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RESEARCH ARTICLE

# Oxidative Stress and Antioxidants in Women with Cervical Cancer patients

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## ABSTRACT

Cervical cancer remains a major health concern among women worldwide and is associated with multiple biochemical and molecular alterations, including oxidative stress.

This work aimed to evaluate the connection between oxidative stress and antioxidant status in women with cervical cancer by measuring serum nitric oxide (NO), plasma vitamin C (VC), and serum zinc (Zn) levels. A total of 120 women were implicated in this case–control study, comprising 60 patients diagnosed with cervical cancer and 60 healthy age-matched controls. Blood samples were gathered and analyzed to evaluate the concentrations of NO, VC, and Zn using ELISA and colorimetric methods. Statistical analysis was done utilizing SPSS software.

The results showed significantly higher levels of serum nitric oxide in cervical cancer participants matched with the controls group ($p < 0.001$). In contrast, plasma vitamin C and serum zinc concentrations were significantly reduced in participants with cervical cancer ($p < 0.001$). Pearson correlation analysis shows a efficient negative correlation between nitric oxide and both vitamin C and zinc concentratinos, while a positive correlation was seen between vitamin C and zinc. (ROC) curve analysis explained that these biomarkers possess diagnostic potential, with nitric oxide showing the highest diagnostic accuracy (AUC = 0.88), followed by vitamin C (AUC = 0.84) and zinc (AUC = 0.81).

These findings suggest that cervical cancer is associated with increased oxidative stress and reduced antioxidant defense, highlighting the potential turn of oxidative stress biomarkers in understanding the biochemical alterations related to cervical cancer.

***Keywords:*** cervical cancer (CaCx); Oxidative stress; vitamin C; Nitric Oxide; Zinc

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## Introduction:

Cancer known as the second reason of death worldwide, with over 11 million new cases diagnosed each year [1]. Within gynecological cancers, cervical cancer (CaCx) represents a complex multistep progression where normal cells evolve into tumor cells. This transformation is regulated by various internal and external cues [2].

Reactive Oxygen Species (ROS) are among these cues. They contribute significantly to the growth of malignancies. ROS production is a natural occurrence in eukaryotic cells, arising as a byproduct of mitochondrial metabolic processes [3]. Typically, cells maintain a low level of ROS, which is crucial for signal transmission, enzyme

activation, gene expression, metabolism, cell division, production of disulfide bonds, and programmed cell death, among the various biological processes [4].

Oxidative stress occurs when there is an elevated production of ROS coupled with a decreased antioxidant capability within the cells. ROS are constantly generated in aerobic cells by the incomplete reduction of molecular oxygen to water via mitochondrial oxidative phosphorylation, as well as in a number of other processes such as inflammation, infections, mechanical and chemical stresses, exposure to UV light, and ionizing radiation [5].

The impact of ROS on cells is dependent on their concentration; low levels can have beneficial effects, supporting cell growth and survival pathways [6]. While elevated levels of ROS can lead to oxidative damage of biological molecules, leading to oxidative stress that can kill cells. ROS can cause damage to DNA that can change its structure, including breaking single and double strands, linking DNA and proteins, making basic sites, and changing bases[7].

In normal conditions, mammalian cells are equipped with a comprehensive range of antioxidant defenses that consist of both enzymatic and non-enzymatic forms. There are both non-enzymatic antioxidants, like tocopherols, retinols, and ascorbate, and enzymatic antioxidants, like (SOD), catalase (CAT), (GPx), directly metabolize reactive oxygen species (ROS) [8].

These antioxidants work to prevent the formation of free radicals or mitigate their harmful effects, protecting cellular components [9].

The compromised antioxidant defense system observed in cancer patients across various tissues indicates an excessive production of free radicals. This is evident in the reduced levels of antioxidants seen in all types of cancer, including cervical cancer [10].

Osmotic fragility, the susceptibility of red blood cells to changes in osmotic pressure, is altered in different pathological conditions; the assessment of erythrocyte osmotic fragility can help determine the integrity of red blood cells [11]. This measurement has been utilized in diagnosing hemolytic diseases, studying membrane permeability, and understanding changes that lead to the destruction of erythrocytes.

Although several studies have searching the turn of oxidative stress in cancer development, limited data are available regarding the connectino among oxidative stress markers and antioxidant status in women with cervical cancer, particularly within the Iraqi population. Understanding these biochemical alterations may provide insight into the mechanisms involved in cervical carcinogenesis and may contribute to identifying potential diagnostic biomarkers. Consequently, the current study sought to assess the correlation between oxidative stress and antioxidant status in women with cervical cancer by measuring serum nitric oxide (NO), plasma vitamin C (VC), and serum zinc (Zn) levels and comparing them with those of healthy controls.

# Materials and Methods:

## Study design and participants:

In a sequential 60-person study, the Gynecological Oncology Department of the Baghdad Teaching Hospital enrolled patients with cervical cancer between April 2023 and January 2024. The Ethics Committee of the Iraqi National Cancer Research Centre at the University of Baghdad in Iraq gave their approval for this study. The research was carried out in alignment with the ethical standards of biomedical research including human subjects. The attending physician informed all participants about the study's purpose and obtained verbal consent from each patient prior to sample collection.

### Sample collection:

Eight milliliters of blood were taken; four milliliters were put into a vial with heparin, and the other four milliliters were left to coagulate. After that, the serum and plasma were centrifuged at room temperature for ten minutes at 3000 rpm, and the samples were kept at 4°C before analysis.

### Determination of Plasma Vitamin C and Serum Nitric Oxide:

Plasma vitamin C (VC) and serum nitric oxide (NO) levels were determined using enzyme-linked immunosorbent assay (ELISA) kits according to the manufacturer's instructions (MyBioSource, USA; Cat. No. MBS160943 for VC and Cat. No. MBS8243214 for NO). Briefly, standards and serum samples were added to the microplate wells pre-coated with specific antibodies and incubated under controlled conditions. After the washing steps, enzyme-conjugated reagents were added, followed by substrate solution. The color intensity was measured spectrophotometrically at the recommended wavelength using a microplate reader, and the concentrations of VC and NO were calculated from the corresponding standard curves.

### Determination of Serum Zinc:

Serum zinc concentration was evaluated utilizing a colorimetric method depending on the reaction of zinc ions with a chromogenic reagent according to the recorded protocol (Agappe Diagnostics, Switzerland). In this method, When the sample is alkaline, the zinc in it makes a colored complex with the reagent. The color intensity is proportional directly to the zinc levels in the sample and was calculated using a spectrophotometer at 560 nm. Zinc levels were calculated by comparing sample absorbance values with those of the provided standard.

### Statistical Analysis:

We used SPSS software (version 24.0, IBM Corporation, headquartered in Armonk, NY, USA) to do the statistical analysis. The data were presented as mean ± standard deviation (SD). The Student's t-test was used to find differences between cervical cancer patients and healthy controls. We used Pearson correlation analysis to find the links between the parameters we looked at, and ROC curve analysis to check how well the biomarkers worked as tests. A p-value of less than 0.05 was considered statistically significant [12].

## Results:

The age distribution of cervical cancer patients showed that the highest proportion of cases was shown in the age group of 35–40 years (33.3%), followed by the age team of 30–35 years (26.6%). The age groups of 20–25 years and 25–30 years each accounted for 16.6% of the patients, while the lowest proportion was recorded in the age group of 15–20 years (6.6%). These findings indicate that the prevalence of cervical cancer directed to increase with advancing age within the studied population.

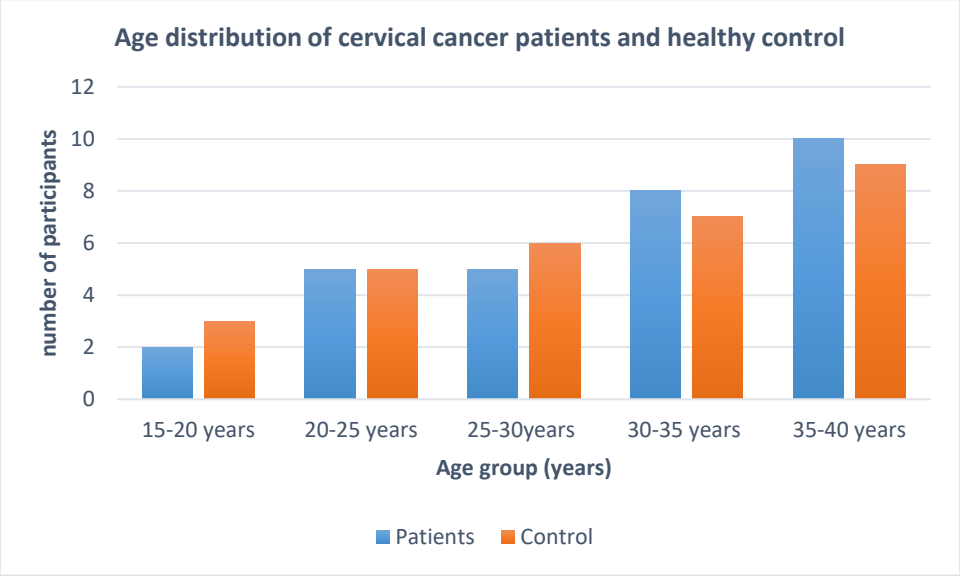


**Figure 1.** Distribution of study participants according to age groups among cervical cancer patients and healthy controls.

As shown in Table 1, patients with cervical carcinoma (CaCx) exhibited significantly more levels of serum nitric oxide (NO) matched with normal controls ($p < 0.001$). In contrast, plasma vitamin C concentrations were significantly lower in CaCx participants as matched in the control group ($p < 0.001$). Similarly, serum zinc concentrations were markedly reduced in patients with cervical cancer matched with healthy participants ($p < 0.001$).

**Table 1.** Overall level of Plasma Vitamin C (VC), serum Nitric Oxide (NO), and Serum Zinc in study groups.

| **Parameters** | **Mean ± SD** | |
|---|---|---|
| | **Control N.O**=60 | **Patients N.O**=60 |
| VC (ng/dl) | 450.6±49.52 | 210.12±31.85 |
| NO• (µmol/ml) | 54.15±8.55 | 77.10±11.51 |
| Zn (µg/dL) | 75.38±10.41 | 56.55±8.75 |
| *P*-value | 0.001 | |

Pearson analysis was done to istemate the relationships among the studied oxidative stress and antioxidant parameters. The results give a significantly negative correlation among serum nitric oxide (NO) levels and both plasma vitamin C and serum zinc concentrations, indicating that increased oxidative stress is associated with reduced antioxidant status in cervical.

**Table 2.** Pearson correlation analysis between serum nitric oxide (NO), plasma vitamin C, and serum zinc levels among cervical cancer patients.

| Variables | NO | Vitamin C | Zinc |
|---|---|---|---|
| NO | | | |
| Pearson Correlation | 1 | -0.62 | -0.58 |
| Sig. (2-tailed) | — | 0.001* | 0.001* |
| Vitamin C | | | |
| Pearson Correlation | -0.62 | 1 | 0.55 |
| Sig. (2-tailed) | 0.001* | — | 0.002* |
| Zinc | | | |
| Pearson Correlation | -0.58 | 0.55 | 1 |
| Sig. (2-tailed) | 0.001* | 0.002* | — |

ROC curve analysis was done to give the diagnostic efficacy of the examined biomarkers in differentiating cervical cancer patients from healthy controls. The analysis demonstrated that serum nitric oxide (NO) exhibited the highest diagnostic accuracy, with an AUC of 0.88, a sensitivity of 86.7%, and a specificity of 83.3% at a cut-off value of 65.0 µmol/mL. Plasma vitamin C exhibited commendable diagnostic efficacy, achieving an AUC of 0.84, a sensitivity of 81.7%, and a specificity of 80.0% at a threshold of 320 ng/dL. Serum zinc exhibited a moderate diagnostic capacity, with an AUC of 0.81, sensitivity of 78.3%, and specificity of 76.7% at a threshold of 65 µg/dL. These findings indicate that oxidative stress and antioxidant biomarkers may possess diagnostic significance in cervical cancer.

**Table 3.** ROC analysis of nitric oxide, vitamin C, and zinc for distinguishing cervical cancer patients from healthy controls.

| Biomarker | Cut-off value | Sensitivity (%) | Specificity (%) | AUC | Std. Error | Sig. (p-value) | 95% CI |
|---|---|---|---|---|---|---|---|
| Nitric Oxide (NO) | 65.0 µmol/mL | 86.7 | 83.3 | 0.88 | 0.04 | 0.001 | 0.80–0.95 |
| Vitamin C | 320 ng/dL | 81.7 | 80.0 | 0.84 | 0.05 | 0.001 | 0.75–0.92 |
| Zinc | 65 µg/dL | 78.3 | 76.7 | 0.81 | 0.05 | 0.002 | 0.71–0.90 |

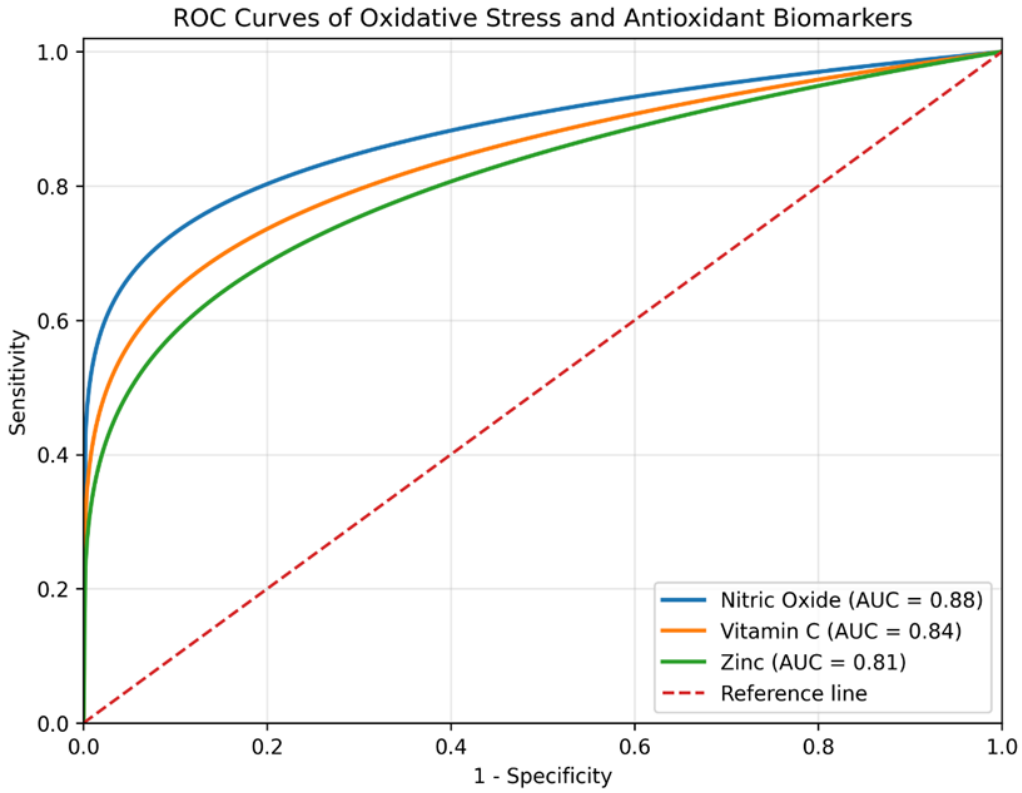


**Figure 2.** ROC curves of nitric oxide, vitamin C, and zinc for distinguishing cervical cancer patients from healthy controls.

## Discussion:

The present study searched the correlation among oxidative stress and antioxidant status in women with cervical cancer by evaluating serum nitric oxide, plasma vitamin C, and serum zinc levels. The findings demonstrated a clear imbalance between oxidant production and antioxidant defense mechanisms in cervical cancer patients[13]. The significantly elevated levels of nitric oxide observed in the patient group compared with healthy controls suggest increased oxidative and inflammatory activity associated with tumor development[14]. Nitric oxide is famous to play a dual role in cancer biology; while physiological levels are involved in normal cellular signaling, excessive production may contribute to DNA damage, genomic instability, and tumor progression through the production of RNS and the enhancement of oxidative stress pathways[15]. The increased nitric oxide levels observed in the present study are therefore consistent with the concept that oxidative stress contributes to the pathophysiology of cervical cancer and mayth reflect an activated inflammatory microenvironment within tumor tissues[16-18].

In contrast, vitamin C concentrations were significantly reduced in cervical cancer patients compared with healthy individuals. Vitamin C is a major non-enzymatic antioxidant which have an essential turn in stopping ROS and protecting cell parts from damage caused by oxidation [19]. The reduction observed in vitamin C levels may reflect increased utilization of antioxidant defenses in response to elevated oxidative stress in cancer patients[20]. Several previous studies have reported similar findings, indicating that depletion of antioxidant vitamins is frequently observed in patients with malignancies, including cervical cancer[21]. Reduced vitamin C availability mayth impair the body's capacity to shows oxidative damage, thereby facilitating carcinogenic processes and disease progression[22, 23].

The current study demonstrated a notable reduction in levels of zinc in the blood in patients alongside cervical carcinoma relative to the control group. Zinc is a necessary trace element which have a turn in many biological cycles, like making DNA.[24], immune regulation[25], antioxidant defense, and cellular repair mechanisms[26]. A lack of zinc has been linked to a weakened immune system and a higher risk of oxidative

stress, both of which may help cancer grow [27]. The lower zinc levels observed in this study may therefore indicate compromised antioxidant and immune defenses in cervical cancer patients. Previous epidemiological and clinical studies have also reported decreased zinc concentrations in various cancer types, suggesting that alterations in trace element metabolism may play an important role in tumor biology[28-30].

The correlation analysis further supported the connection among oxidative stress and antioxidant depletion. A significant negative correlation was seen between nitric oxide and both vitamin C and zinc levels, indicating that increased oxidative stress is associated with decreased antioxidant status in cervical cancer patients[31]. Conversely, a positive correlation among vitamin C and zinc suggests that these antioxidant factors may act synergistically in maintaining cellular redox balance[32]. These findings highlight the interconnected nature of oxidative stress markers and antioxidant defenses in cancer pathology.

In addition to these biochemical alterations, the ROC curve analysis demonstrated that nitric oxide, vitamin C, and zinc possess potential diagnostic value for distinguishing cervical cancer patients from healthy individuals. Nitric oxide showed the biggest diagnostic toool with the largest area under the curve, followed by vitamin C and zinc. These findings suggest that oxidative stress and antioxidant biomarkers may serve as useful indicators for the detection or monitoring of cervical cancer[33]. Although these biomarkers alone may not be sufficient for definitive diagnosis, their combined evaluation may contribute to improving early detection strategies and understanding the biochemical alterations associated with cervical cancer[34].

## Conclusion:

The findings of the current study explain that cervical cancer patients exhibit a clear imbalance between oxidative stress and antioxidant defense mechanisms. Elevated nitric oxide levels together with decreased vitamin C and zinc concentrations suggest increased oxidative stress in affected individuals. The observed correlations between these biomarkers further support their involvement in the oxidative processes associated with cervical cancer. In addition, ROC analysis demonstrated that nitric oxide, vitamin C, and zinc possess potential diagnostic value for distinguishing cervical cancer patients from healthy individuals. These results highlight the importance of oxidative stress biomarkers in understanding the biochemical changes connected with cervical carcinoma and may contribute to improving future diagnostic and monitoring strategies.

## Acknowledgment

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## Conflict of Interest

The authors declare that there are no conflicts of interest regarding the publication of this study.

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