DETECTION OF SURVIVIN IN BREAST CANCER

Thesis

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بسم الله الرحمن الرحيم

"وقـــــل رب زدنـــي عـــــــلماً"

صدق الله العظيم
سورة طه
الآية ١١٤

DEDICATION

To My Dear Parents

For their pray to Allah for me

To My Husband , My Son and My Daughter

For their endurance and loving

For their love and support

Mai Mohamed Nabil

Introduction

Breast cancer is the second leading cause of cancer deaths in general after lung cancer and it is the most common cancer among women worldwide **(Laurance & Jeremy, 2006).**

In Egypt, breast cancer is the most common cancer among women, representing 18.9% of total cancer cases among the Egyption National Cancer Institute (NCI) and represents 37.5% of all reported tumors in Egyptian females ***(Elatar, 2002).***

The diagnosis of breast cancer is established by the pathological examination of removed breast tissue. A number of procedures have been devised to obtain tissue samples like fine-needle aspiration, nipples aspirates, ductal lavage, core needle biopsy, and local surgical biopsy Most of these diagnostic steps, have some limitations as they may not yield enough tissue or miss the cancer, while the surgical biopsy already becomes an invasive procedure. Imaging tests are used to detect metastasis and include chest X-ray, bone scan, CT, & MRI ***(Rusiecki et al, 2005).***

Inspite of the availability of all these diagnostic & prognostic methods but we still need an easy, accurate & non

invasive way to follow up the tumor activity. In this work we will study survivin as a possible candidate to fulfill this goal.

survivin is a recently described molecule that is expressed in most human cancers but not in normal tissues, it is one of the members of inhibitor of apoptosis (IAP) gene family, it is Positioned at the interface between the regulation of apoptosis and the control of Cell proliferation ***(Altieri, 2003).***

Aim of the work:

The aim of this study was to detect survivin in breast tumor tissue and to correlate the data with the different clinical and pathological factors to try to find out a role of survivin in the prognosis and evaluation of aggressiveness of breast cancer.

BREAST CANCER

Breast cancer represents a serious health problem and is currently the most frequent malignancy in female population. It is the most common cause of cancer related mortalities among women worldwide. The basic understanding of breast cancer initiation and progression is still incomplete.

In addition, there is a need to develop improved methods to stratify breast cancer patients into different risk groups more accurately than can be achieved with current clinicopathologic classification methods. Hence, low-risk patients can be spared unnecessary treatment, avoiding side effects and reducing the cost of treatment ***(Li and Brattain, 2006).***

Epidemiology

According to the American Cancer Society, every three minutes a woman in the United States is diagnosed with breast cancer. This cancer incidence in women has increased from one in 20 in 1960 to one in eight nowadays; about 1.3 million women are expected to be diagnosed with this cancer annually worldwide and about 465,000 will die from the disease. Breast cancer death rates have been dropping steadily since 1990

because of earlier detection and better treatment. Also the society reported in 2008 that an estimated 22,400 women will be diagnosed with this cancer and 5,300 will die of it. On average, 431 women will be diagnosed with this cancer every week, 102 of which will die. One in 8 women is expected to develop this cancer during her lifetime and one in 28 will die of it ***(Johnson, 2008).***

According to the National Cancer Institute, Cairo, Egypt, breast cancer is the first most common malignancy in women constitutes 37.5% of all reported tumors in Egyptian females ***(Elatar, 2002).***

There is an international geographical variation in the incidence of Breast Cancer. Incidence rates are higher in the developed countries than in the developing countries. Incidence rates are also higher in urban areas than in the rural areas ***(Vorobiof et al, 2001).***

The mortality rates of breast cancer are declining in the developed world (Americas, Australia and Western Europe) as a result of early diagnosis, screening, and improved cancer treatment programs, the converse is true in the developing world ***(Adesunkanmi et al, 2006).***

The hallmarks of the disease in Africa are patients presenting at advanced stage, lack of adequate mammography screening programs, preponderance of younger pre-menopausal patients, and a high morbidity and mortality ***(Parkin et al, 2005).***

Possible Risk Factors

The precise etiology of breast cancer is largely unknown, but several risk factors have been identified, they include: (table 1).

Age:

The incidence of breast cancer increases with age and is rare before the age of 20 years. The incidence in Caucasians is highest at the age of 50-59, after menopause, dropping after the age of 70 ***(Adebamowo and Ajayi, 2000).***

In Africa and African-Americans the peak age incidence is about one decade less ***(Ijaduola and Smith, 1998).***

Numerous theories have been proposed to explain this difference, including age at menarche, time of first delivery, parity, social factors, and underlying genetic difference ***(Polite and Olopade, 2005).***

Sex:

Breast Cancer is 100 times more common in women than in men with male breast cancer accounting for <1% of all breast cancer cases in the United States and 0.1% of cancer mortality in men ***(Fentiman et al, 2006).***

In Africa this situation may be different as 5-15% of breast cancer in Uganda and Zambia may occur in males ***(Okobia* and Osime, *2001).***

Geographic Variation:

A wide difference in age adjusted incidence and mortality for breast cancer exists between different countries ***(Bray et al, 2004).***

Hormone& Pregnancy Related Factors:

The role of estrogen in the causation of breast cancer has been extensively studied and the general opinion is that estrogen is the primary stimulant for breast epithelial proliferation. Factors that increase exposure to high or prolonged level of estrogen are therefore associated with an

increased risk of developing breast cancer, and these factors include: - early menarche,

- late menopause,
- use of contraceptives and exogenous estrogen,
- nulliparity and increased age at first term pregnancy.

Induced abortion and spontaneous abortion do not increase the risk. Prolonged breast feeding reduces the risk ***(Basu* and Rowan*, 2005).***

As the living standard and health care facilities in Africa improve, it is probable that age at menarche will decrease while that of menopause increases. The demands for education and a career may increase the number of women who delay childbearing, have fewer children, use contraceptives and breast feed for a shorter time. For these reasons, the incidence of breast cancer will increase among African countries ***(Okobia* and Bunker, *2006).***

Previous Breast Disease:

Individuals who have a prior history of invasive carcinoma or ductal carcinoma in situ have a risk of developing a new invasive breast carcinoma. Women with atypical ductal or lobular hyperplasia have a four to five times higher risk of

developing breast cancer. Proliferative lesions without atypia, such as moderate hyperplasia and sclerosing adenosis, are associated with a slightly increased risk. Other common non-proliferative changes such as palpable cysts, fibroadenomas and duct papillomas are not associated with a significantly increased risk ***(Santen* and Mansel*, 2005).***

Enviromental Exposures:

The frequent exposure to radiotherapy for ankylosing spondylitis, Hodgkin's disease, or enlargement of the thymus gland increase the incidence of developing breast cancer, this also occur in survivors of the atomic bombings, painters of radium watch faces and X-ray technicians ***(MacMahon, 2006).***

Environmental exposures to organic chlorines and other synthetic estrogens like cosmetics have also been postulated to increase the risk, but so far there are no conclusive evidence linking organic chlorines to breast cancer ***(Darbre, 2006).***

Life Style Risks:

- Anthropometric indices and physical activity:

Height, obesity and high body mass index are risk factors especially in post menopausal women. In pre-menopausal

women, obesity and high body mass index have an insignificant but inverse relationship to breast cancer risk that is reduced by physical activity ***(Friedenreich, 2004).***

-Diet, Alcohol and Smoking:

Alcohol and Diets rich in fat especially saturated fat raises the risk while smoking does not appear to affect the risk ***(Dumitrescu* and Shields*, 2005).***

Family history and genetics:

A family history of breast cancer increases a woman's risk of developing the disease. A woman is considered to be at increased risk if the family member is a first degree relative with early age onset (< age 50), if both breasts are involved, or if she has multiple primary cancers (such as breast and ovarian cancer). Women with one, two, and three or more first-degree affected relatives have an increased breast cancer risk when compared with women who do not have an affected relative ***(Dumitrescu* and Cotarla*, 2005).***

Women with positive family history of breast cancer in first degree relative are recommended to begin breast cancer screening at an age 10 years younger than the age at which the affected relative was diagnosed. Hereditary breast cancer

caused by an underlying inherited gene mutation accounts for a small proportion (5-10%) of all breast cancers. The majority is accounted for by mutations in two tumor suppressor genes, BRCA-1 (50%) and BRCA-2 (32%), which are inherited in an autosomal dominant fashion *(A form of inheritance in which only one copy of a gene coding for a disease is enough for the disease to be expressed. If either parent has the disease, a child has a 50% chance of inheriting the disease because the altered BRCA is dominant over the normal gene inherited from the other parent).* These two genes are important in the processing of DNA damage and preservation of genomic integrity ***(Buchholz et al, 2002).***

Mutations in BRCA-1 and BRCA-2 genes are most commonly found in the European population, accounting for the high prevalence of breast cancer in the developed world. Up to 50-87% of women carrying a mutated BRCA1 gene develop breast cancer during their lifetime. Risks for ovarian and prostate cancers are also increased in carriers of this mutation. BRCA2 mutations are identified in 10-20% of families at high risk for breast and ovarian cancers and in only 2.7% of women with early-onset breast cancer. BRCA2 is also a risk factor for male breast cancer. BRCA2 mutations are associated with other

types of cancers, such as prostate, pancreatic, fallopian tube, bladder, non-Hodgkin lymphoma, and basal cell carcinoma ***(Kirby & Bland, 2007).***