INSULIN-LIKE GROWTH FACTOR-1 AND BREAST CANCER RISK IN KURDISH WOMEN

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ABSTRACT

Background

Insulin-like growth factor -1 (IGF-1) has mitogenic and antiapoptotic effects on breast cancer cells. High-circulating IGF-1 was found to be associated with increased risk of breast cancer in several previous epidemiological studies, mostly conducted in the Caucasian populations. Little is known about the association between IGF-1 and breast cancer in Kurdish women whose dietary habits and genetic basis differ considerably from their Caucasian counterparts. IGF-1 levels can vary substantially among individuals and have been shown to be regulated in part by diet, age, lifestyle and anthropometric indices. Nutrition and energy balance have an important influence on IGF-1 levels which are decreased in energy-restricted diets and transiently increased with intense physical activity. Despite the number of factors that can influence IGF-1 levels, it has been estimated that up to 60% of the variability has a genetic basis, also age have been shown in some studies to be an important factor. Determinants of IGF-1 levels within racial and ethnic groups are unclear.

Research goal

To investigate the association between IGF-1 and breast cancer in Kurdish women.

Methods

a population-based case-control study was conducted to assess the associations of IGF-1 with breast cancer risk in Kurdish women. The study included 131 incidents of premenopausal ER (+) and PR(+) breast cancer patients diagnosed between June 2016 and March 2017 at Hiwa Cancer Hospital, Slemani, Kurdistan of Iraq and 130 age-matched controls selected randomly from the general population at Marital Screening Center/ Slemani General Hospital.

Results

The results showed no statistically significant differences exist between the case and control in this study.

Conclusion

We have investigated a lack of correlation between circulating IGF-1 levels and breast cancer among Kurdish women patients.

Keywords: *Insulin-like growth factor (IGF)-1, Breast cancer, Case-control study, Sulaimani.*

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INTRODUCTION

Breast cancer is the most common malignancy in women worldwide; the rates vary from 27 cases per 100,000 women in eastern Africa to 96 cases per 100,000 women in Western Europe [1]. Although, the detail of breast cancer etiology is still unclear, it is known to be multifactorial disease and the genetic factor is the main risk factor for the disease. It is well-known that breast cancer (BRCA) 1 and 2 gene mutations may increase the risk of developing hereditary breast and ovarian cancer over the time [2]. Nevertheless, the participation of breast cancer genes has not been fully elucidated. Some authors have shown a significant association between IGF-1 gene polymorphism and breast cancer, however there is a need for further elucidation of the association between IGF-1 polymorphism and increased risk of breast cancer [3-5].

IGF-1 shares significant sequence homology with insulin (6) and acts as a regulator of cell growth and metastasis as well as potent mitogenic and anti-apoptotic effects in both normal and transformed breast epithelial cells [6 , 7]. IGF-1 also activates gene transcription programs strongly associated with poor breast cancer prognosis [8]. Bioactivity of IGF-1 is regulated via IGF Binding Proteins (IGFBPs), and approximately 90% of the IGF-1 in the circulation is bound to IGFBP-3 together with an acid-labile subunit, to form a ternary inactive complex [9, 10]. In addition to its growth-inhibiting properties via competitively binding to IGF-1, IGFBP-3 has intrinsic and independent growth inhibiting effects, such as induction of apoptosis [11, 12]. The IGF-1/IGFBP-3 molar ratio has been proposed as a measure of free unbound IGF-1 [13].. In addition, IGF-1 is also down regulated by tamoxifen [14].

Evidence from some, but not all epidemiologic studies demonstrates an association between circulating IGF-1 levels and increased risk of breast cancer [15-24]. However data on the association between circulating IGF-1 levels and prognosis in breast cancer survivors are limited. One small study (N=110) reported an association between lower levels of IGF-1 and improved survival [25]. Another found no association between IGF-1 and outcome but did find a significant association between elevated IGFBP-3 levels and recurrence [26]. Results from one big study suggest that differences in IGF-1 levels exist in Hispanic and non-Hispanic white women. These differences could be due to the combined effects of genetic and behavioral factors that could account for ethnic differences in the risk of breast cancer and other chronic diseases [27].

MATERIALS AND METHOD

Study Subjects

In the context of case-control investigation conducted in Sulaimani, Kurdistan, we studied 131 women with incident ER (+) and PR (+) breast cancer and compared their IGF-1 blood level with those of 130 healthy controls with frequency-match on age. Hiwa Cancer Hospital was designated to recruit all newly diagnosed breast cancer women during the period between June 2016 and March 2017.

Hormone Receptor Analysis

As part of routine pre-treatment work-up, oncologists from Hiwa Cancer Hospital refer all newly diagnosed breast cancer patients to Shorsh Hospital, Sulaimani to assess the hormonal status of their diseases, including estrogen, progesterone and epidermal growth factor receptors, based on which management plan will be developed. The most common method currently used by Shorsh Hospital pathologists is immunohistochemistry (IHC).

Specimen and Hormone measurements

The blood of ER (+) and PR (+) breast cancer patients were collected in a 10-ml vacationer tube with either EDTA or heparin anticoagulant at the Hiwa Hospital laboratories. Serum was separated immediately after collection and stored at −70°C until analysis. To enhance the comparability between the cases and controls in this study and minimize the effect of confounders, blood samples were collected before any radiotherapy or chemotherapy prescription. The potential controls were randomly selected women from the general population in the Marital Screening Center in Sulaimani General Hospital.

The cases and controls were individually matched on age (±5 years) and date of blood collection (±30 days). The ages of the 131 patients ranged between 25 and 45 years, and the average was 35 years, which was comparable with the average age of the controls group (ranged 25 to 40), the later average age was 32.5 years.

Laboratory Assays for Circulating Levels of IGF-1 in the Serum Samples

The frozen serums were sent from Hiwa Hospital Laboratories to Shar Hospital Clinical Diagnostic Laboratory, Department of Hormones to determine the concentration of IGF-1 by Chemiluminescence analyzer. LIAISON® XL, 2010/Italy was used

for the assay. LIAISON® XL is a fully automated Chemiluminescence analyzer that performe the complete sample processing from sample pre-dilutions, sample and reagent dispensing, incubations, wash processes as well as measurement and evaluation.

All samples were in one batch but were assayed in the same in multiple runs in the lab. Cases and their matched controls were assayed in the same runs. The lab assay personnel were blinded to the case, control and quality control status of the sample analysis. The calibrators used in the assays ranged between 4.5- 640 ng/ml forIGF-1. There were no cross- reaction in each assay with other members of the IGF family.

RESULTS

All data analysis has been conducted in R (v. 3.3.3). The data have been checked for normality with Q-Q plot, density plot and Shapiro Wilk test, and the data is normally distributed. Levene's test was used to test for the homogeneity of variance between the groups. The test has shown that the variances between groups was not significantly different from each other ($F_{1, 259} = 3.57$, p-value = 0.06).

Welch Two Sample t-test has shown that there was no significant difference between the mean concentration of IGF-1 in each group (t = 0.02, df = 259, p-value = 0.98). Mean IGF-1 concentrations were the same in both the cancer patients group (221 ng/ml) and control group (221 ng/ml) (Figure 1 and Table 1).

In contrast to the findings from some but not all epidemiological studies demonstrating an association between circulating IGF-1 levels and increased risk of breast cancer (15-24), the current study showed no statistically significant differences between cases and controls in terms of IGF-1 level and increased risk of breast cancer relationship (Table 1).

There were no statistically significant differences between cases and controls (Figure 1). In contrast to the findings, several but not all epidemiological studies demonstrate an association between circulating IGF-1 levels and increased risk of breast cancer [15-24].

Table 1. Summary of the concentration of IGF-1 (ng/ml) and age of the cancer patients and control groups.

		IGF-1 concentration (ng/ml)	Age (years)
Cancer patients	*n*	131	131
	mean	221	35.5
	standard deviation	56.5	5.9
	median	216	36
	minimum	122	25
	maximum	367	47
Control	*n*	130	130
	mean	221	32.7
	standard deviation	46.3	4.8
	median	222	32
	minimum	127	25
	maximum	307	45

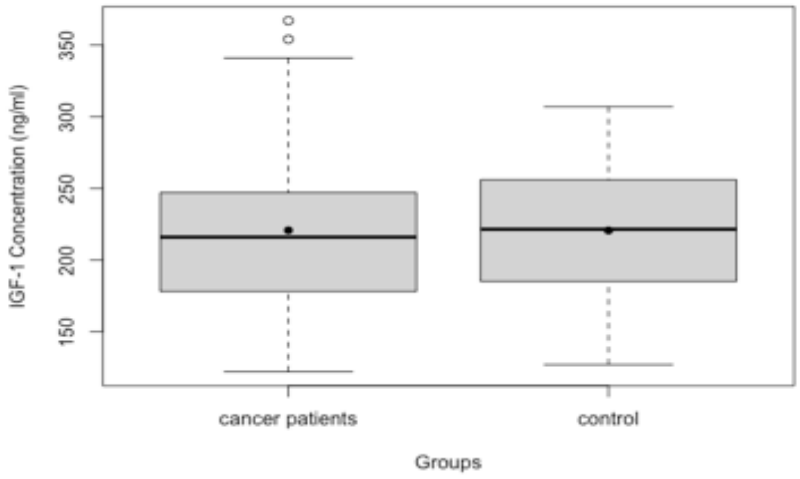

Figure 1. Box plot of IGF-1 concentrations (ng/ml) for cancer patients and control groups. Black dots and solid black lines in the center represent mean and median of each group, respectively (for values, see Table 1).

DISCUSSION

Results from this study suggest that there is no evidence of an increased level of IGF-1 among Kurdish breast cancer women at the time of diagnosis that is comparable to the findings from several but not all epidemiological studies. Several studies are arguing for the presence of an association between circulating IGF-1 levels and increased risk of breast cancer [15-24]. This could be partly due to the combined effects of genetic and life-style factors such as ethnic differences in the risk of breast cancer and other chronic diseases.

However, our finding is inconsistence with the suggestion of the study of Hispanic women with breast cancer who have lower levels of IGF-1 than non-Hispanic white women [28]. Hispanic women are diagnosed with breast cancer at a more advanced stage [23-25] and present with higher grade, larger tumors than non-Hispanic white women after adjusting for age at diagnosis [26]. Meanwhile, studies have shown that breast cancer in Hispanic women are more commonly estrogen receptor (ER)-positive compared with those in non-Hispanic white women [20, 23]. Those studies are inconsistence with Kurdish women breast cancer whose breast cancer mostly is ER and PR- positive.

However, earlier studies on circulating IGF-1 levels and breast cancer risk reported positive associations among pre-menopausal, but not post-menopausal women [29]. The relationships among circulating levels of IGF-1, IGFBP-3 and breast cancer risk have been inconsistent across studies, with positive associations observed for IGF-1 among pre-menopausal but not post-menopausal women in earlier studies [29]. Whereas, several IGF-1 and IGFBP-3 single nucleotide polymorphisms (SNPs) were associated with the corresponding biomarker levels[30-38]. The results among IGF-1, IGFBP-3 genetic variants and breast cancer risk have largely been inconsistent [30, 31, 34, and 38-42]. However, our analysis did not incorporate several variables that are strongly related to breast cancer risk and that commonly vary based on the ethnicity [43] such as breast cancer family history, prior benign breast disease, socioeconomic status, physical activity and mammogram screening frequency.

Conclusion

To our knowledge, this is the first study to examine the associations between circulating level of IGF-1 and breast cancer among Kurdish women. Results from this study suggest that there is no increased level of IGF-1 among Kurdish women with breast cancer. Future studies are recommended for further assessment of this relationship and a broader consideration of the possible confounders. Overall, there was no correlation between circulating IGF-1 levels and breast cancer among Kurdish women patients.

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