PATHOLOGICAL STUDY OF: ESTROGEN RECEPTORS AND CARCINOEMBRYONIC ANTIGEN ASSAY AS PREDICTIVE FOR PROGNOSIS IN BREAST CANCER PATIENTS

THESIS
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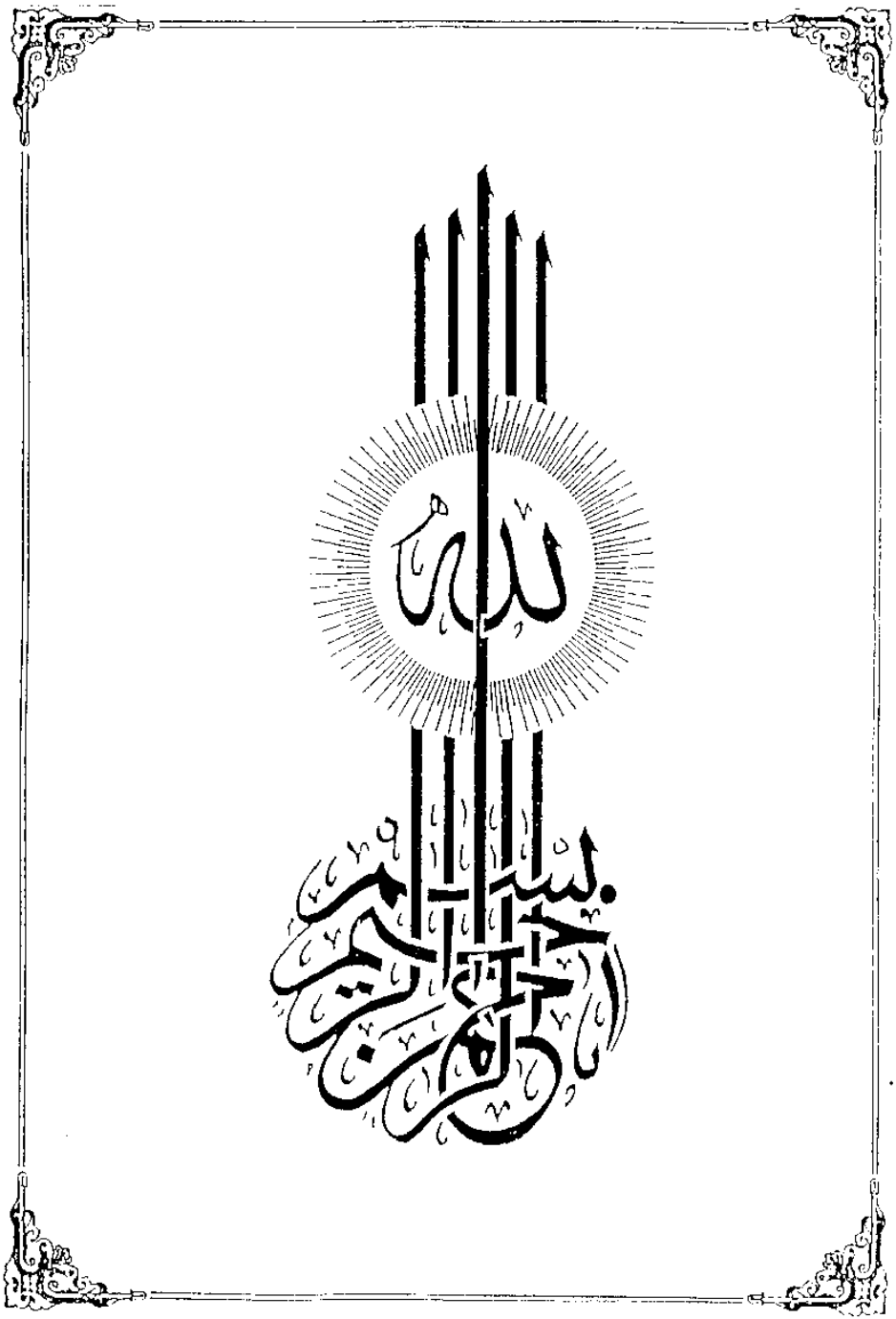

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INTRODUCTION &

AIM OF THE WORK

INTRODUCTION

Assessment of tumor burden remains a major problem in the management of most patients with cancer.

Breast cancer is the commonest malignant tumor affecting females in most parts of the world including Egypt. Statistical reports from National Cancer Institute in Cairo showed that breast cancer accounts for 34.8 percent of total malignancy among Egyptian females (Ibrahim and Aref, 1982).

Scientists and physicians from twelve laboratories around the world compared their results regarding the occurrence of specific estrogen binding proteins in human breast cancer with clinical response data (McGuire et al., 1975). The evidence presented indicated that tumor remission after either endocrine organ ablation or additive hormonal therapy occurred more often in women with either primary or metastatic breast lesions containing estrogen receptors than in those whose carcinomas did not exhibit measurable estrogen binding capacity. Furthermore for breast cancer, a satisfactory tumor marker or a system of markers would be of major clinical importance at all stages of the disease, and especially for early recognition of metastatic disease (Cooke et al., 1979).

It is known that a high percentage of breast cancer

patients who undergo radical mastectomy die of metastatic disease (Hutter, 1980). This necessitates the search for reliable markers that can be used for predicting the presence of metastases at their early and rather undetectable stage.

Cooke (1982) included carcinoembryonic antigen (CEA) as one of the principal means of follow up for patients after mastectomy.

Also estrogen receptor measurements has been established as useful predictive for prognosis and for planning endocrine therapy in carcinoma of the breast (O'Connell and Said, 1983).

AIM OF THE WORK

The present work will deal with immunohistochemical studies of estrogen receptors (ER) as well as of carcinoembryonic antigen (CEA) in breast cancer tissue.

The aim is to correlate their presence with the histopathological data in these tumors in order to declare their importance as useful tumor markers in predicting prognosis and selecting therapeutic regimens for patients with breast cancer.

REVIEW OF LITERATURE

NORMAL BREAST

***Embryology:**

The breast is a modified skin sweat gland that develops into a complex functional structure in the female, but remains as a rudimentary organ in the male. It arises from an epidermal thickening on the ventral surface of the body at approximately the sixth week of fetal development. Bilateral ridges (the milk line) develop between the upper and lower limb buds. These ridges totally atrophy except for several persistent thickenings, which later give rise to the nipples. During the second trimester of fetal life, cords of cells grow downward from the basal layer of the epidermis and later give rise to the primary mammary ducts.

Development of the breast is complete at the time of birth. Progressive growth and branching of the mammary ducts occur at a very slow pace during prepubertal life. Mammary development ceases at about this stage in the male. In the female, before the onset of menstruation, the growth rate increases with branching of ducts and proliferation of the interductal stroma. During adolescence, stromal growth is responsible for most of the increase in the mass of the breast, but at the same time the terminal small ducts give rise to many small, blind, saccular outpouchings.

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* Cotran et al. (1989).

***Anatomy and *Histology:**

The resting mammary gland consists of about 20 lobes, each of which is subdivided into lobules, the functional units of the mammary parenchyma (Diagram 1). Each lobe drains through a separate main excretory or lactiferous duct into the nipple. Just beneath the nipple, the lactiferous ducts exhibit a small dilated segment, called the lactiferous sinus. Successive branchings of the lactiferous ducts distally eventually lead to the terminal ducts. Before puberty, this complex system of branching ducts ends blindly, but at the beginning of menarche, it proliferates distally, giving rise to some 30 epithelium-lined ductules or acini. Each terminal duct and its ductules compose the terminal duct lobular units (Diagram 1).

The areola, nipple, and mouths of the main lactiferous ducts are covered by stratified squamous epithelium. It soon becomes transformed into a pseudostratified columnar and then double-layered cuboidal epithelium that lines the major breast ducts. As the ducts branch and become smaller, the epithelium tends to become a single layer of cells, but in the smaller ducts and sometimes even in the ductules, a low flattened layer of cells (myoepithelial cells) can be identified beneath the more prominent lining epithelium. Myoepithelial cells contain myofilaments oriented parallel to the long axis of the duct. A basement

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* Cotran et al. (1989).

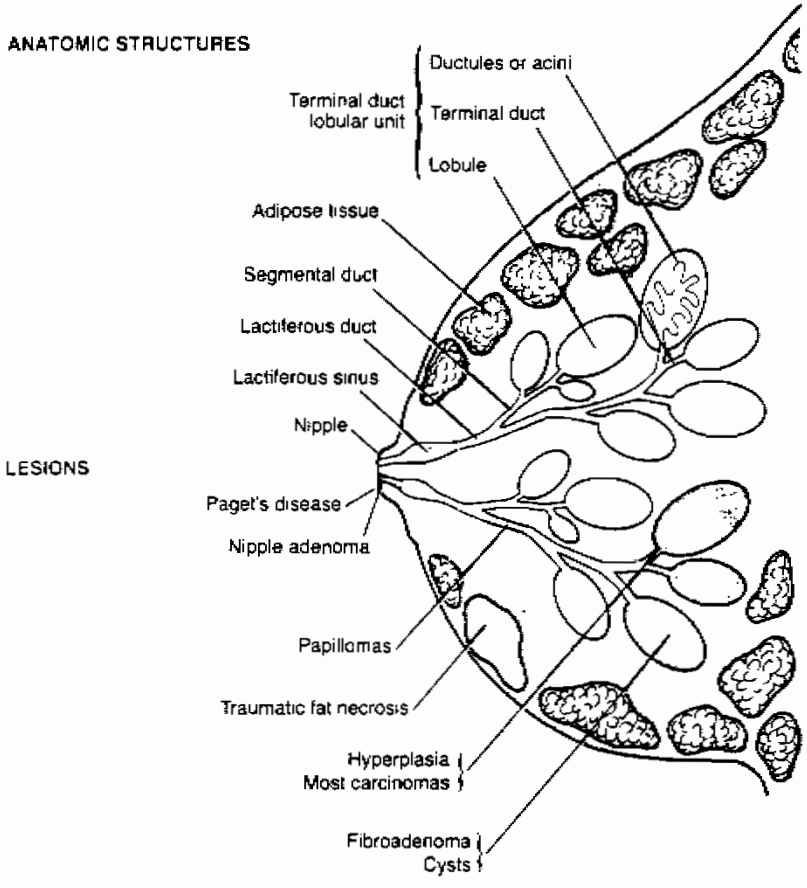

Diagram (1) : Anatomy of the breast and major lesions at each site within the various units.

membrane follows faithfully the contour of ducts and ductules (Stirling and Chandler, 1976). These are enclosed within a denser, collagenous, fibrous interlobular stroma.

Just as the endometrium rises and ebbs with each menstrual cycle, so does the breast (Longacre and Bartow, 1986). Following the menstrual period, with the progressive rise in estrogen, the ductal and ductular cells begin to proliferate and continue to develop throughout the menstrual cycle. During the secretory phase of the menstrual cycle, under the influence of progesterone, proliferation of the terminal duct structure increases, and there is vacuolization and increased mitotic activity of basal epithelial cells. The stromal cells proliferate and there is, in addition, stromal edema. This combined stimulatory effect of estrogen and progesterone on the intralobular breast elements accounts for the sense of fullness commonly experienced by women during the premenstrual phase of the cycle. When menstruation occurs, the fall in estrogen and progesterone levels is followed by desquamation of epithelial cells, atrophy of the intralobular connective tissue, disappearance of stromal edema, and overall shrinkage in the size of the ducts and gland buds. Considerable numbers of lymphocytes accumulate in the periductal tissue.

It is only with the onset of pregnancy that the breast assumes its complete morphologic maturation and functional

activity. From each gland bud, numerous true secretory glands pouch out to form grapelike clusters. As a consequence, there is a reversal of the usual stromal glandular relationship so that, by the end of pregnancy, the breast is composed almost entirely of glands separated by a relatively scant amount of stroma. The secretory glands are lined by cuboidal cells, and in the third trimester, secretory vacuoles of lipid material are found within the cells. Immediately following birth the secretion of milk begins.

Following lactation, the glands once again regress and atrophy, the ducts shrink, and the total breast size diminishes remarkably. However, complete regression to the stage of the normal virginal breast usually does not occur, and some increases of glandular parenchyma remains as a permanent residual.

With the menopause, the ducts and gland buds further atrophy with more shrinkage of the intra and interlobular stroma. The gland buds may almost totally disappear in the very aged, leaving only ducts to create a morphologic pattern that comes close to that of the male. However, in most women there is sufficient persistent estrogenic stimulation, possibly of adrenal origin, to maintain the vestigial remnants of gland buds that differentiate even the very aged female breast from the male breast.

EPIDEMIOLOGY OF BREAST CANCER

Breast cancer is the most common cancer in women, accounting for 27 percent of all the cancers that develop in them. One out of every eleven women, or about 9 percent, will develop it during her lifetime (Leis, 1980a).

Breast cancer is also the leading cause of cancer death in women, accounting for 19 percent of these. It is also the leading cause of death due to all causes in women aged 40 to 44 (Leis, 1980c).

These facts emphasize the magnitude of the breast cancer problem and stress the importance of determining epidemiologic factors responsible for its development and of trying to isolate any preventive measures that might reduce its incidence (Leis, 1980a).

After determining the etiology of breast cancer and defining preventive measures, the most important factor is early diagnosis (Leis, 1981). Early diagnosis offers better cure and long-term survival rates with less extensive surgery, less adjuvant therapy, and decreased local recurrence rates.