients, the drug had been well tolerated for a period averaging 14 months. Conversely, in the control group toxicity due to the supportive treatment was never given as a reason for dropout. This suggests that the mortality rate in the pamidronate patients may have been underestimated.

Quality of life investigations vary from a limited problem-oriented approach to a global overall investigation [12, 17–19]. Generally, a measuring instrument should be suitable for patient self-administration, and for repeated measurements. This implies that the questions should be limited in number and should be comprehensible, allowing for consistent and standard interpretation. The instrument should preferably be cancer specific and should exhibit the acceptable levels of scale validity and reliability [12, 19–21].

The self-report questionnaire designed for this trial proved to be a convenient, valid and reliable measure of important aspects of quality of life relating to morbidity among breast cancer patients with osteolytic metastases. The high response rate (96% returned questionnaires) was facilitated by a number of factors, including: the convenience of the mailed questionnaire, the strict administrative management of the data collection, the use of a simple questionnaire at regular but not too frequent intervals and, perhaps most importantly, the high level of motivation exhibited by the patients themselves.

The results indicate, in accordance with the clinical evaluation, a rapid, beneficial effect of pamidronate on mobility impairment and bone pain. No effect was seen on fatigue. Surprisingly, no relation was found between pamidronate treatment and gastrointestinal complaints. Such complaints appear to be more closely related to disease and cytotoxic treatment related factors.

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APPENDIX: MISSING DATA

In this paper we used a multivariate repeated measurements MANOVA model with two groups of patients, who were observed with respect to four dependent variables on 13 equally spaced points in time (0, 3,. . ., 36 months). The dependent variables of these models were the scores of the individual patients on the four scales (mobility impairment, toxicity, pain, and fatigue) at the 13 points in time.

Let $Y_{itv(i)}$ be the scale score of the vth patient in group i on point in time t(i = 1,2; t = 1,. . 13; v = 1,. ., $n(i)$). Our MANOVA model had the following structure:

$$Y_{itv(i)} = \mu + \alpha_i + \pi_{v(i)} + \tau_t + \alpha\tau_{it} + \epsilon_{itv}, \qquad (1)$$

where μ was the general mean, α_i was the main effect parameter of group i, τ_t was the main time effect of point in time t, $\alpha\tau_{it}$ was the interaction term of group i and point in time t, $\pi_{v(i)}$ was the parameter associated with the vth patient in group i, and ϵ_{itv} was the error term of y_{itv} (nested within the individual observation). The error team was assumed to be independent and identically normally distributed with mean zero. For a further description of this model, see Winer [15].

Most patients were not observed for all scales at all points in time. Patients died during the trial, and patients dropped out due to gastrointestinal problems. Further, as this paper reports on an interim analysis, there was a censoring mechanism involved. Some patients participated longer then others. For these reasons, there were many missing data to be dealt with.

Some of the missing data were not missing at random. One can expect that a patient who died was in very poor health. Hence, she probably had high mobility impairment, toxicity, pain, and fatigue scores. If one compares the means of the observed scales in both groups on the 13 points in time, then the contrasts between the two groups of patients, and the contrasts between points in time are heavily biased.

However, an important characteristic of the model specified in (1) is the absence of patient-within-group-by-time interaction: all patients in the same treatment group were modelled as showing the same pattern over time. Therefore, the difference between two points in time was expected to be the same for all patients in the same treatment group:

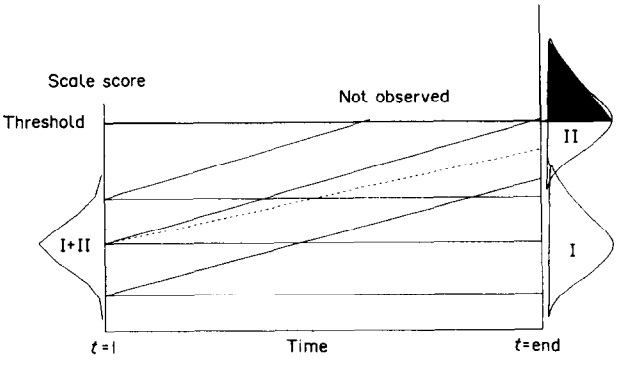

Fig. 3. Threshold mechanism: at t = 1, start of treatment, group I and group II have the same distribution of scale scores. Group I scores are constant over time, while group II scores increase with time. The boldline is the threshold for drop out. At t = end, the black part of the distribution of the scores of group II was not observed. The dotted line is the biased estimate of the change of group II based on the observed means.

$$E(Y_{itv(i)} - Y_{ijv(i)}) = \mu+\alpha_i+\tau_t+\alpha\tau_{it}+\pi_{v(i)}+\epsilon_{itv} - (\mu+\alpha_i+\tau_j+\alpha\tau_{ij}+\pi_{v(i)}+\epsilon_{itv}) = (\tau_t-\tau_j)+(\alpha\tau_{it}-\alpha\tau_{ij}). \quad (2)$$

Hence, with the model as specified in (1) we were able to obtain unbiased estimates of the contrasts with the non-missing data. This is illustrated in Fig. 3. According to the terminology of Little and Rubin [22] all missing data mechanisms are ignorable for the MANOVA model specified in (1).

In Fig. 3 we have graphed the distribution of the scale scores in the two groups at points in time $t = 1$ and $t =$ end. At $t = 1$, the distribution of the scale scores in group I and II were the same. In group I, the scale scores remained constant over time. In group II, the scores increased linearly. Suppose that there was a threshold C such that if the scale score was higher than C, the patient dropped out. Hence, the major part of the distribution group II at $t =$ end would not be observed. If one would compare the means of the observed scales in both groups at $t =$ end, the contrast would be underestimated as well as the rate of the change (dotted line). However, as the rate of the change was assumed to be equal for all patients in one group, the rate of change could be estimated without bias by means of time contrasts within each of the two groups.

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Zinc Alpha-2 Glycoprotein Levels in Serum and Breast Fluids: a Potential Marker of Apocrine Activity

N.J. Bundred, W.N. Scott, S.J. Davies, W.R. Miller and R.E. Mansel

Zinc alpha-2 glycoprotein (ZnGP) was measured in human breast microcysts, breast secretions, breast cyst fluid and serum. Detectable amounts of ZnGP were found in all fluids but the highest levels were found in microcysts. Apocrine macrocysts had a higher ZnGP level than flattened macrocysts. In both cysts and secretions levels of ZnGP correlated with those of dehydroepiandrosterone sulphate. Levels were significantly higher in cyst fluids from women who developed further cysts during follow-up compared with those in fluid from women who did not. Concentrations of ZnGP in serum from breast cancer patients were significantly higher than controls but not women with breast cysts. Women with node positive breast cancer had higher serum levels compared with those in node negative patients. Women with more advanced breast cancer had higher serum ZnGP levels than those with earlier disease. ZnGP is a serum and breast marker of apocrine activity and may prove to be a useful prognostic marker in breast cancer.
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INTRODUCTION

ZINC ALPHA-2 GLYCOPROTEIN (ZnGP) is a 44 000 Dalton molecular weight protein, first isolated and characterised in 1961 by Burgi and Schmid [1]. It is one of the major component proteins of breast cyst fluid [2] and forms 36% of the total protein content of apocrine sweat [3]. Although a recent immunohistochemical study demonstrated that ZnGP is located in apocrine metaplastic epithelium and apocrine glands [4], little is known about the factors affecting the levels of ZnGP in serum and breast fluids.

Women who have had multiple breast cysts aspirated have an increased risk of subsequent breast cancer [5, 6] and Dixon *et al.* have suggested that it is apocrine breast cysts (defined by a low sodium:potassium ratio) which most often recur [7, 8] and give the highest risk of subsequent breast cancer [9].

The aims of this study were to quantitate ZnGP in breast tissue and to determine if ZnGP levels in serum could be used as a marker of breast disease.

PATIENTS, MATERIALS AND METHODS

130 breast cysts were obtained by needle aspiration from 113 women. In 99 women a single cyst was aspirated and in 14 women multiple cysts were drained. 102 women were premenopausal and 11 were postmenopausal (last menstrual period more than 2 years ago). Sodium and potassium levels in cyst fluid were measured by flame photometry [7] and dehydroepiandrosterone sulphate (DHAS) was measured by radioimmunoassay [7] in 66 cysts. 95 women with breast cysts have been followed up for at least one year and the number of cysts they have developed has been recorded.

23 microcysts were dissected from breast biopsy specimens prior to fixation using a dissecting microscope. Fluid within the microcysts was collected after puncture into calibrated capillary tubes. Breast secretions were obtained from 28 women by a

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