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Study Expression of HDAC3 and HDAC6 in Women with Breast Cancer under Chemotherapy and Immunotherapy

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Abstract: Breast cancer exhibits considerable heterogeneity in its molecular and clinical features, and is one of the most common cancers among women worldwide. It has multiple causes, including genetic and non-genetic factors. It also poses a major challenge in diagnosis and therapeutic monitoring, especially in light of the complexity of the tumor's immune environment and the variability of responses to treatment. The current study aimed to investigate some molecular biomarkers. The gene expression of Histone Deacetylase 3 (HDAC3) and Histone Deacetylase 6 (HDAC6) was evaluated in breast cancer patients undergoing chemotherapy and immunotherapy, compared to a control group of healthy women. The study included 40 patients previously diagnosed with breast cancer by the medical staff at the Salah al-Din Oncology Center, during the period from July 2024 to August 2024, in addition to 20 healthy female participants (controls). Women with breast cancer were divided into two groups according to the type of treatment: the first group (chemotherapy group) included 20 samples. The second group (immunotherapy group) included 20 samples. The third group was the control group, with 20 samples. Gene expression was quantified using RT-qPCR. The results showed that HDAC3 gene expression was significantly decreased in the patient group compared to the control group ($p=0.006$), with the decrease being more pronounced in the chemotherapy group, reaching ($p=0.003$) compared to the control group. As for HDAC6, gene expression was significantly decreased in patients compared to the control group ($p=0.047$). Although lower values were recorded in the chemotherapy group, the differences between the groups were not statistically significant ($p>0.05$). Meanwhile, ROC analysis showed that HDAC3 had a higher diagnostic ability ($p=0.009$, AUC=0.701) compared to HDAC6, which had a moderate diagnostic ability ($p=0.042$, AUC=0.659). Correlation analysis results also revealed a strong positive relationship between HDAC3 and HDAC6 ($r=0.679$, $p<0.001$), while no statistically significant correlation was recorded between immune variables and age. These findings suggest that the molecular markers HDAC3 and HDAC6 may play an important role in regulating the tumor immune environment and determining treatment response, and may serve as promising markers for breast cancer diagnosis and monitoring. However, further studies are needed to determine their prognostic significance and therapeutic implications, particularly in the context of combination therapies.

Keywords: Breast cancer, Histone deacetylases, HDAC3, HDAC6, Chemotherapy, Immunotherapy, Biomarkers, Real-time PCR.

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Introduction

Breast cancer is a type of cancer that originates in breast tissue, most often in the inner lining of milk ducts or the lobules that supply these ducts with milk. The disease primarily affects women, but it can also affect men (1)(2). It is one of the most common

types of cancer among women worldwide, with approximately 2.3 million new cases recorded in 2020, representing 11.7% of all diagnosed cancer cases. Approximately 685,000 women died from the disease that same year, according to data from the International Agency for Research on Cancer (3). Furthermore, the development of breast cancer is influenced by multiple factors, including genetic and environmental variables (4). Despite significant advances in diagnostic techniques and traditional treatments, including surgery, chemotherapy, radiation, and molecular targeting, mortality rates remain high due to metastasis and drug resistance (5). Therefore, there remains a need to identify new biomarkers that can contribute to early detection of breast cancer and improve treatment response, especially given the molecular and immunological diversity of the tumor.

In recent years, there has been growing interest in studying the role of the tumor's immune microenvironment in breast cancer progression. Epigenetic modifications, particularly histone acetylation and methylation, have been shown to play an important role in regulating gene expression, and disruption of these processes can lead to the silencing of tumor suppressor genes. In this context, HDACs, particularly HDAC3 and HDAC6, have received increasing attention due to their role in chromatin regulation and inhibiting the expression of genes associated with apoptosis (6). HDAC3, a member of the first class of these enzymes, contributes to maintaining genome stability by primarily targeting histones, affecting chromatin structure and gene expression. It also interacts with nuclear hormone co-repressors such as N-CoR and SMRT. HDAC3 inhibits gene expression by directly binding to these co-repressors. (7). While HDAC6 has unique properties that include its activity in both the cytoplasm and the nucleus, its association with non-histone cellular functions, and its influence on a wide range of signaling pathways and cellular processes, making it a promising potential therapeutic target for cancer treatment (8), its molecular role in breast cancer remains a subject of scientific controversy, with studies showing conflicting prognostic results.

In summary, HDAC3 and HDAC6 are critical for breast cancer progression via regulation of gene expression, tumor microenvironment modulation, and resistance mechanisms to treatment. Understanding their distinct and overlapping functions provides a foundation for the development of more effective therapeutic strategies targeting these enzymes in breast cancer treatment.

Materials and methods

Sample Collection

From July through August of 2024, research samples were gathered from Salah al-Din Oncology Centre located in Tikrit and Oncology. Based on the medical staff's exams and the results of past breast cancer diagnoses, they included 60 research samples from women. The goal of the research was to evaluate the expression levels of HDAC3 and HDAC6 in breast cancer patients receiving chemotherapy and immunotherapy in women in the Salah al-Din Governorate and Mosul city of Iraq who had been diagnosed with breast cancer. Based on the type of treatment, the afflicted women were split into two groups: The first group (chemotherapy-treated patients) included 20 breast cancer patients aged between 35-68 years. The second group

(immunotherapy-treated patients) included 20 breast cancer patients aged between 34-83 years. Additionally, 20 blood samples were collected from healthy women with no history of breast cancer, aged between 30-84 years, to serve as controls. Information about participants was collected through an information form that included much information related to the subject of the study.

Sample preparation for molecular studies:

250 microliters (µl) of blood were placed in an Eppendorf tube containing 750 µl of TRIzol reagent. The contents were mixed well to ensure homogeneity, then the mixture was stored at –20°C until RNA extraction and the necessary molecular analyses were performed.

RNA Extraction

Total RNA was extracted from blood samples using the TransZol Up Plus RNA Kit (TransGen Biotech, China; Cat No. ER501), following the manufacturer's protocol.

cDNA Synthesis

Complementary DNA (cDNA) was synthesized using the 5× RT PCR MasterMix (TransGen Biotech, China; Cat. No. PC5801).

Quantitative Real-Time PCR (qRT-PCR)

Quantitative real-time PCR was performed to evaluate the expression levels of HDAC3 and HDAC6 using the Universal Super SYBR Master Mix (Tinzyme, China; Product Number: PCM60) Table (1).

Table (1): RT-PCR Reaction Program

Number of Cycles	Time/second		Temperature (°C)	Phases
Holding stage1	3min		94	Enzyme activation
40	15sec		94	Denaturation
	45sec		60	HDAC3 primer binding/elongation
	45se		60	HDAC6 primer binding/elongation
95cº/15se-60/1min-95cº/30se-60cº/15se				Dissociation

Primers used in RT-PCR

Primers were designed to detect gene expression of (HDAC3, HDAC6) genes in the study samples based on the information available in NCBI by Prof. Dr. Ahmed Abdul Jabbar Suleiman Antar—University of Anbar. The reference gene's primer pair was standardized for all samples, and the primers were obtained in a lyophilized form Table (2).

Table (2): Primers used in RT-PCR

primer	Sequence	Tm (C°)
HDAC3	F 5`- CCCTTGCCCCTTATTTCTTC -3` R 5`- GCCCCTTCCAAATCTCTCTC -3`	57
HDAC6	F 5`- ACGGTCCCTCTTCACCTTCT -3` R 5`- CAGGGGGAGATCCACAATTA -3`	57
GADPH	F 5`- TGCCACCCAGAAGACTGTGG -3` R 5`- TTCAGCTCAGGGATGACCTT -3`	58

Ethical Considerations

This study was conducted with official approval from the Department of Postgraduate Studies, College of Science, Tikrit University, through a formal task facilitation letter (No. [3024], dated [2024/6/24]) allowing access to the Oncology Centers for sample collection. The approval included permission to interact with patients and collect clinical data and blood samples. All participants were informed of the study objectives and voluntarily provided their consent before participation, in compliance with the ethical standards of the institution.

Statistical analysis

All statistical analyses were performed using R and GraphPad Prism 10 (United States). Descriptive statistics were calculated for all variables, and normally distributed continuous data presented as mean±standard deviation, and non-normally distributed data as median (interquartile range, IQR). Comparisons between control and patient groups, as well as between chemotherapy and immunotherapy groups, were conducted using independent t-tests for normally distributed variables and Mann-Whitney U tests for non-normally distributed variables. Pearson correlation coefficients (r) were calculated to assess relationships between variables, including age, HDAC3, HDAC6. Statistical significance was set at $p<0.05$ for all analyses.

Result

Plots of known standard concentrations of Human HDAC3 and HDAC6 were generated on a logarithmic scale (x-axis) with their corresponding opti-cal density (OD) readings on a logarithmic scale (y-axis). By setting the OD values of the samples on the y-axis, the concentrations of HDAC3 and HDAC6 in the blood samples were determined. The dilution factor was multiplied to calculate the original concentration. Data were analyzed using R and GraphPad Prism 10 statistical software.

Table 3 presents the clinical and demographic characteristics of the study participants, including age, type of treatment of breast cancer. Participants were divided into three groups: control (n=20), chemotherapy-treated patients (n=20), and immunotherapy-treated patients (n=20). The results showed that there were no statistically significant differences in age between the control group and breast cancer patients ($p>0.06$), where the median age was 42.00 years (IQR: 38.00-51.00) in the control group and 47.00 years (IQR: 42.00-57.75) in the patient group.

Table (3): Demographic characteristics of study participants.

	Control (n= 20)	Patient (n= 40)	*P*-value
Age (years)	42.00 (38.00,51.00)	47.00 (42.00,57.75)	0.06

Moreover, no significant differences were observed in the distribution of patients into age groups (≤50 years vs. >50 years) or in their exposure to chemotherapy, immunotherapy. Additionally, no significant associations were found between family history of breast cancer and treatment type ($p>0.05$). Age was expressed using median and interquartile range (median, IQR), while categorical variables were presented as frequency and percentage. The ages of patients in the two groups were compared using Student's t-test for independent samples, while

categorical variables were analyzed using the chi-square test.

To further investigate the molecular differences between the study groups, we analyzed the gene expression levels of HDAC3 and HDAC6 using quantitative real-time PCR (qRT-PCR). Figure 1A depicts the gene expression fold change of *HDAC3* in control subjects and breast cancer patients. The control group exhibited a higher mean expression level (2.697±0.462) compared to the patient group (1.751±0.336). This difference in *HDAC3* expression between control and patient groups was statistically significant (p=0.006). Further analysis of *HDAC3* expression among control, chemotherapy, and immunotherapy groups revealed distinct patterns Figure 1B. The control group maintained the highest mean expression (2.697±0.462), followed by the immunotherapy group (2.343±0.598), while the chemotherapy group showed the lowest expression (1.159±0.265). Statistical analysis indicated that only the chemotherapy group differed significantly from the control group (p=0.003). The immunotherapy group, despite showing a slightly lower mean expression than the control group, did not exhibit a statistically significant difference. These findings suggest that chemotherapy may be associated with a more pronounced downregulation of *HDAC3* expression compared to immunotherapy in breast cancer patients.

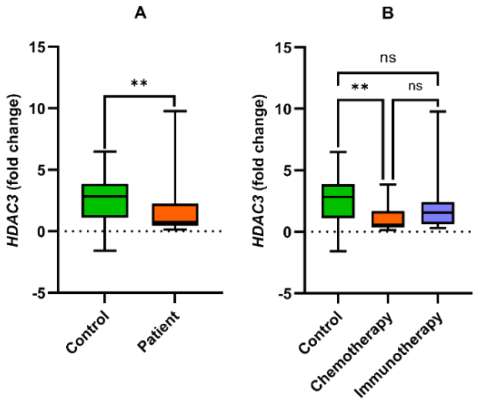

Figure (1): *HDAC3* gene expression fold change in control subjects and breast cancer patients: A) comparison between control and all patients, and B) comparison among control, chemotherapy, and immunotherapy groups.

Analysis of *HDAC6* gene expression revealed statistically significant differences between study groups. In the comparison between control subjects and breast cancer patients (Figure 2A), control individuals exhibited significantly higher HDAC6 expression levels (2.697±0.462) compared to patients (2.009±0.312, p=0.047). This observed difference suggests a downregulation of *HDAC6* in breast cancer patients, which may have implications for disease progression or treatment response. Further investigation into *HDAC6* expression patterns among control, chemotherapy, and immunotherapy groups showed distinct tendencies (Figure 2B), although these differences did not reach statistical significance (all p>0.05). The control group maintained the highest expression levels (2.697±0.462), followed closely by the immunotherapy group (2.437± 0.529). In contrast, the chemotherapy group displayed lower *HDAC6* expression (1.581±0.316).

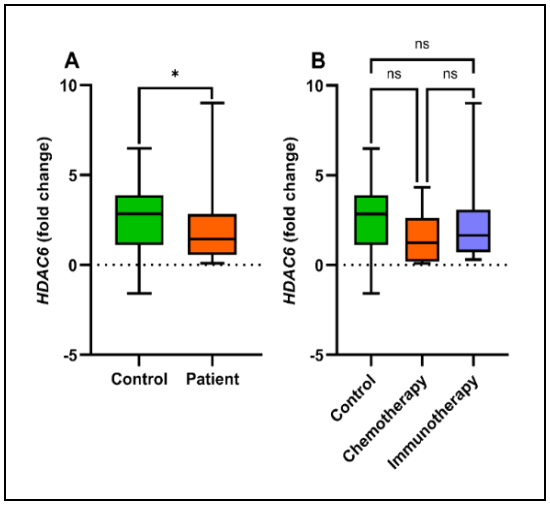

Figure (2): *HDAC6* gene expression fold change in control subjects and breast cancer patients: A) comparison between control and all patients, and B) comparison among control, chemotherapy, and immunotherapy groups.

Table (4): Correlation analysis of age, *HDAC3*, and *HDAC6*.

Variable 1	Variable 2	Correlation	*P*-value
Age	HDAC3	-0.161	0.219
Age	HDAC6	-0.082	0.536
HDAC3	HDAC6	0.679	<0.001

To further explore potential interactions between these histone deacetylases, a Correlation analysis was performed to examine the relationships between age, *HDAC3*, and *HDAC6* (Table 4). The results revealed several noteworthy associations. A strong positive correlation was observed between *HDAC3* and *HDAC6* (r= 0.679, p<0.001) which suggests a probable functional relationship between these two histone deacetylases in the context of breast cancer. Interestingly, age did not show significant correlations with any of the other variables examined (all p>0.05), which suggests that the expression or levels of *HDAC3*, *HDAC6* may not be strongly influenced by patient age in the group.

Receiver Operating Characteristic (ROC) curve analysis was performed to evaluate the diagnostic value of *HDAC3* and *HDAC6* in recognizing breast cancer patients from healthy controls (Table 5).

Table (5): Receiver Operating Characteristic (ROC) analysis of HDAC3, HDAC6 for distinguishing breast cancer patients from healthy controls.

	Cut-off	AUC	Sensitivity (95%CI)	Specificity (95%CI)	*P*-value
HDAC3	≤2.422	0.701	80 (64.4 - 90.9)	65 (40.8 - 84.6)	0.009
HDAC6	≤2.633	0.659	75 (58.8 - 87.3)	65 (40.8 - 84.6)	0.042

In contrast, Figure 3 illustrates that *HDAC3* showed the highest diagnostic accuracy with an AUC of 0.701 (p=0.009). At an optimal cut-off value of ≤2.422, *HDAC3* showed a sensitivity of 80% (95% CI: 64.4% - 90.9%) and a specificity of 65% (95% CI: 40.8% - 84.6%). The *HDAC6* also had significant diagnostic potential (Figure 4), with an AUC of 0.659 (p=0.042). At a cut-off value of ≤2.633, *HDAC6* demonstrated a sensitivity of 75% (95% CI: 58.8% - 87.3%) and a specificity of 65% (95% CI: 40.8% - 84.6%). These findings indicate that while both HDAC3 and HDAC6 hold promise as

diagnostic markers, HDAC3 exhibits slightly superior diagnostic performance in distinguishing breast cancer patients from healthy individuals.

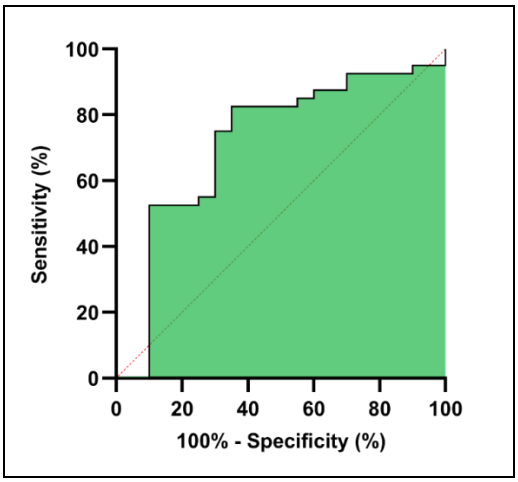

Figure (3): ROC curve analysis of *HDAC3* for differentiating breast cancer patients and healthy controls.

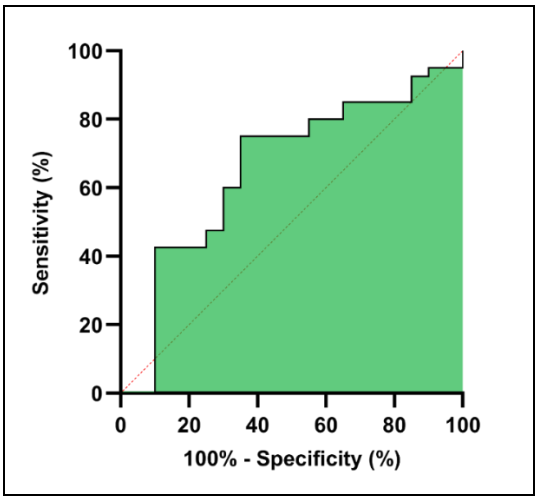

Figure (4): ROC curve analysis of *HDAC6* for differentiating breast cancer patients and healthy controls.

Discussion

The present study investigated the expression levels of HDAC3 and HDAC6 in breast cancer patients who received chemotherapy and immunotherapy versus healthy controls. Our findings indicate a significant downregulation of both HDAC3 and HDAC6 in breast cancer patients compared to controls, with a more pronounced reduction of HDAC3 in chemotherapy-treated patients. In contrast, differences in HDAC6 expression between treatment groups were not statistically significant. These results provide insight into the potential role of HDACs in breast cancer progression and therapeutic response.

HDAC3 Expression in Breast Cancer

Histone deacetylase 3 (HDAC3) a well-established nucleus factors involved in chromatin reorganization and transcriptional repression with the potential to influence pathways associated with the regulation of cell proliferation, apoptosis, and tumor microenvironmental remodeling (9). This study showed the same substantial

downregulating for HDAC3 in breast cancer patients as described by Bhaskara et al.,2010, the down-regulation of HDAC3 expression was observed in breast cancer tissues, speculating that the loss of HDAC3 might be related to effective DNA repair impairement, thus promoting tumor progression(10).

However, our findings contradict those of Rahbari *et al.* (2022), who found that HDAC3 was overexpressed in breast cancer lesions, and that overexpression is more pronounced in aggressive breast cancer subtypes (11). This apparent inconsistency might depend on the different source of samples, since we analysed HDAC3 mRNA expression in peripheral blood, while Rahbari et al. concentrated on tumor tissues, which could be associated with local, not systemic, alterations. There are also some potential sources of variations that are likely due to differences in patient subgroups, treatment exposure and analytical methods (qRT-PCR vs. immunohistochemistry). The enhancement of HDAC3 suppression in chemotherapy-treated patients indicates a possible mechanistic interplay between the action of chemotherapeutic agents and that of HDAC3. Studies showed that inhibition of HDAC3 enhances apoptosis from chemotherapy through suppression of DNA damage repair mechanisms, ultimately rendering cancer cells more- susceptible to treatment (12). This supports the hypothesis that HDAC3 expression is being downregulated by chemotherapy on its own, potentially simply due to cell cycle arrest and possibly also due to negative feedback regulation.

HDAC6 Expression in Breast Cancer

HDAC6, the unique cytoplasmic deacetylase implicated in protein degradation, immune modulation, and epithelial-mesenchymal transition (EMT), demonstrated dramatically reduced expression in the breast cancer patients of our study, This aligns with findings from Zhang and colleagues (2004), who reported that patients expressing elevated HDAC6 mRNA and protein had a better prognosis than those with lower expression levels, in terms of disease-free survival (13). However, this contradicts earlier studies indicating HDAC6 overexpression, particularly in triple-negative breast cancer (TNBC), where higher levels associate with enhanced tumor aggressiveness and resistance to therapy (14). The inconsistency may originate from distinctions in breast cancer subtypes and therapeutic exposure histories, as well as divergences in analytical techniques (tumor biopsies versus blood analyses). While our results note marginally elevated HDAC6 expression in immunotherapy-treated patients, this disparity proved statistically insignificant Prior research suggests that HDAC6 inhibition could improve immunotherapy efficacy by modulating the tumor microenvironment and augmenting T-cell infiltration (15). Thus, additional research should explore whether HDAC6 may serve as a biomarker predictive of immunotherapy response.

Correlation between HDAC3 and HDAC6

The strong positive relationship between HDAC3 and HDAC6 expression levels observed in this study ($r = 0.679$, $p < 0.001$) implies potential co-regulation or functional interplay in breast malignancy. This data correlates with past examinations demonstrating that HDAC3 and HDAC6 can sway similar oncogenic pathways involved in cellular proliferation and survival. Namely, research has revealed that both HDAC3 and HDAC6 play a role in

mediating estrogen receptor signaling and HER2 amplification, which are critical in breast cancer progression (16). However, the exact biomolecular systems behind this correlation remain enigmatic, necessitating additional exploration to decide whether their synchronized expression contributes straight to tumor formation or mirrors broader epigenetic dysregulation in the disease. The interplay between these histone deacetylases warrants supplementary inspection to elucidate how their combined action impacts the disease on a molecular scale.

Diagnostic Potential of HDAC3 and HDAC6

The Receiver Operating Characteristic (ROC) curve analyses uncovered moderate diagnostic aptitude for both biomarkers, with HDAC3 (AUC = 0.701, p = 0.009) outperforming HDAC6 (AUC = 0.659, p = 0.042). While these metrics indicate potential usefulness as diagnostic indicators, they are inferior to traditional markers, for example, HER2 and Ki-67, which regularly exhibit AUC > 0.85 in detecting breast cancer (13). However, amalgamating HDAC3 and HDAC6 with other epigenetic markers could heighten diagnostic accuracy, a strategy that has proven to be successful in recent studies on multi-component cancer detection panels (17).

Conclusions

Our investigation highlights the varying expressions of HDAC3 and HDAC6 in breast cancer and their possible diagnostic and therapeutic implications. HDAC3 suppression in chemotherapy-treated patients was more pronounced, suggesting chemotherapeutic agents may modulate HDAC3 expression levels. However, further exploration is needed to clarify HDAC6 expression patterns and their role in immunotherapy response. To enhance clinical applicability, future studies should examine HDAC3 and HDAC6 in different breast cancer subtypes such as ER-positive versus TNBC. Additionally, investigating HDAC inhibitors combined with chemotherapy and immunotherapy in clinical settings may provide useful insights. Developing multimarker panels integrating HDACs with traditional markers like HER2 and Ki-67 could help refine diagnostic accuracy.

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