Eur J Cancer Clin Oncol, Vol. 21, No. 12, pp. 1553–1554, 1985.
Printed in Great Britain

0277-5379/85$3.00+0.00

Letter to the Editor

Elevated Bioactive Prolactin in Women at Risk for Familial Breast Cancer*

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WHILE the pivotal role of prolactin (PRL) in rat mammary carcinogenesis is well established, clear demonstration of its role in human breast cancer has been elusive. Because a family history of breast cancer has been shown repeatedly to confer increased risk for the disease, women with this history have been studied seeking evidence for an aberration of prolactin regulation [1–5]. The magnitudes of the differences in prolactin found in cases and controls in several studies have been small, and other important variables such as age, body mass, time of the day during which samples were obtained and specific family history may have confounded the findings. The measurement of PRL in these studies has been by a homologous radioimmunoassay (RIA) technique first described by Sinha and co-workers [6]. In 1980, Tanaka *et al.* described a new bioasssay for serum prolactin based on stimulation of growth of Noble 2 rat lymphoma cell cultures [7]. The system assays all three lactogenic hormones—PRL, human growth hormone (hGH) and human placental lactogen—but specificity for PRL is obtained in non-pregnant women by including anti-PRL antiserum in the assay medium. Its sensitivity for PRL is greater than RIA [8]. Further investigations have demonstrated that in a wide range of clinical disorders the correlation between PRL determined by bioassay and that determined by RIA is remarkably high, and that responses to thyrotropin releasing hormone (TRH) are similar in both assay systems [8].

We have studied eight unrelated, healthy, premenopausal women, each of whom had at least two first-degree relatives with breast cancer and a history of familial breast cancer. These subjects were not taking oral contraceptive pills, tranquilizers or thyroid medications. Throughout one menstrual cycle, morning blood samples were collected every other day and, in addition, TRH stimulation tests with a 500 μg dose were performed at the mid-follicular and mid-luteal phases in each woman.

Compared with control specimens from other healthy women assayed at the same time, basal plasma PRL and hGH levels determined by RIA were unremarkable, while basal levels of plasma lactogenic hormone (PRL plus hGH) by bioassay were 3–15 times the RIA levels. In Fig. 1 these

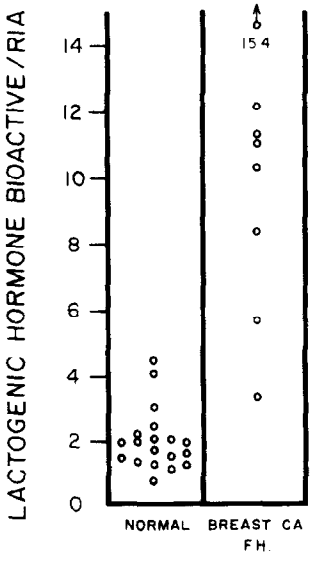

Fig. 1. Ratios of plasma lactogenic hormone (PRL plus hGH) bioactivity to the sum of PRL and hGH determined by radioimmunoassay in normal premenopausal women and those with a strong family history of breast cancer (the samples were collected in the morning during the luteal phase of the menstrual cycle).

Accepted 1 July 1985.
*Supported in part by research grants K07-CA00721 (RRL) and CA 17613 and CA 32617 (D.P.R.) awarded by the National Cancer Institute.

results have been expressed as the ratio of plasma lactogenic hormone (PRL plus hGH) determined by mitogenic bioassay to the sum of PRL and hGH determined by RIA. Thyrotropin stimulation resulted in exaggerated elevations in PRL by bioassay but conventional increases as determined by RIA, and unchanged, low, immunoassayable hGH levels (a typical pattern is shown in Fig. 2). Basal plasma thyroid stimulating hormone (TSH) values, and responses to TRH, were all within normal limits (not shown).

Mittra has demonstrated that a 16K moiety of cleaved prolactin from rat pituitary increases the rate of DNA synthesis and cell division in mammary epithelial cells [9]. Our data suggest that, as in the rat, different forms of bioactive PRL may exist in humans, and that a mitogenic species, not recognized by RIA, is significantly elevated in a homogeneous subset of women at risk for familial breast cancer.

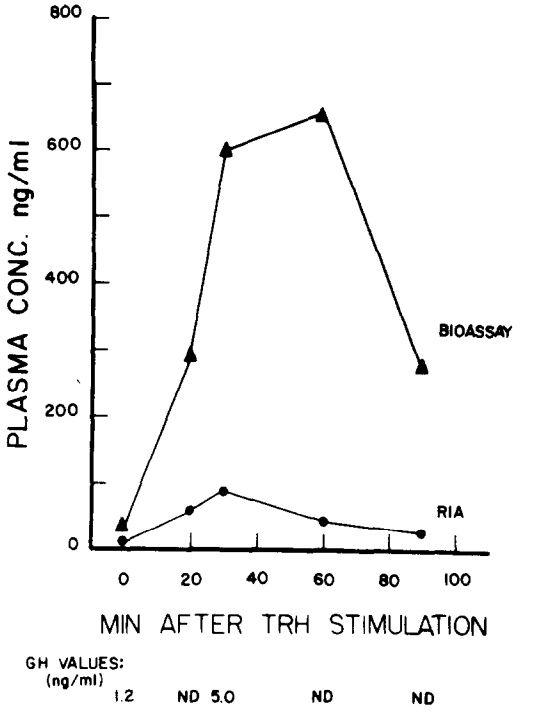

Fig. 2. Prolactin responses, as determined by bioassay and radioimmunoassay, to TRH stimulation in a premenopausal woman with a strong family history of breast cancer (ND: nondetectable serum GH).

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