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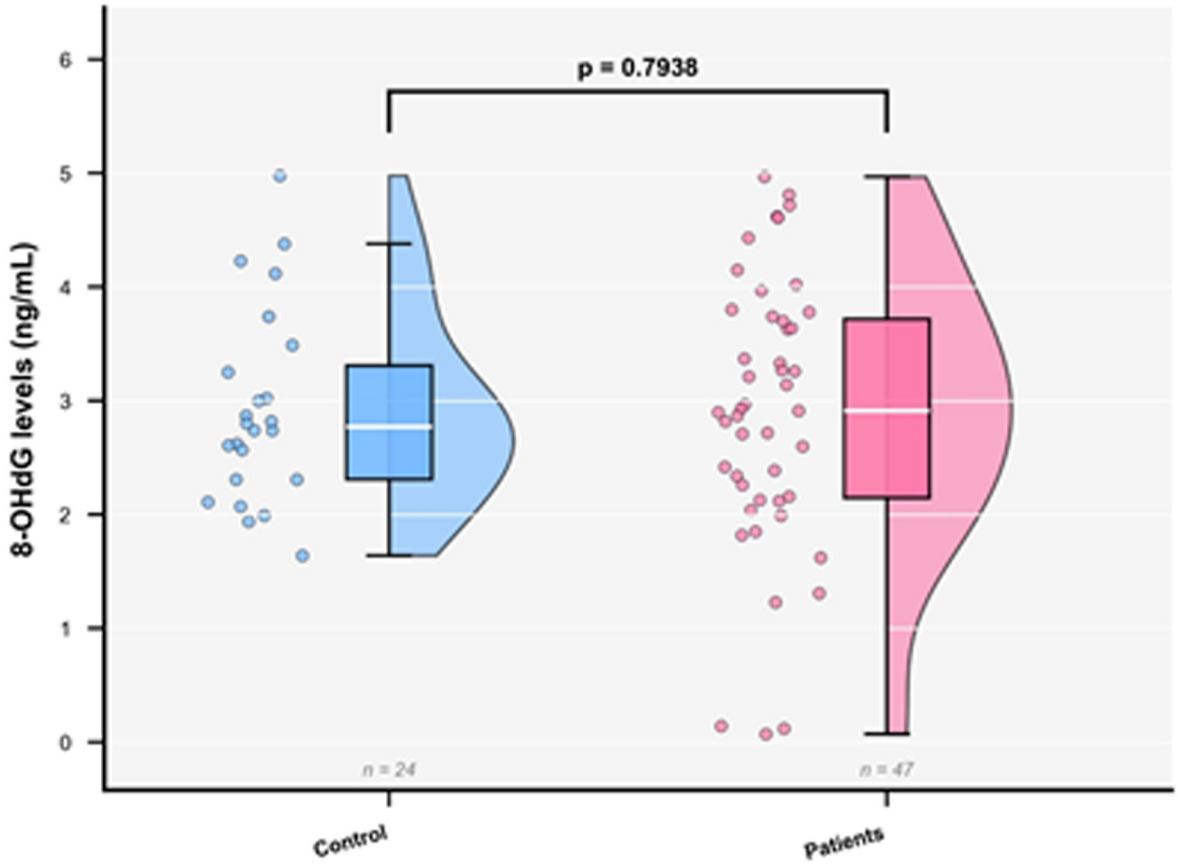

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AIM AND SCOPES
Journal of Cellular Neuroscience and Oxidative Stress is an online journal that publishes original research articles, reviews and short reviews on the molecular basis of biophysical, physiological and pharmacological processes that regulate cellular function, and the control or alteration of these processes by the action of receptors, neurotransmitters, second messengers, cation, anions, drugs or disease.

Areas of particular interest are four topics. They are;

A-Ion Channels (Na^+- K^+ Channels, Cl^- channels, Ca^{2+} channels, ADP-Ribose and metabolism of NAD^+, Patch-Clamp applications)

B-Oxidative Stress (Antioxidant vitamins, antioxidant enzymes, metabolism of nitric oxide, oxidative stress, biophysics, biochemistry and physiology of free oxygen radicals)

C-Interaction Between Oxidative Stress and Ion Channels in Neuroscience
(Effects of the oxidative stress on the activation of the voltage sensitive cation channels, effect of ADP-Ribose and NAD^+ on activation of the cation channels which are sensitive to voltage, effect of the oxidative stress on activation of the TRP channels in neurodegenerative diseases such Parkinson's and Alzheimer's diseases)

D-Gene and Oxidative Stress
(Gene abnormalities. Interaction between gene and free radicals. Gene anomalies and iron. Role of radiation and cancer on gene polymorphism)

READERSHIP

Biophysics	Biochemistry
Biology	Biomedical Engineering
Pharmacology	PhysiologyGenetics
Cardiology	Neurology
Oncology	Psychiatry
Neuroscience	Neuropharmacology

Keywords
Ion channels, cell biochemistry, biophysics, calcium signaling, cellular function, cellular physiology, metabolism, apoptosis, lipid peroxidation, nitric oxide, ageing, antioxidants, neuropathy, traumatic brain injury, pain, spinal cord injury, Alzheimer's Disease, Parkinson's Disease.

RESEARCH ARTICLE

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The Oxidative DNA Damage Marker 8-OHdG Indicates No Clear Association to Newly Detected Breast Cancer in Women

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List of Abbreviations;

***8-OHdG,** 8-hydroxydeoxyguanosine; **BMI,** Body mass index; **DNA,** Deoxyribonucleic acid; **ELISA,** Enzyme-linked immunosorbent assay; **ER,** Estrogen receptor; **HER2,** Human epidermal growth factor receptor 2; **HRP,** Horseradish peroxidase; **IQR,** Interquartile range; **PR,** Progesterone receptor; **ROS,** Reactive oxygen species; **SD,** Standard deviation; **TMB,** 3,3',5,5'-tetramethylbenzidine; **TNM,** Tumor node metastasis; **WHO,** World Health Organization*

Abstract

The role of 8-hydroxydeoxyguanosine (8-OHdG) as a biomarker in breast cancer remains controversial with conflicting results across studies. This case-control study aimed at comparing serum 8-OHdG levels between breast cancer patients and healthy controls, and examine associations with clinical characteristics. Thus, 71 Iraqi women (47 newly diagnosed, treatment-naïve breast cancer patients and 24 controls) were used from November 2024 to June 2025. Demographic data and lifestyle factors were collected through structured questionnaires. No significant difference was found in median 8-OHdG levels between breast cancer patients and controls. No correlations were observed between 8-OHdG and age, BMI, tumor grade, or hormone receptor status. Our findings suggest that 8-OHdG may not serve as a general screening biomarker for breast cancer, as its levels were comparable across all clinical and pathological parameters examined.

Keywords: 8-hydroxy-2'-deoxyguanosine; breast neoplasms; oxidative stress; tumor biomarkers

Introduction

Over the past decades, breast cancer was one of the leading causes of cancer-related mortality among women worldwide (Al-Tameemi et al., 2025). The complex etiology of breast cancer involves multiple factors, yet oxidative stress has gained significant attention as a key mechanism in cancer initiation and progression (Jelic et al., 2021). Nowadays, researchers are increasingly focusing on understanding how oxidative damage contributes to breast carcinogenesis and how multiple factors may influence this process.

Oxidative stress occurs when there is an imbalance between the production of reactive oxygen species (ROS) and the body's antioxidant defense mechanisms (Yağcı et al., 2025; Yaseen et al., 2020; Valavanidis et al. 2009). This imbalance leads to oxidative damage to cellular components, including DNA, which plays a crucial role in cancer development (Kasai et al., 2008). Moreover, the measurement of oxidative DNA damage has become

essential for understanding cancer pathophysiology and identifying potential biomarkers for early detection and prognosis. 8-Hydroxydeoxyguanosine (8-OHdG) has been reported as one of the most reliable and widely used biomarkers for oxidative DNA damage (Huyut et al., 2024; Graille et al., 2020). This modified nucleoside is formed when ROS attack guanine bases in DNA, thus serving as a critical indicator of oxidative stress in various biological systems (Ock, 2012). In recent years, urinary 8-OHdG levels have been extensively used to assess oxidative stress in clinical settings due to their non-invasive nature and correlation with systemic oxidative damage (Loft et al., 1993).

In the context of breast cancer, research has showed complex and sometimes contradictory findings regarding 8-OHdG levels. Several studies have demonstrated that breast cancer patients exhibit elevated levels of 8-OHdG in both tissue and serum samples compared to healthy controls (Nour Eldin et al., 2019; Himmetoglu et al., 2009; Musarrat et al., 1996). However, paradoxically, some investigations have reported that lower levels of 8-OHdG are associated with more aggressive breast cancer phenotypes and poorer prognosis (Liu et al., 2021; Sova et al., 2010). This apparent contradiction suggests that 8-OHdG may play different roles during various stages of breast carcinogenesis. Furthermore, the relationship between 8-OHdG expression and breast cancer subtypes remains unclear. Research has showed that triple-negative breast cancers, which are generally associated with worse outcomes, show lower expression of 8-OHdG compared to other breast cancer subtypes (Jakovcevic et al., 2015). Yet, this finding adds another layer of complexity to understanding the role of oxidative stress markers in breast cancer biology. The prognostic significance of 8-OHdG in breast cancer has been also a subject of considerable debate. While some studies suggest that higher 8-OHdG levels indicate increased cancer risk and more aggressive disease (Nour Eldin et al., 2019; Musarrat et al., 1996), others have found that negative 8-OHdG immunostaining serves as an independent prognostic factor for poorer survival outcomes (Sova et al., 2010). Hence, the interpretation of 8-OHdG levels requires careful consideration of the specific context and methodology used in each study. Interestingly, it has also shown that 8-OHdG levels may decrease during breast cancer progression, potentially supporting tumor growth in later stages (Sova, 2014). This observation agrees with the concept that while high ROS levels may initiate carcinogenesis, lower oxidative stress levels might favor tumor survival and growth in advanced stages of cancer development.

Moreover, the association between oxidative stress markers and breast cancer risk appears to vary depending on menopausal status. Some studies have suggested that DNA damage biomarkers like 8-OHdG may increase the risk of postmenopausal breast cancer, particularly estrogen receptor-positive tumors (Loft et al., 1993). Thus, hormonal factors may play an important role in modulating the relationship between oxidative stress and breast cancer development. Therefore, this study aimed to test whether serum 8-OHdG levels differ between breast cancer patients and healthy controls, and to examine associations with clinicopathological characteristics including tumor grade, hormone receptor status, and molecular subtypes. We hypothesized that 8-OHdG levels would differ between breast cancer patients and healthy controls, potentially serving as a biomarker for disease presence.

Materials and Methods

Study Design and Participants

This case-control study was conducted from November 2024 to June 2025. The participants were recruited from multiple healthcare facilities in Iraq, including Al-Hussain Teaching Hospital and the Cancer's Early Diagnosis Unit in Karbala, the Imam Hussain Oncology and Hematology Center in Karbala. The study protocol was reviewed and approved by the Postgraduate Committee at the Department of Chemistry and Biochemistry of the Medical College of University of Kerbala and the Ethics Committee of the Health Directorate of Karbala (Approval No.: 3986, Date: 03-11-2024). The study was conducted in accordance with the Declaration of Helsinki and Good Clinical Practice guidelines.

The study population consisted of 71 Iraqi women, divided into two groups: 47 newly diagnosed, treatment-naïve patients with histopathologically confirmed breast cancer and 24 healthy controls. For the patient group, inclusion criteria were: female sex, age 18 years or older, histopathologically confirmed diagnosis of primary breast cancer (ductal or lobular carcinoma), newly diagnosed cases who had not received chemotherapy, radiation therapy, or hormonal therapy prior to blood sample collection, and ability to provide informed consent. For the control group, inclusion criteria included: female sex, age-

matched to cases (±5 years), no personal history of any type of cancer, and ability to provide informed consent.

Exclusion criteria for both groups were: pregnancy or lactation at the time of enrollment, previous history of any malignancy other than the current breast cancer diagnosis for the patient group, presence of chronic inflammatory diseases (rheumatoid arthritis, inflammatory bowel disease, or systemic lupus erythematosus), chronic liver or kidney disease, current use of immunosuppressive medications, blood transfusion within the past 3 months, active infection or fever within 2 weeks prior to enrollment, and psychiatric conditions that would impair the ability to provide informed consent. Written informed consent was obtained from all participants prior to enrollment.

Demographic, Life Style and Clinical Data

A comprehensive structured questionnaire was developed and administered through face-to-face interviews to collect detailed demographic and lifestyle information. Demographic data included age, marital status (single, married, divorced, widowed), educational level (uneducated, elementary school, secondary school, or higher education), and current occupation (housewife, employee, or other). For patients, clinical data were extracted from medical records and pathology reports, including tumor characteristics (histological type, grade, size), receptor status (estrogen receptor, progesterone receptor, HER2), TNM staging, and treatment received. Family history of cancer was documented with specific attention to the affected family member and degree of relationship. Moreover, lifestyle factors assessment included smoking status (categorized as never, current, or former smoker), alcohol consumption (recorded as yes/no), and environmental exposure history including questions about occupational or residential exposure to chemicals or radiation. Furthermore, anthropometric measurements were obtained using calibrated equipment. Height was measured to the nearest 0.1 cm using a wall-mounted stadiometer (Seca, Germany) with participants standing barefoot in an upright position. Weight was measured to the nearest 0.1 kg using a digital scale (Seca, Germany) with participants wearing light clothing and no shoes. Body mass index (BMI) was calculated as weight in kilograms divided by height in meters squared (kg/m^2) and categorized according to WHO classification: underweight (<18.5), normal weight (18.5-24.9), overweight (25.0-29.9), and obese (≥30.0).

Blood Sampling and Biochemical Analysis

Venipuncture was performed, to collect 5 mL of venous blood samples from the antecubital vein of all participants, using standard aseptic techniques between 8:00 and 10:00 AM to control for circadian variations in biomarker levels. The collected samples were placed in serum separator gel tubes. Samples were allowed to clot at room temperature for 30 minutes, then centrifuged at 3000 rpm for 10 minutes to separate serum. The resulting serum was carefully aliquoted into 0.5 mL cryovials to avoid repeated freeze-thaw cycles, which can compromise biomarker stability. All frozen samples were maintained in a continuously monitored ultra-low temperature freezer at -80°C.

For oxidative stress assessment, 8-hydroxy-2'-deoxyguanosine (8-OHdG) levels were measured as a biomarker of oxidative DNA damage using a competitive enzyme-linked immunosorbent assay (ELISA) kit (Cat. No. #ab201734, Abcam, UK). All serum samples were diluted 1:2 in assay buffer to fall within the standard curve range. The competitive ELISA protocol involved incubation of samples with HRP-conjugated 8-OHdG antibody, followed by washing and substrate addition. TMB substrate was added and color development was monitored, and finally reactions stopped by the addition of sulfuric acid stop solution when appropriate color intensity was achieved. Absorbance was measured at 450 nm using a microplate reader (BioTek ELx800, USA). Standard curves were generated for each plate using four-parameter logistic regression, with R^2 values ranging from 0.9468 to 0.9754. All samples with coefficients of variation greater than 10% between duplicates were re-analyzed. Quality control included blank wells, positive controls, and verification that all standard curve R^2 values exceeded 0.95. 8-OHdG concentrations were calculated from the standard curves and expressed as ng/mL.

Statistical Analysis

All statistical analyses were performed using Python. Descriptive statistics were calculated for all variables, with continuous data presented as means ± standard deviations or medians with interquartile ranges based on normality distribution assessed by Shapiro-Wilk test, while categorical variables were expressed as frequencies and percentages. For comparison of 8-OHdG levels between breast cancer patients and healthy controls, Mann-Whitney U test was used. Chi-square (or Fisher's exact) test were

Table 1. *Patient demographics and clinical characteristics factors (N= 71).*

Characteristic	Control (n=24)	Breast cancer (n=47)	*P*-value
Age (years)	40.5 (37.0-54.2)	51.0 (41.0-57.0)	0.138
BMI (kg/m²)	30.4 ± 7.8	28.9 ± 5.4	0.354
Marital status			
Married	17 (70.8%)	43 (91.5%)	0.012
Widow	3 (12.5%)	4 (8.5%)	
Single	4 (16.7%)	0 (0.0%)	
Family history			
No	20 (83.3%)	29 (61.7%)	0.102
Yes	4 (16.7%)	18 (38.3%)	
Smoking status			
No	21 (87.5%)	44 (93.6%)	0.399
Yes	3 (12.5%)	3 (6.4%)	
Alcohol consumption			
No	24 (100.0%)	47 (100.0%)	1.000
Grade			
G1	—	6 (12.8%)	NA
G2	—	22 (46.8%)	
G3	—	19 (40.4%)	
Histological type			
Ductal	—	43 (91.5%)	NA
Lobular	—	4 (8.5%)	
ER status			
Positive	—	41 (87.2%)	NA
Negative	—	6 (12.8%)	
PR status			
Positive	—	39 (83.0%)	NA
Negative	—	8 (17.0%)	
HER2 status			
Positive	—	16 (34.0%)	NA
Negative	—	31 (66.0%)	
T stage			
T1	—	12 (25.5%)	NA
T2	—	21 (44.7%)	
T3	—	9 (19.1%)	
T4	—	5 (10.6%)	
N stage			
N0	—	18 (38.3%)	NA
N1	—	16 (34.0%)	
N2	—	9 (19.1%)	
N3	—	4 (8.5%)	
M stage			
M0	—	46 (97.9%)	NA
M1	—	1 (2.1%)	

Data were presented as mean ± SD or median (IQR) based on normality distribution testing.
Categorical variables are presented as frequency (percentage).

used to analyze associations between categorical variables. Pearson or Spearman correlation coefficients were calculated to assess relationships between 8-OHdG levels on one hand and age and BMI on the other hand; and given the significant difference in marital status between groups, correlations with 8-OHdG were adjusted for marital status as a potential confounder. All statistical tests were two-tailed, and *p*-values less than 0.05 were considered statistically significant.

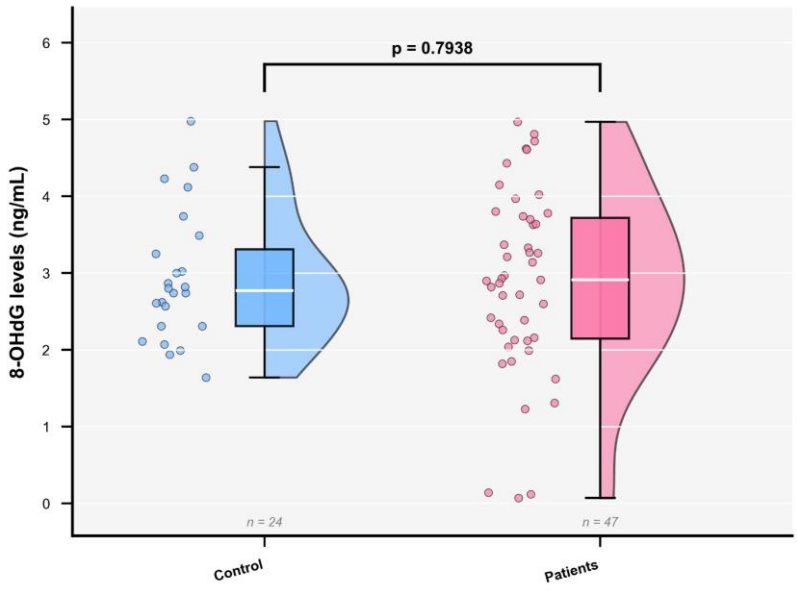

Figure 1*. Comparison of 8-OHdG levels between breast cancer patients (n= 47) and control group (n= 24). Box plots show median (white line), interquartile range (box), and minimum/maximum values (whiskers).*

Results

The overall patient demographics and clinical characteristics were presented in Table 1 and show largely comparable between the breast cancer and control groups, with no significant differences observed in age, BMI, family history, smoking status, or alcohol consumption. However, significant differences were identified in marital status, with a higher proportion of married individuals in the breast cancer group (91.5%) compared to controls (70.8%). Regarding oxidative stress biomarker, Figure 1 shows that 8-OHdG levels were comparable between breast cancer patients 2.91 (2.15-3.72) ng/mL and controls 2.77 (2.31-3.31) ng/mL, with no statistically significant difference (p>0.05). This suggests that oxidative DNA damage marker did not vary significantly between the study groups despite the observed demographic differences.

We also assessed correlations between 8-OHdG and demographic factors (age and BMI) after adjusting for marital status as a probable confounder (Figure 2). 8-OHdG showed no significant correlation with age (r=0.06, p=0.616) or BMI (r=-0.048, p=0.691), which indicates that these fundamental demographic factors do not influence oxidative DNA damage levels in this population even after accounting for marital status differences between groups.

Subgroup analysis of 8-OHdG levels based on various clinical characteristics showed largely consistent oxidative stress patterns (Figure 3). Menopause status showed no significant difference between post-menopausal [3.26 (2.42-4.02) ng/mL] and pre-menopausal patients [2.77 (2.31-3.28) ng/mL, p>0.05]. Similarly, tumor grade also had comparable 8-OHdG levels across G1 [2.38 (2.03-3.18) ng/mL], G2 [2.89 (2.30-3.27) ng/mL], and G3 tumors [3.33 (2.24-4.29) ng/mL, p>0.05]. In addition, hormone receptor status analysis showed no significant variations, with ER-positive tumors displaying 2.91 (2.16-3.70) ng/mL versus ER-negative tumors at 2.63 (0.69-3.71) ng/mL (p>0.05), while PR-positive cases showed 2.91 (2.21-3.69) ng/mL compared to PR-negative cases at 2.83 (1.63-3.77) ng/mL (p>0.05). HER2 status showed virtually identical levels between negative [2.93 (2.21-3.69) ng/mL] and positive cases [2.87 (2.10-3.88) ng/mL, p>0.05].

Discussion

This study found no significant difference in serum 8-OHdG levels between breast cancer patients and healthy controls. Furthermore, 8-OHdG levels showed no significant correlation with age or BMI, and no differences were observed across tumor grades, hormone receptor status, or menopausal status.

The absence of significant differences in 8-OHdG levels between breast cancer patients and controls in our study agrees with several previous investigations. In a

study, Lee et al. reported similar findings in their nested case-control study within the Shanghai Women's Health Study, where urinary 8-OHdG levels did not differ between breast cancer cases and controls (Lee et al., 2010). Similarly, Rossner et al. found no initial association between urinary 8-oxodG levels and breast cancer risk in their analysis of 400 cases and 401 controls (Rossner et al., 2006). Moreover, Yahia et al. recently demonstrated no significant difference in oxidative stress markers between controls and breast cancer patients, concluding that breast cancer patients do not exhibit systemic oxidative stress (Yahia et al., 2025). However, our findings contrast with other studies that reported elevated 8-OHdG levels in breast cancer patients. Musarrat et al. demonstrated significantly higher 8-OHdG levels in malignant breast tissue compared to normal tissue using immune-slot blot assays (Musarrat et al., 1996). Additionally, Li et al. (2001) found that breast cancer patients had significantly higher levels of 8-oxo-dG compared to controls using high-performance liquid chromatography with electrochemical detection (Li et al., 2001). Furthermore, Nour Eldin et al. reported that serum 8-OHdG levels were significantly increased in breast cancer patients compared to controls and showed highest levels in stage I breast cancer (Nour Eldin et al., 2019).

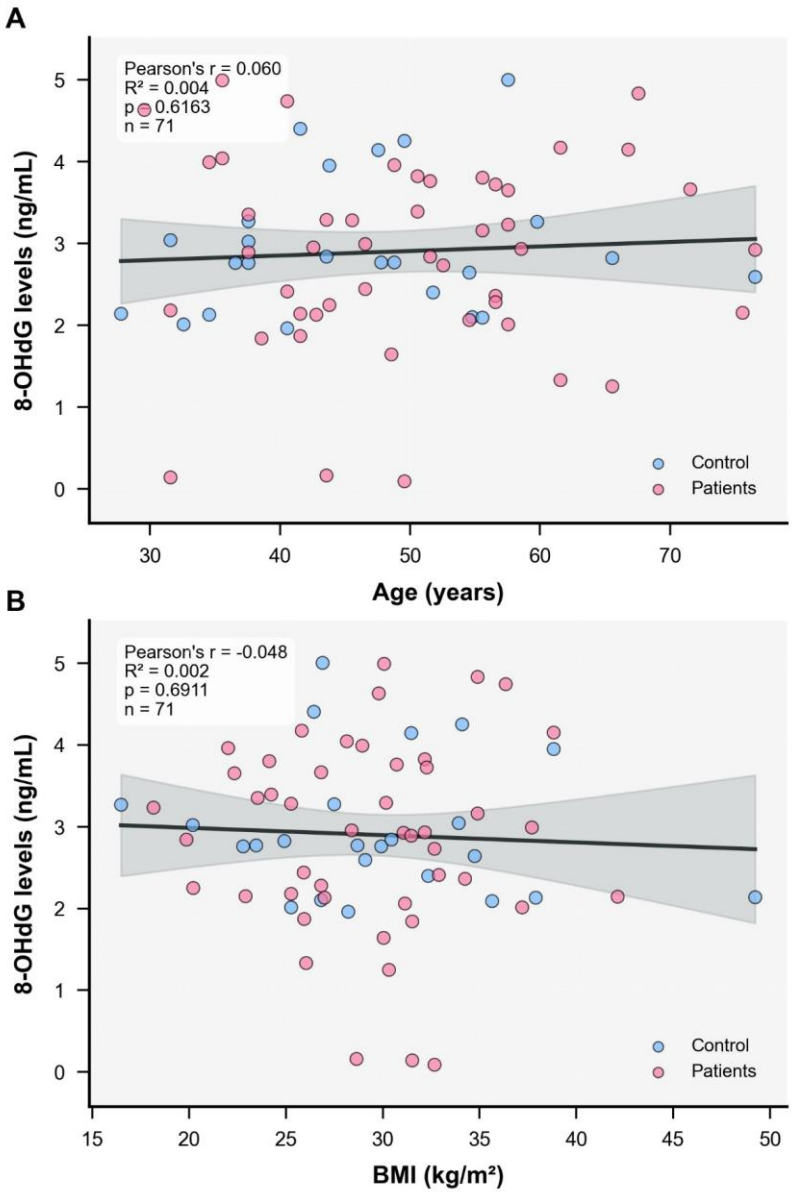

Figure 2. *Correlation analysis of 8-OHdG levels with: A) age and B) BMI, (N= 71), adjusted for marital status.*

The lack of significant differences in 8-OHdG levels across all tumor characteristics examined suggests that this marker may not be useful for breast cancer stratification in clinical practice. Furthermore, the lack of correlation between 8-OHdG levels and traditional prognostic factors such as tumor grade, hormone receptor status, and lymph node involvement suggests that oxidative DNA damage markers may provide independent prognostic information. Loft et al. demonstrated that higher urinary 8-oxodG levels were associated with increased risk of postmenopausal breast cancer, especially estrogen receptor-positive tumors (Loft et al., 1993). In addition, their findings suggested that oxidative stress with DNA damage plays an important role in breast cancer development. However, our study found no significant differences in 8-OHdG levels based on estrogen or progesterone receptor status, which may reflect differences in study populations, measurement techniques, or biological sample types.

Several factors may explain the conflicting results observed across different studies investigating 8-OHdG in breast cancer. First, the choice of biological sample significantly influences results, as showed by studies measuring 8-OHdG in serum, urine, tissue, or saliva. Gornitsky et al. found that salivary levels of 8-oxodG were actually lower in breast cancer patients compared to controls (Gornitsky et al., 2016). Moreover, the analytical methodology used varies considerably between studies, ranging from ELISA-based approaches to high-performance liquid chromatography with electrochemical detection and immunohistochemical staining. Furthermore, the timing of sample collection relative to diagnosis and treatment may significantly influence results. According to our methodology, all samples were collected from treatment-naïve patients, which eliminates the confounding effects of chemotherapy and radiation therapy that have been shown to influence oxidative stress markers. Rossner et al. noted that removing cases with radiation treatment from their analysis revealed a significant inverse trend between 8-oxodG levels and breast cancer risk (Rossner et al., 2006).

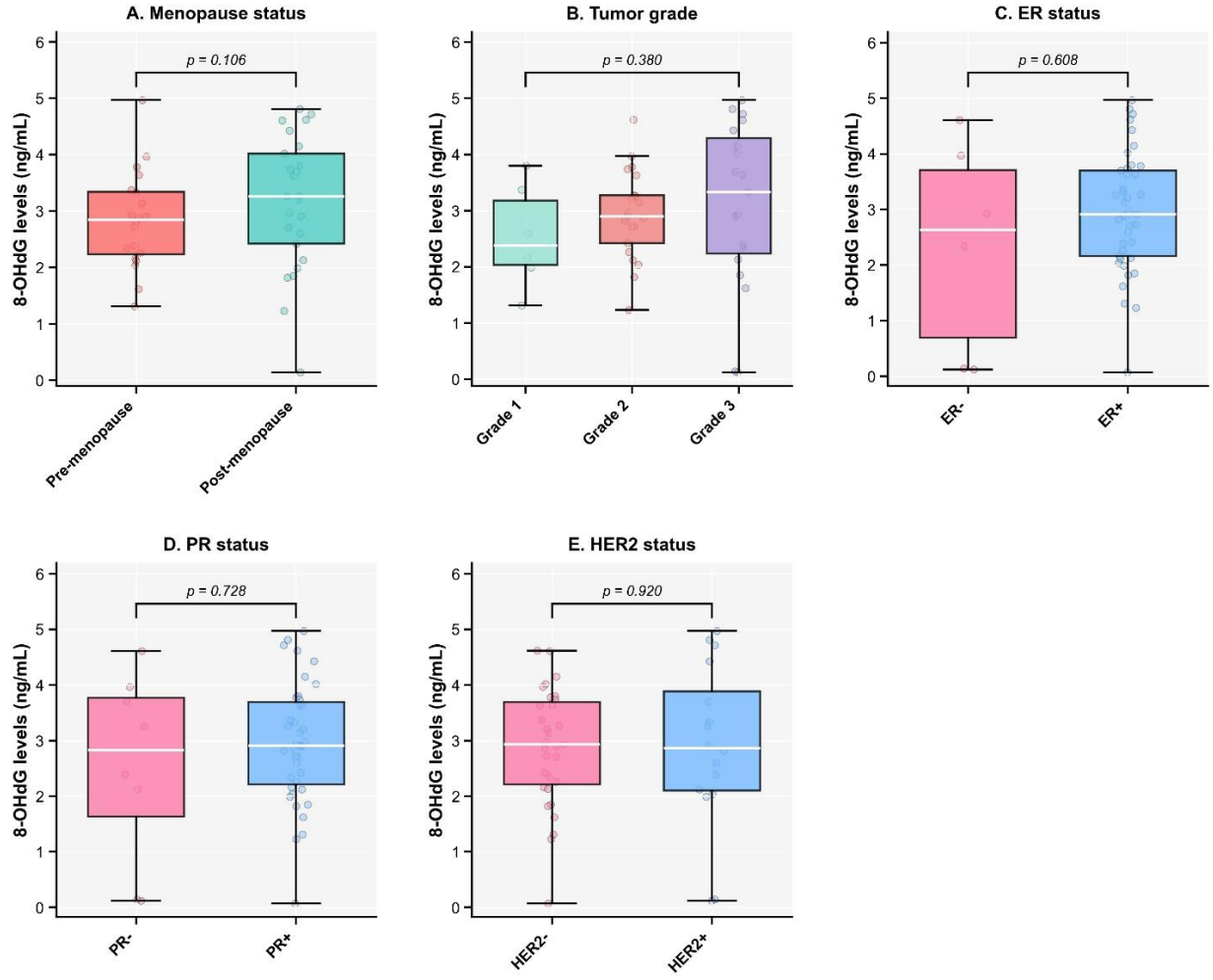

***Figure 3**. Box plots showing 8-OHdG levels across different clinical subgroups based on: A) menopause status, B) tumor grade, C) ER status, D) PR status, and E) HER2 status. Box plots show median (white line), interquartile range (box), and minimum/maximum values (whiskers).*

Our study has several important limitations that should be acknowledged. First, this was a single-center study conducted in Iraq with a relatively small sample size of 71 participants, which may limit the generalizability of our findings to other populations. Second, the cross-sectional design prevents us from establishing temporal

relationships between 8-OHdG levels and breast cancer development. Third, we measured 8-OHdG levels in serum rather than urine or tissue, which may not fully reflect local oxidative stress within breast tissue. Fourth, we did not account for other lifestyle factors that could influence systemic oxidative stress levels. Additionally, the significant difference in marital status between groups, though unlikely to directly influence oxidative stress biomarkers, represents a demographic imbalance that could potentially confound other unmeasured lifestyle factors. Larger multicenter studies with diverse populations are needed to confirm the relationship between 8-OHdG levels and breast cancer molecular subtypes.

Conclusions

In conclusion, our study shows that serum 8-OHdG levels do not differ significantly between newly diagnosed breast cancer patients and healthy controls. Furthermore, 8-OHdG levels showed no association with tumor grade, hormone receptor status, or menopausal status. These results suggest that serum 8-OHdG may not be useful as a differential biomarker for breast cancer screening or characterization. The lack of correlation with traditional prognostic factors indicates that oxidative DNA damage, as measured by serum 8-OHdG, may not play a significant role in early breast cancer detection in our population.

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Authors' Contributions

SAA: Conceptualization, Methodology, Investigation, Data curation, Formal analysis, Writing – original draft, Writing – review & editing, Visualization. RMH: Conceptualization, Methodology, Supervision, Writing - review & editing, Project administration. MFA: Conceptualization, Methodology, Supervision, Writing - review & editing, Validation, Resources.

Conflict of Interest

The authors declare that they have no conflict of interest.

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Data Availability Statement

The data that support the findings of this study are available from the corresponding author upon reasonable request.

Ethical Approve The local human ethics committee of the College of Medicine of University of Kerbala and the Ethics Committee of the Health Directorate of Karbala approved the project. (Protocol Number: 3986).

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