Faculty of Medicine
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An Essay
Subjected for Partial Fulfillment of
The Master Degree in General Surgery(M.S.)

Subject:

Prevention and Management of Breast Cancer

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List of abbreviations

U.S.	United States
DCIS	Ductual carcinoma in situ
LCIS	Lobular carcinoma in situ
NCI	National cancer institute
U.K.	United Kingdom
BRCA	Breast cancer gene
ATM	Ataxia-telangiectasia mutated gene.
MLO	Mediolateral oblique
CC	Craniocaudal
BI-RADS	The breast imaging reporting and data base.
US	Ultrasound
AP	Anteroposterior
NPV	Negative predictive value
MRI	Magnetic resonance imaging.
CT	Computed Tomography
PET	Positron-emission tomography.
FNA	Fine needle aspiration
CEA	carcino embryonic antigen
SSCP	assingle-stranded conformational polymorphism
CSGE	conformation-sensitive gel electrophoresis
LES	Li-Fraumeni syndrome
WHO	World Health Orgnization
BSE	Breast self examination
CBE	CLINICALBreast examination
CAD	Computer- aided detection.

FDA	Food and drug administration
IBC	Inflammatory breast cancer
HRT	HORMONE replacement therapy
TDLU	Terminal duct lobular unit
NOS	NOT otherwise specified
NST	No special type
IDC	Invasive duct carcinoma
ILC	Invasive lobular carcinoma
MC	Medullary carcinoma
ITC	Isolated tumor cell
IHC	Immunohistochemical
BCT	Breast-conserving therapy
BCS	Breast-conserving surgery
MRM	Modified radical mastectomy
ALND	Axillary lymph node dissection
SLNB	Sentinel lymph node biopsy
RFA	Radiofrequency Ablation
ILA	Interstitial Laser Ablation
RT	Radiation therapy
EBCTCG	Early Breasts Cancer Trialists Collaborative Group
APBI)	Accelerated partial breast irradiation
CMF	Cyclophosphamide, methotrexate and 5-fluorouracil
FAC	(5-fluorouracil, adriamycin, and cyclophosphamide)
AC	Adriamycin and cyclophosphamide
ER	ESTROGEN receptor
TAM	Tamoxfen
PR	Progestrone receptor

DVT	Deep Venous Thrombosis
AI	Aromatase inhibitors:
LHRH	Luteinizing hormone-releasing hormone
SERM),	Selective estrogen receptor modulators
COX-2	Cyclooxygenase-2
BCPT	Breast cancer prevention trail
LDL	low-density lipoprotein
ATAC	Anastrozole versus Tamoxifen versus Combination
BMD	Bone mineral density
NSAIDS	Non-steroidal anti-inflammatory drugs
RAREs	Retinoic acid-responding elements
CRBPs	Cellular retinoid-binding proteins
SEER	Surveillance, Epidemiology, and End Results
HER-2	Human epithelial receptor-2.
IGF-1	Insulin growth factor-1.

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Introduction

Breast cancer is the commonest cause of cancer death in women worldwide. Rates vary about five-fold around the world, but they are increasing in the regions that recently had low rates of the disease. It accounts for one-third of cancer diagnoses and 15% of cancer deaths in U.S. women. and second leading cause of cancer death. ***Lacey JV Jr, Devesa SS, Brinton LA. 2002***.

Carcinoma of the breast is the most prevalent cancer among Egyptian women and constitutes 29% of National Cancer Institute cases. ***Omar S, Khaled H, Gaafar R, Zekry AR, Eissa S, el-Khatib O. 2003)***

Many of the established risk factors of breast cancer are linked to oestrogens. *Risk is increased by early menarche, late menopause, and obesity in postmenopausal women, while Childbearing reduces risk, with greater protection for early first birth and a larger number of births; breastfeeding probably has a protective effect.* Both oral contraceptives and hormonal therapy for menopause cause a small increase in breast-cancer risk, which appears to diminish once use stops. Alcohol increases risk, whereas physical activity is probably protective. Mutations in certain genes greatly increase breast-cancer risk, but these account for a minority of cases. ***Key TJ, Verkasalo PK, Banks E. 2001***

Women with a family member diagnosed with breast cancer before age 50 has increased risk of breast cancer compared to women with family members diagnosed at older ages.

Colditz GA, Kaphingst KA, Hankinson SE, Rosner B 2012.

Eight out of nine women who develop breast cancer do not have an affected mother, sister, or daughter. Although women who have first-degree relatives with a history of breast cancer are at increased risk of the disease, most

will never develop breast cancer, and most who do will be aged over 50 when their cancer is diagnosed **.**

Colditz GA, Kaphingst KA, Hankinson SE, Rosner B 2012

The hereditary breast and ovarian cancer syndrome (HBOC) includes genetic alterations of various susceptibility genes such asTP 53, ATM, BRCA1 and BRCA2. Germline mutations of the cancer-susceptibility genes BRCA1 and BRCA2 seem to be the major aetiology of the HBOC. Genetic counselling and identification of high-risk families may be essential:

(1) to provide the best method for genetic testing by explaining the sensitivity and specificity of the methods.

(2) to offer the opportunity to participate in specific early cancer detection programmes (breast (self) palpation, ultrasound, mammography and magnetic resonance tomography for breast cancer; vaginal exploration and ultrasound for ovarian cancer.

(3) to inform them about prophylactic medication (oral contraceptive pill (OCP), chemoprevention (tamoxifen, raloxifen, aromatase inhibitors)) or surgery (bilateral prophylactic mastectomy or oophorectomy) and (4) to provide individualized psychological support. ***Kuschel B, Lux MP, Goecke TO, Beckmann MW.2000***

The incidence of newly diagnosed breast cancer cases world-wide is expected to double by 2020. ***Mokbel K. 2003***

As for all diagnostic methods the most important requirement for diagnostic imaging is to detect breast cancer in its early stage, and to determine accurate tumor staging, in order to select the appropriate therapy. The spectrum of radiological imaging methods in breast cancer became broader in the past two decades; imaging that provides functional or metabolic data and whole body

information such as CT, MRI and PET-CT are now available besides common X-ray and ultrasound mammography.

The MRI is getting more and more important for the detection and characterization of breast cancer. **Godény M, Szabó E, Bidlek M, Fehér K, Nagy T, Kásler M.2012**

Early diagnosis and prevention have the most significant effect on overall disease specific outcome; 90% of all breast cancer cases could be cured if diagnosed early and treated accurately. ***Godény M, Szabó E, Bidlek M, Fehér K, Nagy T, Kásler M.012***

Risk-reducing strategies for breast cancer include lifestyle modifications, chemoprevention and surgery (bilateral mastectomy and/or oophorectomy). Lifestyle modifications include avoidance of postmenopausal obesity and hormone replacement therapy (HRT), regular physical activity, and restriction of alcohol and animal fat intake. Other promising chemopreventive agents currently under investigation include cyclo-oxygenase 2 (COX-2) inhibitors, fenretinide, aromatase inhibitors, and goserelin. Prophylactic mastectomy can reduce breast cancer risk by 90% in high-risk women. Bilateral oophorectomy has the potential of reducing the risk of breast cancer in women carrying BRCA-1 or BRCA-2 mutations. ***Mokbel K. 2003***

Aim of the work

This work aims at studying

- *Early diagnosis of breast cancer*
- *Screening programs of breast cancer*
- *Prevention and management of breast cancer*

Chpter 1

Embryology Of The Breast

Embryologic development of the mammary gland consists of a series of highly ordered events involving interactions among a number of distinct cell types. These interactions are regulated by an array of systemic and local factors such as growth factors and hormones. Development is initially identical among males and females of the same species. **(*Forsyth IA. 2011*)**

During the fourth week of gestation, paired ectodermal thickenings termed mammary ridges or milk lines develop on the ventral surface of the embryo and extend in a curvilinear fashion convex towards the midline from the axillae to the pubis. This is the first morphologic evidence of mammary gland development. In normal human development, these ridges disappear except at the level of the fourth intercostal space on the anterior thorax, where the mammary gland subsequently develops. In other species, such as cats and dogs, multiple paired mammary glands develop along the mammary ridges in the chest, abdominal, and groin regions. The number of paired glands varies greatly among mammalian species and is related to the number of offspring in each litter. **(*Forsyth IA. 2011*)**

During the fifth week of gestation, the remnant of the mammary ridge ectoderm begins to proliferate and is termed the primary mammary bud.

This primary bud subsequently begins growth downward as a solid diverticulum into the underlying dermis during the seventh week. By the 10th week, the primary bud begins to branch, yielding secondary buds by

the 12th week, which eventually develop into the mammary lobules of the adult breast**.(** ***Medina D. 2011)***

This initial downgrowth and subsequent branching has been shown to occur as the result of an inductive influence of the extracellular matrix of the mesoderm on the primary mammary bud. This epithelial-mesenchymal signaling is probably through paracrine and juxtacrine mechanisms where the underlying mesoderm produces growth factors and hormones that interact with receptors on the overlying ectodermal cells of the primary mammary bud. The adipose tissue in the underlying mesoderm represents a significant store of lipids for the production of hormones and growth factors, which are then available to promote and regulate growth of the developing mammary gland.(***Medina D. 2011***)

During the remainder of gestation, these buds continue lengthening and branching. During the 20th week, small lumina develop within the buds that coalesce and elongate to form the lactiferous ducts. The canalization of the mammary buds with formation of the lactiferous ducts is induced by placental hormones entering the fetal circulation. These hormones include progesterone, growth hormone, insulinlike growth factor, estrogen, prolactin, adrenal corticoids, and triiodothyronine.

At term, approximately 15-20 lobes of glandular tissue have formed, each containing a lactiferous duct. Support for the breast comes from both the skin envelope and the fibrous suspensory ligaments of Astley Cooper that anchor the breast to the pectoralis major fascia.**(*****Medina D. 2011*****)**

The lactiferous ducts drain into retroareolar ampullae that converge into a depressed pit in the overlying skin. Each of the 15-20 lobes of the mammary gland has an ampulla with an orifice opening into this mammary pit. Stimulated by the inward growth of the ectoderm, the