Republic of Iraq
Ministry of Higher Education
and Scientific Research
University of Diyala
College of Medicine

Evaluation of erbb2 Gene Polymorphism in Relation with Serum Levels of Soluble HER-2 and Interleukin-2 in Women with Breast Cancer

A Thesis Submitted to
the council of the College of Medicine- University of Diyala in Partial Fulfilment of the Requirements for the Master Degree of Science in Medical Microbiology

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2018 AD

1440 AH

Dedication

To my dear parents……. With respect

To my Beloved husband…… With special thanks

To my Brothers and sister…… With gratitude

To my sons and daughter…… With love

Hiba 2018

Acknowledgements

First, praise and appreciation are due to Almighty Allah who gave me the strength and hope to complete this work.

Special thanks are due to the Ministry of Higher Education and Scientific Research and to the Department of Microbiology/College of Medicine/Diyala University for giving me the opportunity to perform this work. Deepest thanks to my supervisors Assistant Professor Dr. Walaa Najm Abood and Dr. Nameer Fadhel Gaeb for their valuable time, expertise, guidance, and encouragement**.**

I would like to express my sincere thanks to the dean of the College of Veterinary Medicine Professor Dr. Talib Jawad Kadhim and Dean of the College of Medicine Professor Dr. Ismeel Ibrahim Latif and to Assistant Professor Dr. Areej Atiyah Hussein, the head of the Department of Medical Microbiology / College of Medicine/Diyala University and all the teaching staff of the department for their generous help and support during the time of project.

I am deeply thankful to the staff of Baghdad Teaching Hospital and teaching laboratories in the medical city for their kind help and provision of samples.

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Chapter One

Introduction

1.1. Introduction

Breast cancer(BC) has a major impact on the health of women worldwide. The higher incidence was documented in higher income regions (92 per 100,000 in North America), while the lower incidence was documented in lower income regions (27 per 100,000 in Middle Africa and Eastern Asia) (Torre *et al.,* 2016; Ginsburg *et al*., 2016). In Arab countries, the incidence rate ranged from 6.3% in Oman to 34.3% in Sudan (WHO, 2010). While the five-year survival percentage for BC victims in developed countries is 83%, it is 53% in developing countries. This significant difference can be due to early detection using mammography scans and the better health care treatments available in the developed countries (Houssami *et al*., 2012).

The etiology of BC is multifactorial, with genetic and non-genetic (environmental, dietary and reproductive) factors interacting in a complex way. The human epidermal growth factor receptor 2 gene (her-2) is one of the most important documented genes involved in BC aggressiveness and diagnosis (Solomon *et al*., 2017). Polymorphism in this gene can alter the gene expression with a consequence impact on women's susceptibility to BC.

From diagnostic point of view, the detection of amplification / overexpression of her-2 gene is a mandatory for configuration of treatment regime (National Cancer Institute, 2017). This detection is usually based on *in situ* hybridization or with immunohistochemistry (IHC) technique. However, it is well known that the extracellular domain (ECD) of this receptor (also called soluble HER-2 (sHER-2) is continuously shed into tissue and the blood circulation (Tse *et al*., 2012). Therefore, the quantitative evaluation of this domain in the serum may

reflect the amplification / over-expression of her-2 gene, and assist in the diagnosis of BC cases.

Cytokines are known to have both stimulatory and inhibitory effects on BC growth depending on their relative concentrations and the presence of other modulating factors in the tumor microenvironment (RAO *et al*., 2006). Several studies supporting the importance of Th1 cytokines in enhancing antitumor immunity have been published in the past several years (Zhu and Paul, 2008; Kajitani *et al*., 2012; Shrihari, 2017). Interleukin-2 produced by Th1, activates monocytes and macrophages and induces the proliferation of activated T and B lymphocytes. In addition, it induces the T-cell, natural killer (NK) cells and cytotoxicity T-lymphocyte (CTL) to kill tumor cells (Kuby, 2003; Gaffen and Liu .2004). As such, serum levels of this cytokine in association with sHER-2 level could be used as a marker for the evaluation of the immune status of BC patients and as an indicator for the progression of this malignancy.

1.2 Aims of the Study

1- Investigating the association of some demographic characteristics such as age, menopause state, family history and breastfeeding with the development of BC.

2- Evaluating the role of polymorphism (rs2952155) in her-2 gene in the incidence of BC.

3- Assessing the possible association between serum levels sHER-2 with tissue her-2 statuses (positive or negative).

4- Evaluating the role of IL-2 in BC patients and its association with sHER-2.