INCIDENCE OF CYFRA 21-1 AND HEPATITIS B, C VIRUS INFECTION AMONG PATIENTS WITH CERTAIN MALIGNANT TUMORS

A THESIS

Submitted for the Partial Fulfilment of

The Master Degree (M.Sc.)

in

(Biochemistry)

By

HALA FAWZY MOHAMED

M.B.,B.Ch.

612.05 H.F

Supervisors

Prof. Dr. Nawal Abdo Ziada

Professor of Biochemistry, Faculty of Medicine. Ain Shams University.

Prof. Dr. Ali Khalifa Ali

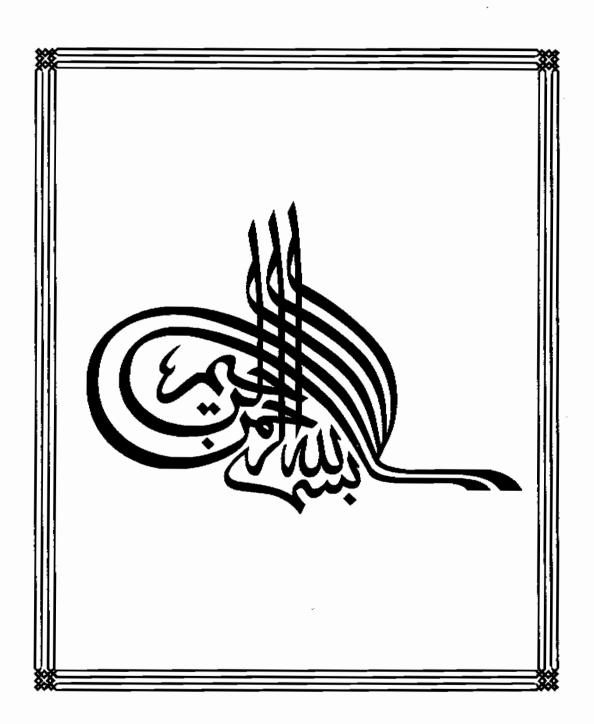
Professor of Biochemistry, & Head Of Oncology Diagnostic Unit Faculty of Medicine, Ain Shams University.

Prof. Dr. Mostafa Mohamed El Rasad

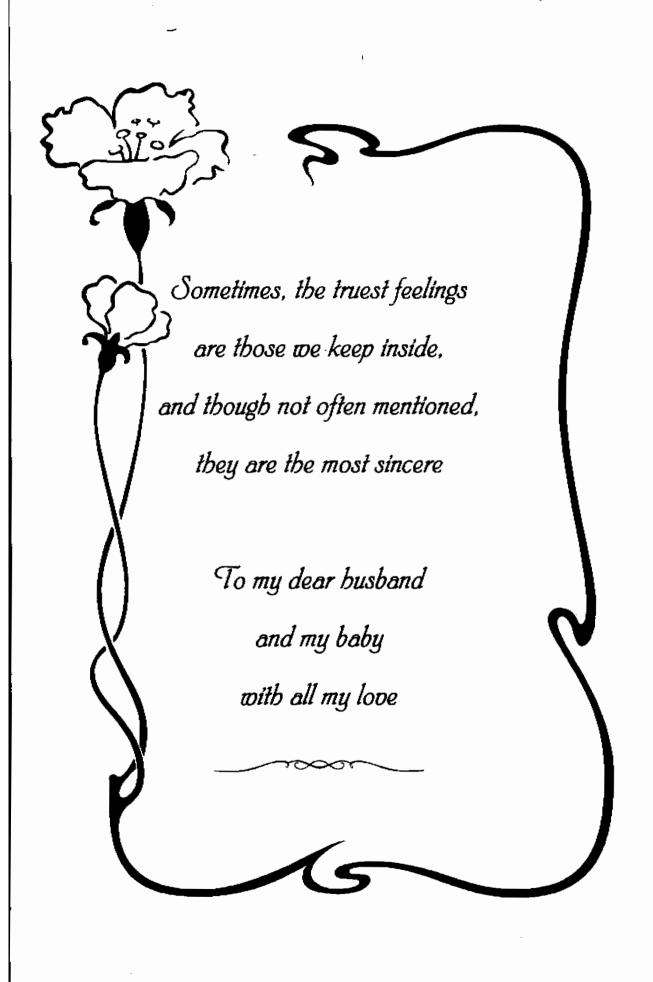
Professor of Biochemistry, Faculty of Medicine, Ain Shams University.

Faculty of Medicine Ain Shams University 1995









ACKNOWLEDGEMENT

I would like to express my deepest thanks and gratitude to **Prof. Dr. NAWAL ABDO ZIADA**, Professor of Biochemistry, Faculty of Medicine. Ain Shams University, for her great help, valuable criticism and continuous encouragement throughout the whole research. I am very much privileged and honoured to have her as my supervisor. To her I am specially indebted.

I am very much obliged to the kindness and great help of **Prof. Dr. ALI KHALIFA ALI,** Professor of Biochemistry, Faculty of Medicine, Ain Shams University. I thank him deeply for the help he provided me during the production of this thesis.

My deepest thanks and gratitude to **Prof. Dr. MOSTAFA MOHAMED EL RASAD**, Professor of Biochemistry, Faculty of
Medicine, Ain Shams University, for his supervision, helpful
criticism and continues encouragement throughout the whole
work.

I would like also to thank **Dr. HANAA EL. TAYEB NASSER,** Assistant Professor of Biochemistry, Faculty of

Medicine, Ain Shams University, for the great help and

assistance she offered me in my research.

I am also grateful to **Dr. MAHA IMAM**, Lecturer of Biochemistry, Faculty of Medicine, Ain Shams University, for her sincere help and advice.

I would like also to express my thanks to **Dr. TAREK EL SHARKAWAY**, Lecturer of Pathology, Faculty of Medicine, Ain

Shams University, for his great help and assistance in this work.



CONTENTS

| | Page | |
|--|------|--|
| INTRODUCTION AND AIM OF WORK | 1 | |
| REVIEW OF LITERATURE | | |
| TUMOR MARKERS | | |
| Classification Of Tumor Markers | 8 | |
| Clinical Applications Of Tumor Markers | 17 | |
| CYTOKERATINS | 22 | |
| CYFRA 21-1 | 30 | |
| HEPATITIS C VIRUS | 34 | |
| HEPATITIS B VIRUS | | |
| LUNG CANCER | 59 | |
| BREAST CANCER | 62 | |
| OVARIAN CANCER | 66 | |
| GASTROINTESTINAL NEOPLASMS | | |
| HEPATOCELLULAR CARCINOMA | 78 | |
| MATERIALS AND METHODS | 81 | |
| RESULTS | 102 | |
| DISCUSSION | 121 | |
| SUMMARY AND CONCLUSION | 130 | |
| REFERENCES | | |
| ARABIC SUMMARY. | | |

LIST OF ABBREVIATIONS

AAG : Alpha-1-acid glycoprotein.

AAT : Alpha-1-antitrypsin.
AFP : Alpha-fetoprotein.
ALP : Alkaline phosphatase.

ASMA : Anti-smooth muscle antibodies.

ANA : Anti-nuclear antibodies.

APRP : Acute phase reactant proteins.

Au : Australia antigen.

CAH : Chronic active hepatitis.
cDNA : Complementary DNA.
CEA : Carcinoembryonic antigen.
CPH : Chronic persistent hepatitis.

EIA : Enzyme immunoassay.

ELISA : Enzyme-linked immunosorbent assay.

FIGO : International Federation of Gynecology and Obstetrics.

FsA : Fetal sulfoglycoprotein.

GGT : Gamma glutamyi transpeptidase.

G.I.T.: Gastrointestinal tract.

HBcAg: Hepatitis B core antigen.

HbeAg: Hepatitis B e antigen.

HBsAb : Hepatitis B surface antibody. HBsAg : Hepatitis B surface antigen.

HBV : Hepatitis B virus.

HCC : Hepatocellular carcinoma.

HCV : Hepatitis C virus.

HRP : Horseradish peroxidase.

Ig : Immune globulin.

IDC : Invasive ductal carcinoma.
ILC : Invasive lobular carcinoma.

Kd : Kilo dalton.

LDH : Lactate dehydrogenase. MCF : Myeloma cell family.

MTGP : Mammary tumor associated glycoprotein.

M.W. : Molecular weight.

NANB : Non-A, non-B hepatitis.

NSE : Neurone specific enolase.

NSCL : Non small cell lung cancer.

OPD : O-phenylenediamine 2 HCl.

ORF : Open reading frame.

PCR : Polymerase chain reaction.

PBMC : Peripheral blood mononuclear cells.

POA : Pancreatic oncofetal antigen.

Pre-C : Precore.

PSA : Prostatic specific antigen.

RIBA : Recombinant immunoblot assay.

SCC-Ag : Squamous cell carcinoma antigen.

TdT : Terminal deoxy nucleotidyl transferase.

TPA: Tissue polypeptide antigen.
WHO: World Health Organization.

LIST OF FIGURES

| | | Page |
|-----------|---|------|
| Fig. (1): | Mean CYFRA 21-1 level and S.E. in different groups; malignant, benign and normal control. | 106 |
| Fig. (2): | Mean CYFRA 21-1 level and S.E. in malignant and benign groups in different organs. | 107 |
| Fig. (3): | Sensitivity and specificity of CYFRA 21-1 in different organs (cut-off 3.3 ng/ml). | 109 |
| Fig. (4): | Mean CYFRA 21-1 and S.E. in different stages of cancer lung. | 111 |
| Fig. (5): | Sensitivity of CYFRA 21-1 in different pathology of cancer lung (cut-off 3.3 ng/ml). | 113 |
| Fig. (6): | Percentage of reactive cases to HCV Ab, HBsAg and HBsAb in different group. | 116 |
| Fig. (7): | Percentage of reactive cases for HCV Ab in different groups. | 118 |
| Fig. (8): | Percentage of reactive cases for HBsAg in different groups. | 119 |
| Fig. (9): | Percentage of reactive cases for HBsAg in different group. | 120 |

| Table (10): | Percentage of reactive cases to HCV antibody in different groups; normal, benign and malignant. | 115 |
|-------------|---|-----|
| Table (11): | Percentage of reactive cases to HBsAg in different groups; normal, benign and malignant. | 115 |
| Table (12): | Percentage of reactive cases to HBs antibody in different groups; normal, benign and malignant. | 115 |
| Table (13): | Percentage of reactive cases for HCV antibody, HBs antigen and antibody in malignant and benign groups in different organs. | 117 |

Introduction And Aim Of Mork

INTRODUCTION AND AIM OF WORK

CYFRA 21-1 is a new tumor marker and it is the first time for this marker to be tested in Egypt using immunoradiometric assay that measures cytokeratin 19 using two mouse MOABKS and BM 19-21, thus it is expressed as CYFRA 21-1.

Cytokeratin 19 is an acidic polypeptide (type 1) subunit expressed in all simple epitheli and in carcinoma with M.W. of 40 Kd. It is one of cytokeratins which are intermediate filaments and part of cytoskeleton of the cell, in contrast to other intermediate filaments cytokeratins, has cell type specificity. CYFRA 21-1 is considered as a useful prognostic factor in lung cancer especially sensitive for squamous cell carcinoma and lowest in small cell carcinoma (*Pujol et al.*, 1993).

In comparison with other tumor markers in lung cancer as CEA (carcinoembryonic antigen) and squamous cell carcinoma antigen (SCC-Ag) and neurone specific enclase (NSE), CYFRA 21-1 was the most accurate marker using a 3.6 ng/ml threshold (*Pujol et al.*, 1993).

During the 2nd International Cancer Molecular Biology Symposium, there were two articles about CYFRA 21-1.

Klapdor et al., (1993) studied sensitivity and specificity of CA 125, CA 15-3, CA 72-4, CEA and other markers as TPS, TPA, CYFRA 21-1 in

patients with breast cancer, ovarian cancer, liver cancer, pancreatic cancers compared with benign G.I.T., breast and liver diseases.

Rastel et al., (1993) measured CYFRA 21-1 in serum of cancer lung patients and confirm that it is sensitive tumor marker for non-small cell cancer especially squamous cell carcinoma.

Among viruses which are implicated in development of human cancer are virus B, C as risk factor for development of hepatocellular carcinoma. Both hepatitis B, C virus infection may function independently in the pathogenesis of hepatocellular carcinoma (Resnick et al., 1993). Few studies were done about association of hepatitis B, C virus infection with other malignant tumors as in breast cancer patients that carriage of hepatitis B virus surface antigen is one of the unfavorable prognostic factors (Mamedov et al., 1992) and associated with lower complete and partial remission rates, lower three years survival rate and higher rate of combination chemotherapy toxic effect in treatment results in breast cancer patients with bone metastasis (Tenialov et al., 1992).

The aim of the present work is to search for CYFRA 21-1 positivity and incidence of hepatitis B and C virus infection in patients with certain malignant tumors.

Review Of Literature