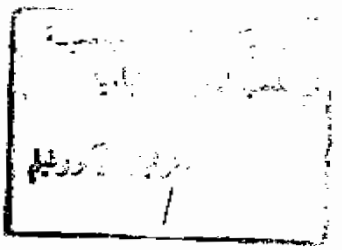
THE PREDICTIVE VALUE OF EGFR AND CATHEPSIN D IN BREAST CANCER

THESIS



Submitted for partial fulfilment of
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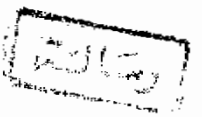

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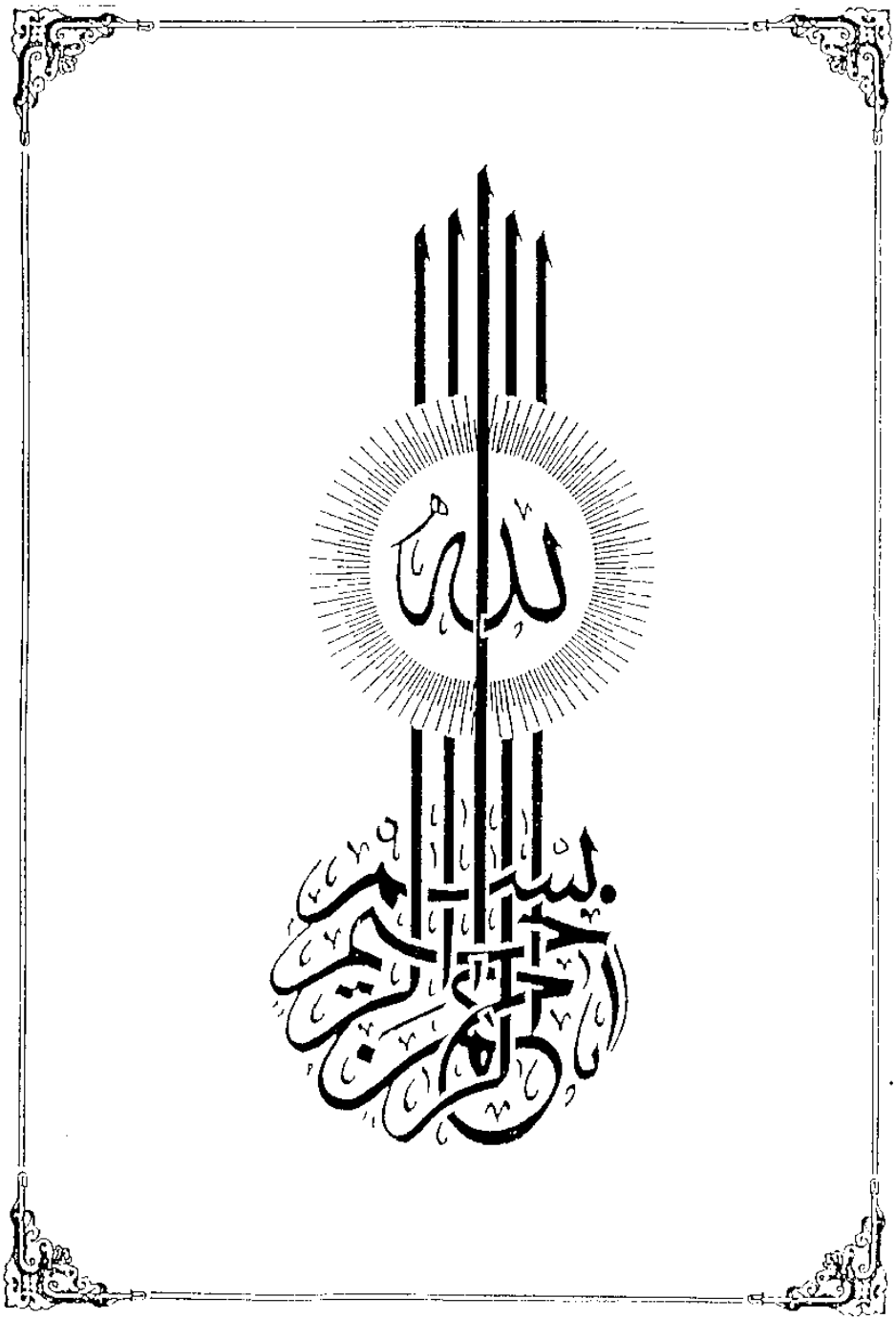
بسم الله الرحمن الرحيم

« وعلمك ما لم تكن تعلم

وكان فضل الله عليك عظيما »

صدق الله العظيم

(سورة النساء آية ١١٣)



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LIST OF ABBREVIATIONS

AJCC	American Joint Committee for Cancer
AEV	Avian erythroblastosis virus
CA 15.3	Cancer antigen 15.3
CEA	Carcinoembryonic antigen
CD or Cath D	Cathepsin D
cDNA	Complementary DNA
c-erb-B	Normal cellular counterpart of v-erythroblastosis B gene
cpm	Counts per minute
DTT	Dithiotreitol
ELISA	Enzyme linked immunosorbent assay
EGF	Epidermal Growth Factor
EGF-R	Epidermal Growth Factor-Receptor
ER	Oestrogen Receptor
GFR	Growth factor receptor
HEPES	N–[2–Hydroxy ethyl] piperazine–N´ {2–ethane sulfonic acid]
IGF I, II	Insulin-like growth factors I and II
LDL	Low density lipoprotein
mM	Millimolar
MCA	Mucin like Carcinoma associated Antigen

MAb	Monoclonal antibodies
Man 6-P	Mannose-6 phosphate
nm 23	Non metastic protein product (23 kd)
NSCLC	Non small cell lung cancer
OS	Overall survival
PR or PgR	Progesterone receptor
PDGF	Platelet derived growth factor
RFS	Recurrence free survival
SHR	Steroid hormone receptor
SCLC	Small cell lung cancer
TNM	T: tumour, N: lymph nodes, M: metastasis
TGFα	Transforming growth factor α
TPA	Tissue polypeptide antigen
TMB	3, 3′, 5, 5′ tetramethyl benzidine
TRIS	Hydroxy methyl amino methane
v-erb-B	Viral erythroblastosis-B gene
VVGF	Vaccinia virus growth factor

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Introduction and Aim of Work

INTRODUCTION AND AIM OF WORK

Breast cancer, the most common cause of cancer death in women, results from the complex interaction of genetic, physiologic and environmental factors. In each case, the ability to predict the clinical outcome, determine the probability of recurrence, and make decisions on adjuvant chemotherapy or radiotherapy relies on tumour stating using several independent prognostic indicators (*Donovan-Peluso et al.*, 1991).

Cathepsin D is an independent prognostic factor associated with high risk for metastasis in breast cancer (*Rochefort et al.*, 1987; *Spyratos et al.*, 1989 and *Tandon et al.*, 1990). Because of its relationship to tumour growth and invasiveness, cathepsin D concentration may be useful to identify patients who would benefit from adjuvant therapy (*Tandon et al.*, 1990).

Epidermal growth factor (EGF) is one of the peptide growth factors whose molecular mechanism of action has provided an understanding of the biochemistry that underlies the regulation of cell proliferation (*Carpenter*, 1987). The mitogenic action of EGF is

mediated through the binding to their membrane receptors, which after internalization, transduces the mitogenic signal (*Fitzpatrick et al.*, 1984).

The clinical importance of epidermal growth factor receptor (EGFR) has recently been outlined as a prognostic factor, an indicator of response to hormonal therapy and possibly a target for blocking of cytotoxic agents (*Sainsbury et al.*, 1985a, 1987; *Macias et al.*, 1987 and *Grimaux et al.*, 1989).

Mucin like carcinoma associated antigen (MCA) belongs to the group of mucin like glycoproteins (*Stähli et al.*, 1988) released from breast cancers. Invasive tumour cells may disrupt tissue architecture sufficiently so that antigen release in the blood stream may occur, as a result, antigens can be detectable in the serum.

This study will deal with the estimation of EGFR in the membrane fraction of benign and malignant breast tissue. Also, the proteolytic enzyme cathepsin D will be estimated in the cytosol fraction of the same tissue. In addition, MCA will be estimated in serum and tissue studied. These biological parameters will be evaluated to highlight their biological behaviour in tumours as well as their predictive value.

Review of Literature

REVIEW OF LITERATURE

The natural history of breast cancer is characterized by a long duration and marked heterogeneity within and among patients. Breast cancer is among the more slow-growing tumours, and the preclinical period before diagnosis and the clinical phases after initial treatment and even after the appearance of metastasis are measured in years and decades.

Nevertheless, some patients have aggressive forms of the disease and do poorly. Other patients have such indolent forms of the disease that it is difficult to demonstrate that therapy has any effect on survival. During the long clinical phase, there is ample opportunity for clonal mutation and evolution, and it seems probable that individual patients may have multiple tumour clones, each with its own growth rate, propensity to metastasize and sensitivity to drugs (*Harris et al.*, 1993).

Advances in molecular biology during the next decade should enable a more precise estimate of a patient's clinical course than is now possible based on clinical criteria.