

واى كى آل – 40 كدلالة لمرض سرطان الثدي فى مرحلة الأولى والمتطورة

رسالة

توطئة للحصول على درجة الماجستير
فى الباثولوجيا الإكلينيكية والكيميائية

مقدمة من

الطبيبة / علياء إبراهيم على حسن سيف
بكالوريوس الطب والجراحة العامة
كلية الطب – جامعة عين شمس

تحت إشراف

الأستاذ الدكتور / هان زاده إبراهيم عبد
الفتاح

أستاذ الباثولوجيا الإكلينيكية والكيميائية
كلية الطب – جامعة عين شمس

الدكتورة / نيرمين حلمى محمود

أستاذ مساعد الباثولوجيا الإكلينيكية والكيميائية
كلية الطب – جامعة عين شمس

الدكتور / رانيا صالح الدين كامل

شاهين

مدرس الباثولوجيا الإكلينيكية والكيميائية
كلية الطب – جامعة عين شمس

كلية الطب
جامعة عين شمس

2010

**SERUM YKL40 AS A TUMOR MARKER IN
PRIMARY AND METASTATIC BREAST CANCER**

Thesis

*Submitted for Partial Fulfillment of Master Degree
in Clinical and Chemical Pathology*

By

Aliaa Ibrahim Aly Hassan Seif

M.B., B.Ch., Ain Shams University

Supervised By

Professor / Hanzada Ibrahim Abdel Fattah

*Professor of Clinical and Chemical Pathology
Faculty of Medicine
Ain Shams University*

Doctor / Nermine Helmy Mahmoud

*Assistant Professor of Clinical and Chemical Pathology
Faculty of Medicine
Ain Shams University*

Doctor / Rania Salah El Din Kamle Shahin

*Lecturer of Clinical and Chemical Pathology
Faculty of Medicine
Ain Shams University*

Faculty of Medicine
Ain Shams University

2010

Acknowledgement

*Thanks first and last to **ALLAH** as we owe him for his great care, support and guidance in every step in our life.*

Words do fail me when I come to express my sincere indebtedness and profound gratitude to my Prof. Dr. Hanzada Ibrahim Abdel Fattah, Professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University, who guided this work and helped whenever I was in need. Her great patience, close supervision, and constant encouragement throughout this work are beyond my words of thanks.

Special thanks are due to Dr. Nermien Helmy Mahmoud, Assistant Professor of Clinical and Chemical Pathology, Faculty of Medicine, Ain Shams University, for dedicating so much of her precious time and effort to complete this work.

I would like to express my deep obligation to Dr. Rania Salah Eldin Kamle Shahin, Lecturer of Clinical and Chemical Pathology, faculty of Medicine, Ain Shams University, for her valuable and generous help, faithful supervision and great cooperation. I would like to take this opportunity to thank her for her continuous encouragement and support throughout the whole work.

List of Contents

Title	Page No.
Introduction.....	1
Aim of the Work.....	3
Review of Literature	
• CHAPTER I: BREAST CANCER.....	4
A- Incidence	4
B- Risk Factors	5
C- Histopathology	12
D- Spread	15
E- Staging	15
F- Diagnosis	19
G- Prognostic Factors.....	21
• CHAPTER II: SERUM TUMOR MARKERS OF BREAST CANCER	23
A- Definition	23
B- Ideal Cancer Biomarker.....	23
C- Specific Tumor Markers for Breast Cancer	24
1. Carcinoembryonic antigen (CEA)	25
2. Mucin Markers (MUC-1).....	26
a) Cancer antigen 15.3 (CA15.3).....	27
b) Cancer antigen 27.29 (CA27.29).....	28

List of Contents (Cont...)

Title	Page No.
c) Cancer antigen 549 (CA549)	29
d) Mucin like Carcinoma Associated antigen (MCA)	29
e) Krebs Van Den Lungner-6 (KL-6)	30
3. Plasminogen Activator System (PAs)	30
4. Matrix Metalloproteinases (MMPs)	30
5. Cytokeratins	31
6. YKL-40.....	33
D- Molecular Diagnosis of Breast Cancer	31
1. Oncogenes	34
a) Human epidermal growth factor receptor (HER-2).....	34
b) Human cervical cancer oncogenes (HCCR)	35
2. Tumor suppressor genes	36
a) Protein 53 kd gene (P53 gene)	36
b) Breast cancer gene 1 and 2 BRCA 1 and BRCA2.....	37
3. Mammoglobin	38
• CHAPTER III: YKL-40	39
A- Chemical Structure of YKL-40.....	39
B- Tissue Distribution of YKL-40	43
C- YKL-40 in Different Diseases	45

List of Contents (Cont...)

Title	Page No.
D- YKL-40 in Malignant Diseases.....	47
1. In ovarian cancer	49
2. In prostatic carcinoma	49
3. In malignant glioma	50
4. In lung cancer	51
5. In colorectal cancer	51
6. In melanoma	52
7. In acute myeloid leukemia	53
E- YKL-40 in Breast Cancer	54
F- Determination of YKL-40 in Tissue and Body Fluids	57
Subjects and Methods	69
Results	84
Discussion	101
Summary.....	110
Recommendations.....	114
References.....	115
Arabic Summary	—

List of Tables

Tab. No.	Title	Page No.
Table (1):	The international classification (TNM) of breast cancer.....	17
Table (2):	Stage grouping and survival rate	18
Table (3):	Descriptive statistics of the different studied parameters in patients with early stage breast cancer with no metastasis (TNM: Stage I and II) (GP IA) and breast cancer patients with distant metastasis (GP IB) and control group (GP II).	87
Table (4):	Statistical comparison between all breast cancer patients (GP I) and control group (GP II) regarding the different studied variables using Wilcoxon's rank sum test for non parametric data or student's t test for parametric data.	88
Table (5):	Statistical comparison between early stage breast cancer with no metastasis (TNM: stager I and II)(GP IA) and control group (GP II) regarding the different studied variables using Wilcoxon's rank sum test for non parametric data or student's t test for parametric data.....	89
Table (6):	Statistical comparison between breast cancer patients with distant metastasis (GP IB) and control group (GP II) regarding the different studies variables using Wilcoxon's Rank sum test for non parametric data or student's t test for parametric data.	90
Table (7):	Statistical comparison between early stage breast cancer patients with no metastasis (TNM: stage I and II) (GP IA) and breast cancer patients with distant metastasis (GP IB) regarding the different studied variables using Wilcoxon's Rank sum test for non parametric data or student's t test for parametric data.	91

List of Tables (Cont...)

Tab. No.	Title	Page No.
Table (8):	Correlation study between each of CA15.3 (ng/mL) and YKL-40 levels (ng/mL) versus all the studied parameters in the whole patients group using spearman's rank correlation coefficient test.	92
Table (9):	Correlation study between CA15.3 (ng/ml) and YKL-40(ng/mL) in the whole patients group using spearman's rank correlation coefficient (r_s) test.	93
Table (10):	Statistical comparison between ER (+ve and –ve patients) regarding CA 15.3 (ng/mL) and YKL-40 (ng/mL) in all patient group using Wilcoxon rank sum test	95
Table (11):	Statistical comparison between PR (+ve and –ve patients) regarding CA 15.3(ng/mL) and YKL-40 (ng/mL) in all patient group using Wilcoxon rank sum test	95
Table (12):	Diagnostic performance of YKL-40 (ng/mL) in breast cancer patients collectively versus healthy control group.	96
Table (13):	Diagnostic performance of YKL-40 (ng/mL) breast cancer patients (GPIA versus GPIB).	96
Table (14):	Descriptive statistics of the median values of YKL-40 levels (ng/mL) and different metastatic sites in breast cancer patients with distant metastasis (GPIB) (n=15)	97

List of Figures

Fig. No.	Title	Page No.
Figure (1):	Ribbon diagrams of YKL-40.....	40
Figure (2):	Comparison between metastatic breast cancer patients, primary breast cancer patients and control group as regards median values of serum YKL-40 (ng/mL)	93
Figure (3):	Comparison between metastatic breast cancer patients, primary breast cancer patients and control groups as regards median values of serum CA 15.3. (ng/mL).....	94
Figure (4):	ROC curve analysis showing the diagnostic performance of YKL40 for discriminating Breast cancer patients versus healthy control	98
Figure (5):	ROC curve analysis showing the diagnostic performance of YKL40 for discriminating GPIA patient group versus GPIB patient group.....	99.
Figure (6):	ROC curve analysis showing the diagnostic performance of CA 15.3 for discriminating GPIA patient group versus GPIB patient group.....	100

LIST OF ABBREVIATIONS

Abbrev.	Meaning
BRCA1,2	Breast cancer genes
CA (27-29)	Cancer antigen (27-29)
CA (549)	Cancer antigen 549
CA15.3	Cancer antigen 15.3
CEA	Carcinoembryonic antigen
COC	Combined oral contraception
CSF	Cerebrospinal fluid
CYFRA 21-1	Cytokeratin fragments
DSB	Double strand break
ECD/HER-2	Human epidermal growth factor receptor-2 extracellular domain
ECM	Extracellular matrix
ELISA	Enzyme linked immunosorbent assay
ER	Estrogen receptor
FFTP	First full term pregnancy
FN	False negative
FNA	Fine needle aspiration
FP	False positive
HCCR	Human cervical cancer oncogenes
HER-2	Human epidermal growth factor receptor-2
H-MAM	Human mamoglobin
HRT	Hormonal replacement therapy
ISH	In situ hybridization

LIST OF ABBREVIATIONS (Cont...)

Abbrev.	Meaning
KL-6	Krebs van den Lunger-6
mAbs	Molecular antibodies
mAbs	Monoclonal antibodies
MCA	Mucin-like carcinoma associated anigen
MMPs	Matrix metalloprotinases
MRI	Magnetic resonance imaging
P53 gene	Protein 53 kd gene
PCR	Polymerase chain reaction
PR	Progesterone receptor
RIA	Radioimmunoassay
ROC	Receiver operating characteristic
rs	Spearman's rank correlation coefficient
SD	Standardized deviation
SSO's	Sequence specific oligonucleotides
TN	True negative
TP	True positive
TPA	Tissue polypeptide antigen
TPA	Tissue polypeptide antigen
TPs	Tissue polypeptide specific antigen
TPS	Tissue polypeptide specific
UPA	Urokinase plasminogen activatorq

LIST OF ABBREVIATIONS

CEA		Carcinoembryonic antigen
UPA		Urokinase plasminogen activator