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Perspectives in Cancer Research

Prolactin and Human Breast Cancer: a Review

HIROSHI NAGASAWA

Pharmacology Division, National Cancer Center Research Institute, Tsukiji 5-1-1, *Chuo-ku, Tokyo* 104, *Japan*

I. INTRODUCTION

WHEREAS the role of prolactin in experimental mammary tumourigenesis is well established [1], its importance in human breast cancer is not well understood. Literature reports on the influence of human prolactin (hPRL) on breast cancer are conflicting and confusing. An up-to-date literature survey of the profile of hPRL in breast cancer patients and under the different physiological conditions, factors affecting hPRL secretion, and their possible relation to the development of breast cancer is thought to be of value for future studies. Emphasis has been placed on the discussion of factors increasing the risk of breast cancer.

II. PLASMA LEVELS OF HUMAN PROLACTIN IN BENIGN AND MALIGNANT BREAST DISEASES

The amount of hormone in the circulation and the responsiveness of the target tissue to the specific hormone are the two primary factors for manifestation of hormone effects. From this point of view, data have been accumulated on the differences in plasma hPRL levels between patients with benign and malignant breast diseases and women free from them.

A. *Human prolactin in benign breast diseases*

Several reports on plasma hPRL levels in patients with various benign breast diseases have been based on single samples and the possibility of abnormal profiles due to menstrual stages and emotional and other conditions cannot be excluded. In order to avoid these influences, hPRL levels have been estimated in serum samples taken daily throughout the menstrual cycle of patients with benign breast diseases; abnormal daily or weekly hPRL profiles during the menstrual cycles were found in these patients [2]. Moreover, a significant positive correlation was present between age and hPRL in cystic breast disease, but not in mammary fibroadenosis or normal women [2]. Basal hPRL levels before surgery for a lump in the breast were not different in patients with benign breast diseases from those with breast cancer regardless of menstrual status [3].

B. *Human prolactin in breast cancer*

Higher plasma hPRL levels have been reported in breast cancer patients than in healthy controls [4, 5], but this could not be confirmed by other studies [3, 6, 7]. Sarfaty *et al.* [8] compared plasma hPRL levels in women and in patients with primary or metastatic breast cancer. Whereas hPRL levels were generally higher in normal premenopausal women or breast cancer patients than in respective postmenopausal subjects or in women after ovariectomy, within each category breast cancer patients had significantly increased hPRL values [8]. Following ovariectomy, hPRL levels dropped more sharply in responders than in nonresponders to endocrine therapy [8].

In some cases, high hPRL levels in patients fell to normal after mastectomy, suggesting that emotional stress before the operation and the physical stress of the operative procedure may partly be the cause of elevation of hPRL in breast cancer patients. When menstrual phase, mental and physical stress were excluded as factors for increase in hPRL secretion, no difference in plasma hPRL levels was observed between breast cancer patients and controls [9]. The mean 24 hr plasma levels before breast surgery were significantly lower in postmenopausal breast cancer patients and significantly higher in premenopausal breast cancer patients than in those of respective normal women and patients with benign breast disease [10]. Nevertheless,

although disordered hPRL regulation has been found in women with breast cancer, its significance in the etiology of breast cancer is uncertain [10]. Sequential analysis of plasma samples revealed that there was no difference in hPRL levels between breast cancer patients and the controls matched for age, years since menopause and parity [11].

Reported periovulatory changes of plasma hPRL levels in premenopausal breast cancer patients after mastectomy [2, 9] and disordered nocturnal hPRL regulation in women with breast cancer [10] may infer the possible role of hPRL in breast cancer.

As will be discussed in the subsequent Sections, pituitary hPRL secretion varies according to age, menstrual stage, drug usage, etc.; also it fluctuates by the time of day and changes in response to emotional condition. Since hormonal differences may become blunted with increasing age and/or debility, increased hPRL secretion in older women with breast cancer for instance may be masked by normal old-age related decline of hPRL secretion. Accordingly, it is difficult or almost impossible to exclude in clinical studies, all or even part, of these factors influencing hPRL secretion and plasma levels; this is a great obstacle for the proper evaluation of the role of hPRL in breast cancer.

III. ONTOGENESIS AND PROFILE OF HUMAN PROLACTIN

Breast cancers almost never develop without preceding proliferations of normal mammary epithelium, for which sex steroids and hPRL act as a physiological stimulus. The major benign neoplastic changes are; (i) lobular adenosis, (ii) sclerosing adenosis, (iii) lobular hyperplasia, (iv) duct hyperplasia, (v) intraductal papillary lesions, (vi) fibrocystic diseases, (vii) fibroadenoma. Therefore, long term exposure of mammary glands to hPRL and sex steroid hormones, especially oestrogens, may be causally related to development of preneoplastic and neoplastic lesions; pregnancy or ages of menarche and menopause, which are largely controlled by these hormones, are well known to affect breast cancer [12]. If indeed endogenous hPRL is a factor for initiation and/or promotion of breast cancer, some differences are expected to be observed during the early induction years, prior to the clinical appearance of the breast cancer, even if little differences have been observed at advanced ages between normal women and patients with benign and malignant breast diseases as detailed in Section II. It seems therefore essential to discuss ontogenesis and profile of hPRL secretion and plasma levels under physiological conditions.

A. *Human prolactin during fetal life and childhood*

Human PRL is detectable in fetal pituitaries and plasma after 16 and 12 weeks of pregnancy, respectively and it markedly increases with advancing pregnancy independent of fetal sex [13, 14]. Amniotic fluid hPRL level rose steeply between 12 and 16 weeks of pregnancy and then declined to term. The concentration consistently exceeded fetal serum hPRL levels even during the last trimester [14].

An intact mature hypothalamus is not necessary for attainment of high plasma hPRL levels at term, since anencephalic infants show plasma hPRL levels similar to healthy newborns. This is in contrast to the very low plasma levels of hGH, FSH, LH, TSH and ACTH in the umbilical cord blood of anencephalic newborns [15].

In the neonate, plasma hPRL remains high during the first day of life [15, 16], dropping gradually in response to progressive decrease of plasma oestrogen-induced pituitary stimulation for hPRL secretion finally to prepubertal levels by 4–6 weeks of age [15].

B. *Human prolactin at puberty*

Corresponding to the rise of oestrogens in the circulation of puberal girls leading to the onset of menses, the basal hPRL levels increase gradually to adult female levels [15, 17]. Meanwhile, Parker *et al.* [18] reported no difference in the level between children at 2–12 yr old and non-pregnant adults at 21–32 yr. Plasma concentration of hPRL in boys during different ages is low and the puberal changes is rather minimal [19, 20].

C. *Human prolactin in premenopausal and postmenopausal women*

Toward the end of the fertile phase of life, plasma hPRL levels decline as a consequence of reduction in ovarian steroidogenesis. In post-menopausal women, basal hPRL levels are significantly lower than in premenopausal females [3, 8, 21–24]. In contrast, hPRL levels in men tend to increase after 45 yr of age [3]. Pituitary hPRL content was 1.5 and 1.3 μg/mg for an 80 yr old male and a 27 yr old female, respectively [25].

The pituitary hPRL reserve is thought to be reduced in older women as demonstrated by the diminished response to TRH-stimulation [19], but not confirmed by Yamaji *et al.* [26], who concluded that hPRL secretion is enhanced in female subjects throughout life after puberty and that aging, *per se*, is not associated with an alteration in hPRL secretion. Azizi *et al.* [27] also found no difference with age in thyrotrophin secretion by TRH.

1. *Circadian rhythm of human prolactin secretion.* Plasma hPRL shows a peak usually between 1 and 5 a.m. [28, 29]. It is considered to be sleep-related, beginning to rise 1/2–1½ hr after the onset of sleep and to coincide with non-REM episodes [29, 30]. Pituitary hPRL release may also occur during day-naps and it is shifted when the period of sleep is changed. Recently, Kwa *et al.* [31, 32] reported abnormally elevated plasma hPRL at 7 p.m. of luteal phase in women with family history of breast cancer. The absence of light, *per se*, seems to be of no influence on hPRL secretion [33, 34]. Nocturnal elevation of plasma hPRL levels is absent in patients with hPRL secretory pituitary adenoma [35]. This circadian rhythm of circulating hPRL is labile and may be modified in physiological–pathological conditions and under the influence of drugs. While the physiological significance of circadian variation in hPRL secretion is still unknown, it may participate in breast cancer, if it is in cooperation with the changes of other hormones and carcinogenic factors.

2. *Human prolactin during the menstrual cycle.* Plasma hPRL levels were reported to be significantly higher during the luteal phase than during the follicular phase of the menstrual cycle; the mean hPRL value at ovulation was higher than that early follicular phase, which is highly correlated with the pattern of circulating oestrogen [9, 36]. During the luteal phase, the mean plasma hPRL values at day 5 after ovulation were found higher than those at days 4 and 6 postovulation [37]. However, other authors did not observe a significant variation in circulating hPRL levels during the menstrual cycle [21, 38, 39]. It has been reported that the distribution of basal hPRL levels during early follicular phase is significantly higher in ovulatory, but infertile women than in the control [40]. It is still premature to speculate about the direct effect of high hPRL on infertility; it may partly account for the higher breast cancer incidence in nulliparous women than in parous women [12].

D. *Human prolactin during pregnancy*

Plasma hPRL levels increase steadily throughout pregnancy and reach maximal values at term [19, 41, 42]. Although it has been reported that during pregnancy no diurnal rhythm of hPRL secretion exists, it was also suggested that the hPRL sleep-related secretory "programme" is maintained during pregnancy in a qualitative manner, albeit at a higher set point [43]. The reason for these changes in hPRL rhythm during pregnancy is obscure, however, an increase in the quantity of hPRL secreted per secretory episode would partly participate in them.

E. *Human prolactin postpartum*

A relatively rapid decline to non-pregnant baseline values occurs within 3–5 weeks postpartum in non-lactating mothers. On the other hand, in lactating mothers, baseline levels of plasma hPRL are still raised 6 weeks after delivery and they do not return to pre-pregnant values as long as the mother is nursing; high hPRL concentrations were found in lactating mothers even later than 13 weeks postpartum [44, 45]. During the baby's suckling a spurt release of hPRL occurs causing a 5-fold or more increase of baseline plasma levels [21, 44–46].

IV. FACTORS PROMOTING HUMAN PROLACTIN SECRETION AND THEIR RELATIONSHIP TO BREAST CANCER

A. *Oestrogenic agents*

Changes in plasma hPRL levels are correlated with alteration of oestrogen levels in the circulation [24, 47, 48]. Oestrogens or oestrogenic contraceptives [49] promote hPRL secretion directly or through increased response of lactotrophs to TRH. In healthy cycling women, ethinyloestradiol stimulates hPRL release and reduces the nocturnal release of hPRL [50]. In postmenopausal patients with metastatic breast cancer, diethylstilboestrol (DES) increases hPRL, yet causes a 50% remission [51]. This is principally attributable to the peripheral antagonism of oestrogen against hPRL [1].

Postmenopausal women given conjugated oestrogens were followed more than 10 yr and were found to have a higher breast cancer risk than the controls, but this higher risk was related to previous benign breast diseases, whereas not to multiparity and ovariectomy [52]. Since literature reports [53–59] reveal no association between oestrogen replacement

therapy with an increased risk of breast cancer, oestrogen elevation of hPRL itself does not appear to be directly related to an increased risk.

B. *Oral combination contraceptives*

Plasma hPRL concentration of women on oral contraceptives for over 9 months was not different from that of women with normal cycles, suggesting that oestrogen stimulation of hPRL secretion is counteracted by the pill's progestin content [24, 49]. In contrast, a significant increase in hPRL levels was noted in pill users [60]. Nevertheless, oral contraceptives do not appear to be associated with breast cancer. Rather, several groups of investigators have reported a decrease in incidence of benign breast diseases in woman on the pill [61–63]. Meanwhile, the relative risks of breast cancer from current use, from 2 to 4 yr of ever-use, from 6 or more years of use by women with prior benign breast disease, and from use before first child birth increased significantly. From these observations, it has been suggested that, in addition to the duration of oral contraceptive use, future observations should pay special attention to use by women before first child-birth and by women with already established benign breast disease [64].

C. *Rauwolfia derivatives and phenothiazines*

Rauwolfia drugs and phenothiazines are widely used as tranquilizers and they are well known to stimulate pituitary hPRL secretion [65]. Since these tranquilizers are used rather chronically, a possible relation between drug usage and breast cancer has extensively been investigated from the view point of hPRL participation. Some literature reports indicated that rauwolfia and phenothiazine therapy is associated with increased risk of breast cancer [66–68]. However, most investigators find little correlation between tranquilizers, increased hPRL levels and breast cancer [69–74]. While the reason for this discrepancy is far from conclusive, as described previously, there would be some factors in each subject which are intangible, but may affect the genesis of breast cancer. Alternatively the participation of elevated hPRL by these drugs may vary with different conditions of the subjects.

D. *Intrauterine device (IUD)*

Increased hPRL values have been reported in women using various types of copper IUD's [49]. On the other hand, IUD use or the history of previous intake of hormonal contraceptives did not affect the serum hPRL [75]. A connection between breast cancer and IUD use has not been established.

E. *Thyrotrophin-releasing hormone (TRH)*

Stimulation of pituitary hPRL secretion by TRH has repeatedly been reported 76–78]. TRH can directly stimulate pituitary hPRL secretion in female and male subjects [25, 41], the response being significantly greater in the former than in the latter [79]. TRH-induced hPRL release is not altered by pretreatment with oestrogens or androgens [41] or during pregnancy [77]. There was no significant difference between basal plasma hPRL levels and hPRL response to TRH in normal subjects and breast cancer patients [80]. At this time, it is not clear how changes in the activity of endogenous TRH can possibly be related to the development of breast cancer.

F. *Alcohol*

It has been hypothesized that alcohol intake is associated with an increased occurrence of breast cancer, and this may be due to the alcoholic stimulation of pituitary hPRL secretion [81].

G. *Diet*

High fat diet has been associated with an increased risk of breast cancer [82–84]. A higher breast cancer incidence in European or American women than in Japanese or Asian women is considered to be partly due to higher intake of fatty food by the former than by the latter. Changes from a Western diet to a vegetarian diet resulted in the decrease in plasma hPRL levels and a shortening of the menstrual cycle [85]. To what extent diet, besides racial and genetic factors, can influence the risk of breast cancer via an alteration of endogenous hPRL and/or oestrogen levels remains to be determined.

V. HUMAN PROLACTIN AS A POTENTIAL RISK FACTOR OF BREAST CANCER

A. *Family history of breast cancer*

Daughters of breast cancer patients had higher levels of oestradiol, oestrone and hPRL than controls. Furthermore, the sisters, but not daughters, of breast cancer patients had earlier menarche and later first full-term pregnancy than the controls [86]. On the other hand, Kwa *et al.* [31] determined plasma hPRL in healthy women on the

Island of Guernsey, who had a mother, sister or maternal aunt with breast cancer and found that the increased risk of breast cancer due to family history was not associated with a raised mean hPRL level. Also, plasma hPRL level was found not to be associated with age at menarche, age at first child or interval between them, which are considered to influence breast cancer risk [12] as well as body weight which is reported to have no relation with breast cancer risk [87]. From these observations, the authors [31] have concluded that hPRL has no obvious function in the etiology of breast cancer and that, if it is involved, the mechanism by which it acts must be subtle and concerned with the homeostatic control governing nychemeral hPRL rhythms. In these experiments, however, hPRL level was significantly higher only at luteal phase of the menstrual cycle in daughters of breast cancer patients than in the controls [31, 32]. At that time, both oestradiol and progesterone levels were also elevated and the synergistic effects of these hypersecreted hormones on breast cancer process may be plausible [32].

B. *Race*

Japanese and Asian women have a much lower incidence of breast cancer than Caucasian women. Plasma hPRL concentrations were measured in normal adolescent, premenopausal, menopausal and postmenopausal Japanese and Caucasian (British) women and it was found that hPRL was similar in both races for all age categories studied [88]. No differences in the basal plasma hPRL levels were found between Bantu, Caucasian and Japanese women under different menstrual and menopausal conditions as well as in relation to parity. However, plasma hPRL concentrations were higher in Caucasian women with breast cancer than in Bantu and Japanese patients [89]. These results would indicate that further studies on the effect of the life style and diet on basal and stimulated hPRL release are required to resolve the race relationship of hPRL in regard to breast cancer risk [89].

C. *Human prolactin in breast fluid*

Hormones contained in breast fluid bathe the mammary epithelium and thus may exert proliferative and/or secretory effects on parenchymal tissue. Recently, Wynder and Hill [90] reported that hPRL and oestrogens were 8–10 and 30–75 times higher, respectively, in breast fluid than in plasma. These authors concluded that the high concentrations of hPRL and oestrogen found in the ductal fluid of Western women may be relevant to development of breast cancer. Although they have not done such breast fluid studies on Japanese women, they propose that high fat intake, typical of the Western diet but not Japanese diet, promotes the growth of preneoplastic lesions by specifically altering the concentrations of hPRL and oestrogen in the ductal fluid [90]. However, Miller *et al.* [91] did not observe an increase of oestrogen concentration in breast fluid over that in plasma. Independent of their concentrations in breast fluid, it remains to be investigated whether hPRL and/or oestrogens in breast fluid or breast cyst fluid are related to the risk of breast cancer.

D. *Human prolactin and dehydroepiandrosterone (DHEA)*

An androgen of potential importance in the hormonal milieu of women with breast cancer is Δ^4-androstenedione. It serves as the major prehormone of oestrone; 80–100% of the total daily oestrone production rate in postmenopausal women is originated from androstenedione secreted by both adrenals and ovaries [61]. From the view point that androstenedione is a metabolite of DHEA, serum and urinary levels of these hormones as well as others have been compared between normal women and women with benign and malignant breast diseases [92, 93] or between women with high (English) and low (Bantu or Japanese) breast cancer risks [94–96] and considerable differences were observed. Recently, it has been claimed that hPRL can stimulate the secretion by adrenals of DHEA and DHEA sulphate from the results of assay of several hormones in patients of amenorrhoea with hyperprolactinemia [97]. This might postulate one of the possible indirect roles of hPRL on breast cancer, while its importance or significance is still unclear.

VI. RESPONSE OF BREAST CANCER TISSUE TO HUMAN PROLACTIN—PROLACTIN RECEPTOR

A. *Response of breast cancer tissue to prolactin*

If indeed a hPRL dependence of mammary neoplasia could be predicted, new implications for the therapy of breast cancer may become apparent. In such patients, lower circulating hPRL with drugs and other agents

may be desirable in the course of therapy. Hobbs *et al.* [98] found that approximately 40% of breast cancers were prolactin responsive and treatment with bromocryptine was much more effective in the specimens showing *in vitro* responsiveness to prolactin stimulation. Beeby *et al.* [99], however, could not confirm Hobbs' results.

B. *Prolactin receptor*

The initial event of manifestation of the hPRL effect is its binding to prolactin (hPRL) receptor on plasma membrane of mammary tumours. Therefore, prolactin receptor assay as a quantitative index of the responsiveness of the tumour tissues has been emphasized. While there are several reports on prolactin receptors in normal and neoplastic mammary glands in experimental animals [100], only a few preliminary studies have appeared on prolactin receptors of human breast cancer [101–104]. Specific binding of prolactin of greater than 1% was seen in 20% of tumours, but the capacity was very low when compared to prolactin responsive experimental mammary tumours [102].

By means of *in vitro* studies, it was found that mammary cancer tissues in approximately 15% of patients respond to prolactin with increased DNA synthesis [105], but not by the other investigators [106, 107]. In these experiments, ovine prolactin (oPRL) was used. Welsch and McManus [108] found the increase in DNA synthesis of human benign breast tumours by human placental lactogen (HPL), but much less by oPRL. From these results, they hypothesized that human breast tissues (tumours) contain the receptors to hPRL or HPL, but lack the receptors to oPRL.

Relevance of hPRL receptors as an index of mammary cancer responsiveness to the specific hormone is uncertain until the hormone dependency of human breast cancer is better understood. Recent studies point to the fact that some tumours are dependent only upon high levels of hPRL, while some others are dependent only upon low levels, indicating the complexity of mammary tumour responsiveness to hPRL [109].

VII. FACTORS INHIBITING HUMAN PROLACTIN SECRETION AND THEIR RELATIONSHIP TO BREAST CANCER

A. *Bromoergocryptine and* L-*Dopa*

Bromoergocryptine and other ergot alkaloids reduce markedly pituitary prolactin secretion in humans as well as in experimental animals [78, 110–116] by acting on both pituitary and hypothalamus. L-Dopa also may induce a significant fall in circulating hPRL levels mainly by altering hypothalamic function [41, 110, 111, 117]. Episodic release of hPRL during sleep was also significantly suppressed by intravenous infusion of L-Dopa [118]. Thus, at present, pharmacological methods can be used, instead of surgical removal of the pituitary gland, to reduce hPRL. Nevertheless, despite drastic reduction of plasma hPRL concentrations by antiprolactin drugs, striking regression of recurrent breast cancer has not always been observed; this is in contrast to the beneficial effect of prolactin suppressants in experimental tumours [1]. Inhibition of hPRL by bromoergocryptine or L-Dopa has been reported to be of benefit by some [6, 119], but the other investigators found that these hPRL suppressants were of only slight value for the treatment of metastatic breast cancer [4, 120, 121].

While it is not established that L-Dopa treatment has a beneficial effect on remission rate or survival of breast cancer, several investigators have proposed the relief by L-Dopa from bone pain of breast cancer patients in response to the decrease in serum hPRL levels [41, 122].

B *Hypophysectomy*

In 58% of patients with metastatic breast cancer, hypophysectomy brought about remission of the disease; the highest incidence of remission occurred in women with osseous metastases or with previous remission after both therapeutic ovariectomy and androgen administration [123]. On the other hand, some breast cancers regressed after pituitary stalk section, which is known to increase hPRL secretion [124]. Since hypophysectomy greatly affects adrenal and ovarian secretion of androgenic and oestrogenic steroids, it appears that the beneficial effect of hypophysectomy in patients with metastatic breast cancer is due to the combined effect of suppression of sex steroid production rather than elimination of only hPRL secretion.

VIII. CONCLUSION AND FUTURE OUTLOOK

At present, the role of hPRL in the development and progression of breast cancer is still little understood. Literature reports on the influence of hPRL on breast cancer as

well as described effects of hPRL inhibitors on advanced breast malignancy are so conflicting. Kim and Furth [125] state emphatically that all mammary cancer risk factors described for human subjects and animals point to a role of hPRL in mammary carcinogenesis, albeit it has been suggested that hPRL, if associated with breast cancer, must do so at normal levels [69]. According to Robyn [126], hPRL may favour both development and progression of breast carcinoma, but evidence for that is still indirect and rather speculative. While it has been proposed, even if endogenous hPRL by itself may not be an etiologic factor, it would, in conjunction with sex steroids, contribute to accelerated malignant mammary growth as indicated in the more fulminant course of breast cancer during pregnancy [12], further research is essential to establish unequivocally whether hPRL is an important hormone in human breast cancer process.

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