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Postoperative Hyperprolactinaemia and Early Recurrence Rate in Breast Cancer

P. Lissoni, A.L. Sormani, G. Tancini, G. Cattaneo, C. Archili, D. Mandelli, S. Crispino, F. Paolorossi and S. Barni

Serum levels of prolactin before and after surgery were measured in 90 women with breast cancer until the 5th postoperative month. Sugery-induced hyperprolactinaemia occurred in 51 patients, without significant correlation to any other clinical variable. After a median follow-up of 39 months, irrespective of each other variable (i.e. nodal involvement, oestrogen receptor status, adjuvant therapies), patients with postoperative hyperprolactinaemia had a significantly lower recurrence rate than those in whom surgery was not followed by an abnormal increase in prolactin secretion (3/51 vs. 13/39, $P < 0.001$). These results suggest that, despite the stimulatory role of prolactin on mammary tumours, the lack of postoperative hyperprolactinaemia is an unfavourable prognostic factor because of its association with a higher relapse rate.
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INTRODUCTION

THE CLINICAL course of breast cancer depends not only on the tumour's biological properties but also on host factors, mainly endocrine status and immune functions. In addition to the stimulatory role of oestrogens, prolactin stimulates experimental breast cancer growth [1–3]. However, the role of prolactin in human breast cancer has still to be established. Preliminary clinical data suggest that this hormone is also stimulatory in human mammary tumours [4–6], since increased prolactin secretion was associated with a less favourable prognosis in patients with advanced breast cancer [5, 6]. Moreover, breast surgery can induce increased prolactin secretion in both premenopausal and postmenopausal women with breast cancer [5, 7, 8]. However, the influence of surgery-induced hyperprolactinaemia on the growth of micrometastases already present at the time of the surgical removal of tumour and on the clinical course of breast cancer has never been investigated. We have studied whether such hyperprolactinaemia is a new prognostic variable, capable of influencing the clinical history of operable breast cancer.

PATIENTS AND METHODS

From December 1985 to July 1987, 90 consecutive women with histologically proven breast carcinoma, stage T1-2, NO-2, MO, entered the study (Table 1). Median age was 57 years (range 33–79). All were inpatients at the First or Second Surgery Division of San Gerardo Hospital, Monza. Patients with high blood levels of prolactin before operation were excluded. None of the patients received any drug affecting prolactin secretion for at least 4 days before blood sampling. Moreover, all patients received the same type of anaesthesia with fluorane. Surgery was followed by adjuvant chemotherapy with (cyclophosphamide/methotrexate/fluorouracil (CMF) in premenopausal patients with axillary node involvement and/or negative

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Table 1. Postoperative hyperprolactinaemia in relation to clinical characteristics of 90 breast cancer patients

Characteristics	No.	Hyperprolactinaemia (%)
Menopausal status		
Premenopausal	25	13 (52)
Postmenopausal	65	38 (58)
Surgery		
Halsted	38	23 (61)
Patey	36	20 (56)
Quadrantectomy	16	8 (50)
Histology		
Ductal	75	43 (57)
Lobular	11	6 (55)
Medullary	4	2 (50)
Nodal status		
Node negative	41	26 (63)
Node positive	49	25 (51)
≤ 3 nodes	26	14 (54)
> 3 nodes	23	11 (48)
ER status		
Positive	36	20 (56)
Negative	27	14 (52)
Unknown	27	17 (63)
Adjuvant therapy		
CMF	32	17 (53)
Tamoxifen	21	12 (57)
None	37	22 (59)

oestrogen receptor (ER) status; postmenopausal patients with node involvement were treated with CMF if ER negative or adjuvant hormonotherapy with tamoxifen for at least 2 years if ER positive. Adjuvant therapies were begun within a month after surgery.

To assay serum prolactin levels, venous blood samples were collected from each patient at 0900 on the day immediately before and 7 days after surgery, then every 15 days until the 5th month. We decided to collect the first postoperative sample on the 7th day to exclude any influence of anaesthesia. To avoid interference due to the stress, blood samples were drawn at least 15 min after the positioning of an indwelling catheter in an antecubital vein. Serum was obtained by centrifugation and stored at −20°C until assay in duplicate with a double-antibody radioimmunoassay kit (Sclavo, Milan). Intra-assay and interassay coefficients of variation were 3% and 5%, respectively. Normal values in our laboratory from 150 age-matched healthy women (95% confidence limits) were below 20 ng/ml. Patients were defined as having surgery-induced hyperprolactinaemia when postoperative levels of prolactin persisted above three S.D. for at least 15 days compared with normal values.

Data were analysed by t test and χ^2 test, as appropriate. The influence of the most important clinical variables for breast cancer (node involvement, ER status, adjuvant therapy, menopausal status) on recurrence rate was studied with Cox's proportional hazard regression model.

RESULTS

Surgery was followed by hyperprolactinaemia in 51/90 (57%) patients, with no significant difference in relation to the type of surgery. Neither menopausal status, axillary node involvement, nor status significantly influenced the frequency of hyperprolactinaemia.

In patients with surgery-induced hyperprolactinaemia, prolactin levels became normal within 3 months in all but 2 cases, in whom prolactin remained abnormally high until the 5th month after surgery. Mean prolactin levels observed before and after surgery in patients with or without surgery-induced hyperprolactinaemia are illustrated in Fig. 1. Levels in patients with surgery-induced hyperprolactinaemia remained significantly higher than those in patients with no hyperprolactinaemia until the 45th day after surgery; no significant difference was seen at 2 and at 3 months. However, starting at the 4th month, prolactin levels were significantly lower in patients with than in those without postoperative hyperprolactinaemia.

Each patient was followed up for at least 3 years after surgery. Median follow-up was similar in patients with or without hyperprolactinaemia (40 months, range 36–55, vs. 38, 36–51). The two groups of patients with or without surgery-induced hyperprolactinaemia were similar for all main prognostic factors for breast cancer, including axillary node involvement, ER status, adjuvant therapies and menopausal status. After a median follow-up of 39 months, a relapse was observed in 16 patients (Table 2). Sites of relapse were: soft tissues 6, bone 5, lung 3, liver 1 and brain 1. Relapse occurred after a median of 19 months (10–40). As expected, recurrence rate was significantly higher in patients with node involvement than in node negative cases (Table 2). Moreover, recurrence was higher in ER negative than in ER positive patients, even though this difference did not reach statistical significance. Recurrence rate was significantly higher in patients without hyperprolactinaemia than in those with postoperative hyperprolactinaemia. The difference in relapse rate between patients with or without hyperprolactinaemia was statistically significant also in relation to each main other prognostic variable, including axillary node involvement.

Multivariate logistic regression showed that the probability of tumour relapse also depended on postoperative prolactin secretion independently of each other known prognostic variable and that the relative risk of recurrence was greater than 19% in patients without postoperative hyperprolactinaemia.

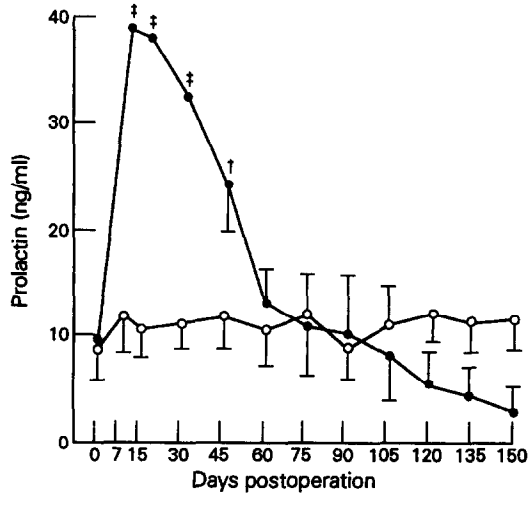

Fig. 1. Mean serum levels of prolactin before and after surgery in breast cancer patients with (●) or without (○) postoperative hyperprolactinaemia. Significant difference, $P <$: *0.025, †0.01 and ‡0.001.

Table 2. Recurrence rates after median follow-up of 39 months in relation to each clinical variable

	No.	Recurrence (%)	
All patients			
Hyperprolactinaemia	51	3	(6)
No hyperprolactinaemia	39	13	(33)§
Menopausal status			
Premenopausal			
Hyperprolactinaemia	13	1	(8)
No hyperprolactinaemia	12	4	(33)*
Postmenopausal			
Hyperprolactinaemia	38	2	(5)
No hyperprolactinaemia	27	9	(33)‡
Nodal involvement			
Node negative			
Hyperprolactinaemia	26	0	
No hyperprolactinaemia	15	4	(27)‡
Node positive			
Hyperprolactinaemia	25	3	(12)
No hyperprolactinaemia	24	9	(37)‡
ER status			
Positive			
Hyperprolactinaemia	20	0	
No hyperprolactinaemia	16	4	(25)†
Negative ER			
Hyperprolactinaemia	14	1	(7)
No hyperprolactinaemia	13	5	(38)*
Unknown			
Hyperprolactinaemia	17	2	(12)
No hyperprolactinaemia	10	6	(40)†
Adjuvant therapies			
CMF			
Hyperprolactinaemia	17	2	(12)
No hyperprolactinaemia	15	5	(33)*
Tamoxifen			
Hyperprolactinaemia	12	1	(8)
No hyperprolactinaemia	9	3	(33)*

Significant difference, $P <$: *0.05, †0.002, ‡0.01 and §0.001.

Site of recurrence was soft tissue in all 3 patients with surgery-induced hyperprolactinaemia who relapsed. Among patients who relapsed, the mean disease-free period was significantly lower in patients without than in those with postoperative hyperprolactinaemia (18 [S.D. 5] vs. 30 [9] months, $P < 0.05$).

DISCUSSION

Despite the stimulatory role of prolactin on breast cancer growth [1–5], we found that postoperative hyperprolactinaemia was associated with a significantly lower tumour recurrence rate in women with operable breast carcinoma independently of each other main prognostic variable, including axillary node involvement, ER status and the influence of both chemotherapeutic and endocrine ajuvant therapies. Therefore, surgery-induced hyperprolactinaemia is a new independent prognostic variable, capable of influencing the clinical history of breast carcinoma, and related to host neuroendocrine response rather than to tumour biological characteristics. However, our results, even though unexpected, do not necessarily disagree with those previously reported [4, 6], in which enhanced prolactin secretion was associated with a less favourable prognosis in advanced breast cancer, since we limited prolactin assays to the period immediately following surgical removal of tumour.

It is difficult to biologically explain the mechanisms responsible for the association between lack of postoperative hyperprolactinaemia and increased recurrence rate in human breast carcinoma. We hypothesise that, similarly to oestrogens which may either stimulate or inhibit breast cancer growth at physiological or at pharmacological doses [9], respectively, prolactin might also exert opposite effects on the development of breast carcinoma depending on its blood concentration. Alternatively, since circulating prolactin values starting on the 4th month following surgery became lower in patients who had had postoperative hyperprolactinaemia than in those without such a prolactin rise, we might hypothesise that in patients with hyperprolactinaemia, a hypoprolactinaemia phase might ensue in the successive months and the patients might have less total exposure to this hormone. A similar hypothesis has been proposed to explain the lower breast cancer incidence in parous than in nulliparous women [10]. Since we monitored prolactin levels only up to the 5th postoperative month, we do not know about the subsequent behaviour of prolactin. A third hypothesis could simply consider postsurgical hyperprolactinaemic status as a reflection of changes in brain neurotransmitter content that has appeared to influence tumour growth [11]. Since breast manipulation *per se* may stimulate prolactin secretion, the lack of prolactin increase after breast surgery could be interpreted as a consequence of alterations in the neuroendocrine mechanisms involved in the regulation of mammary tissue growth. However, since the biological significance of the transient hyperprolactinaemia following tumour removal remains to be understood, it is not possible to establish the best clinical management to improve the prognosis of patients who do not have surgery-induced hyperprolactinaemia. Additionally, since it is unknown whether the reduced recurrence rate observed in patients with postoperative hyperprolactinaemia depends on increased prolactin *per se* or on other mechanisms, pharmacological enhancement of prolactin secretion postoperatively cannot be recommended in patients without a surgery-induced prolactin rise. On the other hand, because of its association with a longer disease-free period, the treatment of postoperative hyperprolactinaemia with dopaminergic agents cannot be justified.

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DNA Ploidy in Intraductal Breast Carcinomas

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Cellular DNA-ploidy in 74 clinically detected intraductal breast carcinomas (IDCs) was analysed by flow cytometry. The histograms were classified as either diploid or aneuploid, and the DNA ploidy pattern compared with that of invasive breast carcinomas and normal breast tissue. All normal breast tissues were diploid while 28 (38%) of the IDCs were aneuploid, the DNA indices ranging from 1.32 to 2.00. The frequency of aneuploidy in invasive ductal carcinomas (73%) was significantly higher ($P = 0.003$), DNA index ranging from 1.34 to 2.92, compared with that in IDCs. Retrospectively, 14.5% of the patients had invasive breast cancer 16–166 months after the diagnosis of IDC. Neither DNA ploidy nor histopathological classification alone predicted clinical outcome, but patients with DNA diploid non-comedo IDC had a more favourable course.
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INTRODUCTION

THE INCIDENCE of intraductal carcinoma (IDC) is not known but among the tumours reported to the Norwegian Cancer Registry between 1976–1986, IDC acounted for only 2.4% of all breast cancer. However, because of screening, an increasing number of IDC cases are being detected, accounting for 15–40% of all breast malignancies [1, 2]. Retrospective studies indicate that 25–50% of IDC is likely to progress to invasive cancer [3, 4]. Histological differentiation and nuclear grading [2] and growth patterns [5] may be related to the clinical outcome of IDC.

Analysis of DNA content in some solid tumours has revealed that recurrence and survival is adversely affected by increasing DNA abnormality [6]. In breast cancer DNA ploidy may be an independent prognostic factor [7, 8] or associated with other more powerful prognostic factors [9–11]. Limited information is available on DNA ploidy in IDC based on flow cytometry [12], while static cytometry from a few screening detected lesions has indicated that aneuploidy may be of value in predicting the most biologically aggressive pre-invasive lesions [13].

Our aim was to compare DNA ploidy in pre-invasive and invasive ductal breast carcinomas and to examine the prognostic value of DNA ploidy in IDC.

PATIENTS AND METHODS

Breast tissues

Formalin-fixed and paraffin-embedded breast tissues, histologically classified as IDC, from 106 women with tumours clinically detected during 1965–1983, samples from 30 invasive carcinomas and from 30 cases with morphologically normal breast tissue were retrieved from the files of the Department of Pathology, Regionsykehuset, University of Trondheim, and the Department of Pathology, Fylkessjukehuset in Molde, Norway. On pathological review of the material classified as IDC, 11 cases (10%) were excluded because of probable foci of invasion. 1 case (1%) showing axillary lymph-node metastases was also excluded. 6 cases (6%) with diagnosed invasive carcinoma in the ipsilateral breast less than 12 months after biopsy were excluded and 4 cases (4%) were reclassified as atypical hyperplasia. Thus, 84 cases were included in the study.

Histological classification

IDC with areas of advanced cytological atypia and necrotic cellular debris in ductal spaces was classified as comedo type [14]. All other IDCs were classified as non-comedo type, since they often contained a mixture of histological patterns. Among the cases accepted as IDC the median number of blocks examined was 7 (range 2–38) per patient.

Clinical information

Due to failure in reporting 5 cases of IDCs, complete clinical information was available in 69 cases analysed by flow cytometry, including reports from the Norwegian Cancer Registry and death certificates from the National Bureau of Statistics.

The cut-off date for recurrence-free survival analysis was 31 December 1987. The median observation period for the 69 patients with IDC was 75 months (range 1–273, mean 88). The following were recorded: (a) invasive recurrences in the ipsilateral breast; (b) metastases with no evidence of a new primary tumour; and (c) patients officially classified as dead from mammary carcinoma with no mammary malignancy other than the IDC.

14 patients (20%), had been treated with biopsy or wide local excision only. 55 (80%) underwent some type of mastectomy. 10 of these patients had mastectomy with no previous biopsy,

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