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ESTROGEN AND BREAST CANCER

The breast is a highly modified sweat gland that develops as an ingrowth from ectoderm. Anatomically, the primary secreting units consist of groups of terminal ductules with sac-like ends (alveoli), which are embedded in a fine specialized connective tissue to form the breast lobules. It is now firmly believed that breast cancer commonly starts in the epithelium which lines the terminal ductules within the lobule. Physiologically, the human female breast is under the primary control of different hormones; the role of estrogen appears to be central. Estrogen is responsible for the development of the ductal system, whereas progesterone is necessary for lobular development. Therefore, the etiology of breast cancer has a strong hormonal component. Once an epithelial cell of ductal system is transformed into a malignant phenotype, it is no longer subject to normal growth controlling mechanisms. A malignant cell may be non-invasive, *ie.* unable to penetrate the basement membrane (in situ cancer). Ductal carcinoma in situ (DCIS) is the most common histological variant of the non-invasive stage of breast cancer. Similarly, invasive or infiltrating duct carcinoma (IDC) is the commonest form of breast cancer accounting for 85 to 90% of all cases. These phenomena signify the important role of estrogen in the development of breast cancer.

Breast cancer is the second most common cancer in women world-wide with 1.05 million new cases being estimated in the year 2001[1]. In developed countries, it is the most common cancer in women. Populations from countries of North America are at high risk of breast cancer, with incidence rates in US white women going up to 103.7 per 100,000. High rates are also reported from Europe and Australia[2]. In the United Kingdom, nearly 30,000 new cases of breast cancer are diagnosed every year with nearly 15,000 deaths reported from this disease[3]. The incidence rate of breast cancer has been rising both in the developed and developing countries[4-6] and it is becoming frequent in some developing countries like Egypt and Tunisia[5,7]. Carcinoma breast is the second most common cancer among Indian women, and an increasing trend in its incidence has been observed in most of the metropolis with Mumbai toping the list[8].

Sex-hormones have been implicated in various human cancers such as endometrial cancer[9], breast and prostatic cancer[10] (among sex-organ related neoplasm) or colon cancer[11], gall-bladder cancer[12], kidney cancer[13,14], *etc.* (non sex-organ related neoplasm). However, the association between estrogen and breast cancer assumes special significance since breast cancer represents an enormous public health problem. Breast cancer risk is

enhanced by increasing the duration of exposure to endogenous ovarian hormones, so early menarche or late menopause increases the risk. Further, the risk of breast cancer is directly related to the age at which women bear first child. An early first, full-term pregnancy seems to have a protective effect. Women whose first pregnancy is delayed to their late 30s are at a higher risk than multiparous women. Unmarried women tend to be at a higher risk than married women[5]. Further, nulliparity increases and high parity decreases the risk of breast cancer, at least after the age of 50[15,16]. Nevertheless, the endocrine mechanisms concerning pregnancy and risk of breast cancer are poorly understood. Exogenous hormonal factors such as estrogen replacement therapy and combined oral contraceptive use may cause a small increase in the risk for breast cancer[9].

Historical Aspect

Estrogens appear to hold the key to the understanding of breast cancer. Before 18th century, breast cancer was considered as a systemic disease caused by some problem in body fluids *viz.* blood and lymph. In 1713, a higher prevalence of breast cancer was observed among nuns in Padua[17]. Interestingly, 129 years after this observation, Rigoni-Stern found nuns to be at more than three times higher risk of breast cancer compared to other women and linked it with nulliparity[18]. In 1889, Schinzinger stated (reported by Haagensen, C.D.[17]) that the disease grew more slowly in postmenopausal women and even suggested castration as a mean for hastening the benefit of menopause. Beatson also reported tumour regression in advanced breast cancer patients after surgical castration[19]; and for the first time, a systemic treatment became available for patients with breast cancer[20].

Breast Cancer vs. Prostate Cancer

Epidemiologically, breast cancer occupies a unique position in the field of oncology. There are interesting similarities between carcinomas of the breast and prostate[21] and an alarming increasing trend in the incidence of both breast and prostate cancers world-wide. Like breast cancer, the populations with a high incidence of prostate cancer are those of northern Europe and North America, while the Far East population shows the lowest rates[22,23]. Both prostate and breast cancers are strongly related with age; two-third cases of breast cancer occur during the postmenopausal period. Furthermore, both are mainly adenocarcinomas arising in sexually differentiated organs and both are strongly influenced by sex-steroid hormones. The incidence of both breast and prostate cancers are closely related to the consumption of fat, probably through the increase in serum sex-hormone levels – a possible risk factor[24]. The risk of carcinoma breast and prostate is also associated with genetic predisposition and familial history of the disease[10,25] as well as some pathological entities of corresponding benign diseases[3,26]. It has been observed that prostate cancer in some families can significantly increase the breast cancer risk[27]. Interestingly, carcinoma of the prostate (in husband) and carcinoma of the breast (in wife) were found to be more frequent in married couples than in the general population[28]; indicating the involvement of similar factors.

Postmenopausal Estrogen

Estradiol, the most potent endogenous estrogen, is the important secretory product of the ovary which represents the principal source of estrogen for breast cancer in premenopausal women. After the menopause, most of the circulating estradiol is derived from estrone which in itself is produced by the peripheral conversion of androstenedione, the precursor of testosterone. In postmenopausal women, androgens (*eg.*, testosterone, androstenedione, dehydroepiandrosterone and its sulfate) come mainly from the adrenal cortex[29]. All steroid hormones are formed from cholesterol via pregnenolone through a series of reactions that occur in either the ovary or adrenal cortex. In the ovary, the conversion of cholesterol to pregnenolone is promoted by luteinizing hormone (LH). On the other hand, in case of adrenal cortex, adrenocorticotropic hormone (ACTH) stimulates the identical reaction[30]. The peripheral-type benzo-diazepine receptors (PBRs) located on the outer mitochondrial membrane, are involved in the regulation of cholesterol transport from the outer to the inner mitochondrial membrane, the rate-determining step in steroid biosynthesis[31,32]. Notwithstanding, ACTH is an anterior pituitary hormone and is processed from the precursor pro-opiomelanocortin (POMC) molecule along with other peptides such as melanocyte-stimulating hormone (MSH), endorphins, β-lipotropin (β-LPH), *etc*. Further, the POMC peptides have been detected in several human non-pituitary tumours including breast cancer[33,34]. The POMC gene is located on chromosome 2 and exists as a single copy. The ACTH has a wide range of activities in various physiological as well as pathological conditions

such as principal stimulator of steroidogenesis, immunological role, ectopic expression in tumor tissue, *etc*. On the other hand, aromatase is the cytochrome P450 enzyme complex that converts androgens to estrogens[35] and is encoded by the human CYP19 gene (15q21.1, a single gene) spanning about 123kb with a coding region of 9 exons (about 30kb, exon II to exon X)[36]. The enzyme is present in various tissues such as adipose tissue, skin, ovary, brain, bone, placenta, *etc*[37]. Also, it has been demonstrated that certain breast carcinomas have the ability to produce estrogen through intratumoral aromatase[38]. Moreover, aromatase activity has been observed in breast tissue *in vitro*, and expression of aromatase is highest in or near breast tumour sites[39]. In situ aromatization contributes to the estrogen content of breast tumours to a major extent and alterations of aromatase activity could serve as a major determinant of tissue estradiol content[40]. After menopause, these extraovarian sources of estrogen may play an important pathophysiological role since two-thirds of breast cancers occur during the postmenopausal period, and about 33-50% of human breast cancers respond to hormonal treatment[41,42].

Diet and Estrogen Metabolism

Over-nutrition and obesity are the common features in developed countries with significantly higher incidence of carcinoma breast. Similarly, the incidence of breast cancer is higher in women from higher socio-economical status in any society. Obese women are at higher risk for breast cancer. Therefore, factors like higher intake of total calories and more fat consumption seem to increase the risk[43]. Apart from the dietary and life-style related factors, genetic factors also contribute to obesity; and hyperlipidaemia is common in the obese persons[44]. Weight gain has been associated with increased blood cholesterol and triglycerides levels, in turn with the risk of cardiovascular diseases[45], and some studies have even detected more cardiovascular disease among breast cancer patients[46]. Fat intake is directly related to the obesity and the degree of obesity is a major determinant of blood cholesterol and triglycerides levels[47]; on the other hand, dietary fat and obesity may play an important role in sex-steroid hormone metabolism[48-51].

The link between nutrition and cancer is highly controversial particularly the association between dietary fat or more specifically the intake of saturated fats of animal origin and the development of breast cancer (*ie.*, hormonal pathology)[52]. Wu *et al*[53] have suggested that dietary fat reduction can result in the lowering of serum estradiol levels and such dietary modification may offer an approach to breast cancer prevention. It has been observed that a low-fat and/or high-fiber diet in premenopausal women can reduce estrogen levels without affecting ovulation, thereby providing a rationale for the prevention of breast cancer[54-56]. Goldin *et al*[57] noticed a significant decrease in serum concentrations of testosterone and androstenedione in premenopausal women when the diet was changed to low-fat and higher-fiber. Further, Barbosa *et al*[58] found that plasma concentrations of estradiol were significantly lower in vegetarian than non-vegetarian postmenopausal women. These factors may contribute to the lower risk of breast cancers. Interestingly, studies revealed that sex hormone binding globulin (SHBG) was positively associated with high density lipoprotein (HDL)-cholesterol[59,60] and negatively associated with triglycerides[61,62]. Therefore, due to an inverse relationship between serum SHBG and serum triglycerides levels, increased level of serum triglycerides leads to an elevation of percentage free estradiol (active form)[63]. Prentice *et al*[64] found that 17% reduction in average plasma estradiol concentration was accompanied by an average reduction of 12mg/dl in total plasma cholesterol. Recently, Mady[65] demonstrated that tissue contents of total lipids, triglycerides and cholesterol were significantly higher in breast cancer, and they were also significantly correlated with estradiol levels. Thus, it could be concluded that the uptake of lipids from plasma by the tumour tissue is greatly correlated to estradiol and this situation may confirm the possible role of lipids as risk factor in breast cancer.

Adipose Tissue and Estrogen Metabolism

Adipose tissue has a role to play in storage of lipid and its supply to various tissues when required. The free fatty acids absorbed from gastrointestinal tract and the fatty acids derived from triglycerides of chylomicrons (intestinal absorption) and lipoproteins (from liver and intestines) after their release through hydrolysis by enzyme lipoprotein lipase, are all taken up by the adipose tissue and resynthesized into triglycerides and stored. Besides, the carbohydrate (glucose) is converted by adipose tissue into fatty acids and stored as triglycerides. Also, adipose tissue is a site of uptake, storage, action and metabolism of sex-steroids. After menopause, aromatization of androgens to estrogens in adipose tissue is one of the

most important sources of estrogen in the circulation and for peripheral tissues[66]. Several studies have documented that body weight and body mass index (BMI) were inversely related to serum levels of SHBG in both premenopausal and postmenopausal women[67,68]. In the same manner, Sulkes *et al*[69] noticed that SHBG plasma levels were significantly influenced by the breast cancer patients' body weight, particularly in those who were premenopausal. In the blood, all steroid hormones exist in either a free (unbound) state or bound to serum proteins. The major and specific binding proteins are corticosteroid-binding globulin (CBG) or transcortin which binds both cortisol and progesterone, and SHBG which binds testosterone and estradiol (testosterone more tightly than estradiol). Until recently, it was generally accepted that the sole function of SHBG and CBG is to regulate the concentration of free steroids in plasma. However, the discovery of specific SHBG and CBG receptors in cell membranes from a variety of tissues suggested a broader role for these glycoproteins. Membrane receptor for SHBG is a physiological component of estrogen- sensitive tissues including breast[70]. The effect of steroid hormones on SHBG membrane receptor interaction has been the subject of a debate. Nevertheless, the serum SHBG concentrations are the result of a balanced effect of stimulatory and inhibitory factors. Estrogens represent the principal stimulatory hormones; whereas insulin, excess body fat and the pattern of body fat distribution have inhibitory effects. Furthermore, Lonning *et al*[71] observed that SHBG correlated negatively with plasma androstenedione and estrone sulfate. Recently, existence of a close link between estrogen-dependence of breast cancer and SHBG has also been shown[72,73].

Androgens in Breast Cancer

The major circulating androgens in women are testosterone, dihydrotestosterone (DHT), androstenedione, dehydroepiandrosterone (DHEA), and DHEA-sulfate. Free testosterone enters the target cells and is either reduced to DHT by 5a-reductase or aromatized to estradiol within these cells. DHT binds to the intracellular androgen receptor, inducing a conformational change that ultimately leads to androgenic actions. Testosterone is the principal circulating androgen in normal women. Both the ovaries and the adrenals normally secrete testosterone. Approximately 50% of the testosterone in blood is derived from the peripheral conversion of steroid precursors, mainly from androstenedione and to a lesser extent from DHEA. Both androstenedione and DHEA are metabolized to androstenediol and its sulfate. Moreover, these androgens are converted to etiocholanolone and androsterone (17-keto compounds) which may be further converted to etiocholanediol and androstanediol, respectively. A study by Bulbrook supported the hypothesis that adrenal androgens are fundamentally involved in breast cancer[74]. Subsequent studies revealed that women who developed carcinoma of the breast had lower levels of androsterone and etiocholanolone[75,76]. Furthermore, it was observed that patients who had a relatively low excretion of androgen metabolites in relation to corticoid metabolites responded less favourably to endocrine ablation than did those with a higher ratio[77]. However, etiocholanolone has no known biological function, and Japanese women were found to have a low (rather than the expected high) excretion of the hormone[78], hence, the role of androgens remains obscure[79-82].

Several studies have revealed that the risk of breast cancer is positively associated with serum levels of testosterone[83-85]. Testosterone may affect breast cancer risk through a direct growth promoting effect or indirectly through the peripheral conversion of testosterone to estrogen. It has been stated that higher serum level of testosterone among patients with breast cancer is a consequence of the stress associated with its diagnosis[86]. However, subsequent investigation did not reveal any such effect of stress[87]. Androgens might be taken up from blood, and thus there could be a storage of these steroid hormones inside the breast tissue and/or perhaps some alterations in their local metabolism; androgens could play a different role in breast carcinogenesis in relation to the circulating levels of estrogen and to the expression of estrogen receptors[88]. Also, it is hypothesized that androgens stimulate the synthesis of epidermal growth factor (EGF) and possibly of other growth factors inside breast epithelium and thus play a role in the autocrine and paracrine growth regulation of human breast cancer[89]. More recently, studies have been undertaken on the possible immunological effects of DHEA[90]. Administration of DHEA was found to reduce elevated interleukin-6 (IL-6) levels in aging mice[91], and since IL-6 is one of the factors that can stimulate aromatase activity, and in turn estrogen production[92]; this might explain the role of DHEA. As the conversion of T-cells to Th2 (T helper type 2 cells) – the source of IL-6, is mediated by the ratio of cortisol to DHEA; an increase in cortisol or a fall in DHEA increases conversion to Th2 and production of IL-6[93]. These immunological effects of DHEA led to the belief that the low ratio of DHEA to corticoid

metabolites in the cancer cases is indicative of the exposure to an immunosuppressive environment. Increased production of IL-6 is also indicative of the increased production of estrogen in the breast tumour[94].

Immune Cells and Estrogen Metabolism

Infiltration by lymphoid cells is a common feature of many human tumours, including breast carcinoma, and the degree of infiltration has been suggested to be a measure of the host-immune response. However, lymphocyte infiltration in breast cancer can give information on both good and poor prognosis[95]. Often, it could be observed that human breast cancers grow progressively despite the presence of extensive lymphocytic infiltration. The function of breast tumour infiltrating lymphocytes (TIL) *in vivo* and their possible role in the suppression of an anti-tumour immune response are largely unknown. Nevertheless, the majority of breast cancer samples have revealed a preponderance of T-cell infiltrates[96-98]. On the other hand, Toomey *et al*[99] observed that a predominant macrophage infiltrate denoted poor prognosis. Similarly, several studies reported that an increased infiltration of macrophages was associated with high tumour grade, overexpression of c-erbB-2 or epidermal growth factor receptor (EGF-R), increased angiogenesis, worsened relapse-free and overall survival in breast cancer[100-102]. Recently, a close relation between sex-steroid hormones and cells of the immune system like macrophages and lymphocytes have been observed[103-105] and considerable amount of aromatase was detected in breast tissue macrophages. Further, it has been noticed that macrophages could convert DHEA to estrogens[106]. Inflammatory cytokines such as IL-6 and IL-1 beta exist at high concentrations in breast cancer tissue. Both IL-6 and IL-1 beta are able to stimulate the activity of aromatase and steroid sulfatase, which are estrogen-producing enzymes[107]. Macrophages and lymphocytes, which infiltrate breast tumours, are thought to be an important source of these cytokines[108]. Recently, aromatase gene (CYP19) expression has been documented in tumour-infiltrating lymphocytes of breast cancer[109]. Interestingly, immune cells including macrophages and lymphocytes can be the source of neuropeptide hormone ACTH and other peptides of POMC[110-112]. The IL-1 (released by macrophages) may elicit POMC production from lymphocytes[113]. Also IL-6 stimulates both ACTH secretion and POMC gene expression[114].

Estrogen and ER in Breast Cancer

Estrogen is an important steroid hormone involved in regulating the differentiation and proliferation of normal breast epithelial cells. The chemical pathways of steroid biosynthesis, including the major enzymes and their intracellular localizations, are similar in the ovary and adrenal. At the initial step, cholesterol is converted to pregnenolone by the enzyme P450scc. This reaction or group of reactions is the rate-limiting step in the biosynthetic process. Pregnenolone may be converted either to progesterone or to 17a-hydroxypregnenolone and these compounds ultimately form androgens. Estradiol, the most active estrogen produced by the ovary, is synthesized from androgens by the enzyme aromatase[115]. However, the effects of estrogen are manifold and incompletely understood. Estrogen is influenced by several environmental factors[116] on one hand, and on the other hand, estrogen influences cells (estrogen-sensitive cells) by interacting with the estrogen receptor (ER) in the nucleus, eliciting a cascade of transcriptional regulatory activity[117]. The steroid hormones are also well known for their ability to modulate directly the expression of cell-cycle regulatory genes (nuclear proto-oncogenes) such as c-myc and the EGF-R/c-erbB-2 growth factor receptor pathways[118,119]. Thus, estrogen is linked with both environmental as well as genetic factors. In the same manner, breast cancer is considered as the outcome of a complex interplay amongst genetic, hormonal, and environmental factors. In addition to modulating growth factor genes, estrogen may increase the production of proteases such as pro-cathepsin D which can enhance the invasiveness of tumour cells[120]. Polyamines have also been found to play a role in estrogen-regulated breast cancer cell growth[121]. The bcl-2 is a key protein involved in the control of apoptosis, and studies have indicated estrogenic regulation of bcl-2[122]. Steroid hormone receptors are also considered to play a potential oncogenic role due to recognition that steroid hormone receptors have structural homology with the avian erythroblastosis viral oncogene v-erb-A which has been shown to transform avian erythrocytes[123,124]. Recent research, studying the molecular mechanism of transcriptional regulation of target genes by steroid receptors has revealed a very complex network of protein-protein interactions in addition to protein-DNA interactions necessary for proper function of steroid hormones. Disruption in this intricately regulated mechanism can disturb steroid receptor signaling. Specifically, mutations in the ER as also altered receptor

expression have been found in breast cancer, and are associated with cancer progression and hormonal resistance[125,126].

Environmental Estrogens

The general agreement is that the estrogens are involved in the etiology of breast cancer, although, there is no general consensus on precise estrogen environment that defines risk in this disease[127]. Interestingly, the estrogenic materials are present in the environment as different chemical substances[128]. Numerous environmental chemicals have also been shown to possess estrogenic activity by virtue of their ability to bind to the ER[129]. However, beta-hexachlorocyclohexane (beta-HCH) may not act through the classic pathway of binding and activating the ER; beta-HCH may represent a new class of xenobiotics that produces estrogen-like effects through nonclassic mechanisms[130]. Chemicals such as pesticides and herbicides have been suggested to be able to interact with the endocrine system[131].

Environmental factors probably play a prominent role in breast cancer etiology. Breast cancer incidence has been rising steadily in many countries and it has been suggested that part of the increase may be due to the unexplained environmental factors[132]. General population have greater contact with pesticides than with any other group of toxic chemicals including industrial chemicals. In a recent study, human tissue samples have been investigated for pesticide residues; samples of fat from children living in farm areas contained a total of 14 pesticides, including lindane, HCH, heptachlor, aldrin, dieldrin, endrin, endosulfan, o,p'-DDE and o,p'-DDD, *etc.*[133]. Associations with breast cancer risk were demonstrated for some polychlorinated biphenyls (PCBs) measured in breast adipose tissue[134,135]. Further, it has been found that free-radical mediated oxidative stress is associated with some of the organochlorine pesticide residues in human breast tumours[136]. Straube *et al*[137] found changes in androgen concentrations and lymphocytes in relation to pesticide exposure; effects of chronic exposure were expressed by a higher level of testosterone[137,138] and an alteration of testosterone/SHBG ratio[139].

Unlike pesticides and related industrial estrogenic chemicals, vegetarian diets are rich in natural estrogenic substances 'phytoestrogens' and have been shown to prevent or affect breast cancer incidence[140]. The isoflavonoid glycosides and plant lignans are 2 main groups of phytoestrogens, found in foods like whole-grain rye products, soya beans, *etc*. The main phytoestrogens derived from the diet are genistein, daidzein and glycitein (all are isoflavones); however, 3 most estrogenic substances are coumestrol, genistein and daidzein. Phytoestrogens may reduce breast cancer risk by affecting ER; or alternatively, these naturally occurring chemicals may alter the actions/ metabolism of steroid hormones[141] and stimulate the production of SHBG in liver cells[140]. Lamartiniere concluded that genistein at physiological concentrations can reduce EGF-R expression[142]. Further, the equol is produced from daidzein in the gut by intestinal bacteria. People who produce high concentrations of equol have an increased ratio of 2-hydroxyestrone to 16α-hydroxyestrone, which is thought to decrease breast cancer risk[140]. Other possible beneficial effects of phytoestrogens include alteration of growth factor activity, inhibition of enzymes like 5a-reductase and aromatase or apoptosis in cancer cells[140,143,144].

Conclusions

Breast cancer is appearing to represent an enormous public health problem. The etiology of breast cancer is thought to involve a complex interplay of genetic, hormonal and environmental factors that influence the physiological status of the host. However, there are substantial experimental, epidemiological and clinical evidences, which show that breast cancer risk is influenced by endogenous sex-steroid hormones. Physiologically, estradiol is the most active estrogen, whereas testosterone is the most potent androgen in women. Besides, the major and specific binding protein for testosterone and estradiol in blood is SHBG. In peripheral tissues, particularly in adipose tissue, aromatase enzyme converts androgens to estrogens. After menopause, these extraovarian sources of estrogen play an important role in the body. More adipose tissues or obesity are related to dietary fat, specifically the intake of saturated fats of animal origin. Also, the degree of obesity is a major determinant of blood cholesterol and triglycerides. All these factors affect the metabolism of sex-steroid hormones. Recently, several studies have demonstrated a close relationship between sex-steroid hormones and immune system. Further, it has been demonstrated that tumour-infiltrating lymphocytes and macrophages could play a significant role in steroidogenesis.

In the process of carcinogenesis, steroid hormones can modulate the growth factor receptor pathways, apoptosis, signaling of steroid receptors, *etc*. Interestingly, numerous environmental chemicals have been shown to possess estrogenic activity; exposure to pesticides and related industrial chemicals increase the risk of breast cancer, whereas naturally occurring phytoestrogens have been suggested to have a preventive effect. Only a clear pathophysiological understanding could lead to an efficient policy of breast cancer prevention and decrease in the mortality due to this. In the near future, an increasing number of various pathophysiological factors will be used as targets for new treatment modalities. Indeed, different concepts are emerging as a valuable approach to the treatment of hormone-dependent breast cancer.

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