Eur J Cancer Clin Oncol, Vol. 23, No. 8, pp. 1141–1145, 1987.
Printed in Great Britain

0277-5379/87$3.00+0.00

Effects of Radical Mastectomy on Prolactin Blood Levels in Patients with Breast Cancer

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Abstract—*The role played by PRL in human breast cancer is still obscure. Several observations, however, demonstrated that antitumor therapies for breast cancer are associated with changes in PRL secretion, clinical significance of which remains to be determined. The present investigation was carried out to further clarify the effects of mastectomy on PRL levels in breast cancer women. The study included 34 patients at clinical stage $T_{1-2}N_{0-2}M_0$ treated with radical mastectomy. In each patient, venous blood samples were drawn before, and 15 days, 1 month, 45 days, 2 months and 3 months after surgery to determine PRL serum levels. As controls, 14 women surgically treated for reasons other than neoplastic disease were included in the study. Mastectomy was followed by hyperprolactinemia in 18 of the 34 cases (52.9%). PRL remained elevated for at least 1 month, and it became normal within 2 months. On the contrary, no PRL increase was seen in controls. Among breast cancer women, PRL increase was irrespective of the type of surgery, the histology of the tumor and the menopausal status. In contrast, PRL increase was significantly higher in patients without node involvement and with negative hormonal receptors, with respect to that observed in cases with node involvement and positive receptors, respectively.*

The mechanisms by which mastectomy induces enhanced PRL secretion are still obscure. They might depend, however, on changes in feed-back systems operating in the regulation of PRL secretion, due to the removal of a target organ for PRL itself.

Longitudinal studies, by evaluating the percentage of relapse either in patients with surgery-induced hyperprolactinemia or in those with normal hormonal values, will be needed to clarify the prognostic significance of the enhanced PRL secretion induced by mastectomy.

INTRODUCTION

In some animal species, prolactin (PRL) is involved in the stimulation of mammary carcinoma growth [1] and the administration of PRL inhibitors blocks the development of breast cancer and causes tumor regression in mice and rats [2]. In humans, the role played by PRL in breast cancer growth has not yet been clarified although some observations suggest a stimulatory effect of the hormone. Most human mammary carcinoma cells are stimulated by PRL *in vitro* [3].

As far as blood levels of PRL in women with breast cancer are concerned, most authors have observed values substantially within the normal range [4–7]. An exaggerated PRL release has been described after stimulation either with TRH [7–9] or with sulpiride [9] and a correlation between PRL release and the clinical course of the disease has been reported [8, 10]. This finding, however, has not been confirmed by other authors [11]. Finally, most antitumor therapies for breast cancer are associated with changes in PRL secretion; both CMF [12] and tamoxifen [9, 11] adjuvant therapies induce a significant fall in PRL increase after TRH stimulation. On the other hand, an enhanced PRL secretion has been observed after mastectomy [13].

The present study was carried out to further clarify the effect of mastectomy on PRL levels and to correlate the changes in PRL secretion after surgery with the clinical data of patients with breast cancer including node involvement and receptor status.

Accepted 12 March 1987.

MATERIALS AND METHODS

From February to September 1986, 34 consecutive untreated women with histologically proven breast cancer at clinical stage $T_{1-2}N_{0-2}M_0$ were evaluated. All patients were hospitalized at the First and Second Surgery Division of San Gerardo Hospital of Monza. Clinical data are reported in

Table 1. Clinical data of breast cancer women

Cases	Age	Menopausal status	T N M	Histology	RE*	RPg	Surgery	Therapies after mastectomy
1	59	Menopausal	$T_2N_0M_0$	Lobular	+	+	Halsted	None
2	62	Menopausal	$T_2N_0M_0$	Ductal	+	+	Halsted	None
3	51	Premenopausal	$T_2N_0M_0$	Ductal	−	−	Halsted	None
4	44	Premenopausal	$T_2N_1M_0$	Ductal	−	−	Halsted	CMF
5	53	Menopausal	$T_1N_1M_0$	Ductal	−	−	Halsted	CMF
6	68	Menopausal	$T_2N_0M_0$	Lobular	+	+	Halsted	None
7	52	Menopausal	$T_2N_0M_0$	Ductal	+	+	Halsted	None
8	39	Premenopausal	$T_1N_1M_0$	Lobular	+	+	Halsted	CMF
9	61	Menopausal	$T_2N_2M_0$	Ductal	+	+	Halsted	Tamoxifen
10	38	Premenopausal	$T_1N_0M_0$	Ductal	+	+	Patey	None
11	63	Menopausal	$T_1N_0M_0$	Ductal	−	−	Patey	None
12	66	Menopausal	$T_1N_0M_0$	Lobular	+	+	Patey	None
13	68	Menopausal	$T_2N_2M_0$	Ductal	+	+	Halsted	Tamoxifen
14	65	Menopausal	$T_2N_2M_0$	Ductal	−	−	Halsted	CMF
15	49	Menopausal	$T_2N_2M_0$	Ductal	−	−	Patey	CMF
16	62	Menopausal	$T_2N_2M_0$	Ductal	+	+	Halsted	Tamoxifen
17	65	Menopausal	$T_1N_1M_0$	Ductal	+	+	Halsted	Tamoxifen
18	52	Menopausal	$T_1N_0M_0$	Ductal	−	−	Patey	None
19	61	Menopausal	$T_1N_0M_0$	Ductal	+	+	Halsted	None
20	65	Menopausal	$T_1N_0M_0$	Ductal	+	+	Patey	None
21	49	Premenopausal	$T_1N_1M_0$	Ductal	+	+	Patey	CMF
22	44	Premenopausal	$T_2N_0M_0$	Ductal	−	−	Patey	CMF
23	63	Menopausal	$T_2N_2M_0$	Ductal	+	+	Halsted	Tamoxifen
24	33	Premenopausal	$T_2N_2M_0$	Lobular	−	−	Patey	CMF
25	47	Premenopausal	$T_1N_0M_0$	Ductal	+	+	Patey	None
26	56	Premenopausal	$T_2N_2M_0$	Ductal	+	+	Patey	CMF
27	40	Premenopausal	$T_2N_2M_0$	Ductal	+	+	Halsted	CMF
28	55	Menopausal	$T_2N_2M_0$	Ductal	+	+	Halsted	Tamoxifen
29	62	Menopausal	$T_2N_0M_0$	Lobular	−	−	Patey	None
30	48	Premenopausal	$T_1N_0M_0$	Lobular	+	+	Halsted	None
31	59	Menopausal	$T_1N_0M_0$	Ductal	−	−	Patey	None
32	43	Premenopausal	$T_1N_0M_0$	Lobular	−	−	Patey	CMF
33	58	Menopausal	$T_1N_1M_0$	Lobular	+	+	Halsted	Tamoxifen
34	46	Premenopausal	$T_2N_1M_0$	Ductal	−	−	Patey	CMF

*RE: estrogen receptors; RPg: progesterone receptors; CMF: cyclophosphamide, methotrexate, fluorouracil.

Table 1. All patients underwent radical mastectomy. To evaluate PRL serum levels, venous blood samples were drawn from each patient after an overnight fast 1–2 days before surgery, and 15 days, 1 month, 45 days, 2 months and 3 months after mastectomy. Blood samples were collected through an indwelling catheter inserted in an antecubital vein. The PRL values reported are the mean of three blood samples drawn at 5 min intervals. None of the patients received any drug affecting PRL secretion for at least 4 days prior to blood sampling.

In patients with axillary node involvement, surgery was followed by adjuvant therapy with CMF (cyclophosphamide, methotrexate, fluorouracil) or tamoxifen within 1 month after mastectomy.

As controls, PRL was measured in a group of 14 women of same age as the patients, surgically treated for reasons other than neoplastic disease, who received the same type of anesthesia.

Sera were obtained by centrifugation and stored at −20°C until assayed. PRL serum levels were determined with the double antibody RIA method using commercially available kits (Sclavo, Milan, Italy). Intraassay and interassay coefficients of variation were 3 and 5%, respectively. Results are reported as mean ± S.D. PRL levels were considered as elevated when they were greater than 2 S.D. with respect to those found in controls. The data were analyzed by Student's t test or the chi-square test, as appropriate.

RESULTS

The individual values of PRL observed in women with breast cancer are listed in Table 2. Figure 1 shows the mean serum PRL levels found in controls and patients before and after surgery.

None of the breast cancer patients had high PRL values before mastectomy, and no significant differences were seen between patients and controls in mean basal PRL levels. No significant PRL increase was found after surgery in subjects treated for reasons other than neoplastic disease. In contrast, mastectomy was followed by hyperprolactinemia in 18 cases (53%), with an increase greater

Table 2. Individual PRL serum levels before and after mastectomy in 34 breast cancer women

Cases	PRL (ng/ml) Before surgery	After surgery 15 days	1 month	45 days	2 months	3 months
1	9.8	30.7	23.7	22.4	13.6	2.1
2	9.2	33.5	30.9	25.7	5.7	6.4
3	11.1	38.1	32.5	24.7	4.9	5.9
4	12.8	50.4	30.4	25.4	5.4	2.7
5	7.6	8.0	4.2	7.7	10.0	4.3
6	9.6	17.7	13.1	12.4	9.4	3.3
7	8.2	32.2	25.6	18.8	8.4	7.4
8	11.1	11.4	10.6	9.1	6.5	7.2
9	2.9	8.8	9.4	7.8	9.3	6.6
10	8.3	9.0	4.8	5.8	7.4	6.4
11	4.5	61.1	41.9	27.1	13.4	7.6
12	6.6	13.1	16.6	17.1	15.7	15.2
13	3.6	32.1	24.6	23.6	13.5	5.4
14	6.1	25.4	29.8	26.1	16.9	2.7
15	7.5	10.9	3.6	4.3	5.8	3.4
16	2.5	37.9	20.5	16.7	15.3	6.3
17	4.6	10.2	16.6	15.1	14.0	12.6
18	8.8	42.4	35.4	28.0	20.4	9.5
19	5.8	19.8	6.1	7.4	6.4	5.8
20	5.5	15.0	12.3	12.9	10.4	10.6
21	6.3	6.8	5.9	6.7	7.3	7.1
22	12.1	51.6	54.9	31.9	5.0	4.2
23	12.6	15.9	14.8	13.5	12.4	13.1
24	6.4	5.2	2.6	2.8	3.4	3.9
25	9.6	50.5	38.1	30.9	18.9	10.5
26	5.4	6.8	7.6	5.8	7.6	6.2
27	12.5	26.1	20.0	18.6	15.2	9.8
28	9.8	11.9	18.5	15.2	16.0	13.6
29	6.7	44.5	35.3	29.2	12.7	12.6
30	5.1	26.7	24.9	18.9	6.7	7.4
31	9.9	29.9	25.9	24.8	10.6	9.9
32	9.0	32.6	28.1	25.4	12.7	6.8
33	3.6	6.1	5.8	6.6	5.6	6.3
34	8.7	22.9	25.7	24.9	3.8	9.7

than 100%, while no significant change in PRL circulating levels was seen in the other 16 patients compared with those observed before surgery. In patients with mastectomy-induced hyperprolactinemia, PRL levels remained elevated for at least 1 month, and fell to the normal range within 2 months either in women who received no other therapy after surgery, or in those who underwent adjuvant therapy. In one case only, PRL remained elevated until the second month after mastectomy. Mean serum PRL levels were significantly higher in patients with surgery-induced hyperprolactinemia at 15 days ($P < 0.001$), 1 month ($P < 0.01$) and 45 days ($P < 0.05$) after mastectomy compared with those observed either in control subjects or in women with breast cancer with no PRL rise after surgery.

The percentage of cases with hyperprolactinemia induced by mastectomy was significantly higher in patients without node involvement compared with those with axillary node involvement (12/17 vs. 6/17; $P < 0.05$). Moreover, the percentage of hyperprolactinemia was higher in negative estrogen receptor patients than in those with positive receptors (10/13 vs. 8/21; $P < 0.05$). Finally, among patients with node involvement, the percentage of PRL rise was higher in T_2 cases than in T_1 patients (6/12 vs. 0/5; $P < 0.05$).

No significant differences in the percentage of mastectomy-induced hyperprolactinemia cases were seen between premenopausal and post-menopausal patients (8/13 vs. 10/21; NS); similarly, no significant differences were seen between patients treated with Halsted's mastectomy and those who underwent Patey's mastectomy (10/19 vs. 8/15; NS) and no differences were observed between patients with ductal carcinoma and those with lobular carcinoma (14/25 vs. 4/9; NS). Among patients without node involvement, no differences were seen between T_1 and T_2 patients (6/10 vs. 6/7; NS). Overall patients at clinical stage T_2 had a higher percentage of hyperprolactinemia caused by mastectomy compared with T_1 cases, but this difference was not statistically significant (12/19 vs. 6/15; NS).

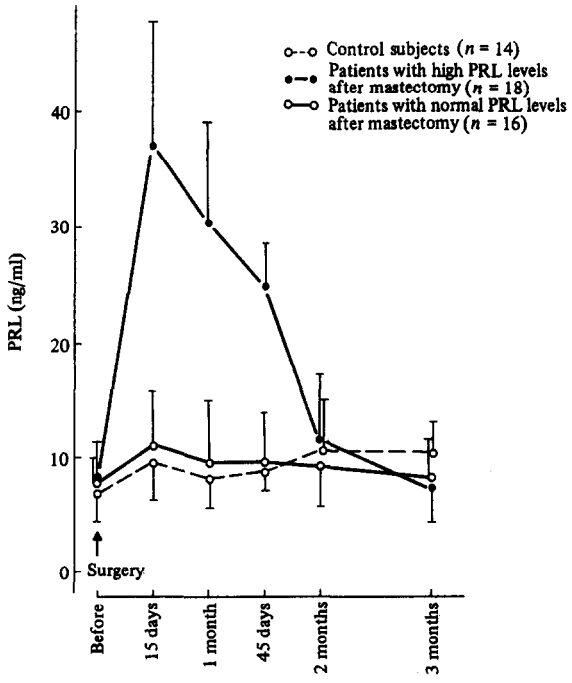

Fig. 1. PRL serum levels (mean ± S.D.) before and after surgery in 34 breast cancer women and in 14 controls.

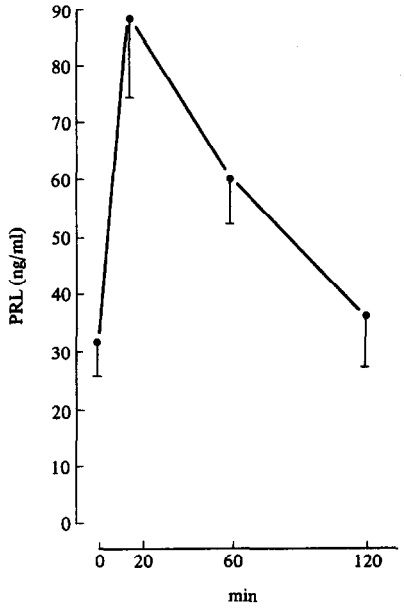

Fig. 2. PRL serum levels (mean ± S.D.) after TRH administration in 8 breast cancer women with hyperprolactinemia afer mastectomy.

In 8 of the 18 patients with elevated levels of PRL after mastectomy, PRL secretion was evaluated after TRH stimulation. TRH was given intravenously at a dose of 200 μg as a bolus, and venous blood samples were drawn through an indwelling catheter at zero time, and at 20, 60 and 120 min after TRH administration. In all patients, a normal PRL rise was seen in response to TRH, with an increase greater than 100% and a peak àt 20 min (Fig. 2).

DISCUSSION

The results of the present study show that radical mastectomy is followed by hyperprolactinemia in approximately half of patients with breast cancer of at least one month's duration. This finding is in agreement with the results of other authors [13].

The exaggerated secretion of PRL induced by mastectomy is difficult to explain. It does not seem to depend on surgical stress *per se*, since no PRL increase was seen in patients treated with the same type of anesthesia who underwent surgery for reasons other than breast cancer. Moreover, the type of radical mastectomy was irrelevant in influencing PRL secretion, nor was menopausal status or the histology of tumor related to the percentage of hyperprolactinemia caused by surgery. On the contrary, our data show that the PRL increase induced by mastectomy was significantly higher in patients without node involvement and in those with negative hormonal receptors compared with that observed in patients with axillary node involvement and positive receptors, respectively. Finally, the percentage PRL rise was higher in T_2 than in T_1 cases in the only patients with node involvement.

Hyperprolactinemia caused by mastectomy could depend on a rearrangement of the hypothalamic–putuitary–breast axis following the removal of a tissue with high content in PRL receptors, such as the mammary gland. In other words, the removal of a target organ for PRL might induce changes in feed-back mechanisms involved in the regulation of PRL secretion. However, even if the relation between mastectomy and hyperprolactinemia is obscure, the present study would seem to demonstrate that the exaggerated PRL release induced by surgery is mediated by the physiological mechanisms that are normally involved in regulating PRL secretion, since a normal response of PRL to TRH, which represents the physiological stimulus for PRL release, was seen in all patients.

The clinical significance and prognostic value of PRL increase after radical mastectomy remains to be determined. If there is a stimulatory role of PRL on breast cancer cells in humans, the high levels of PRL after mastectomy could stimulate the growth of micrometastases and this might represent a risk factor for relapse. Moreover, since mastectomy-induced hyperprolactinemia is more frequent in patients without node involvement, it would be interesting to analyze, particularly among breast cancer women without axillary node involvement, if the relapse percentage is higher or not in cases whose PRL secretion is enhanced by surgery compared with those in whom mastectomy does not induce any significant change. If there is an increased percentage of relapse in patients with hyperprolactinemia caused by surgery, mastectomy could be followed by adjuvant therapy with bromo-

criptine or other dopaminergic agents for a period of at least 2 months, in an attempt to block PRL increase.

Further investigations evaluating PRL receptors and correlating them with the clinical data and with PRL blood levels will be needed to clarify the different patterns of PRL secretion after tumor removal, and to establish if mastectomy-induced hyperprolactinemia is an unfavorable prognostic factor in human breast cancer.

Acknowledgements—We wish to thank Sister Carla, Mr L. Manzoni, Mrs R. Brambilla, and Mrs L. Giani for their much appreciated cooperation.

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