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Original Article

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# Lack of Association between Selenium Level and Human Epidermal Growth Factor Receptor *2 (*HER2) Expression in Breast Cancer Tissue

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## ABSTRACT

**Background and Objectives:** H*uman epidermal growth factor receptor 2 (HER2)* is a gene involved in development of breast cancer. Normally, HER2 receptors control breast cells growth and division. HER2 overexpression is the cause of almost 20% of all breast cancer incidents. The phosphoinositide 3 kinase (PI3K) pathway is important in the oncogenic function of HER2. It has been reported that compounds, such as selenium significantly attenuate oxidative stress-induced activation of the PI3K pathway, and can exert antitumor effects by downregulating PI3K activation. In this study, we evaluated association of selenium level and HER2 expression in breast cancer tissue.

**Methods:** Atomic absorption spectrometry and immunohistochemistry were used to evaluate selenium content and HER2 expression in 30 tissue sets (tumor and adjacent tissue) collected from 30 women diagnosed with breast cancer.

**Results:** HER2 was expressed in about 30% of the samples. In HER2-positive tissues, mean level of selenium was 268.15 µg/L in tumors and 165.36 µg/L in tumor margins. In HER2-negative tissues, mean level of selenium was 206.43 µg/L in tumors and 184.39 µg/L in tumor margins. There was no significant association between selenium level and HER2 expression ($P>0.05$).

**Conclusion:** Based on the results, we conclude that there is no association between Se level and HER2 expression in breast cancer tissue.

**Keywords:** Selenium, HER2, Breast Neoplasms.

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## INTRODUCTION

Breast cancer is the second leading cause of death among women (1). Human epidermal growth factor receptor 2 (HER2) gene amplification and/or protein (tyrosine kinase receptor) overexpression occur in many carcinomas, especially in breast cancer (2). HER2 overexpression also stimulates downstream signaling and promotes cell proliferation and survival. HER2 status is both a prognostic and a predictive factor for HER2-targeted therapies. Therefore, it is necessary to accurately determine HER2 status in every breast cancer case (3).

Some dietary micronutrients, such as selenium (Se) are thought to have cancer protective and antioxidant effects (4). The potential role of Se in cancer prevention may be due to its effects on carcinogen metabolism, cellular immune response, cell proliferation, cell cycle, tumor cell invasion and estrogen and androgen-receptor expression (5). However, few epidemiological studies have investigated the relationship between dietary Se and breast cancer (4,6-8). For decades, epidemiological and preclinical evidence supported the notion that higher dietary intake of Se decreases the incidence of cancers (9). However, the results of most animal studies indicate that the cancer preventive properties of Se occur at supranutritional levels. It is believed that active Se metabolite is a monomethylated Se species, such as methylselenol. In this study, we evaluated association of Se level and HER2 expression in breast cancer tissue.

## MATERIALS AND METHODS

Sixty tissue samples (30 tumors and 30 tumor margins) were collected from 30 breast cancer patients in Imam Khomeini hospital in Tehran, Iran. A pathologist performed histopathological evaluations independently. Tumors containing tumor cells less than 50% of total cell mass as well as tumor margins containing any tumor cell were excluded from analysis. The tissue samples were stored at -80 ℃ until analysis. After the samples were cut and weighed (0.02-0.03 g), phosphate buffer saline (PBS, pH 7.2-7.4) was used to remove blood. The samples were frozen with liquid nitrogen and maintained at 2-8 ℃ after melting. Two hundred µg/L of 0.2M PBS (pH 7.4) were added and the samples were homogenized by vortexing. Centrifugation was done at 13,000 rpm for 20 min and the supernatant was removed. All Se measurement in both tissue fluid and serum were carried out in Kavosh Laboratory (Gorgan, Iran) using an atomic absorption spectrometer with longitudinally heated graphite atomizer (Agilent-AA240) and Zeeman background correction. In brief, 50 µL of sample were diluted with 450 µL of an aqueous solution of Triton, which was prepared by diluting 600 µL Triton X-100, 5 mg ascorbic acid and 2.5 ml nitric acid in 500 ml water. After diluting the samples and the calibration standard materials, 30 µL of the diluted samples and 20 µL of the freshly prepared matrix modifier (500 mg/L palladium chloride) were injected into the furnace with an auto-sampler (Varian-PSD120). Se hollow cathode lamp (Agilent Technologies) was also used for the analysis. HER2 expression in breast cancer tissues was evaluated by immunohistochemistry tests. Chi-square test was performed using IBM SPSS Statistics (version 25) for data analysis.

## RESULTS

About 30% of the samples were positive for HER2 expression. Mean level of Se in tumors and tumor margins of HER2-positive tissues was 268.15 µg/L and 165.36 µg/L, respectively. Mean level of Se in tumors and tumor margins of HER2-negative tissues was 206.43 µg/L and 184.39 µg/L, respectively. There was no significant association between Se level and HER2 expression in breast cancer tissues ($P>0.05$).

## DISCUSSION

The association between Se intake and breast cancer incidence is still unclear. We found no association between Se level and HER2 expression in breast cancer tissues. In addition, there was no significant relationship between Se level and breast cancer.

Khandelwal et al. reported that Se is cytotoxic to triple negative (ER-/PR-/HER2-) breast cancer cell lines (10). In another study, Se could synergistically enhance the growth-inhibitory effect of chemotherapeutic agents against triple negative breast cancer cells (11). It has been also claimed that Se can increase oxidative stress, stimulate growth-inhibitory effects, and induce apoptosis in triple negative breast cancer cell lines but not in non-tumorigenic cells (12). It has been also suggested that organic Se supplementation

may reduce/delay breast cancer metastasis (13). A study on Japanese women reported a significant difference in Se levels between newly diagnosed breast cancer patients and healthy counterparts (14), whereas other studies found no relationship between Se level and breast cancer risk or incidence (15-17).

## CONCLUSION

Based on the results, we conclude that there is no association between Se level and HER2 expression in breast cancer tissue.

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## CONFLICT OF INTEREST

The authors declare that there is no conflict of interest.

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