INTRODUCTION

Breast cancer is the most common cause of cancer death among women worldwide. Incidence rates are high in more developed countries whereas rates in less developed countries and in Japan are low but increasing ***(Ries, 1999)***. In Egypt, breast cancer is the most common cancer among women, representing 18.9% of total cancer cases (35.1% in women and 2.2% in men) among the Egypt National Cancer Institute (NCI) series of 10 556 patients during the year 2001***(Elatar, 2002),*** with an age-adjusted rate of 49.6 per 100 000 population ***(Ibrahim, 2001).***

Interest in novel prognostic markers is based on the fact that a significant number of patients with early-stage breast cancer harbour microscopic metastasis at the time of diagnosis. Many molecular markers that have been studied have both prognostic and predictive values. Prognostic markers are indicators of aggressiveness, invasiveness, extent of spread of tumors, and thus, correlate with survival independent of systemic therapy and can be used to select patients at risk ***(Kuderer and Lyman, 2009)***.

To date, a series of experimental and clinical evidences have been reported to support a correlation between galectin expressions and neoplastic transformation.

Galectin-1 participates in tumor transformation by binding oncogenic H-Ras and resulting Ras membrane anchorage. ***(Paz et al., 2001). Yamaoka et al., 2000*** demonstrated the correlation of galectin-1 mRNA with malignant phenotype transformation in glioma cells. Galectin-1 is also involved in the regulation of cell growth, but recent studies suggest the multifaceted functions of galectin-1 in cell growth ***(Wells, 1999; Yamaoka et al., 2000; Kopitz , 2001)***. Another important role of galectin-1 in cancer progression is its interactions with extracellular matrix (ECM) molecules such as laminin, fibronectin, 90 K (MAC-2BP) and integrin ***(Hughes, 2001)***. By these interactions, galectin-1 regulates cell-cell or cell-ECM adhesion, and alters cell motility and aggregation which are important steps in cancer cell invasion and metastasis.

AIM OF THE WORK

1- Evaluate Galectin-1 expression in cancerous breast tissue spicemens.

2- Correlation of the results with the various clinicopathological data.

3- Find a new diagnostic and/or prognostic molecular biomarker for breast cancer.

Breast cancer

Breast cancer is the most common cancer in women and a leading cause of cancer death worldwide ***(Rakha et al., 2010)***, It is the most common malignancy-affecting women in North America and Europe and the second leading cause of cancer death in American women after lung cancer. ***(Armstrong et al., 2000).***

Management of breast cancer relies on the availability of robust clinical and pathological prognostic and predictive factors to guide patient decision making and the selection of treatment options ***(Rakha et al., 2010)***.

Epidemiology:

The age-adjusted incidence of breast cancer varies greatly around the world, with higher rates in developed than in developing regions ***(Curado et al., 2007)***.

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

The American National Cancer Institute estimates that a woman in the United States has a 1 in 8 chance of developing invasive breast cancer during her lifetime. This risk was about 1 in 11 in 1975 ***(ACS, 2003)***.

In general, incidence rates are high in Western and Northern Europe, Australia/New Zealand and North America; intermediate in South America, the Caribbean, and Northern Africa; and low in sub-Saharan Africa and Asia ***(Jemal et al., 2011)***

Possible Risk Factors

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).***

Dumitrescu and Cotarla (2005) showed that 48% of all new cases of breast cancer occur in women over 70 years of age and there is a similar increase with age as regards mortality.

Sex:

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

Men with gynaecomastia do not have a higher risk of developing breast cancer. There may be an increased incidence of breast cancer in men with prostate cancer ***(Giordano et al., 2004)***.

Race:

Breast cancer incidence rates are highest among white women. Rates among Asians and Hispanics are half to two thirds those of whites; American Indian women are at notably low risk ***(Lacey et al., 2002).***

Black women are more likely to have steroid receptor negative tumors and high grade tumors such as medullary carcinoma. On the other hand, white women are more likely to have steroid receptor positive tumors and low grade tumors such as lobular carcinoma or tubular carcinoma ***(Chlebowski et al., 2005).***

Family history:

Many studies have examined the relationship of family history and the risk for breast cancer. These studies can be summarized as follows:

1- First degree relatives (mothers, sisters and daughters) of patients with breast cancer (especially those who have premenopausal onset and bilateral breast cancer) have twofold to threefold excess risk of the disease.

2- Risk decreases quickly in women with distant relatives affected with breast cancer (cousins, aunts, grandmothers).

In families with multiple affected members, particularly with bilateral and early-onset cancer the absolute risk in first-degree

relatives approaches 50%, consistent with an autosomal dominant mode of inheritance in these families ***(Iglehart and smith, 2008)***

HORMONAL FACTORS:

Breast cancer risk is increased in women with the longest known exposures to sex hormones, particularly estrogen. Therefore, breast cancer risk is increased in women who have history of:

- early menarche (before age 12)
- late menopause ***(Mcpherson et al., 2000)***
- Exogenous estrogens, either the combined oral contraception (COC) or hormone replacement therapy (HRT), also confer increased risks of breast cancer, depending on the duration of exposure and whether the estrogen is used alone or in combination with progesterone ***(Antoine et al., 2004).***
- 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).***

Genetic Mutations:

Genetic factors are estimated to cause 5-10% of all breast cancer cases but, may account for 25% of cases younger than 30 years ***(Iglehart and smith, 2008).***

In 1994, the breast-cancer susceptibility genes, BRCA1 was identified and accounts for up to 40% of familial breast cancer. One year later a second susceptibility gene, BRCA2, was discovered. In addition to increased breast cancer risk, women with mutations in BRCA1 or BRCA2 are at increased risk for ovarian cancer (45% lifetime risk for BRCA1 carriers) ***(Iglehart and smith, 2008).***

BENIGN BREAST DISEASAE:

Women with severe atypical epithelial hyperplasia have a four to five times higher risk of developing breast cancer than women who do not have any proliferative changes in their breasts. Also, women with palpable cysts, complex fibroadenomas, duct papillomas, sclerosis adenosis, and moderate or florid epithelial hyperplasia have a slightly higher risk of breast cancer (1.5-3 times) than women without these changes, but this increase is not clinically important ***(McPherson et al., 2000).***

Previous Breast Cancer:

Personal history of cancer in the other breast is a major risk factor for development of primary breast cancer. However, many second cancers can appear in the same breast. Most recurrent breast cancers arise within the first five years following treatment. Recurrence rates are very low in patients with primary tumors

smaller than 1 cm and negative axillary nodes ***(Armstrong et al., 2000).***

Exposure to Ionizing Radiation:

Female breast tissue is sensitive to the carcinogenic effects of radiation, particularly when exposure takes place at younger age. Risk of radiation- induced breast cancer is evidenced in the sub-population of female patients who have undergone radiotherapy for either malignant or non-malignant diseases, including benign breast diseases in their childhood or young age ***(Golubicic et al., 2008).***

Dietary Factors:

The human diet contains a great variety of natural and chemical carcinogens and anti-carcinogens. Some of these carcinogenic compounds may act through the generation of free oxygen radicals, which can lead to DNA damage or other deleterious components ***(Bissonauth et al., 2009).***

A high intake of fat, especially unsaturated fatty acids, has been reported to be significantly associated with an increased breast cancer risk. while, particular type of polyunsaturated fatty acids and omega-3 seem to be protective ***(Saadatian-Elahi et al., 2004).***

Alcohol intake:

Numerous epidemiological studies have demonstrated a positive association between alcohol intake and the risk of developing breast cancer in both pre- and postmenopausal women with an overall risk of 1.6 fold ***(Singletary and Gapstur, 2001).***

Histopathologic Classification of Breast cancer

Breast cancer includes a heterogeneous group of malignant tumors of variable natural history. It can be classified histologically based upon the types and patterns of cells that compose them. Carcinomas can be invasive (extending into the surrounding stroma) or non-invasive (confined just to the ducts or lobules). It is important to recognize that in invasive category, special types of tumors are associated with favorable prognosis **Table (1-a) & (1-b).**

Table (1-a):Non-invasive Carcinoma of the Breast

Histologic type	**Frequency**
Intraductal Carcinoma	3.6
lobular Carcinoma in situ (LCIS)	1.6
Intraductal & LCIS	0.2
Papillary Carcinoma	0.4
Comedocarcinoma	0.3

(Breast cancer pathology, 2005)

Table (1-b): Invasive Carcinomas of the Breast

Histological type	**Frequency (%)**
Infiltrating Ductal Carcinoma	63.6
Infiltrating Lobular Carcinoma	5.9
Infiltrating Ductal & Lobular Carcinoma	1.6
Medullary Carcinoma	2.8
Mucinous (colloid) Carcinoma	2.1
Comedocarcinoma	1.4
Paget's Disease	1.0
Papillary Carcinoma	0.8
Tubular Carcinoma	0.6
Adenocarcinoma	7.5
Other combinations	3.5

(Breast cancer pathology, 2005)

Non-invasive Carcinoma:

The enthusiasm for screening has led to the increasing detection of breast cancer at early carcinoma in situ (CIS) stage. Before mammography, the incidence of non-invasive carcinoma was only 5%, but increased to 15% and more in screening series. By definition, the carcinoma is confined by the basement membrane within the ducts or lobules, and it is classified into ductal carcinoma in situ (DCIS) and LCIS with an incidence ratio of 4:1 respectively. Three mammographic growth patterns are described namely: the microfocal, tumor forming, and diffuse.

DCIS A non invasive proliferation of malignant epithelial cells within the duct system (some consider this to be pre-cancer) ***(Silverberg&Masood, 1997).*** It accounts for about 18% of all breast cancers in the U.S (invasive and non-invasive) and is usually diagnosed by mammography, where it can be seen with or without calcifications. DCIS is occasionally found by clinical breast examination, but usually not palpable. It can be classified into subtypes based on cell features and named for their histopathological architectural growth patterns ***(Rosai, 1996).***

LCIS is an incidental and uncommon lesion (1% of breast biopsies). It is often multicenteric (50%) and bilateral (40%).

Histologically, the acini of the lobular unit are distended by uniform cells with obliteration of the lumen.

Lobular carcinoma may extend to proximal duct in pagetoid fashion. **LCIS** has low risk to progress into invasive carcinoma with an annual cumulative risk of 1% only. The developing invasive tumors are commonly ductal rather than lobular carcinomas ***(Rosal et al., 2004).***

Invasive carcinoma:

Invasive ductal carcinoma:

It is the most common form of invasive carcinoma, it has the worst prognosis. It may be preceded and accompanied by an in situ component characterized by a proliferation of cells within the ducts without interruption of the basal membrane; when this membrane is altered, the carcinoma is invasive. It may be pure or mixed with other carcinomas most commonly lobular carcinoma. It is characterized by its solid core, which is usually hard and firm on palpation. An associated ductal carcinoma in-situ is frequently present and comedo necrosis may occur in both invasive areas and areas of intraductal carcinoma. Invasive ductal carcinoma commonly spreads to the regional lymph nodes and carries the

poorest prognosis among various carcinomas in the breast ***(Raju et al., 2001).***

Invasive, lobular carcinoma:

It is the second common type of breast cancer, characterized by greater proportion of multicentricity in the same or the opposite breast. The lesions tend to have ill-defined margins, and occasionally the only evidence is subtle thickening or induration, Patients with infiltrating lobular carcinoma are especially prone to have bilateral carcinoma. Stage by stage, invasive lobular carcinoma has a similar prognosis to infiltrating ductal carcinoma ***(Tavassoli and Devilee, 2003)***.

Medullary carcinoma:

Typically has a prominent lymphocyte infiltrate. Patients with medullary carcinoma tend to be younger than those with other types of breast cancer. The prognosis is generally better than for invasive ductal cancer ***(Pedersen et al., 1995).***

Tubular carcinoma:

It is the most favourable tumor, but with high risk of bilaterality (20%). It is composed of tubules oval in shape with angular end (teardrop) and dense fibrous stroma. It is lined by a single layer of cuboidal or columnar epithelium. Invasive cribriform carcinoma is related cytologically and biologically to tubular carcinoma ***(Mc Boyle et al., 1997).***

Mucinous carcinoma:

Is common in older women. Grossly, it shows a glistening appearance. Microscopically, it is composed of small islands of tumor cells suspended in abundant mucin in the stroma ***(Fentiman et al., 1997).***

Paget's disease*:*

It is a rare type, about 1-4% of all breast cancers characterized by neoplastic cells in the epidermis of the nipple areolar complex. It most commonly presents with eczema of the areola, bleeding, ulceration, and itching of the nipple. The diagnosis is often delayed because of the rare nature of the condition and confusion with other dermatologic conditions. Because of this, it is recommended that any ulcerated or irritated lesion on the nipple areolar complex undergo a punch biopsy under local anesthesia. There is an associated cancer elsewhere in the breast in up to 80% of cases ***(Cotran et al., 1994).***

Papillary carcinoma:

This type of carcinoma is rare occurring more in postmenopausal women. The term papillary carcinoma is applied only to tumors in which true papillary and micro papillary (without a stromal core) structure with focal solid areas are present ***(Silverberg& Masood, 1997).***