

IMMUNOHISTOCHEMICAL EXPRESSION OF ANDROGEN RECEPTOR IN ESTROGEN RECEPTOR NEGATIVE BREAST CANCER

Thesis

Submitted for Partial Fulfillment of Master Degree
in Pathology

By

Heba Ahmed Abd Elsattar

M.B.B.Ch

Supervised by

Professor: Sanaa Abd Elmaged Sammour

Professor of Pathology

Faculty of Medicine Ain Shams University

Professor: Laila Nabegh Mohamed Naguib

Professor of Pathology

Faculty of Medicine Ain Shams University

Dr: Naglaa Samier Ahmed

Assistant Professor of Pathology

Faculty of Medicine Ain Shams University

**Faculty of Medicine
Ain Shams University**

2012

Acknowledgement

First, thanks are all directed to **ALLAH** for blessing this work until it has reached its end, as a part of generous help throughout my life.

It is with immense gratitude that I acknowledge the support and help of **Prof. Sanaa Abd Elmaged Sammour**, Professor of Pathology, Faculty of Medicine, Ain Shams University, it was a great honor to work under her supervision and guidance.

I am profoundly grateful to **Prof. Laila Nabegh Mohamed Naguib**, Professor of Pathology, Faculty of Medicine, Ain Shams University, for her faithful guidance, meticulous revision and tremendous support .

My warmest thanks are expressed to **Dr. Naglaa Samier Ahmed**, Assistant Professor of Pathology, Faculty of Medicine, Ain Shams University, for her help, valuable comments and careful supervision.

Last but not least I would like to express my best regards and deepest thanks to all who gave me a hand while working in this thesis and I would like to dedicate this work to my beloved supportive **family**, who encouraged me to complete this work and guided me throughout my life. Without their kind help and support this work could not have come to completion.

List of Contents

	<i>Page</i>
LIST OF ABBREVIATIONS	I
LIST OF FIGURES	IV
LIST OF TABLES	VII
INTRODUCTION	1
AIM OF THE WORK	4
REVIEW OF LITERATURE	5
I-ANATOMICAL HINTS	5
A-Embryology:	5
B-Anatomy :	6
C-Histology	6
II-BREAST CARCINOMA	10
A-Epidemiology of Breast Carcinoma	11
B-Risk Factors for Breast Carcinoma	12
1-Age	12
2-Geographical Variation	13
3-Hormones And Hormonal Replacement Therapy	14
4-Reproductive Factors	14
5-Breast Conditions	16
6-Environmental Factors	16
7-Lifestyle Factors	17
a) Cigarette Smoking	17
b) Light at Night	18
c) Physical Activity	18
d) Body Weight	19
e) Alcohol Consumption	19
8-Genetic Factors	19
a) Breast Cancer type 1 susceptibility protein and Breast Cancer type 2 susceptibility protein	20

b) Tumor protein p53	22
c) Checkpoint kinase 2 gene	23
d) Ataxiateleangiectasia mutated gene	23
e) Cadherin 1, E-cadherin gene	23
f) Phosphatase and tensin homologue gene	24
C-Breast Carcinoma Classification	25
1-Invasive Carcinomas	27
a) Invasive duct carcinoma	27
b) Invasive lobular carcinoma	29
c) Tubular carcinoma	31
d) Invasive cribriform carcinoma	32
e) Medullary carcinoma	33
f) Mucin producing carcinomas	34
i-Mucinous carcinoma	34
ii-Other mucin producing carcinomas	36
g) Neuroendocrine carcinomas	36
h) Invasive papillary carcinoma	38
i) Invasive micropapillary carcinoma	39
j) Apocrine carcinoma	40
k) Metaplastic carcinoma	40
l) Lipid Rich Carcinoma	42
m) Secretory carcinoma (Juvenile Carcinoma)	43
n) Oncocytic carcinoma	44
o) Adenoid cystic carcinoma	45
p) Acinic cell carcinoma	46
q) Glycogen-rich carcinoma clear cell carcinoma	46
r) Sebaceous carcinoma	47
s) Inflammatory carcinoma	48
2-Noninvasive carcinomas	49
a) Ductal carcinoma in situ	49
i-Architectural classification of DCIS	50
• Comedocarcinoma	50

• Cribriform type	50
• Solid type	51
• Micropapillary type	51
• Flat ductal intraepithelial neoplasia (Clinging type)	51
• Apocrine intraductal carcinoma	52
• Cystic hypersercretory DCIS	52
• Signet ring cell DCIS	52
• Endocrine (Argyrophilic) ductal carcinoma in situ	53
• Papillary ductal carcinoma in situ	53
ii- Grading of DCIS	53
• High nuclear grade DCIS	55
• Low nuclear grade DCIS	55
• Intermediate nuclear grade DCIS	56
b) Lobular carcinoma in situ	57
D- Diagnosis of Breast Carcinoma	59
1- Clinical Assessment	59
2- Radiological Assessment	59
a. Mammography	59
b. Ultrasonography	60
c. Magnetic resonance imaging	60
3- Pathological Assessment	61
a) Fine needle aspiration biopsy	61
b) Core needle biopsy	61
c) Excisional biopsy	62
d) Frozen section	62
E- Prognostic factors of breast carcinoma	64
1-Clinical features	64
a) Age	64
b) Lymph node status	65
c) Tumor size	66

2- Pathological features	66
a) Histological type	66
b) Histological grade	66
c) TNM classification for breast carcinoma	68
d) Tumor cell proliferation	71
e) Lymphatic and blood vessel invasion	71
f) Perineural invasion	72
g) Tumor necrosis	72
h) Extent of the carcinoma in situ	72
i) Tumor stroma	73
j) Inflammatory cell infiltrates	73
3- Molecular Markers and Gene Expression	74
a) Steroid Hormone Receptors (Estrogen receptor and Progesterone receptor)	74
b) The C-erbB-2 / HER2/neu oncogene	75
c) P53 mutations	76
d) DNA ploidy	76
F- Treatment of Breast Carcinoma	77
1- Surgery	77
2- Radiation Therapy	78
3- Systemic Therapy	79
a) Targeted Therapy	80
b) Hormone Therapy	81
i) Ovarian Ablation or Suppression	82
ii) Tamoxifen	82
iii) Aromatase inhibitors	83
4- Chemotherapy	85
5- Antiangiogenic Therapy	85
III- STEROID RECEPTORS (ER, PR and AR)	87
A- Estrogen and Progesterone Receptors (ER and PR)	87
B- Androgen Receptor	88
1- Androgen Receptor Structure	90

2- Molecular Basis of Androgen Action	91
3- Androgen receptor expression in breast carcinoma	92
MATERIAS AND METHODS	94
RESULTS	102
DISSCUSSION	141
SUMMARY	153
CONCLUSIONS	158
RECOMMENDATIONS	159
REFERENCES	160
ARABIC SUMMARY	—

List of Abbreviations

AC	Apocrine carcinoma
ACC	Adenoid cystic carcinoma
ACCA	Acinic cell carcinoma
AI	Armoatase inhibitors
AKT	Serine/Threonine-specific protein kinase
ALH	Atypical lobular hyperplasia
AMC	Atypical medullary carcinoma
ARE	Androgen response element
AT	Ataxia teleangiectasia
ATM	Ataxia teleangiectasia mutated gene
BRCA1	Breast Cancer type 1 susceptibility protein
BRCA2	Breast Cancer type 2 susceptibility protein
BRIP1	BRCA1- interacting protein 1
CBE	Clinical breast examination
CBS	Conservative breast surgery
CDH1	Cadherin 1, E-cadherin gene
C-erb-B2	Human epidermal growth factor receptor 2
CHEK2	Checkpoint kinase 2 gene
Chr	Chromosome
CLCIS	Classic lobular carcinoma in situ
CNB	Core needle biopsy
DAB	Diaminobenzidine tetrahydrochloride
DBD	DNA- binding domain
DCIS	Ductal carcinoma in situ
DHEAS	Dehydroepiandrosterone sulfate
DIN	Ductal intraepithelial neoplasia
DNA	Deoxyribonucleic acid
DPX	Distyrene, a plasticizer, and xylene
EEC	European Economic community
ER	Estrogen receptor
ERα	Estrogen receptor- alpha

ERβ	Estrogen receptor- beta
FDA	Food and drug administration
FNA	Fine needle aspiration
GnRHa	Gonadotropin releasing hormone agonist
GR	Glucocorticoid receptor
GRCC	Glycogen rich carcinoma
HER2/neu	Human epidermal growth factor receptor 2
HPF	High power field
HR	Hormonal receptor
HRT	Hormonal replacement therapy
Hx&E	Hematoxyline and Eosin
IBC	Invasive breast cancers
ICC	Invasive cribriform carcinoma
IDC	Invasive ductal carcinoma
IHC	immunohistochemistry
ILC	Invasive lobular carcinoma
IMC	Invasive micropapillary carcinoma
IPC	Invasive papillary carcinoma
LAN	light at night
LBD	Ligand- binding domain
LCIS	Lobular carcinoma in situ
LHRHa	luteinizing hormone releasing hormone agonist
LN s	Lymph nodes
LPR	Lymphoplasmacytic reaction
LRC	Lipid rich carcinoma
LVI	Lymphovascular invasion
MC	Medullary carcinoma
MIC	Microinvasion
MPC	Metaplastic carcinoma
MR	Mineralocorticoid receptor
MRI	Magnetic resonance imaging
MRM	Modified radical mastectomy
MTC	Mixed tubular carcinoma

NBS1	Nibrin
NEC	Neuroendocrinal carcinoma
NHSBSP	National Health Service Breast Screening Program
NOS	Non otherwise specified
NPI	Nottingham Prognostic Index
NST	No special type
NTD	N- terminal regulatory domain
OC	Oncocytic carcinoma
OCP	oral contraceptives
OS	overall survival
P	Short arm of chromosome
PAS	Periodic acid schiff
PALB2	Partner and localizer of BRCA2
PBS	Phosphate buffered saline
PR	Progesterone receptor
PTC	Pure tubular Carcinoma
PTEN	Phosphatase and tensin homologue gene
q	Long arm of chromosome
RAD50	DNA repair protein
RFP	Relapse-free period
RT	Radiation therapy
SBR	Scarff-Bloom-Richardson
SC	Sebaceous carcinoma
SCC	Small cell carcinoma
SERM	Selective Estrogen receptor modulator
SLN	Sentinel lymph node biopsy
SPF	S-phase fraction
SPSS	Statistical program for social science
STK11/ LKB1	Serine/threonine kinase 11gene
TC	Tubular carcinoma
TDLU	Terminal ductal lobular unit
Tis	In situ tumor

TNM	Tumor node metastasis
TP53	Tumor protein p53
TSR	Tumor stromal ratio
USA	United States of America
WHO	World Health Organization

List of Figures

<i>Figure No.</i>	<i>Page</i>
Fig. (1): Percentage of different age groups	102
Fig. (2): Percentage of different surgical procedures	103
Fig. (3): Percentage of T1, T2 and T3	104
Fig. (4): Percentage of multi-centricity	105
Fig. (5): Percentage of IDC, ILC and MC	106
Fig. (6): Percentage of different tumor grades	107
Fig. (7): Percentage of lymph node metastasis	108
Fig. (8): Percentage of associated in situ component in the studied cases	109
Fig. (9): Percentage of associated LPR in the studied cases	110
Fig. (10): Percentage of associated desmoplastic reaction in the studied cases	111
Fig. (11): Percentage of HER2/neu overexpression	112
Fig. (12): percentage of AR expression	113
Fig. (13): Correlation between AR expression and different age groups	115
Fig. (14): Correlation between AR expression and tumor size	117

Fig. (15): Correlation between AR expression and tumor multi-centricity	119
Fig. (16): Correlation between AR expression and tumor type	121
Fig. (17): Correlation between AR expression and the tumor grade	123
Fig. (18): Correlation between AR expression and the lymph node status	125
Fig. (19): Correlation between AR expression and the associated in situ component	127
Fig. (20): Correlation between AR expression and LPR	129
Fig. (21): Correlation between AR expression and desmoplastic reaction	131
Fig. (22): Correlation between AR expression HER2/neu overexpression	133
Fig. (23): Invasive duct carcinoma grade II .Hx&E (X200)	134
Fig. (24): Invasive duct carcinoma grade III, Hx&E (X400)	134
Fig. (25): Invasive lobular carcinoma - Indian filing. Hx&E (X200)	135
Fig. (26): Medullary carcinoma. Hx&E (X100)	135

Fig. (27): Metastatic deposits in a lymph node in a case of invasive duct carcinoma grade III. Hx&E (X200)	136
Fig. (28): In situ comedo component.. Hx&E (X200)	136
Fig. (29): In situ cribriform component.. Hx&E (X200)	137
Fig. (30): In situ lobular carcinoma.. Hx&E (X200)	137
Fig. (31): Lymphoplasmacytic reaction in a case of invasive duct carcinoma grade II. Hx&E (X200)	138
Fig. (32): Negative nuclear immuno-expression for AR- No expression (X400)	138
Fig. (33): Negative nuclear immuno-expression for AR- Low expression (X200)	139
Fig. (34): Positive nuclear immuno-expression for AR- Intermediate expression (X200)	139
Fig. (35): Positive nuclear immuno-expression for AR- High expression (X200)	140

List of Tables

<i>Table No.</i>	<i>Page</i>
Table 1: Incidence of Breast Carcinoma by Age	13
Table 2: WHO Histological Classification of Malignant Breast Tumors	25
Table 3: Criteria for the differential diagnosis of mucin producing carcinomas	36
Table 4: Classification of Metaplastic carcinomas	42
Table 5: Proposed classification for ductal carcinoma in situ	54
Table 6: Minimal criteria for low grade DCIS	56
Table 7: Summary of Intraductal Carcinoma grading	57
Table 8: Scarff-Bloom-Richardson (SBR) grading system	67
Table 9: TNM Classification for Breast cancer	69
Table 10: Percentage of different age groups	102
Table 11: Percentage of different surgical procedures	103
Table 12: Percentage of T1, T2 and T3	104
Table 13: Percentage of multi-centricity	105
Table 14: Percentage of the different histologic types	106
Table 15: Percentage of different Tumor grades of IDC cases	107