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Tumor Markers and Some Heamatological Factors as Diagnostic Signs for Early Diagnosis of Female Breast Cancer

A Thesis Submitted to

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Chapter One

Introduction

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1.1. Introduction

Breast cancer is the most frequently diagnosed type of cancer among women in all world regions. About 1.7 million cases of breast cancer are diagnosed every year (Ferlay *et al.*, 2015; Ferlay *et al.*, 2012). With higher incidence documented in higher income regions (92 per 100,000 in North America) and lower incidence documented in lower income regions (27 per 100,000 in Middle Africa and Eastern Asia) Ferlay *et al.* (2012); Torre *et al.* (2016); Ginsburg *et al.* (2016). Breast cancer is the leading cause of cancer death among women worldwide (Ferlay *et al.*, 2015). There were approximately 0.5 million deaths worldwide from breast cancer in 2012, which mean almost one death per minute and accounts for 15% of all cancer deaths (Ferlay *et al.*, 2012). Breast cancer survival rate being significantly lower in low and middle income countries compared to high income countries (Ginsburg *et al.*, 2016).

Breast tissue is composed of lobules which are glands involved in milk production, ducts that connect the lobules to the nipple and connective tissue, fatty tissue, and lymphatic tissue. Breast cancer occurs when cells within any of the components of the breast undergo an unregulated growth, especially in the lobules (American Cancer Society, 2017). By routine self-breast examination, mammographic screening, or once signs or symptoms have been developed breast cancer whether in situ or invasive could be detected (American Cancer Society, 2017). Painless breast lump is the most common physical sign that can be appreciated, other less common signs which are considered as a substantial indicator of breast malignancy and maybe more evident with

advanced stages of disease are nipple discharge, heaviness, redness, swelling, breast deformity, or retractions. During the early stages of breast cancer swollen and enlarged lymph nodes may be present within the axillary region (Ginsburg *et al.*, 2016). As there are few early signs, it is recommended that all females should follow the current breast cancer screening guidelines to identify those with abnormal breast tissue during the early stages. Currently, there are 21 histologically distinct breast cancers and four different molecular variations. Each subtype differs in their overall presentation and type of treatment required (American Cancer Society, 2017).

Many risk factors for breast cancer development have been identified in many population which are Non-modifiable (intrinsic) and modifiable (extrinsic) risk factors. The non-modifiable risk factors include gender, increasing age, race and ethnicity, and a genetic/family predisposition to breast cancer (Chlebowski *et al.*, 2005; Biunno *et al.*, 2014). Other risk factors include prolonged exposure to endogenous sex hormones and growth factors, which result from early age at menarche and late menopause and taller stature. Excess weight at post-menopausal ages also increases the risk of breast cancer. Alcohol consumption and limited physical activity also influence breast cancer risk (World Cancer Research Fund Report, 2014). In contrast, young maternal age at first birth, high parity and breastfeeding reduce breast cancer risk (Okobia *et al.*, 2005).

Breast cancer has many treatment options, which include surgery, chemotherapy, radiation therapy, target therapy and hormonal therapy depending on the stage, as well as on the histological and molecular subtypes (National Cancer Institute, 2017). The stage of breast cancer at the time of diagnosis is a major determinant of survival from breast cancer, patients with early stage disease being associated with a better

prognosis compared to late stage disease. Earlier stage of breast cancer at the time of diagnosis was a major contributor to the sharp reductions in breast cancer mortality (Allemani *et al.*, 2015).

The majority of breast cancer are of the invasive type which means that the malignancies have been extended beyond the ducts and glands into the surrounding tissues and lymph nodes also evaluated by molecular techniques to determine if hormone receptors are present, and if there is an excessive concentration of human epidermal growth factor receptor 2 (HER2). These molecular techniques prove that the majority of invasive breast malignancies are either estrogen or progesterone receptor positive, but human epidermal growth receptor 2 negative (luminal A) which are characteristically slow growing and less aggressive (National Cancer Institute, 2017). Triple negative cancers have the poorest short term prognosis largely because there are no targeted therapies (National Cancer Institute, 2017).

On the other hand, breast malignancies which are hormone receptor negative, but human epidermal growth factor receptor 2 positive (HER2- enriched) are also more aggressive and have a poorer short-term prognosis than hormone positive types (American Cancer Society, 2017). Prediction the response to anti-HER2 therapy in the neo-adjuvant, adjuvant and advanced disease settings is the main clinical use of HER2 measurement by either immunohistochimestry (IHC) or in situ hybridization (ISH) Eroglu *et al. (*2014). Recently, there are four anti-HER2 therapies are approved for the treatment of HER2-positive breast cancer, trastuzumab, lapatinib, pertuzumab and trastuzumabemtansine American Cancer Society, (2017). The National Comprehensive Cancer Network (NCCN) recommended that the first-line therapy for patients with HER2-positive advanced breast cancer should be trastuzumab,

pertuzumab and a taxane, if not previously treated with trastuzumab (Giordano *et al.*, 2014).

Several serum tumor markers have been evaluated in breast cancer. Most of these markers are of prognostic value. Tumor markers are molecules which undergo important alterations during cancer and carry high clinical significance. Tumor markers may be proteins, nucleic acids, isoenzymes, metabolites or hormones and are classified as prognostic, predictive and diagnostic (Sankara *et al*., 2017). Diagnostic biomarkers are used for the detection of the disease, whereas prognostic biomarkers give information about course of recurrence of the disease. On the other hand, predictive markers are important to evaluate the response to treatment (Fong and Winter, 2012). Any change in the level or presence or absence of specific biomarkers within a cell often is an indication of cancer development. Cancer-specific detection and identification of these biomarkers could help in early monitoring and diagnosis of disease progression (Chatterjee and Zetter, 2005).

CA15-3 and CA27-29 are the most important serum biomarkers used for the diagnosis and monitoring of breast cancer (Tothill, 2009; Duffy, 2006). CA 15-3 and CA27-29 often mostly used in monitoring therapy in advance breast cancer cases. Hence their values rise by 10%, 20%, 40% and 75% in 1st, 2nd, 3rd and 4th stages of breast cancer respectively (Duffy, 2006).

1.2Aims of the study

The aims of the study are to:

1. Determine the significant difference in the preoperative serum (CA15-3 & CA27-29) tumor markers levels between patients and control groups.
2. Establish the relation between serum tumor markers (CA15-3 & CA27-29) of patients with age and clinic-pathological parameters which are: receptor status, tumor stage, tumor grade, tumor size, lymph node involvement, and metastasis, in order to evaluate the prognostic significance of serum CA15-3 and CA27-29 in the early detection of breast cancer.
3. Determine if there is any significant association between HER2 scores of breast cancer patients and serum levels of tumor markers (CA15-3 & CA27-29).
4. Determine the significant difference in complete blood count parameters between patients and control groups.
5. Evaluate the prognostic significance of complete blood count parameters in the early detection of breast cancer by correlating them with the studied serum tumor markers and with the clinic-pathological parameters of patients.
6. Find a possible association between socio-demographic variables which are: residence nearby industries and incinerators, breast feeding history, and family history of breast cancer with the studied markers in patients and control.