Abstract. This report compares the xeromammographic patterns of 35 patients with hyperprolactinaemia and 70 (age-matched) normoprolactinaemic controls. It is shown that nulliparous patients have less frequent mammary dysplasia and more patterns of involution than the nulliparous controls. The groups of parous patients and parous controls were similar to each other and both had more involutions and less dysplasia than the nulliparous controls. Hyperprolactinaemia in parous women is not associated with any changes in the xeromammographic breast patterns as compared to parous controls. The changes described in hyperprolactinaemic patients can be understood in terms of their low oestrogenic activity.

The role of prolactin in the development of breast disease is far from clear. The hormone dependence of rodent mammary tumours to prolactin has been demonstrated in vitro and in vivo (Smithline et al. 1975; Welsch & Nagasawa 1977). In humans, however, it is controversial whether prolactin levels differ in normal women and in women with breast cancer (Nagasawa 1979). The treatment of this disease with inhibitors of prolactin secretion is not followed by remission (Heuson et al. 1972; Engelsman et al. 1975). In mammary dysplasia the serum prolactin concentrations are usually normal (Franks et al. 1974; Boyns et al. 1973; Gorins & Netter 1974) although moderately elevated values (< 50 ng/ml) have been found in some series (Franks et al. 1974). When average nycthemeral prolactin concentrations are estimated in patients with cystic dysplasia it is found that the values, although within the normal range, are significantly higher than those observed in control populations (Cole et al. 1977).

The present report describes a radiographic study of the breasts of 35 consecutive patients with sustained hyperprolactinaemia and a control group of normoprolactinaemic women.

Materials and Methods

Thirty five consecutive female patients with sustained hyperprolactinaemia — elevated basal values (> 20 ng/ml) on different days — and otherwise unselected were studied at the Endocrine Clinic of the Portuguese Cancer Institute. The mean age of the patients was 30.8 years (range 19–45). Sixteen were nulliparous and 19 were parous. The average prolactin concentration was 276 ng/ml (range 22–3.500). All had plain skull X-ray studies and hypocycloidal tomographies of the sella turcica. In 19 there was radiological evidence of a pituitary tumour. None of the patients had used hormonal contraception in the year preceding the study and only 2 had ever used it. Twenty-three patients had amenorrhoea, two had oligomenorrhoea and ten had regular menstrual periods. As a control population a group of 70 normoprolactinaemic women was selected from patients presenting to the same clinic with benign non-functioning thyroid nodules or with dysfunctional complaints unrelated to the breast, namely nervousness or bolus hysterics without evidence of organic disease. Other criteria for selection were age (similar to the patients'), regular menstrual cycles and no use of hormonal contraception for at least one year before the study. The mean age of the controls was 32.3 years (range 18–50). Twenty were nulliparous and 50 were parous. Forty-one of the parous controls had their first child between 20 and 32 years of age, 6 at or before 20 and 3 after 32. This distribution was comparable to the one of the patients (15/19, 2/19 and 2/19, respectively). The average prolactin concentration of the controls was 9.1 ng/ml (range 0–17).
The serum prolactin and plasma oestradiol concentrations were measured by radioimmunoassay using CEA-CIS-SORIN kits.

Xeromammographies were obtained from all the subjects and classified by a radiologist specially trained in breast studies (C.C.) who was aware only of the age and parity status of each woman. Each xeromammograph was classified into one of the three following categories: normal fibro glandular pattern, involution or dysplasia (classification 1). The radiographs were also classified into low and high breast cancer risk patterns (classification 2). This classification (Wolfe 1976a) distinguishes four radiographical patterns: N1 - breasts consisting almost entirely of fat; P1 - breasts with a predominance of fat but where up to one fourth of the subareolar area exhibits cord like structures corresponding to prominent ducts; P2 - the prominent duct pattern involves more than one fourth of the breast; DY - most of the breast has a density greater than that of fat.

For the calculation of the significance of the differences a chi-square non-homogeneity test was used.

Results

The results are summarized in Table 1 and Fig. 1. From the data in Table 1 it is apparent that the distribution of the radiographical patterns of the breast in hyperprolactinaemic parous women is similar to that of normoprolactinaemic parous controls. This statement applies to both radiographic classifications employed. The nulliparous patients, however, behave differently. The hyperprolactinaemic nulliparous patients show significantly more breast involution ($P < 0.01$) and low risk patterns ($P < 0.05$) than the control nulliparous women while normal fibro glandular tissue ($P < 0.01$), dysplasia ($P < 0.01$) and high risk patterns ($P < 0.05$) predominate in the controls.

The prolactin values of the patients are shown in Fig. 1. The prolactin levels of the 3 hyperprolactinaemic patients with dysplasia were only marginally elevated (22, 23 and 35 ng/ml). The other subgroups of patients (nulliparous or parous, and with normal or involuted breast patterns) had widely scattered prolactin values not significantly different from one another. Within the control population the average prolactin values of each group - dysplasia, normal fibro glandular pattern or involution, parous or nulliparous - were similar and varied between 8.4 and 10.7 ng/ml.

The average plasma oestradiol concentration in the amenorrhoeic patients was 51 pg/ml (range 6.5–135 pg/ml). The average values for normal women are: early follicular phase - 65 pg/ml (range 42–130); periovulatory – 233 pg/ml (range 131–316); luteal phase 123 pg/ml (range 65–250).

<table>
<thead>
<tr>
<th>Classification 1</th>
<th>Classification 2</th>
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<tr>
<td>Normal</td>
<td>Dysplasia</td>
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Hyperprolactinaemic

| Nulliparous | 9 | 1 | 6 | 11 | 5 |
| Parous | 12 | 2 | 5 | 12 | 7 |

Controls

| Nulliparous | 15 | 5 | 0 | 8 | 12 |
| Parous | 32 | 4 | 14 | 34 | 16 |

The arrows connect the significantly different populations. $* P < 0.05$, $** P < 0.01$.  

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Discussion

Our observations are consistent with the well-established concept that previous pregnancies influence the subsequent development of breast tissue (Egan 1972). This influence can be characterized by the induction of mammary involution, predominance of low risk patterns and protection against dysplasia. According to our results the importance of previous pregnancies is so great that hyperprolactinaemia later in life does not appear to induce any further changes. In fact, parous hyperprolactinaemic and normoprolactinaemic women show similar radiographic breast patterns. For the nulliparous however the situation is different. Hyperprolactinaemic nulliparous patients behave similarly to parous women in that they show significantly less dysplasia and high-risk patterns than age-matched nulliparous controls.

The ultimate significance of these findings is open to discussion. The prognostic value of Wolfe's classification is not universally established. Moreover the radiographic patterns of the breast change with age (Wolfe 1976b) and age at birth of the first child (Andersson et al. 1981). These variables were considered in the selection of the control women for this prospective study. Although a larger population of patients and controls would be necessary for a final statement our results strongly suggest that hyperprolactinaemia in nulliparous patients provides some protection against mammary dysplasia (classification 1) and presumably breast cancer (classification 2). The only three hyperprolactinaemic patients with mammary dysplasia had slightly elevated prolactin levels. It has been demonstrated that moderate hyperprolactinaemia is frequently associated with luteal insufficiency (Seppälä et al. 1976; Mühlenstedt et al. 1978; del Pozo et al. 1979) while higher prolactin levels are associated with hypooestrogenism as observed with our patients and as reported by Davajan et al. (1978) and Franks (1979). It is thus likely that moderate degrees of hyperprolactinaemia may be associated with mammary dysplasia due to luteal insufficiency and unopposed oestrogen predominance as suggested by Mauvais-Jarvis' group (Sitruk-Ware et al. 1977, 1979) and others (Dargent et al. 1977; Lignières 1976). The hypo-
oestrogenism associated with higher prolactin levels could be responsible for the involuted, low risk radiographic appearance of the breasts.

Prolactin levels may have no direct influence upon the state of activity of the breast tissue as judged radiographically. The modifications observed in hyperprolactinaemic patients may be explained simply on the basis of the abnormalities in ovary function that accompany the hyperprolactinaemic states.

References