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Neuroendocrine Abnormalities and The Pathogenesis of Estrogen-Receptor-Positive Breast Cancer

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Abstract

Breast cancer in women appears to have different manifestations, depending on the presence or absence of the estrogen receptor (ER). Although both ER-negative and ER-positive breast cancers are likely to be associated with the presence of an oncogene, ER-positive breast cancer is also associated with two clinical neuroendocrine abnormalities involving the pineal gland and olfaction, both of which may result from a defect in tryptophan metabolism along the kynurenine pathway.

Recent studies of the epidemiology, genetics, and endocrinology of breast cancer suggest that this neoplasm occurs in at least two distinct forms, depending on estrogen receptor (ER) status.

Epidemiology

There is marked variation in the incidence of breast cancer in different areas of the world (1, 2). The disease is five times more common in the United States than in Japan or other areas of the Far East (3). This disparity is not genetic, since first- and second-generation Japanese women in San Francisco have rates higher than do women in Japan (4).

The geographic variation of breast cancer incidence correlates with dietary differences, particularly fat intake (5). In Japan, average dietary fat intake is low, whereas in the United States dietary fat intake is high (6). In addition, Seventh-day Adventists, who have lower-than-average fat intake because many are vegetarians, have lower breast cancer death rates than the general population (7); however, socioeconomic status may be a confounding variable (8).

Even within low- and high-risk countries, breast cancer incidence varies. In Japan, a "low-risk" country, the rate of breast cancer decreases after menopause, while in Sweden, a "high-risk" country, there is a continued increase of incidence with age beyond menopause. These patterns suggest multiple etiologies and manifestations of breast cancer (9).

Genetics

Family history is a key risk factor in breast cancer (1) and is particularly important if the cancer is bilateral or if there is male or female breast cancer in other family members (10). Further evidence of the genetic nature of breast

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cancer may be inferred from the weak association with HLA antigens (11) and cerumen type (12).

This genetic evidence has spurred the search for a specific transforming gene, an oncogene, that is responsible for human breast cancer. One study, for example, demonstrated that the same or closely related transforming genes were activated in six different mouse mammary carcinomas induced by the mouse mammary tumor virus or the carcinogen dimethylbenzanthracene (13). Another study reported the detection and cloning of a Harvey H-ras oncogene from the HS578T human mammary carcinoma cell line derived from a rare, highly malignant tumor with histopathologic features of both carcinoma and sarcoma (14).

A third study described the amplified function of a novel v-erb-B–related gene in a human mammary carcinoma (15). This gene appears to encode a truncated version of the receptor for epidermal growth factor, which may be responsible for the proliferation of malignant cells.

Despite these data, transforming genes appear to occur at a relatively low frequency in human mammary tumors. Krause et al (14) observed no oncogenes in four human breast carcinoma cell lines and 16 primary human breast carcinomas. Furthermore, truly hereditary breast cancer is not common. Only about 5% of all patients fulfill criteria allowing their disease to be classified as autosomal dominant (10).

Some oncogenes seem to render the tumor hormone independent and estrogen receptor (ER) negative. One experiment confirming this effect was performed by Kasid et al (16) on the MCF-7 human breast cancer cell line. MCF-7 cells require substantial estradiol levels for tumor formation in vivo. However, when the v-ras^h oncogene is inserted into these cells, they no longer demonstrate augmented growth in culture in response to estrogen, and proliferation is minimally inhibited by antiestrogens (16). Moreover, in a study of 104 primary human breast tumors, Sainsbury et al (17) found that the epidermal growth factor receptor, which is associated with the erb-B oncogene, is also associated with ER-negative lesions.

Endocrinology

A strong association has been found between breast cancer and hormones, especially estrogen, progesterone, and possibly prolactin (18). The risk of breast cancer is 100 times greater in women than in men, and the disease does not occur before puberty. The risk of breast cancer increases as the age at menarche decreases and as the age of menopause increases; that is, the longer a woman has normal ovarian function, the greater her risk. Furthermore, daughters of women with breast cancer have elevated mean 24-hr prolactin levels and a partial resistance of prolactin to dopamine suppression (19). This aberration suggests a neuroendocrine abnormality, since the secretion of estrogen, progesterone, and prolactin are under neuroendocrine control. Hourly pulses of gonadotropin-releasing hormone (GnRH), produced by the arcuate nucleus of the hypothalamus, stimulate the anterior pituitary to elaborate the gonadotropins follicle-stimulating hormone (FSH) and luteinizing hormone (LH). FSH and LH stimulate the ovary to produce estrogen and progesterone. Prolactin production by the anterior pituitary is regulated by prolactin-inhibiting factor (PIF). The control mechanism for PIF appears closely related to that for GnRH and resides within the same area of the hypothalamus (20).

We postulate that a neuroendocrine defect within this control mechanism might promote or predispose to ER-positive breast cancer. Recently identified abnormalities involving the pineal, olfaction, and tryptophan metabolism suggest such a defect is associated with ER-positive breast cancer. The data to support this hypothesis are as follows.

The pineal gland, its principal hormone melatonin, and breast cancer are strongly interrelated (21). There is a decreased nocturnal plasma melatonin peak in women with ER-positive breast cancer (22, 23), and melatonin inhibits, whereas pinealectomy enhances, dimethylbenzanthracene-induced mammary tumors in the rat (24).

Pineal function is related to sense of smell (25), and women with ER-positive breast cancer have abnormally diminished olfaction (26). Since efferent olfactory impulses pass via the median forebrain bundle to the entire lateral extent of the hypothalamus (27), and since normal mammalian pineal function is dependent on the suprachiasmatic nucleus of the hypothalamus (28), we hypothesize that both the pineal and olfactory abnormalities share a common hypothalamic origin, possibly the result of a neurotransmitter defect involving serotonin.

The amino acid L-tryptophan is a precursor of both melatonin and serotonin. Moreover, tryptophan abnormalities are associated with breast cancer (29, 30). After an oral 2-gm load of trypto-

phan, urinary levels of tryptophan metabolites of the kynurenine pathway are high in most women with breast cancer. Using the assay method of Arend et al (31), we recently measured total kynurenine in 24-hr urine samples from women with early-stage breast cancer given a 2-gm oral tryptophan load. The following values were obtained for women with ER-positive and -negative tumors:

	ER+	ER−
No. of subjects	11	10
Kynurenine (μmol/day)	33.0 ± 28.7	12.2 ± 5.6
Significance	$p < 0.05$	

The higher kynurenine excretion in ER-positive subjects suggests a defect in tryptophan metabolism. Whether this abnormality is responsible for the melatonin abnormality of these subjects and the olfaction abnormality, however, cannot be determined from these observations. Nonetheless, it is interesting to speculate that these derangements are the result of a genetic defect in tryptophan metabolism, which diverts tryptophan from the serotonin pathway to the kynurenine pathway. The observation of high kynurenine excretion associated with a reduced relapse rate in premenopausal women with stage I or stage II breast cancer (32) is consistent with this hypothesis, since ER-positive breast cancer has a longer natural history than ER negative (33).

Further evidence for a neuroendocrine abnormality is suggested by the relationship of body fat to both the onset of menarche and the risk of mammary neoplasms. Girls who are fat have menarche early, whereas girls who are very slender have a considerable delay in the onset of menses (34). This delay appears to result from a modification of the activity of the arcuate nucleus of the hypothalamus (35). Furthermore, thin women have a decreased risk of breast cancer, whereas fat women have an increased risk (1). Thus, body habitus appears to influence the same neuroendocrine regulatory mechanism that is responsible for both fertility and the predisposition to breast cancer. This influence might result from the fact that free fatty acids disturb the ratio of bound to free tryptophan in plasma. The free fatty acids cause increased free tryptophan, which is able to cross the blood-brain barrier (36).

Other recent findings suggest that the described neuroendocrine defects function in concert with an oncogene to induce ER-positive breast cancer. First, the human estrogen receptor c-DNA shows sequence, expression, and homology to the erb-A oncogene (37). Second, the normal mouse myc gene, with large portions replaced by hormonally inducible mouse mammary tumor virus (MTV) DNA, has been inserted into mouse embryos. The resulting transgenic mice spontaneously develop mammary carcinomas, but only during the second or third pregnancy (38). The MTV/myc fusion gene alone is not sufficient to induce breast cancer. Therefore, hormonal and possibly neuroendocrine changes, perhaps somewhat comparable to those associated with a predisposition to develop human breast cancer, are needed to induce the breast cancer in the transgenic mice.

An interesting psychoendocrine feature of breast cancer is its relationship to depression. In early breast cancer, recurrence-free survival is reduced in depressed patients who respond to their disease with stoic acceptance or feelings of helplessness and hopelessness; survival is much better in women who initially react to their cancer with denial or who have a "fighting spirit" (39). In addition, the nocturnal melatonin peak is reduced in depressed patients (40), just as it is in women with ER-positive breast cancer. Also, cortisol is elevated in both depressed patients (41) and women with breast cancer (42–44). If the pathogenesis of ER-positive breast cancer and certain forms of depression share anything in common, antidepressant drugs might be of value in breast cancer chemoprevention in high-risk women.

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