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Research Article

OVERVIEW OF BREAST CARCINOMA

***R. Yadav[1], R. Sen[2], P. Chauhan[1] and D. Phougat[3]**
[1]M.D. University, Rohtak
[2]Health University, Rohtak
[3]Dept. of Genetics, M. D. University, Rohtak, Haryana
**Author for Correspondence*

ABSTRACT
Breast cancer is a major concern and one of the leading causes of cancer-related death worldwide. Geographic variation in breast cancer incidence can be attributed to racial and genetic differences, cultural differences, as well as environmental exposures that vary throughout the world. The traditional prognostic factors such as nodal status, tumor size and tumor grade and lymph vascular invasion used identify the breast cancer patients. There are different kinds of risk factors like a person's age, reproductive factors and environment factors. Others are heterogeneous group of chemicals (xenoestrogen) that are hormonally active agents and these xenoestrogens promote the development of cancer by inducing cell proliferation. Analysis of hormonal receptor HER2 (Human epidermal receptor 2) as well as estrogen and progesterone receptors (ER and PR, respectively) is used for predictive purposes in routine breast cancer patient management. Incidences of breast cancer increasing in urban areas are as compared to rural areas. This review focuses on receptors status, risk factors, xenoestrogens and the benefits from therapies with the ultimate goal of understanding causes, treatments and management in future.

Key Words: *Breast Cancer, Estrogen, Progesterone, Xenoestrogen, Hormonal Receptor, Risk factors*

INTRODUCTION
Breast carcinoma the most common cancer malignancy in women, is the third most common cancer in the world and accounting for the highest morbidity and mortality in women. It is of serious concern owing to the rising incidence of the disease in the last 5-10 years (Parkin *et al*., 1990). Breast cancer is a major medical problem with significant public health and societal ramifications and is a leading cause of cancer death in women.

Carcinoma of breast is a malignant neoplasm results from the combined influence of endogenous and exogenous estrogen exposure as well as genetic susceptibility. The increasing global incidence of breast cancer emphasizes the need to understand the various mechanisms involved in breast tumorgenesis. Although a number of studies have been reported the role of estrogens as well as the imbalance in oncogenes and tumor suppressor genes in breast cancer, there are very few reports available on oxidant - antioxidant profile in breast cancer patients,. Many studies have now focused on changes in circulation or tumor tissue (Mirunalini *et al*., 2010).

Breast cancer is a typically sex hormone dependant neoplasm and estrogen is believed to play an important role in the pathogenesis and initial proliferation of this tumor. Estrogen binds to the estrogen receptor (ER) resulting in an activated complex that acts as a transcription factor through binding to the target genes. Estrogens play an important role in the aetiology of breast cancer through the expression of their receptors. Estrogen diffuses passively through ligand-receptor complex process and activates upstream promoter region of target genes (Wolf *et al*., 1997). Estrogen dependant growth can be blocked by anti-estrogen, which competes for binding to the estrogen receptor. The evaluation of ER expression in the breast tissue has brought about prominent developments in the treatment of breast cancer, especially in the area of endocrine therapy (Azam *et al*., 2009a).

Hormonal status of a breast cancer patient is usually determined only on the basis of ER content in the primary carcinomas. Metastatic tumors have been reported as being less frequently receptor positive than primary tumor (Azam *et al*., 2009 b). ER positive expression in breast cancer patients has a prognostic value and show significantly longer survival and disease-free intervals.

Xenoestrogen

The most common risk factor in the development of breast cancer is the cumulative exposure to 17 Beta - estradiol. This exposure may be endogenous or exogenous. Increased life time exposure to estrogens especially estrone and estradiol has long been linked to the promotion and progression of breast cancer because of their physiological action on the mammary gland (Dorgan *et al*., 2001 and Clemons *et al*., 2001).

Role of Xenoestrogen

Other unknown estrogenic risk factors also increase the risk of breast cancer, mostly later in life. Such estrogenic risk factors are diverse group chemicals called xenoestrogens related to industrial development These xenoestrogens include chemicals in plastics such as bisphenol-A (BPA), phthalates and polyvinyl chloride (PVC), pesticides and insecticides like DDTs, polychlorinated biphenyls (PCBs), parabens and placental extracts in cosmetics, aromatic amines, industrial solvents like benzene and toluene and air pollutants such as polyaromatic hydrocarbons (PAHs). Xenoestrogens pervade almost all areas of modern life in developed parts of the world (Grey *et al*., 2009). There is increasingly reported evidence that xenoestrogens are related to breast cancer (Brody *et al*., 2007 and Grey *et al*., 2009) and primarily cause ER positive breast cancer (Robison *et al*., 1985, Dewailly *et al*., 1994 and Woolcott *et al*., 2001).

Urban/Rural Effects

ER positive cancer is increasing in the industrialized parts of the world mainly due to estrogenic risk factors. On the other hand most of the hereditary and environmental risk factors also explain only up to 50% of breast cancer risks (Madigan *et al*., 1995 and Rockhill *et al*., 1998).

In developing countries, urban and rural populations are differentially exposed to xenoestrogens. There have been multiple studies from various parts of the world that clearly demonstrate the higher presence and exposure to xenoestrogens in urban areas (Kumari *et al*., 2005 and Zhang *et al*., 2007, Pentamva e*t al*., 2007, Jafari *et al*., 2008 and Kidata *et al*., 2008). Women in urban areas are prone to using more plastics and electrical appliances, household insecticides, detergents, cosmetics, etc. Dey and his coworkers in 2009 have also shown that incidence of breast cancer is indeed higher in urban areas than rural areas in Egypt (Dey *et al*., 2009). A recent study (2010) in Egypt showed that the urban ER positive rate was 2 to 4 times higher than the rural ER positive rate (Dey *et al*., 2010). The reasons for higher incidence of ER positive cancer in urban areas are multi-factorial.

Xenoestrogens might play an important role in increasing ER positive cancer in major cities. It is quite possible that women in urban areas have better nutrition and development which leads to early menarche. They might be more educated resulting in higher age of marriage, lesser number of children and reduced breast feeding (Kelsey *et al*., 1996). All of these reproductive factors result in higher lifetime exposure of women to endogenous estrogens and thus can increase ER.

Previous studies also demonstrated that urban women have higher levels of 7, 8-dihydro-8-oxo-20-deoxyguanosine (8-oxo-dG) indicating higher DNA damage and thus higher exposure to carcinogens (Soliman et *al*., 2004). Since xenoestrogens have estrogenic effects and related to ER positive Cancer (Robison *et al*., 1985, Dewailly *et al*., 1994 and Woolcott *et al*., 2001).

These studies clearly suggested that estrogen risk factors/ environmental exposure chemicals such as organochlorine pesticides and polychlorinated biphenols which mimic estrogens increase the risk of breast cancer. These chemicals can contaminate the food, water and air and can accumulate in human breast fat (Darbare *et al*., 2006 and Salehi *et al*., 2008).

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Role of Hormonal Receptor and Other Risk Factors

Estrogens play an important role in the etiology of breast cancer. Effect is seen in the established reproductive risk factors, such as early menarche and late menopause, suggesting that prolonged estrogen exposure could play a role (Ma *et al*., 2006).

Positive status of estrogen, progesterone receptor breast cancer was most closely related to most of the risk factors and estrogen receptor-negative, progesterone receptor-negative breast cancer was unrelated to the risk factors (Yoo *et al*., 1997).

Epidemiologic studies have shown that the percentage of ER positive breast cancers has been increasing over time (Pujol *et al*., 1994 and Li *et al*., 2003). The reason for this increase is unclear, but may be due to environmental factors (Darbare *et al*., 2006 and Salehi *et al*., 2008).The risk factors responsible for ER or progesterone (PR) positive and ER or PR negative breast cancers appear to be different. The presence (estrogen receptor positive) or absence (estrogen receptor negative) of specific estrogen binding protein in breast cancer is related to the biologic characteristics of the tumor. Receptor negativity is associated with larger tumor size and more rapidly proliferating tumor tissue. Estrogen receptor status also varies according to some breast cancer risk factors, notably age, menstrual status and race (Salehi *et al*., 2008).

In one case control study in Japan have examined the suspected breast cancer risk factors stratified separately by estrogen receptor and progesterone receptor status. There is some evidence that certain risk factors may differ by progesterone receptor status, but not by estrogen receptor status. Data from 1988-1989 has reported that risk factors for breast cancer varied by progesterone receptor status, but not by estrogen receptor status (Yoo *et al*., 1993).

Age has been reported to be a stronger risk factor for estrogen receptor-positive breast cancer than for estrogen receptor-negative breast cancer (Habel *et al*., 1993). Most of the data suggest that progesterone receptor-positivity is more closely associated with age than is estrogen receptor positivity (Yoo *et al*., 1997). Incidence rates for breast cancer are consistent with prior clinical and epidemiologic observations suggested the increase in the proportion of estrogen receptor positive cancer with advancing age (Donegen *et al*., 1992, Fisher *et al*., 1987, Hildreth, 1983 and Tiernen, 1986).

Age, ethnicity, stage and grade are strong determinants of ER positivity. Early menarche, nulliparity, late age at first birth and late menopause are all correlated with increased risk of breast cancer (Pathak *et al*., 2000). According to some old studies, exogenous hormone intake increases overall risk to 2.5 fold (Kelseyy *et al*., 1991). Ethnicity also appears to be a factor in the occurrence of ER positive breast cancers (Gapstur *et al*., 1996, Joslyn *et al*., 2002 and Chu *et al*., 2002).

Early age at menarche, menstrual regularity at ages 20-29 years, late age at menopause, late age at first full-term pregnancy, fewer full-term pregnancies and less breastfeeding should have been most closely associated with estrogen receptor-positive, progesterone receptor-positive breast cancer (Handerson *et al*., 1985, Kelsey *et al*., 1993 and Colditz *et al*., 2004).

Estrogen receptor concentrations are lower in tumors of premenopausal women than in those of post menopausal woman (Silfversward *et al*., 1980 and Honma *et al*., 2003). Ethnicity, age has also been significantly associated with ER positivity in various studies published in 2000 and 2002, with postmenopausal women having higher rates of ER positive tumors (Chow *et al*., 2000 and Tarone *et al*., 2002). Correlation of breast cancer with age reported the ER positive rates remain lower in postmenopausal Asian women than reported data from Western studies (Chow *et al*., 2000). Most of women aged 40 years and older were more likely to have ER positive tumors; however, age became insignificant when adjusted for covariates, as age was also associated with grade and ethnicity. Malay women were previously reported in 2006 as presenting at a younger age (Yip *et al*., 2006).

Several risk factors for the development of breast cancer have been established and proposed that the common denominator for most of these factors is prolonged estrogen stimulation operating on a genetically susceptible background (Moor *et al*., 1993). Numerous studies suggest a strong link between the female hormone, estrogen and the development of breast cancer. Distribution of risk factor are

different in patients with hormonal receptor and it showed that increase a woman's lifetime exposure to endogenous estrogens resulting in ER positive Cancer (Haung *et al*., 2000 and Althuis *et al*., 2004).

There is two to three times increased risk of breast carcinoma if a first degree relative has breast cancer (Skolnick *et al*., 1992). Potter *et al*., (1995) noticed that progesterone receptor-positive breast cancer is most associated with family history (Potter *et al*., 1995). It is also hypothesized estrogen receptor negative, progesterone receptor-negative breast cancer to have the strongest association with alcohol consumption (Potter *et al*., 1995). Other risk factors such as genetic factor, radiation and smoking may give rise to ER- cancers (Haung *et al*., 2000 and Manjer *et al*., 2001). Overall, these differences imply that ER positive and ER- cancers denote different subtypes of breast cancer with different risk factors, clinical pictures and outcomes (Chen *et al*., 2007).

Most studies have found there is weak association between cigarette smoking and breast cancer. Intake of exogenous hormone increases overall risk to 2.5 fold (Kesley *et al.,* 1991). Other risk factors such as genetic risks, radiation and smoking give rise to ER- cancers (Haung *et al*., 2000 and Manjer *et al*., 2001). Several studies has been reported the incidence of ER positive breast cancer increase with time (Pujol *et al*., 1994). Increase in breast cancer incidence could be due to the increase in hormone-receptor positive breast cancers. Li *et al.,* reported the incidence rate of hormone receptor-negative tumors remained fairly constant in the United States between 1992 and 1998, despite the overall increase in incidence of breast cancer (Li *et al*., 1998).

Breast cancer with ER status also related to the period of exposure to various risk factors. There are three critical periods in the development of mammary glands: the intrauterine period especially just before birth, the peripubertal period and the period of pregnancy and lactation (Fenton et *al*., 2006). Mammary stem cells research, which is now considered to be the origin of breast cancer, shows that during the intrauterine period all stem cells which are the progenitor stem cells are ER-ve (Bartow *et al*., 1998, Keeling *et al*., 2000, Reya *et al*., 2001, Marx *et al*., 2003, Singh *et al*., 2003 and Al et *al*., 2003). Postnatally ER- stem cells differentiate into ER positive cells which later form mammary glands during puberty under the influence of estrogen (Bartow *et al*., 1998). Exposure to xenoestrogens in early life intrauterine period or around birth studies showing excretion of xenoestrogens in human milk in Egypt and across the world (Solomon *et al*., 2002, Soliman *et al*., 2003 and Lakind *et al*., 2004). However, progenitor stem cells are few in number and quite hardy and resistant to mutations (Dontu *et al*., 2004). ER positive cancer must be higher in exposed populations because ER positive stem cells is more numerous later in life and are less resistant to mutations (Dontu *et al*., 2004).

A large cohort of case control study have provided strong evidence for a greater increase in breast cancer risk in women using hormone replacement therapy than in those using estrogen alone (Ross *et al*., 2000). In December 2002, the hormone estrogen was declared a known human carcinogen by the National Toxicology Program. Presence of hormone receptors in tumour tissue correlates well with response to hormone therapy and chemotherapy (Barnes *et al*., 2001). Differences in ER positive and ER negative cancers denote different subtypes of breast cancer with different risk factors, clinical pictures and outcomes (Chen *et al*., 2007).

In several studies Stage and grade have been associated with ER status, with ER negative tumors associated with higher stage and grade (Grann *et al*., 2005). ER positive cancers were significantly associated with early stage breast cancer (stage I and II) and a lower grade. Study from Malaysia has reported that Malay women present with larger tumors and later stage of disease than Chinese and Indian women, (Yip *et al*., 2006). Grade is another independent factor associated with ER positivity. Grade 1 cancers were shown to be almost 9 times more likely to be ER positive compared with grade 3 breast cancers. Because ER negative tumors are more aggressive, it is not surprising that it is also more likely to be of a higher grade (Yip *et al*., 2011). Some studies found that presence of estrogen receptors to be significantly associated with high nuclear and low histological grades, absence of tumor necrosis, presence of marked tumor elastosis and old patient's age groups (Fisher *et al*., 1980). Hormone receptor

positivity also correlates with bcl-2 immunoreactivity (Cote et *al*., 1988) and absence of mutations (Caleffi *et al*., 2001), p53 and it correlates inversely with the presence of epidermal growth factor receptors (Agthoven *et al*., 1994).

Increase in the proportion of estrogen positive cases was unlikely to be related to changes in technology, age, size of tumor or lymph node status and that this rise may be related to changes in tumor biology or hormonal events that influence breast cancer genesis and growth (Pujol *et al*., 1994). Most of study shows that there was a clear increase of ER positivity over time in population. This increase was not explained by age, ethnicity, stage or grade of women with known ER status.

Estrogen receptor (ER) status is an important predictive and prognostic factor in breast cancer (Rastelli *et al*., 2008). Determination of hormonal status in breast cancer is helpful in selecting the patients most likely to receive benefit from endocrine therapy and provide prognostic information on recurrence and survival. The highest response rates to endocrine therapy are observed in estrogen and progesterone receptors positive tumors (Haider *et al*., 2001). Evaluation of breast carcinoma for presence of hormone (estrogen and progesterone) receptors in the tumor tissue correlates well with response to hormone therapy and chemotherapy has been found (Hawkins *et al*., 1980 and Barnes *et al*., 2001).

Epidemiology

Surveillance Epidemiology and End Results (SEER) studies showed ER positive cancers are more frequent after menopause and more common among Caucasians than other races (Anderson *et al*., 2001, Parkin *et al*., 2002, Li *et al*., 2002, Brey *et al*., 2004 and Chlebowski *et al*., 2005). In addition to this many international studies have clearly indicated that ER positive breast cancer is higher in developed countries (Desai *et al*., 2000). Li *et al*., 2003 have reported that most of the breast cancer incidence increase in US due to an increase in ER positive breast cancer cases.

The breast is the most common site of primary cancer in both Black and White women in the United States (Edwin *et al*., 1985). Although Black women have a lower risk of developing breast cancer than White women, the survival of Black women following diagnosis is worse than that of Whites (Edwin *et al*., 1985). Survival time of white patients have average of 6.6 years, whereas Black patients survive only about 3.7 years (National Cancer Institute, 1974). Many Studies in United States showed that African Americans, Asians, Native Americans and Hispanic Whites were more likely to have ER negative tumors than non-Hispanic Whites (Gapstur *et al*., 1996 and Li *et al*., 2002**)**. Reason for the hormonal receptor status differences is unknown; diet and lifestyle differences between the ethnic groups may be play a role. There also appears to be a geographical difference in the proportion of ER positive breast cancer, with lower rates reported in developing countries. The ER positive rates in asia are an average of 60% compared with 70% in Western countries (Yip *et al*., 2009). This may be related to the younger age of diagnosis in Asian countries. Chinese women are significantly more likely to have ER positive cancers compared to Malay women. In another study on Chinese women in Hong Kong which reported an ER positive rate 53% in premenopausal women and 61.6% in postmenopausal women (Chow *et al*., 2000). In Western countries, breast cancer is the most common female cancer and the leading cause of cancer mortality (Tarone *et al*., 2006). Breast cancer incidence of Kingdom of Saudi Arabia (KSA) is lower than in Western countries (Kuraya *et al*., 2005) and highest amongst all the malignancies seen in Saudi females comprising 21.8% (Registry *et al*., 2007). In Asian populations, breast cancer patients are of younger age onset and premenopausal stage but features of breast cancer vary among Asian countries (Duijm *et al*., 2007 and Choi *et al*., 2003). Some studies have reported higher rates of hormone receptor negative or high-grade breast tumor in Asian populations (Aggarwal *et al*., 2007). Race differences affect the prevalence of breast cancer subtypes and prognosis (Carey *et al*., 2006).

In Cancer Registry of Tunisia, breast carcinoma is the most frequent malignant neoplasm affecting Tunisian female patients with an incidence of 23.6/100.000 inhabitants (Hsairi *et al* 2002). Women with breast carcinoma in Tunisia are relatively in younger than in Western countries, with an average age of 51 years (Maalej *et al*., 2008). This may suggest that breast carcinoma in Tunisia may have some biological

features that need to be explored. Besides, the increasing incidence and significant breast cancer mortality (Overall survival rate = 50.5% after 5 years) highlight the need for new therapeutic development, especially targeted treatment (Ahmed *et al.,* 2002).

Study on Vietnamese and Australian Caucasian women with breast cancer found that ER expression in Vietnamese women was no different from the Australian Caucasian counterpart, suggesting that ER expression in breast cancer among women from other countries in Asia is also higher than other previously studies (Tran *et al*., 2004). Nigeria and Kenya also found ER status to be higher than previously reported for African ancestry (Adebmowo *et al*., 2008 and Bird *et al*., 2008). Many studies on race specific incidence reported a lower prevalence of estrogen positive breast cancer among black women compared to white women (Fisher *et al*., 1987 and Hildreth, 1983). Studies done in the United States, prior to 2002, among Asians, Africans and other non-Whites living in the United States, found the rate of ER expression to be lower in these ethnic groups compared to Caucasians, assuming the variables were standardized across studies.

In countries, where there is a population-based mammography screening program for differential selection of women for status determination. It was found ER positive cancers number increase as screen-detected cancers are generally slower growing and hence more likely to be ER positive (Brown *et al*., 1986). In most LMCs like Malaysia, where there is no population-based mammography screening program, the proportion of ER positive cancers reported is likely to remain lower than in high-resource countries (Yip *et al*., 2011).

A substantial proportion of primary breast cancers contain estrogen receptors and/or progesterone receptors (Wittliff *et al*., 1984, Thorpe *et al*., 1988, Rayter *et al*., 1991 and Donegan *et al*., 1992). The incidence of breast cancer in Malay women is significantly lower than that in Chinese and Indian women and it may be that the rate of ER positive breast cancer increases with the overall incidence of breast cancer (Yip *et al*., 2006). Increase in the incidence of breast cancer is also in high income countries (1992 to 1998) are believed to be due to the increase in the incidence of ER positive breast cancer.

MATERIALS AND METHODS

Management of Breast Cancer

ER status in breast tumor is essential for optimal management of breast cancer. ER positive tumors are associated with a better overall survival compared with ER negative tumors (Dunnwald *et al*., 2007). Tamoxifen has been shown to improve overall survival in ER positive breast cancer and has been thought to be one of the reasons for improving survival rates in breast cancer (Lancet, 1998). Hormone status of breast tumors and their responsiveness to endocrine therapy are highly correlated, with receptor-positive tumors responding favorably. Patients with receptor positive tumors have a somewhat better prognosis than patients with receptor-negative tumors and receptor positive cancers tend to have less aggressive biologic properties than receptor-negative cancers (Wittliffet *et* al., 1984, Thorpe *et al*., 1988, Rayter *et al*., 1991 and Donegan *et al*., 1992).

The clearest clinical and biologic distinctions between tumors positive for both estrogen receptors and progesterone receptors versus tumors that is negative for both receptors (Wittliffet *et al*., 1984, Thorpe *et al*., 1988, Donegan *et al*., 1992 and Fisher *et al.*, 1987). The behavior of tumors that are estrogen receptor-positive and progesterone receptor-negative is intermediate.

It is not yet clear whether breast cancers of differing hormone receptor status represent etiologically distinct forms of the disease with different risk factor profile (Habel *et al*., 1993 and Potter *et al*., 1995). The characterization of the small proportion of breast cancers determined to be estrogen receptor-negative, progesterone receptor-positive is controversial.

Response to hormonal therapy leads to the hypothesis that estrogen receptor- positive; progesterone receptor-positive tumors would be most closely related to reproductive risk factors that are probably

mediated by endogenous hormones (Kelsey *et al*., 1993 and Potter *et al*., 1995) while estrogen receptor-negative, progesterone receptor-negative tumors would be unrelated to these risk factors.

Cancer chemoprevention, by biologically active or non dietary supplements has generated immense interest as putative role in allenuating the risk of developing cancer. Additional studies are warranted to determine the effects of compounds in inhibiting cancers in humans. The changes in estrogen receptor and progesterone receptor breast cancer patients were also evident in carcinoma patients placing them in a high risk category.

Certain plant-derived dietary constituents have estrogenic activity on breast cancer. These include pulses and legumes rich in the isoflavone phytoestrogen (genistain, dieldrin and coumestrol). These exert anti carcinogenic effects by functioning as estrogen antagonists, antioxidants, inhibitors of aromatase enzymes and by altering hormone levels (Davis *et al*., 1997). Diets rich in vegetables, fruits and grains products can prevent the breast carcinogenesis (Brown et al., 2000). Many studies have suggested that breast cancer could be prevented by developing drugs to block estrogen action in the breast (Fisher *et al*., 1969). Selective estrogen receptor modulators (SERMs) such as tamoxifen, raloxifen etc., which are competitive inhibitors of estrogen binding at estrogen receptors alpha and beta play a major role in the prevention and treatment of breast cancer. PgR expression vectors were transfected into estrogen receptor (ER)-alpha and PgR-negative breast cancer cells MDA-MB-23 thus the functions of progesterone could be studied independent of estrogens and ERs (Barnes *et al*., 2001). Breast Cancer may be characterized in terms of histologic grade as well as histologic type.

CONCLUSION

Percentage of ER positive breast cancers has been increasing over time in several high income countries. A significantly high incidence of ER positivity was seen in different population. The reason for this increase is unclear, but it may be due to environmental factors and genetic factors. Xenostrogen might be significant cause of higher incidence of ER positive cases. We also need a future research plans to investigating a correlations of xenoestrogens exposure and hormonal receptor positivity. Population of hormonal receptor positivity increases with other risk factors age, ethnicity, stage and grade. The role of hormone receptors as prognostic and therapeutic tools has widespread acceptance in the management of breast cancer.

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