

2-23-2026

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Fouad Najm Najm Abed

Department of Biotechnology, College of Science, University of Baghdad, Baghdad, Iraq,
fouad.najm1106a@sc.uobaghdad.edu.iq

Suhad Saad Saad Mahmood

Department of Biotechnology, College of Science, University of Baghdad, Baghdad, Iraq,
suhad.mahmood@sc.uobaghdad.edu.iq

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How to Cite this Article

Abed, Fouad Najm Najm and Mahmood, Suhad Saad Saad (2026) "Investigating Interleukin-19 and Interleukin-33 in Breast Cancer of Iraqi Women: An Immunohistochemical Study," *Baghdad Science Journal*: Vol. 23: Iss. 2, Article 8.

DOI: <https://doi.org/10.21123/2411-7986.5200>

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RESEARCH ARTICLE

Investigating Interleukin-19 and Interleukin-33 in Breast Cancer of Iraqi Women: An Immunohistochemical Study

Fouad Najm Abed¹, Suhad Saad Mahmood¹ *

Department of Biotechnology, College of Science, University of Baghdad, Baghdad, Iraq

ABSTRACT

Cytokines are immune elements that have been found as marker either for tumor-promoting or inhibiting effects on breast tumor development, depending evidently on their exact quantities as well as the existence of additional modifying variables. The study aims to evaluate the relationship between breast cancer tissue and the expression level of IL-19 and IL-33. This study includes using breast cancer tissue (30 specimens) and normal breast tissue (20 specimens) to analyze the expression level of IL-19 and IL-33. Using immunohistochemical technique, the results indicated that IL-33 and also IL-19 were strongly elevated in patients with stage II and stage III of BC, compared to stage I. Also, IL-33 and IL-19 were highly expressed in patients with grade II and grade III BC, compared to grade I. In cancer tissues, expression of IL-33 and IL-19 was higher than in normal breast tissues. These data imply that IL-33 and IL-19 may play a significant role in the progress of BC and may be helpful biomarkers to identify the progress and metastasis of BC.

Keywords: Breast cancer, Cytokines, Immunohistochemistry, IL-19, IL-33, Stage

Introduction

Breast cancer is one of the most prevalent malignancies, represents 15% of the latest incidences of cancer in women, posing a major threat to their health, and lives.¹ It also accounts for 11.6% of all neoplasms around the world in 2018.^{2,3} The prognosis for aggressive and metastatic breast cancer continues to be dismal despite significant advancements in surgery, radiation, chemotherapy, and endocrine therapy.³ Breast cancer is the second leading cause of cancer-related fatalities in Iraq and one of the major causes of female carcinoma, accounting for nearly one-third of all female cancers reported in the most recent Iraqi cancer registry.³ Cytokines produced by endothelial cells and cancer cells play important roles in cancer by promoting angiogenesis, promoting cancer growth, enhancing cancer cell migration and allowing them to evade immune surveillance through

autocrine or paracrine processes. Endothelial cells and cancer cells can respond to chemoattractants as chemokines and growth factors.⁴ Chemokines may also improve cancer cells' capacity to spread through metastatic processes;⁵ however, the exact processes are still unknown. Investigation of diverse cytokine expression levels in a number of human malignancies, such as human breast cancer, has proven that cytokine expression is enhanced in a variety of cancers and that the rise has a cancer promoting effect.⁶ This is consistent with the hypothesis that cancer cells use the production of chemokine receptors and chemokines to activate the immune system, cause cancer angiogenesis and cancer development, modify the cancer microenvironment, and promote metastasis.⁷ Cytokines are key intercellular regulators for angiogenesis as well as the invasion of leukocytes in breast tumors, and based on their exact quantities and the presence or absence of distinct regulatory

Received 5 March 2024; revised 29 September 2024; accepted 1 October 2024.
Available online 23 February 2026

* Corresponding author.

E-mail addresses: fouad.najm1106a@sc.uobaghdad.edu.iq (F. N. Abed), suhad.mahmood@sc.uobaghdad.edu.iq (S. S. Mahmood).

<https://doi.org/10.21123/2411-7986.5200>

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elements in the tumor microenvironment, they can either promote or hinder the progression of the disease.⁸ Breast cancer proliferation and invasion are influenced via variations in the proportional levels of various cytokines, including transforming growth factor (TGF- β 1), IL-19, IL-11, IL-6 and IL-1, which are mediated either directly or indirectly by the cancer.⁹

The cluster of genes that make up the IL-10 family contains IL-19, IL-20, IL-22, IL-24 (MDA-7), IL-26 (AK155), IL-28, and IL-29.^{10,11} Many reports have shown that IL-19 has Pro-inflammatory effects.^{12,13} Conversely, IL-19 has anti-inflammatory properties that have been identified in inflammatory bowel disease¹⁴ and inflammatory vascular disease.¹⁵ IL-19 expression is elevated when monocytes are activated by cytokines (IL-4, IL-6, IL-17, and TNF- α), lipopolysaccharide (LPS) and granulocyte-macrophage colony-stimulating factor (GM-CSF).^{16,17} Monocytes' synthesis of IL-6 and TNF- α and T cells' release of Th2 cytokines are both stimulated by IL-19.¹⁸ Nuclear translocation and Tyrosine phosphorylation of STAT3 are stimulated by IL-19.¹⁹ IL-19 was largely produced by macrophages, with minor contributions from B cells and non-immune cells like skin keratinocytes, endothelial cells, and fetal membranes.²⁰ IL-19 is associated with several diseases and conditions, including asthma,²¹ breast cancer,²² periodontal and vascular disease, endotoxic shock,²³ psoriasis,²⁴ uremia,²⁵ and rheumatoid arthritis.²⁶

The cytokine interleukin-33 (IL-33) is a member of the IL-1 family and is essential for cancer immunity.²⁷ One of IL-33's natural receptors is suppressing tumorigenicity 2 (ST2). The destruction of stromal cells triggers necrosis and produces IL-33, which bonds with heterodimeric ST2 on the outer layer of a variety of immune cells. The IL-33/ST2 signal stimulates transcription of downstream anti-inflammatory and inflammatory genes by activating several intracellular kinases and proteins, resulting in an appropriate immune response even in the tumor microenvironment.²⁷ It is believed that IL-33 is a modulator of the elements regulating T helper (Th)2 activities, including the disorders connected to its ligand. Allergies, cancer, and cardiovascular illnesses are just a few of the conditions that are strongly associated with the IL-33-ST2 axis.²⁸ By enhancing CD8 + T cell function and increasing IFN- γ production, IL-33 creates a cancer microenvironment that encourages the full remission of the tumor.²⁹ In a CD8 + T cell-dependent way, recombinant IL-33 significantly contributes to extending the surviving duration of rats suffering acute myeloid leukemia (AML).³⁰ Recombinant IL-33 significantly contributes to extending the surviving

duration of rats suffering acute myeloid leukemia (AML).²⁹ Myeloid and lymphoid cell viability and survival are controlled by IL-33, which is essential for the synthesis of type 2 immune mediators.³¹ Th2 cells, Treg cells, and ILC2 are among the lymphoid cells that have ST2. Th2 cells are the first to express ST2. The Th1 response predominates in anti-cancer immunity. When the body primarily displays the Th2 phenomenon, it means that the body's ability to fight tumors is being inhibited.³² The study aims to evaluate the relationship between breast cancer tissue and the expression level of IL-19 and IL-33.

Materials and methods

Collection of specimens

Thirty-five fresh pieces of malignant breast tissue were collected from BC patients at Baghdad Teaching Hospital, a medical city. The age range of women patients was from 35 to 76 years old. Fifteen fresh normal breast tissues were collected from dead women at the medico-legal directorate in the Baghdad Department of the Dead, the range of age was from 26 to 53 years old. All specimens were fixated on 10% formalin. Those specimens were examined and diagnosed by using hematoxylin and eosin-stained histopathological examination as carcinoma and normal tissues by histopathologists at the pathology Lab of the National Center of Teaching Labs in Medical City.

Preparing paraffin-embedded tissue blocks

After fixation of specimens in 10% formalin, specimens were cut with a surgical knife to 2.5 mm * 2 mm. Then, it was transferred to a special plastic cassette. Formalin-fixed (10%) specimens dehydrated with series alcohol concentrations (70% for 1hr, 80% for 1hour, 90% for 1hour, and 100% for 12 hours) were then transferred into a xylene bath for 1 hour and changes of xylene then repeat xylene path for 1 hour. After clearing by xylene, specimens were infiltrated with paraffin wax (which melted at 54–60 °C) in a beaker and two changes of paraffin wax for 1 hour each.³³

Removing paraffin, rehydration, and staining

10% formalin-fixed Paraffin-embedded specimen blocks were cut into 4-m sections and mounted on charge slides before being fixed for 30 minutes in a hot air oven at 65 °C. Dewax the slides with xylene for three adjustments for 5 minutes each. The excess liquid was whisked off and hydrated slides by series

alcohol concentration as below: 100%, 90%, 80%, 70%, then D.W. for 5 min each. Staining the slides with hematoxylin for 5 minutes, then washing by D.W. The slides are then stained with eosin for 5 seconds before being washed with D.W. Dehydration of the slides by series alcohol concentrations as follows: 70%, 80%, 90%, and then 100% for 1 minute each clearing by xylene for 1 minute and covered by cover slide slipping with Dibutylphthalate Polystyrene Xylene (dpx). Those paraffin-embedded tissue blocks were examined and diagnosed as carcinoma and normal tissues by histopathologists at the pathology Lab of The National Center of Teaching Labs in Medical City.³⁴

Immunohistochemistry experiments

Immunohistochemistry for Interlukin-19 and Interlukin-33

Human IL-19 and IL-33 ELISA Kit-Elabscience employed.

Antigen retrieval

The antigen retrieval solution was completed and ready for use. The slides were washed with deionized distilled water and placed in a plastic staining jar containing the antigen retrieval solution. The plastic staining jar was laid in the water bath at 97 °C for 40 minutes, ensuring the slides were still covered with the retrieval solution. The cooling time was at least 20 minutes at room temperature.

Preparation of working solutions

To prepare each working solution, freshly prepared buffers were employed. The following supplies were used in this process:

EnVision FLEX substrate working solution

EnVision FLEX Substrate Working Solution is prepared by mixing it thoroughly with 1 drop of EnVision FLEX DAB+ Chromogen (3,3N-Diaminobenzidine Tertrahydrochloride) per 1 mL of EnVision FLEX Substrate Buffer (Buffered solution containing hydrogen peroxide and preservative).

Procedure of staining

Reading slide and scoring method

Pathologist examining was performed for each slide using the double-blind procedure. The pathologist was demanded to recount any counts where there was a variance of more than 10%. After DAB formation, the presence of brown-yellow pigmentation

or brown-yellow granules in the cell was interpreted as indication that IL-19 and IL-33 was present. Utilizing the semi-quantitative integration method,³⁴ the results were calculated. In particular, three randomly selected locations were examined using a light microscope with a magnification of x200, and the percentage of cells that stained positive and the staining intensity were used to calculate scores. 1 point was given for staining less than 1/3 of the total cells, 2 points for staining between 1/3 and 2/3 of the cells, and 3 points for staining more than 2/3 of the cells. Having a score of 0 means there was no color, a score of 1 means there was light yellow coloration, a score of 2 means there was brownish yellow coloration, and a score of 3 means there was brown color. Thus, two scores were obtained for each segment. The following criteria were used to assess the positive of studied interleukin in the section: 3 points (1+); 4-5 points (2+); and 6-9 points (3+). The two values were summed to produce a final score. The sections were considered IL-negative if their overall IL score was less than two.³⁵

Statistical analysis

The data were analyzed using IBM Corp.'s SPSS 22.0 software, and the results were displayed as percentages. Using the χ^2 test, the groups were compared, and the association between IL-19 and IL-33 was evaluated using Spearman's correlation analysis. A difference with statistical significance was defined as $P < 0.05$.

Results and discussion

Table 1 demonstrates that all of the breast cancer tissues had positive expression of IL-19, with positive staining primarily found in the cytoplasm and cell membrane with a scattered pattern, Fig. 1. It was shown that IL-19 was negatively expressed in all normal breast tissues. In contrast to breast normal tissues, breast cancer tissues had a much greater positive expression rate of IL-19. The current findings agree with those described in the research.³⁶

IL-19 both directly and indirectly influences cancer proliferation, migration, and progression by triggering other mediators. We indicate that IL-19 is an essential, specific regulator in the microenvironment that influences the growth of breast cancer cells. The current results imply that elevated IL-19 expression in breast cancer cells may be an important factor influencing cancer development and a predictor of poor prognosis among people with this type of cancer.³⁷ The presence of IL-19 receptors

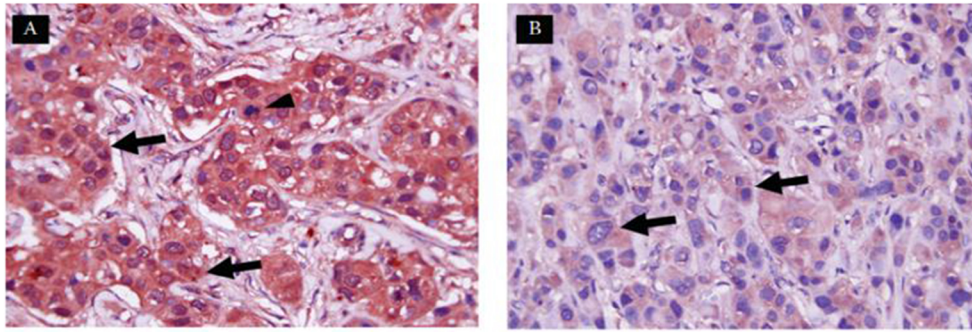


Fig. 1. Expression of IL-19 and IL-33 in tissues with cancer (immunohistochemical staining at x40 magnification). The cytoplasm of the cells in breast cancer tissue was shown to have positive expression of IL-19 (A) and IL-33 (B) (arrows).

Table 1. Summary of IL-19 score on normal and breast cancer tissues.

		IL-19 score in BC tissues				IL-19 score in normal tissues
		No score	+	++	+++	No score
Age groups (year)	20-29	0	0	0	0	2
	30-39	0	0	2	2	6
	40-49	1	1	3	2	5
	50-59	0	2	3	4	2
	60-69	0	2	2	7	-
	70-79	0	2	1	1	-
Total		1	7	11	16	15

in breast cancer cells suggests that IL-19 acts as an autocrine mediator in breast cancer. IL-19 influences breast cancer migration, cell proliferation, and cancer growth. Additionally, it raised the expression of TGF- β , MMP-1, and CXCR4, inflammatory mediators that are involved in angiogenesis (MMP-1), metastasis and migration (CXCR4 and MMP-1), and the proliferation of cancer cells (TGF- β).³⁸

Table 2 indicates that all of the breast cancer tissues had positive expression of IL-33, with the majority of the positive staining being found in the cytoplasm and nucleus as present in Fig. 1. The expression of IL-33 was negative in all normal breast tissues. The current findings agree with those described in the research.³⁰ The current results imply that elevated IL-33 expression in breast cancer cells may be an important factor influencing cancer development and

a predictor of poor prognosis among people with this type of cancer. IL33 is a multifunctional regulator secreted by fibroblasts, epithelial cells, endothelial cells, macrophages, and dendritic cells; it has an immunosuppressive function during cancer development, reducing the participation of cancer-related cytokines and triggering immune escape and cancer growth.³⁹

In the current investigation, cancer cells were shown to express IL-33 in practically all breast cancer patients. Normal breast tissue, on the other hand, lacked IL-33 expression. It was evident that breast cancer tissues had a greater percentage of IL-19 positive than normal breast tissues. The findings demonstrated a significant positive correlation ($P < 0.01$) between the positive expression rates of IL-19 and IL-33.

Table 2. Summary of IL-33 score on normal and breast cancer tissues.

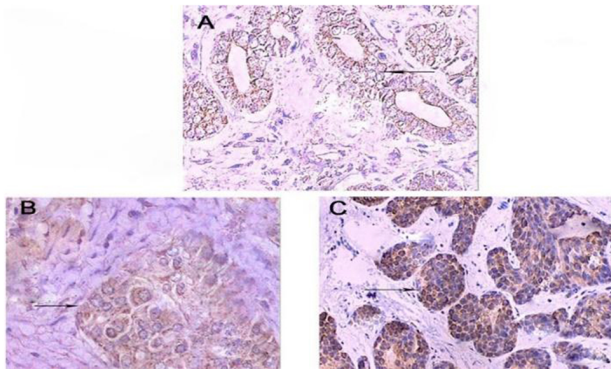
		IL-33 score in cancer tissues				IL-33 score in normal tissues
		No sore	+	++	+++	No score
Age group	20-29 year	0	0	0	0	2
	30-39	0	1	2	1	6
	40-49	2	0	1	4	5
	50-59	1	1	4	3	2
	60-69	1	2	3	5	-
	70-79	0	1	3	0	-
Total		4	5	13	13	15

Table 3. IL-19 and IL-33 score on breast cancer tissues in different stages.

		IL-33 score in cancer specimens				IL-19 score in cancer specimens			
		No score	+	++	+++	No score	+	++	+++
stage	I	4	1	0	0	1	4	0	0
	II	0	4	10	1	0	3	9	3
	III	0	0	3	12	0	0	2	13
total		4	5	13	13	1	7	11	16

Table 4. IL-19 and IL-33 score on breast cancer tissues in different grades.

		IL-33 score in cancer specimens				IL-19 score in cancer specimens			
		No score	+	++	+++	No score	+	++	+++
grade	I	4	5	5	0	1	7	6	0
	II	0	0	8	5	0	0	5	8
	III	0	0	0	8	0	0	0	8
total		4	5	13	13	1	7	11	16

**Fig. 2.** IL-19 expression in cancer tissues stage I (A), stage II(B) and stage III (C), (immunohistochemical staining magnification, x40) In breast cancer tissues.

Relationship between cancer stage and grade with IL-19 and IL-33 expression

As shown in Table 3, the expression of IL-19 and IL-33 in stages II and III was significantly higher than that in stage I ($P < 0.05$) Fig. 2. Table 4 shows the expression of IL-19 and IL-33 in the grade II and III was significantly higher than that in the grade I ($P < 0.05$) Table 4. IL-19 and IL-33 expression in breast cancer is clearly related to cancer stage and grade. Several studies indicated that IL-33 and IL-19 levels were considerably higher in patients with stage III breast cancer compared to other stages and controls.³³ The finding could be explained by the following mechanism: Cancer cells, tumor-associated macrophages, DCs, and regulatory T cells in the cancer microenvironment can all produce IL-33, which inhibits the production of IL-2 and TNF- α , inhibiting T cell proliferation and death.³⁸

Furthermore, cytokines are effective mediators of acquired and innate cellular immunities, and they are most likely engaged in the process of cancer cell escape from the immune surveillance network.

This could likely be one of the pathways by which IL-19 accumulation enhances cancer progression in vivo in breast cancer cells. Several studies found an association between cancer and an inflammatory environment.⁴⁰

TGF- β was found to be increased in cancer patients, according to Takahashi et al.⁴¹ IL-33 was eventually classified as a member of the IL-1 family of cytokines based on its structural features and interaction with a heterodimer receptor composed of IL1RAcP and ST2, both of which are members of the IL-1 family of receptors.⁴² However, significant differences were not observed between positive IL-19 as present in Table 1 and IL-33 result with age as presented in Table 2.

Conclusion

IL19 expression was positively linked with IL33 expression in breast cancer. The expression of IL-19 and IL-33 did not appear to be related to patient age. IL19 and IL33 expression, on the other hand, were related to breast cancer stage and grade. Therefore, the basic mechanisms may be based on IL19 and IL33's ability to influence each other and their cooperative involvement in the progression of breast cancer. These findings suggest that IL-19 and IL-33 may play a crucial role in the development and advancement of breast cancer. Further research is needed to fully understand the relationship between these two interleukins and their impact on the disease. Targeting the IL-19 and IL-33 pathways could potentially lead to new therapeutic strategies for the treatment of breast cancer.

Acknowledgment

We would like to express our gratitude to the medical staff of the Baghdad Hospital at the Medical City

/ Baghdad - Iraq. We would also like to show our deep appreciation to the medico-legal directorate/ Baghdad - Iraq.

Authors' declaration

- Conflicts of Interest: None.
- All the Figures and Tables in the manuscript are ours. Any Figures and images, that are not ours, have been included with the necessary permission for re-publication, which is attached to the manuscript.
- No animal studies are present in the manuscript.
- Author(s) signed on ethical consideration's approval.
- Ethical Clearance: The project was approved by the local ethical committee at University of Baghdad.

Authors' contributions statement

F.N.A. conceived the idea, designed, acquired the data and drafted the manuscript. While S.S.M interpreted the results of the study, did the revision, paraphrasing and proofreading of the manuscript.

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دراسة الإنترلوكين-19 والإنترلوكين-33 في سرطان الثدي لدى النساء العراقيات: دراسة مناعية كيميائية

فؤاد نجم عبد، سهاد سعد محمود

قسم التقنيات الاحيائية، كلية العلوم، جامعة بغداد، بغداد، العراق.

الخلاصة

السيتوكينات هي عناصر مناعية لوحظ انها لها دور إما للتأثيرات المعززة للورم أو المثبطة لتطور ورم الثدي، وهذا يعتمد بشكل واضح على كمياتها الدقيقة بالإضافة إلى وجود عوامل اخرى . تهدف الدراسة إلى تقييم العلاقة بين أنسجة سرطان الثدي ومستوى التعبير عن IL-19 و IL-33. تتضمن هذه الدراسة استخدام أنسجة سرطان الثدي (30 عينة) وأنسجة الثدي الطبيعية (20 عينة) لتحليل مستوى التعبير عن IL-19 و IL-30. باستخدام تقنية المناعة الكيميائية، أشارت النتائج إلى أن IL-33 و IL-19 كانا مرتفعين بشدة في المرضى الذين يعانون من المرحلة الثانية والثالثة من سرطان الثدي، مقارنة بالمرحلة الأولى. أيضًا، تم التعبير عن IL-19 و IL-33 بشكل كبير في المرضى الذين يعانون من الدرجة الثانية والثالثة من سرطان الثدي، مقارنة بالدرجة الأولى. في أنسجة السرطان، كان التعبير عن IL-19 و IL-33 أعلى من الأنسجة الطبيعية للثدي. تشير هذه البيانات إلى أن IL-19 و IL-33 قد يلعبان دورًا مهمًا في تقدم سرطان الثدي وقد يكونان بمثابة مؤشرات حيوية مفيدة لتحديد تقدم سرطان الثدي وتطوره.

الكلمات المفتاحية: سرطان الثدي، IL-19، IL-33، التحليل الكيميائي المناعي، السيتوكينات، الدرجة.