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Evaluation of Interleukin-17 A Levels in Patients with Breast Carcinoma

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Abstract

Breast cancer is a highly common form of cancer that impacts a considerable proportion of women on a global scale. Interleukin 17A (IL-17A) is a cytokine that has both anti-tumor and pro-tumor effects, which can vary depending on the specific tumor microenvironment. The aim of this study was to determine whether IL-17A can be used as a biomarker for diagnosis of breast cancer. Therefore, we compared concentrations of serum IL-17A in patients suffering from breast carcinoma and normal control women by an enzyme-linked immunosorbent assay (ELISA). This study included 86 women, 44 patients that were diagnosed with breast carcinoma, and 42 normal control women. Serum IL-17A levels in both case and control groups were measured by sandwich ELISA kits. The IL-17A serum level was significantly higher among patients with breast carcinoma than in the control group (p<0.001). The serum IL-17A concentration was significantly higher in estrogen receptor-positive cases than in estrogen receptor-negative cases (p=0.033). The highest levels of IL-17A were detected in patients with stage 2 breast carcinoma rather than stage 3 with no significant correlation. There was no correlation between IL-17A level and tumor size, lymph node invasion, or metastasis in patients with breast cancer. In conclusion, a high level of IL-17A in breast carcinoma patients compared to the control group was detected in our study. It indicates that IL-17A could be a promising biomarker for diagnosis of breast cancer and may play a role in tumor development. High levels of IL-17A were not a predictor of poor prognosis in breast cancer patients as it was not related to tumor size, lymph node invasion, or metastasis.

Keywords: Interleukin-17A, breast carcinoma, enzyme-linked immunosorbent assay (ELISA).

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Introduction

Breast cancer is presently the most widespread form of cancer that affects women globally. In Egypt, it accounts for around 33% of female cancer cases and more than 22,000 new cases being identified annually.[1] While it was previously believed that breast cancer incidence increased with age, recent studies have indicated that the majority of cases occur in women between the ages of 40 and 49.[2]

Interestingly, around 7-10% of cases are detected in women who are younger than 40 years old.[3]

Breast cancer has complex causes that can be divided into genetic and non-genetic factors.[4] Genetic risk factors are evaluated through testing for four high-penetrance genes. Non-genetic factors include female hormones and lifestyle habits such as alcohol consumption and obesity. Both genetic and non-genetic factors can influence the microenvironment of breast cancer patients.[5] The presence of inflammation is a crucial factor in the advancement and occurrence of breast cancer, chronic inflammation can trigger the transformation of cells to malignant ones and obstruct anti-tumor immunity, eventually resulting in the development and spread of cancer. This relationship between inflammation and cancer has been the focus of many studies.[5,6]

Interleukin-17 (IL-17) is a pro-inflammatory cytokine that triggers the proliferation, invasion, and metastasis of breast cancer cells and is linked to poor prognosis.[7] Recently, IL-17 was associated with programmed cell death.[8] While IL-17 was produced mainly by Th17 cells, now it is known that many cells, including Tumor-Infiltrating Lymphocytes (TILs), neutrophils, mast cells, and macrophages, can produce IL-17.[9] IL-17 levels may increase due to autoimmune diseases, infections, or malignant tumors.[10]

In breast cancer, IL-17 has both direct and indirect effects. It directly promotes angiogenesis and changes gene expression profiles making tumor cells more aggressive.[11] Indirectly, IL-17 relies on neutrophils that trigger the growth of primary breast tumors.[12] IL-17 also inhibits apoptosis by activating the nuclear factor-κB (NF-κB) pathway, leading to the expression of anti-apoptotic genes in tumor cells and promoting immune resistance.[13]

Our study aimed to determine whether IL-17A can be a biomarker for diagnosis of breast cancer. Therefore, we evaluated concentrations of IL-17A in the serum of patients suffering from breast carcinoma and normal control women by an enzyme-linked immunosorbent assay (ELISA) sandwich method.

Subjects and Methods

The study population included 86 women attending the clinic at Baheya Center for Early Detection and Treatment of Breast Cancer. Participants were divided into two groups. The first group included 44 newly diagnosed patients with breast carcinoma as confirmed by histopathological examination before the start of treatment. Patients data including age, stage of the tumor, tumor size, lymph node invasion, metastasis, estrogen receptors, progesterone receptors, Herceptin II, and histopathology, were obtained from the hospital pathological records of the patients. The second group included 42 normal control women, without a history of autoimmune diseases or malignancies.

A blood sample (5 ml) was withdrawn from each case and control participant, sera were separated and stored at −80°C until used in ELISA analysis.

Assessment of IL-17A concentration in the blood by Enzyme-Linked Immunosorbent Assay (ELISA)

Measurement of IL-17A serum levels in all participants was performed by a commercially available sandwich ELISA kits (Cat. No. EH3267, Fine Biotech, China) according to the manufacturer's instructions. The optical densities of the final ELISA products were measured using a microtiter reader (Multiskan FC, Thermo Scientific, USA).

Statistical Analysis

Data were analyzed using the Statistical Package for the Social Sciences (SPSS) version 24. Numerical data are expressed as mean and standard deviation (±SD), median, interquartile range, or range as appropriate. Qualitative data are expressed as frequency and percentage. The Chi-square (Fisher's exact) test was used to examine the relation between qualitative variables as appropriate. The Student t-test was used to compare the mean and SD of 2 sets of quantitative normally distributed data, while the Mann Whitney test was used when this data were not normally distributed. Finally, Spearman's correlation was used to study the correlation between two variables when data

was not normally distributed. A *p-value* less than or equal to 0.05 was considered statistically significant.

Results

This study included 86 women, 44 patients with breast carcinoma, 42 of them were diagnosed with invasive ductal carcinoma (IDC) and two patients with invasive lobular carcinoma (ILC) of the breast, confirmed by histopathological examination and the control group which included 42 normal control women. Measurement of IL-17 level in blood was done by ELISA.

Demographic data of patients

The age of the patients ranged between 31 and 76 years, with a mean of 55.18 ± 10.466 years, while the mean age of the control group was 51.93 ± 10.28 with no difference between the two groups. Breast carcinoma was more common between the age group 51-60 years (43.2%), followed by 41-50, 61-70 years (both were 20.5%), patients less than 40, and more than 70 years were the least affected group (7.7%).

Clinical characteristics of patients

Of the 44 breast carcinoma patients enrolled in this study, 33 (75%) patients were positive for both estrogen (ER) and progesterone (PR) receptors (81.4% ER^+, 90.7% PR^+), 9 (20.9%) positive for human epidermal growth factor receptor-II (HER-II), and 2 (4.5%) triple negative. Most of the cases, 33 (75%) were in stage 2 breast carcinoma and the rest of them in stage 3. Twenty-six cases (59.1%) had lymph node invasion, while 10 cases (22.7%) were positive for distant metastasis (Table 1).

Table 1. Clinical characteristics of the 44 patients with breast carcinoma.

Clinical data	Status	Case group No. (%)
Histopathology	IDC	42 (95.5%)
	ILC	2 (4.5%)
Stage	2	33 (75%)
	3	11 (25%)
ER	Positive	35 (81.4%)
	Negative	9 (20.5%)
PR	Positive	39 (90.7%)
	Negative	5 (11.4%)
HER-II	Positive	9 (20.9%)
	Negative	35 (81.4%)
Tumour Size	Mean ± SD	3.417 ± 2.143
	Min - Max	1.5 – 14 cm
Lymph node invasion	Positive	26 (59.1%)
	Negative	18 (40.9%)
Distant Metastasis	Positive	10 (22.7%)
	Negative	34 (77.3%)

IDC: invasive ductal carcinoma, ILC: invasive lobular carcinoma, ER: estrogen receptors, PR: progesterone receptors, HER-II: human epidermal growth factor receptors II

Assessment of IL-17A concentration and its relation to clinical characteristics of patients

The IL-17A serum levels were significantly higher among breast cancer patients than in the control group (p <0.001) (Table 2, Figure 1). The concentrations of IL-17A were significantly higher in ER-positive cases than in the negative cases (p= 0.033). The highest levels of IL-17A were detected in patients with positive ER, positive PR, and negative HER-II receptors.

Table 2. Comparison between IL-17 levels among control and breast carcinoma groups.

IL-17	Cases (no=44)	Controls (no= 42)	*p-value
Mean ± SD	79.2818 ± 109.152	16.63 ± 13.148	
Median	33.8	11	<0.001
Min-max	9.8 – 442 pg/ml	3.4 – 50 pg/ml	

*The Mann-Whitney test was used. $p \leq 0.05$ is significant.

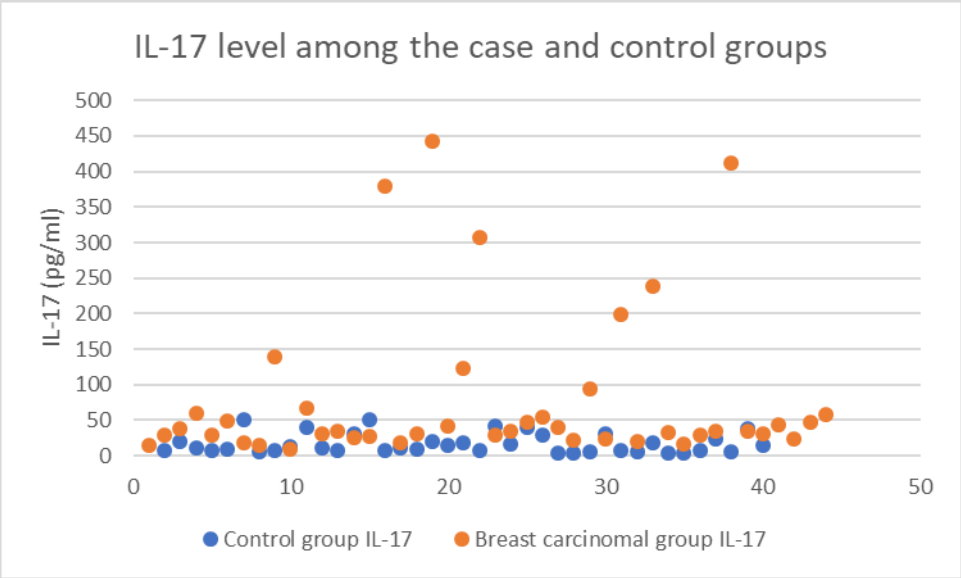

Figure 1. Interleukin 17A (IL-17A) levels among the breast carcinoma group and the control group.

The highest levels of IL-17A were detected in patients with stage 2 breast carcinoma rather than stage 3, but the difference did not reach statistical significance. There was no statistically significant difference in IL-17A concentrations regarding the state of lymph nodes or distant metastasis. There was no relation between the tumor size, local inflammatory reaction, or lymphatic infiltration and the IL-17A levels (Table 3).

Table 3. Association between IL-17 and clinical characteristics of patients.

Clinical data	Status	IL-17 Median (IQR)	*p-value*
Histopathology	IDC	38.2 (25.6)	NS*
	ILC	33.8 (36.55)	
Stage	2	35.85 (62.35)	NS*
	3	33.7 (17.6)	
ER	Positive	39.7 (65.7)	0.033*
	Negative	26.45 (9.3)	
PR	Positive	34.2 (36.5)	NS*
	Negative	29.55 (265.1)	
HER-II	Positive	33.7 (20)	NS*
	Negative	34 (55.15)	
Age	r=0.3		NS**
Tumour Size	r= -0.074		NS**
Lymph Node invasion	Positive	33.0 (97.9)	NS*
	Negative	37.5 (25.6)	
Distant Metastasis	Positive	29.0(28.6)	NS*
	Negative	34.2(65.9)	
Local Inflammatory Reaction	Positive	33.7 (24.9)	NS*
	Negative	35.8 (100.4)	
Local Lymphatic Infiltration	Positive	33.8 (28.7)	NS*
	Negative	33.8 (32.6)	

ER: estrogen receptors, PR: progesterone receptors, HER-II: human epidermal growth factor receptors II
r is the coefficient of Spearman correlation. *Mann-Whitney test was used. **Spearman correlation was used
$p > 0.05$ is not significant (NS).

Discussion

Breast cancer is one of the most prevalent types of female malignancies, and the leading cause of death in these patients, attributed to the metastasis of cancer cells to other organs.[14] The cytokine IL-17 is predominantly secreted by Th17 cells, and it is known to induce inflammation and plays a role in both innate and adaptive immune responses. It is implicated in several diseases, including autoimmune diseases, infections, and cancer.[15] Recent studies suggested that IL-17 has both oncogenic and antitumor effects, it can promote tumor progression by enhancing tumor immune evasion and activating tumor angiogenesis through its signal transduction pathway, leading to increased secretion of vascular endothelial growth factor (VEGF) in the tumor.[16] On the other hand, IL-17 can enhance the activation of natural killer (NK) cells and cytotoxic T lymphocytes (CD8) and recruit neutrophils, NK, CD8, and helper T cells (CD4) to tumor tissue, thus exerting an antitumor effect.[15,17] This dual role of IL-17 makes it a "double-edged sword" in oncology.[15]

The present study was designed to compare serum IL-17A concentrations in breast carcinoma patients and normal control women by ELISA. In the current study, the IL-17A serum levels were significantly higher among patients with breast carcinoma than in the control group. This result was similar to what was reported by many other authors. The study by Liu *et al.,* 2022,[18] compared the expression levels of IL-17 and other cytokines (IL5, IL-6, IL 8 and VEGF) among patients with benign and malignant breast tumors and found that IL-17 levels were higher in the breast cancer group than in the group with benign breast disease. They concluded that the levels of IL-17, IL-6, and VEGF in serum are significantly linked to the onset, advancement, and spread of breast cancer, and that these biomarkers have the potential to serve as monitoring parameters for evaluating clinical prognosis and treatment efficacy.

A study by Ali *et al.,* 2020,[19] employed immunohistochemical staining techniques to assess the expression of IL17 in both benign and malignant breast tumors. The results indicated that malignant cells exhibit considerably elevated levels of IL17 expression when compared to benign tumor cells. A study conducted by Borj *et al.,* 2017,[20] measured the concentrations of IL-17, and other cytokines in the serum and tumor tissues of patients with malignant and benign breast tumors, they revealed a significant increase of IL-17 in both serum samples and tumor tissues of patients with malignant tumors compared to the other group. The study by Chen *et al.,* 2013,[21] utilized immunohistochemistry to examine IL-17 expression in 207 breast carcinoma samples. They observed that increased IL-17-producing cells within the breast cancer tumor microenvironment is a predictor of poor prognosis.

On the other hand, Avalos-Navarro *et al.,* 2019,[22] observed lower levels of serum IL-17E in breast cancer patients compared to healthy controls. The variation of IL-17 levels in breast carcinoma patients may be due to several reasons, including the stage of breast cancer, the presence of other inflammatory conditions, and genetic factors. Another factor that may contribute to these discrepancies is the variation in breast cancer phenotypes within patients. Different phenotypes of breast cancer patients have distinct immune responses, disease pathogenesis, and responses to treatment. It is important to further investigate these factors to better understand the role of IL-17 in breast cancer and potentially develop new therapeutic strategies.[23]

Several research studies have explored the role of IL-17 in various types of cancer. For instance, Baharlou *et al.,* 2014,[24] found that reduced levels of IL-17 and tumor growth factor-β (TGF-β) could be important predictors for monitoring the progression of bladder cancer. Wang *et al.,* 2010,[25] also observed a significant increase in IL-17 and IL-6 mRNA expression in skin cancer, which promoted tumor growth. The study by Zhang *et al.,* 2009,[26] observed high levels of IL-17 in hepatocellular carcinoma tissues. In ovarian cancer, high expression of IL-17 was found to play a significant role in tumor growth through angiogenesis.[27] In a study by Radosavljevic *et al.,* 2010[28], it was found that patients with colorectal carcinoma had notably elevated levels of IL-17 in their serum compared to the control group.

Regarding the relation between IL-17 levels and the clinical characteristics of patients, there was no relation between the tumor size and the IL-17A levels in the current work. Similarly, Chen *et al.,* 2013,[21] revealed that there was no correlation between tumor size, stage, or nodal invasion and the increased abundance of IL-17-producing cells. However, Ariyanaa *et al.,* 2020,[29] reported that the concentration of IL-17 in tissue was related to tumor size, with an increase in its level observed in tumors with a size of ≥ 50 mm. On the other hand, Oda *et al.,* 2012,[30] observed that the presence of IL-17F^{+} T-cells in tumor infiltrates was linked to smaller tumor size.

In the current work, patients with stage 2 breast carcinoma exhibited the greatest concentrations of IL-17A compared to patients in stage 3 with no statistically significant difference. The findings of Ariyanaa *et al.,* 2020,[29] were similar to the present study, as they also observed that the highest increase in

IL-17 levels occurred in patients with stage 2 cancer compared to other stages.

In this study, there was no statistically significant difference between IL-17A and lymph node invasion or distant organ metastasis in breast cancer patients. Similar results were reported by Liu *et al.* (2022).[18] Conversely to our study findings, several other studies found positive correlations between the abundance of IL-17-expressing cells and the histological grade of tumors, cancer aggressiveness, and a shorter duration of disease-free survival.[21,31,32] According to Cochaud *et al.,* 2013,[9] breast cancer patients with IL-17A-positive tumors are more likely to have lymph node metastasis. This could be due to the notion that IL-17A, triggers the migration and invasion of breast cancer cells, as previously reported by Zhu *et al.,* 2008.[33]

IL-17 has been found to have pro-tumoral effects on several cell lines and mouse models, including proliferation, angiogenesis, invasion, migration, and resistance to treatments. These effects may occur through direct signaling *via* IL-17 receptors that activate mitogen-activated protein kinase and nuclear factor kappa B (NF-Kb). Additionally, IL-17 cytokines can indirectly affect cytokine secretion in both immune and non-immune cells surrounding the tumor.[34]

Breast cancer can be categorized into different subtypes based on molecular markers' expression, including ER, PR, and HER-II. The triple-negative subtype is one of these types characterized by the absence of ER and PR expression, as well as the lack of HER-II amplification. This subtype is not responsive to hormonal therapy or HER-II targeted agents.[35] Research studies have indicated that tumor cells of triple-negative breast carcinoma exhibit increased expression of IL-17. The overexpression of IL-17 may contribute to the promotion of active tumor angiogenesis through its signal transduction pathway, which results in the elevation of VEGF secretion within the tumor, ultimately leading to the progression of cancer.[16]

Regarding the association between IL-17A level and the expression of hormonal receptors (ER, PR, and HER-II), 44 patients with breast carcinoma were enrolled in our study, among these patients, 33 (75%) patients were diagnosed as hormone receptor-positive, 9 (20.9%) as HER-II positive, and 2 (4.5%) as triple negatives. The concentration of IL-17A was significantly higher in ER-positive cases than in negative cases (p= 0.033). Patients with positive estrogen and progesterone receptors and negative HER-II receptors had the highest levels of IL-17A.

In accordance with our result, Fuseini *et al.,* 2019,[36] showed a direct relation between IL-17 and ER, they concluded that there was a signaling pathway *via* ERα results in the enhancement of IL-17A production in Th17 cells, through the upregulation of IL-23R expression, and the stimulation of mitochondrial respiration and proliferation. However, the study by Ali *et al.,* 2020,[19] reported that there was no significant correlation between IL17 expression in breast tissue and the ER, PR, and HER-II. Furthermore, Slattery *et al.,* 2014,[37] suggested that the function of IL17 in breast cancer may be independent of hormonal receptor expression. Conversely to our study, Liu *et al.,* 2022,[18] indicated that IL-17 concentrations were higher in HER-II receptor-positive and triple-negative patients than in hormone receptor-positive patients, and this difference was significantly significant. A study by Chen *et al.,* 2013,[21] indicated that a higher abundance of IL-17-producing cells was linked to negative ER/PR status and the triple-negative molecular subtype.

Several other studies have demonstrated the relationship between estrogen status and IL-17A, ER signaling deficiency was shown to promote the differentiation of Th17 cells.[38] In breast cancer, high levels of estrogen receptors can reduce the expression of programmed cell death protein-1 and the infiltration of CD8 T cells by suppressing the infiltration of Th17 cells and the signal transduction of IL-17.[39]

In our opinion, the current study had one limitation, the relatively small sample size, particularly for patients with advanced breast cancer. In conclusion, a high level of IL-17 in breast carcinoma patients compared to the control group was detected in our study. It indicates that IL-17 could be a promising biomarker for diagnosis of breast cancer and

that this cytokine may play a role in tumor development. High levels of IL-17 were not a predictor of poor prognosis for patients with breast cancer as it was not related to tumor size, lymph node invasion, or metastasis.

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Author Contributions

HME, collected data, processed the necessary methods & techniques for conducting the study, analyzed the data, and reviewed the research. NMG, determined the study objectives & designed the research protocol, wrote, edited, evaluated, and analyzed the results of the research. MMK, supervised the technical and scientific work of the study. IM, conducted statistical analysis and interpretation of the data.

Declaration of Conflicting Interests

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Ethical approval

The study protocol was reviewed and approved by the Baheya Research Ethics Committee, Cairo, Egypt (approval number: 202302200005).

Informed consent

Informed verbal consents were obtained from all women participating in this study.

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