Prognostic and predictive value of molecular markers in early breast cancer

an essay submitted for partial fulfillment of master degree in radiation oncology and nuclear medicine

by:

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LIST OF CONTENTS

LIST OF ABBREVIATIONS

AC	Adriamycin/Cyclophosphamide
ADEPT	Antibody-dependent enzyme prodrug therapy
ADH	Atypical ductal hyperplasia
AI	Aromatase inhibitor
AIB1	Amplified in breast 1
AJCC	American Joint Committee on Cancer
ALTTO	Adjuvant Lapatinib and/or Trastuzumab Treatment Optimization
ATAC	Arimidex, Tamoxifen, Alone or in Combination
BIG	Breast International Group
BRCA	Breast cancer susceptibility protein
CAF	Cyclophosphamide/doxorubicin/fluorouracil
CAF–T	CAF–tamoxifen
CDK	Cyclin-dependent kinase
cDNA	Complementary DNA
CEF	cyclophosphamide/epirubicin/fluorouracil
CHERLOB	Preoperative Chemotherapy plus Lapatinib or Trastuzumab or Both in HER2-positive Operable Breast Cancer
CI	Confidence Interval

CISH	Chromogenic in situ hybridization
CMF	cyclophosphamide/methotrexate/fluorouracil
DC	Docetaxel/Cyclophosphamide
DCIS	Ductal carcinoma in situ
DDFS	Distant disease-free survival
DFS	Disease-free survival
DH	Docetaxel/Herceptin
DHCarbo	Docetaxel/Herceptin/Carboplatin
EBPs	Estrogen-binding proteins
ECOG	Eastern Cooperative Oncology Group
EGFR	Epidermal growth factor receptor
EORTC	European Organization for Research and Treatment of Cancer
ER	Estrogen receptor
ERE	Estrogen response element
ERK	Extracellular signal regulated kinases
ERα	Estrogen receptor alpha
ERβ	Estrogen receptor beta
FAC	Fluorouracil/doxorubicin/cyclophosphamide
FDA	Food and Drug Administration
FGF	Fibroblast growth factor
FISH	Fluorescent in situ hybridization
H&E	Hematoxylin and eosin
HER2	Human Epidermal growth factor Receptor 2

HR	Hazard ratio
IGF1-R	Insulin-like growth factor-1 receptor
IHC	Immunohistochemistry
IMPACT	Immediate Preoperative Anastrozole, Tamoxifen, or Combined with Tamoxifen
IRS1	Insulin receptor substrate-1
IRS1	insulin receptor substrate-1
JNK	Jun kinase
MAPK	Mitogen-activated protein kinase
MCF-7	Michigan Cancer Foundation - 7
MEK	MAPK/ERK kinase
MINDACT	Microarray In Node-negative Disease may Avoid ChemoTherapy
MISS	Membrane-initiated steroid signaling
MKP3	MAP kinase phosphatase 3
mRNA	Messenger ribonucleic acid
mTOR	Mammalian target of rapamycin
MVD	Microvessel density
NCCTG	North Central Cancer Treatment Group
NCI	National Cancer Institute
NCOR1	Nuclear receptor co-repressor 1
NHEJ	Non-homologous end joining
NISS	Nuclear-initiated steroid signaling
NPV	Negative predictive value

NSABP	National Surgical Adjuvant Breast and Bowel Project
NST	No special type
OS	Overall survival
pCR	Pathological complete response
PI3K	Phosphatidylinositol-3-kinase
PIKK	Phosphoinositide-3-kinase-related kinase
PKA	Protein kinase A
pMAP kinase	Phosphorylated MAP kinase
POETIC	PeriOperative Endocrine Treatment for Individualizing Care
PPV	Positive predictive value
PR	Progesterone receptor
PTEN	Phosphatase and tensin homolog
RFS	Recurrence Free Survival
RR	Relative risk
RS	Recurrence score
RT–PCR	Reverse transcription polymerase chain reaction
SAPK	Stress activated protein kinase
SEER	Surveillance, Epidemiology and End Results
Ser	Serine
SERMs	Selective estrogen receptor modulators
SISH	Silver enhanced in situ hybridization

SLN	Sentinel lymph node
SNP	single nucleotide polymorphism
SRC-1	Steroid receptor coactivator-1
SSA	Single-strand annealing
sVEGFR-1	Soluble vascular endothelial growth factor receptor-1
TAILORx	Trial Assigning IndividuaLized Options for Treatment (Rx)
TEACH	Tykerb Evaluation After CHemotherapy
TGFα	Transforming Growth Factor Alpha
TNBC	Triple negative breast cancer
TNM	Tumour, Node and Metastasis
TOP2A	Topoisomerase 2 alpha
TSP-1	Thrombospondin-1
UICC	Union Internationale Contre le Cancer
UK	United Kingdom
VEGF	Vascular endothelial growth factor
VEGFR	Vascular endothelial growth factor receptor

LIST OF FIGURES

LIST OF TABLES

Introduction and aim of the work

Breast cancer is a major public health problem for women throughout the world. It is the most frequent cancer in women and the second most frequent cause of cancer death. However, it is the leading cause of cancer death in women aged <65 years ***(Pegram & Casciato, 2009).***

The stage distribution based on SEER (Surveillance, Epidemiology and End Results) Summary Stage 2000 shows that 60% of breast cancer cases are diagnosed while the cancer is still confined to the primary site (localized stage); 33% are diagnosed after the cancer has spread to regional lymph nodes or directly beyond the primary site; 5% are diagnosed after the cancer has already metastasized (distant stage) and for the remaining 2% the staging information was unknown. The corresponding 5-year relative survival rates were: 98.3% for localized; 83.5% for regional; 23.3% for distant; and 57.7% for unstaged ***(Horner et al., 2009)***.

In Egypt, Breast cancer accounted for as high as 37.6% of all reported tumors in females ***(Freedman et al., 2006).*** Between January 2002 and December 2003, there

were 3,519 new cases of breast cancer attending the NCI (National Cancer Institute). These cases accounted for 19% of all 18,496 newly diagnosed proven malignant cases. There were 82 males (0.9% of all cancer types) and 3,437 females (37.5% of all cancer types). The median age for males was 53.5 years and 49 years for the females. The distribution of the cases by year and gender is shown in Table 1. Breast cancer ranked 1st most common cancer site among females ***(NCI, 2003).*** In the department of Clinical Oncology at Ain Shams University Hospitals, breast cancer accounted for 25.7% of all new cases in 2009.

	2002	2003	2002-03
Gender	n (%)	n (%)	n (%)
Males	41 (0.9)	41 (0.9)	82 (0.9)
Females	1719 (38.0)	1718 (37.1)	3437 (37.5)
Total	1760 (19.2)	1759 (18.9)	3519 (19.0)

Table 1: New Cases of Breast Cancer by Gender, NCI 2002-03 ***(NCI, 2003).***

Although breast cancer has traditionally been less common in non-industrialized nations, its incidence in

these areas is increasing. Estrogen-receptor-negative tumors tend to occur earlier in life and estrogen-receptor-positive tumors are more common in older women, and they seem to have different underlying causes and pathobiology. Reproductive and lifestyle factors have opposing effects, with nulliparity, obesity, and oral contraceptive use decreasing the risk of early-onset breast cancers while increasing the risk in older women ***(Benson et al. 2009).***

Breast cancer is a heterogeneous disease encompassing a wide variety of pathological entities that are reported to have distinct clinical behaviors ***(Geyer et al., 2009)***. Invasive duct carcinoma accounts for 70% to 80% of breast cancers with a highly variable clinical prognosis. Lobular carcinoma comes next with 10% to 15% of cases ***(Pegram and Casciato, 2009***).

Traditional prognostic factors include the axillary lymph node status, the tumor size, and the nuclear and histologic grade ***(Esteva & Hortobagyi, 2004)***. Although clinicopathological and IHC (Immunohistochemistry) factors that are commonly used for breast cancer provide prognostic information and have been proven to be

clinically useful, they are not able to predict perfectly. For example, the lymph node status is the best available prognostic marker for survival, but there are about 50% of node-positive breast cancer patients who will not develop recurrence, even without adjuvant chemotherapy treatment, whereas 25% of node-negative patients will develop micro-metastatic disease and may suffer from the recurrence. ***(Modlich et al., 2006)***

Interest in novel prognostic markers is based on the fact that a significant number of patients with early-stage breast cancer harbor microscopic metastasis at the time of diagnosis. It is now well established that adjuvant systemic therapy improves survival in such patients ***(Early Breast Cancer Trialists' Collaborative Group, 2005).***

Systemic therapies are potentially toxic, and identifying the individual patients who are at high risk and likely to benefit remains a major challenge. Unfortunately, the histologic information is clearly not sufficient to accurately assess individual risk and to possibly avoid adjuvant systemic therapy ***(Esteva and Hortobagy, 2004).***