Familial Breast Cancer

An Essay

Submitted for partial fulfillment of master degree of general surgery

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2011

سرطان الثدى العائلى

رسالة مقدمة توطئة للحصول على درجة الماجستير
فى الجراحة العامة
مقدمه من الطبيب

عبد الرحمن نصحى عبد المجيد
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بسم الله الرحمْن الرحيم

صدق الله العظيم

البقرة٢٨٢

Acknowledgement

*My first and last thanks to **GOD**, as we owe Him His great care, support and guidance in every step of our lives.*

I would like to express my sincere gratitude to

***Prof. Dr. Reda Abdel Tawab Khalil,** Professor of General Surgery, Ain Shams University, who devoted much of his precious time, kind guidance and meticulous supervision.*

*I would like to thank **Ass. Prof. Mohamed Elsayed Elshinawi** Assistant Professor of General Surgery, for his sincere advice, generous help, kind assistance and guidance throughout this work.*

*Special thanks to **Dr. Tarek Youssef Ahmed** who have assisted me and supported me.*

Last but not least, I would like to thank my parents, brothers and friends for their constant support and encouragement.

Abdelrahman Nosehi 2011

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List of abbreviations

ACS	American Cancer Society.
ACR	American college of Radiology.
ADH	Atypical ductal hyperplasia.
AIS	Aromatase Inhibitors.
A-J	Ashkenazi – Jewish.
ALH	Atypical Lobular Hyperplasia.
ASCO	American Society of Clinical Oncology.
ATM	Ataxia Telangiectasia mutated gene.
BASC	BRCA1 Associated genome surveillance Complex**.**
BCLC	Breast Cancer linkage consortium.
BIC	The Breast Cancer Information core.
BI-RADS	Breast imaging Reporting Data System.
BRCA1	Breast cancer gene 1.
BRCA2	Breast Cancer gene 2.
BSE	Breast Self Examination.

BSO	Bilateral Salpingo – Oopherectony
CARE	Contraceptive And Reproductive Experiences.
CBE	Clinical Breast Examination.
CBC	Contra- lateral Breast cancer
CCND1	Cyclin D1.
CDH1	Cadherin 1 gene.
CHEK2	Check point kinase2 gene.
CI	Confidence Interval.
CK	Cytokeratin.
CNB	Core Needle Biopsy.
CPM	Contra lateral Prophylactic Mastectomy.
CR	Czech Republic.
DCIS	Ductal Carcinoma In Situ.
DSB	Double Stranded Breaks.
EGFR	Epidermal Growth Factor Receptor.

EM	Extensive Metabolizers.
ERα	Estrogen Receptor alpha.
ERβ	Estrogen Receptor beta.
FA	Fanconi Anaemia.
FGFR2	Fibroblast growth factor receptor 2.
FNA	Fine Needle Aspiration.
HBOC	History of Breast / Ovarian Cancer.
HER-2	Human Epidermal Growth Receptor 2.
HIF-1	Hypoxia – Induced Factor 1.
HOC	History of Ovarian Cancer.
HR	Homologous Recombination.
HRM	High Resolution Melting analysis.
IBS	Inflammatory Breast Cancer.
ID4	Inhibitor of DNA binding 4.

LCIS	Lobular Carcinoma In Situ.
LHRH	Luteinising Hormone Relapsing Hormone.
LOH	Loss Of Heterozygosity.
MLPA	Multiplex – Ligation dependent Probe Amplification.
MMR	Post replication Mismatch Repair.
MMCI	Masaryk Memorial Cancer Institute.
MRI	Magnetic Resonance Imaging.
NBS1	Nijmegen Breakage Syndrome.
NCI	National Cancer Institute.
NCCN	National Comprehensive Cancer Network.
NHS	National Health Service.
NICE	National Institute of health & clinical Excellence.
NO	No positive lymph nodes.
NSABP	National Surgical Adjuvant Breast and Bowel Project.
PARP	Poly ADP Ribose polymerase.

PM	Poor Metabolizers.
POETIC	Peri- operative Endocrine Treatment for Individualized Care.
SNB	Sentinel lymph Node Biopsy.
SS DNA	Single Stranded DNA
STK11	Serine/ theronine kinase 11 gene.
TNBC	Triple Negative Breast Cancer.
TN-BLBC	Triple –Negative Basal Like Breast Cancer.
TP53	Tumour Protein p53.

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INTRODUCTION

By studing familial breast cancer there may be a genetic contribution to breast cancer risk is indicated by the increased incidence of breast cancer among women with a family history of the disease and by the observation of families in which multiple members have breast cancer in a pattern compatible with autosomal dominant inheritance of cancer susceptibility. **(Hall JM et al , 1990).**

Linkage analysis studies of families have led to the identification of highly penetrant genes as the possible cause of inherited cancer risk in many cancer-prone families **(Hall JM et al , 1990).** However, mutations in these genes are rare, and account for no more than 5–10% of breast cancer cases. It is probably that other background genetic factors contribute to the etiology of breast malignancies **(Hopper JL ,2001).**

Autosomal dominant inherited predisposition to breast cancer is characterized by early age at onset, bilaterality, vertical transmission through both maternal and paternal lines, and familial association with tumors of other organs. Three principal syndromes are associated with autosomal dominant inheritance of breast cancer risk: (i) hereditary breast and ovarian cancer due to *BRCA1* or *BRCA2* germline mutations **(Lindor NM et al,1998);** (ii) Li-Fraumeni syndrome due to germline mutations in the *p53* gene, identified in over 50% of families, with a

penetrance of at least 50% by age 50 years **(Lindor NM et al,1998),(Garber JE et al,1991);** germline mutations in another gene, *hCHK2,* have been implicated in the etiology of classical and variant Li-Fraumeni families **(Bell DW et al,1999);** and (iii) Cowden syndrome due to *PTEN* germline mutations **(Lindor NM et al,1998).**

Other genetic syndromes, which may include breast cancer, are ataxia telangiectasia and Peutz-Jeghers syndrome. Ataxia telangiectasia is an autosomal recessive disorder; it is estimated that ~ 1% of the general population may be heterozygote carriers of the *ATM* gene **(Savitsky Ket al,1995).**

Over 200 mutations have been identified in the gene to date, the majority of which are truncating mutations **(Telatar M et al,1998).** A number of epidemiological studies have suggested a statistically increased risk of breast cancer among female heterozygote carriers, with an estimated relative risk ranging from 3.9 to 6.4 **(Olsen JH et al,2001).**

Peutz-Jeghers syndrome is an early onset autosomal dominant disorder **(Jenne DEet al,1998).** Germline mutations in *STK11* appear to be responsible for ~ 50% of Peutz-Jeghers syndrome cases **(Westerman AM et al,1999).** Patients with this syndrome have a very high risk of developing breast cancer **(Giardiello FM et al,2000).**

Identification of the *BRCA1* and *BRCA2* genes marked an important step in understanding the molecular basis of the hereditary susceptibility to cancer**(Miki Y et al,1994) (Wooster R et al,1995).**