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Comparison of Ovarian and Cervical Cancer Prevalence in Iraqi Women with Lowered Serum Antioxidant Levels

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Abstract

Objective: This study aimed to assess the correlation between a decline in serum endogenous enzymatic antioxidant levels and cervical and ovarian cancer incidence and to determine which type of cancer was more significantly influenced by the decrease in endogenous enzymatic antioxidants among Iraqi patients.

Methods: It's a retrospective study comprising a total of 100 adult females, including 50 patients with ovarian and cervical cancer, recruited from the Oncology Teaching Hospital in Baghdad, Iraq, between January and March 2024. The patient's history was acquired with the patient's consent. Biochemical tests were performed using a spectrophotometric technique to estimate serum endogenous enzymatic antioxidant levels, including catalase, superoxide dismutase, and glutathione peroxidase.

Result: The study demonstrated a significantly lower serum level of catalase, superoxide dismutase, and glutathione peroxidase among the study population with cancer compared with healthy women. Among the positive cases, The number of patients with cervical cancer was significantly higher than that of those with ovarian cancer. Further, the level of endogenous enzymatic antioxidants in patients with cervical cancer was lower than that in patients with ovarian cancer.

Conclusion: The findings of this study indicate that the serum level of endogenous enzymatic antioxidants may serve as a marker for predicting the incidence of cervical cancer, particularly associated with human papillomavirus infection, with a lesser association with ovarian cancer.

Keywords: Cervical cancer, ovarian cancer, antioxidant, cancer diagnosis

Introduction

Gynecologic malignant tumors, specifically cervical, endometrial, and ovarian cancer, are associated with significant morbidity and mortality rates. Diagnosing and treating these cancers requires understanding their characteristics, including prevalence, stages, treatment methods, and survival rates.[1] Cervical cancer is one of these cancer forms, and it is the second most prevalent malignancy among women globally. Human papillomaviruses (HPVs) are recognized as the principal causative agents in cervical carcinogenesis. Harold Zur Hausen initially proposed the idea of linking HPV infection to cervical neoplasia in the early 1970s.[2] Conversely, ovarian cancer is one of the fatal gynecologic malignancies, resulting in more mortality than cervical and uterine cancers combined.[3] Over the last decade, roughly 26,700 new instances of ovarian cancer were detected annually, resulting in almost 14,800 mortality per year.[4]

Numerous studies demonstrate that oxidative stress contributes to the initiation and progression of various cancers, including melanoma, prostate, lung, liver, gastric, brain, cervical, breast, bladder, ovarian, pancreatic, oral, lymphoma, and leukemia.[5–8] Oxidant and oxidant imbalance generate oxidative stress. Boosting oxidants results in the overproduction of free radicals, primarily reactive oxygen species (ROS), which in turn causes cellular damage.[9] Hydrogen peroxide (H_2O_2), hydroxyl radical (•OH) and Superoxide anion (O_2•−) are reactive oxygen species generated from the partial reduction of atmospheric O_2. Increased concentrations of nitric oxide, regarded as a free radical with potent vasodilatory effects in the body, lead to the overproduction of reactive oxygen species (ROS). Furthermore, nitric oxide can engage with O_2−• to generate peroxynitrite (ONOO−), classified as a reactive nitrogen species (RNS).[10] Reactive oxygen species (ROS) are crucial in regulating metabolic pathways and the immune response to pathogens.[11] However, The overproduction of reactive oxygen species (ROS), resulting from either endogenous or exogenous factors, adversely affects cellular structures and the functionality of proteins, carbohydrates, nucleic acids, and lipids.[9] The degradation of these macromolecules significantly affects cancer pathogenesis by altering several cellular processes, such as cell replication, programmed cell death, migration, angiogenesis, and therapeutic resistance.[9,12,13] As a consequence, Glutathione (GSH), vitamins, and carotenoids are examples of the organism's nonenzymatic antioxidant defense mechanisms; enzymatic antioxidant defense mechanisms include the thioredoxin system, SOD, GPx, GSTs, and catalase.[14,15]

Recent studies across the past two decades demonstrate the increasing importance of antioxidant enzymes. Biomarkers serve as tools for diagnostics, monitoring patient conditions, predicting chemotherapy outcomes, and providing insights into cancer stage and type.[16] Enzymes such as CAT and SOD are particularly significant in the diagnosis and predictive factors of bladder cancer.[17] SOD, CAT, and GST in lung cancer.(Zalewska-Ziob et al., 2019),[18] XOR, CAT, and SOD ovarian cancer. (Arafa and Faqihi, 2019).[19] or SOD, CAT, GPx, GR in colorectal cancer.[20] More clinical studies are essential regarding significant advancements in examining antioxidant enzymes as biomarkers. The discovery of the substantial potential of antioxidant enzymes in cancer treatment necessitates their incorporation into standard diagnostic tests.[16] These studies continue to exhibit limitations in identifying the effect

of reduced enzymatic antioxidant levels on the incidence of cervical and ovarian cancer in Iraqi patients without a comparative analysis of the prevalence of the two gynecological cancers. In this study, we attempted to ascertain the relationship between the reduction in enzymatic antioxidant levels and the prevalence of gynecological cancers among Iraqi women, specifically cervical and ovarian cancer, while determining which type of cancer is more frequently associated with diminished levels of enzymatic antioxidants, particularly catalase, glutathione peroxidase, and superoxide dismutase.

Patients and Methods

Study Population

This cross-sectional retrospective study comprised a total of 100 adult females, including 50 patients with ovarian and cervical cancer, recruited from the Oncology Teaching Hospital in Baghdad, Iraq, between January and March 2024. The doctors checked the patients, and particular tests corroborated the diagnosis.

In the same period, we identified 50 control participants without cervical cancer from the Baghdad Teaching Hospital, utilizing daily census records or referrals from medical staff. The participants predominantly originated from three departments: Orthopaedics, Ophthalmology, and Infectious Diseases. The study population comprised individuals aged 45 to 65.

Informed consent was secured from every participant in the study before conducting the interview and collecting samples. The study protocol received approval from the University of Baghdad's medical faculty's ethics committee. The procedures were executed in alignment with the established protocols.

Sampling

Five milliliters of blood were obtained from a vein for each ill and healthy control individual. Upon centrifugation for 10 minutes at 3000 rpm, the blood sample was transferred to a gel tube and let to coagulate on a bench for 20 minutes. The collected serum was preserved in a refrigerator at −20°C for further analysis.[21]

Biochemical Tests

The assay technique described below was employed to assess the endogenous levels of antioxidants in the serum of the study population.

Determination of Catalase (CAT) Activity

The concentration of the catalase enzyme is determined by quantifying absorbance. 1.4 ml of 30% H_2O_2 is added to the test tube, followed by 0.1 and 1.4 ml of each phosphate buffer and sample, respectively. Followed by measuring the cuvette solution every 30 s on a three-phase wavelength of 240 nm. E.U = (2.3/Δx) × (log A1/logA2) activity = U/L. Δx = 30 seconds.[22]

Screening of Superoxide Dismutase (SODs)

The SOD screening technique entails SOD catalyzing the dismutation of hydrogen peroxide and molecular oxygen from superoxide radicals produced during oxidative energy production. The method is predicated on quantifying the optical density generated by xanthine and xanthine oxidase, which catalyses the formation of superoxide radicals from the blue formazan dye of nitro blue tetrazolium (N.B.T) at a wavelength of 560 nm. The superoxide dismutase in the serum sample inhibits the formazan process by sequestering superoxide radicals from the environment. In the experimental conditions, 1 unit of SOD equates to a 50% reduction in the N.B.T. decline rate.[23]

$$\%\ Inhibition = [(Blank\ OD - Sample\ OD)/Blank\ OD] \times 100$$

Glutathione Peroxidase Activity (GPx)

The activity of Glutathione in plasma was assessed using the Paglia and Valentine technique. This method employs t-butyl hydroperoxide as a substrate and observes the rate of NADPH oxidation via its paired reaction with glutathione reductase. A 340 nm reduction in absorbance, indicative of GPx activity, was quantified using the Unicam UV4 UV/Vis spectrophotometer (Cambridge, UK). The intraassay variation (CV) was 2.7% (n = 8) for GPx1 and 2.3% (n = 7) for GPx3. The samples underwent individual measurements for analysis. The measurement was repeated anytime the value fell beyond the designated range.[24]

Ethical Approval

The University of Baghdad's medical faculty ethics committee approved the study protocol, and the procedures were executed according to the established protocols.

Statistical Analysis

Results are presented as mean ± standard deviation (SD). The one-way analysis of variance (ANOVA) test was utilized. Various groups were compared employing T-tests and the Least Significant Difference (LSD). The study used IBM SPSS version 20 software. The significance threshold is set at $P < 0.05$.[25]

Results

The sociodemographic distribution study revealed that, of 50 targeted samples, 44 cases were positive for cancer (cervical or ovarian). The majority, 68.2%, were aged between 56 and 65, while 31.8% were aged between 45 and 55.

Out of the total positive cancer cases, 32 females were diagnosed with cervical cancer, and 12 were diagnosed with ovarian cancer. The predominant age group of individuals with cervical cancer was between 56 and 65, accounting for 50% of all cases, while those aged 45 to 55 comprised 22.7% of the cases.

Furthermore, the predominant demographic of females diagnosed with ovarian cancer was aged 56 to 65, with 18.1% of total cases, while those aged 45 to 55 accounted for 4%. Moreover, among the total positive cancer cases, educated females constituted 25%, while uneducated females accounted for 75%.

Patients having a history of cancer constituted 81.8%, while patients without such a history were 18.1% (Table 1).

Furthermore, screening of endogenous antioxidant levels within the study population indicated significant variations in glutathione peroxidase, catalase, and superoxide dismutase levels between healthy females and those diagnosed with cancer. There is significant variation between cases of cervical cancer and those of ovarian cancer. (Tables 2–4).

Table 1. **The most commonly cited factors for gynecologic cancer disparities**

Questions	Categories	Numbers and Ratios	Positive case No *N* = 50	Cervical cancer *N* = 44	Ovarian cancer *N* = 44	Gynecological cancer *N* = 44
Age	45–55	No.	14	10	4	14
		%	28 %	22.7 %	9 %	31.8%
	56–65	No.	30	22	8	30
		%	72%	50 %	18.1 %	68.2 %
	45–65	No.	44	32	12	44
		%	88%	72.7 %	27.2%	100%
Education	Educated	No.	12	7	4	11
		%	27.2 %	15.9 %	9 %	25 %
	Uneducated	No.	38	25	8	33
		%	72.7%	56.8 %	18.1 %	75 %
Family history	Yes	No.	39	17	19	36
		%	78 %	38.6 %	43.1 %	81.8 %
	No	No.	11	5	3	8
		%	22 %	11.3 %	6.8 %	18.1%

Table 2. **Comparison of serum antioxidant concentration across healthy women versus those with gynecological cancer**

Parameters	Mean ± S.D[a]		*P*-value
	Healthy women Control (*n* = 50)	Women with gynecological cancer, Case (*n* = 44)	
GP_x (U/g Hb)	70.67 ± 2.316	34.16 ± .1451	**0.0001***
CAT (G/L)	128.30 ± 3.316	71.78 ± 3.316	**0.0001***
SOD (U/mg Hb)	189.10 ± 2.270	93.63 ± 3.316	**0.0001***

GP_x: glutathione peroxidase, CAT: catalase, SOD: superoxide dismutase. *: significant at ($P < 0.05$).

Table 3. **Comparison of control, cervical, and ovarian cancer serum antioxidant concentrations**

Parameters	Mean ± S.D[a]			LSD[b]
	Healthy women Control (*n* = 50)	Women with cervical cancer	Women with ovarian cancer	
		Case (*n* = 44)		
GP_x (U/g Hb)	**A** 70.67 ± 2.316	**B** 46.430 ± 1.290	**C** 21.90 ± 4.316	**3.347**
CAT (G/L)	**A** 128.30 ± 3.316	**B** 82.10 ± 3.446	**C** 61.46 ± 2.226	**5.776**
SOD (U/mg Hb)	**A** 189.10 ± 2.270	**B** 118.17 ± 1.976	**C** 69.10 ± 3.606	**5.601**

GP_x: glutathione peroxidase, CAT: catalase, SOD: superoxide dismutase. *: significant at ($P < 0.05$).

Table 4. **Comparison of serum antioxidant concentration across cervical cancer cases versus those with ovarian cancer**

Parameters	Mean ± S.D[a] Case (*n* = 44)		*P*-value
	Women with cervical cancer	Women with ovarian cancer	
GP_x (U/g Hb)	46.430 ± 1.290	21.90 ± 4.316	**0.0001***
CAT (G/L)	82.10 ± 3.446	61.46 ± 2.226	**0.0001***
SOD (U/mg Hb)	118.17 ± 1.976	69.10 ± 3.606	**0.0001***

GP_x: glutathione peroxidase, CAT: catalase, SOD: superoxide dismutase. *: significant at ($P < 0.05$).

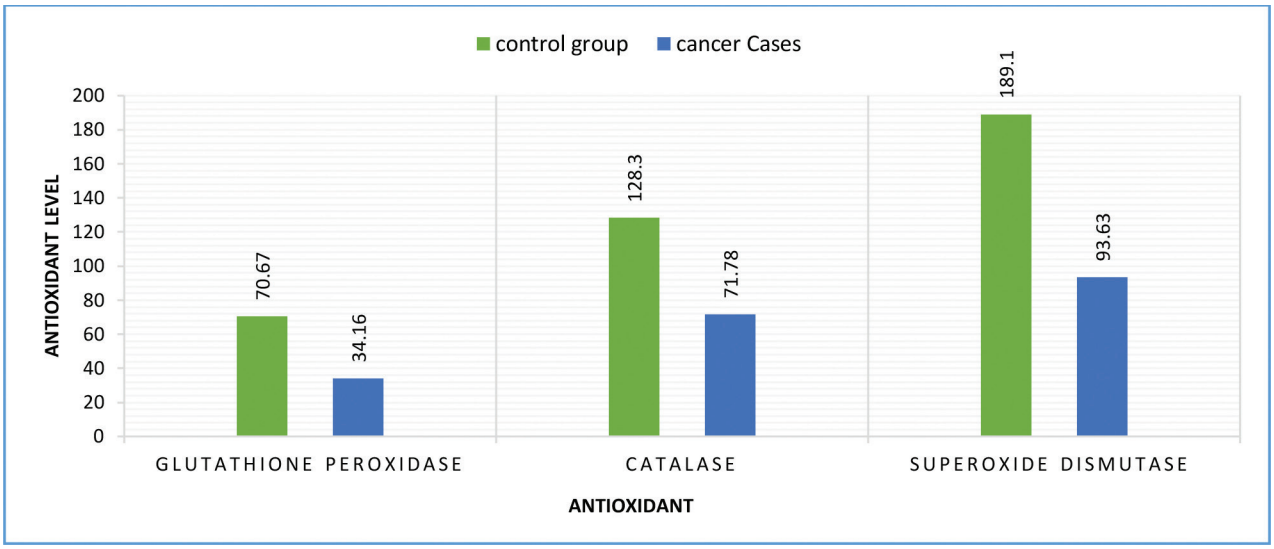

Fig. 1 **Comparison of serum antioxidant concentration across healthy women versus those with gynecological cancer.**

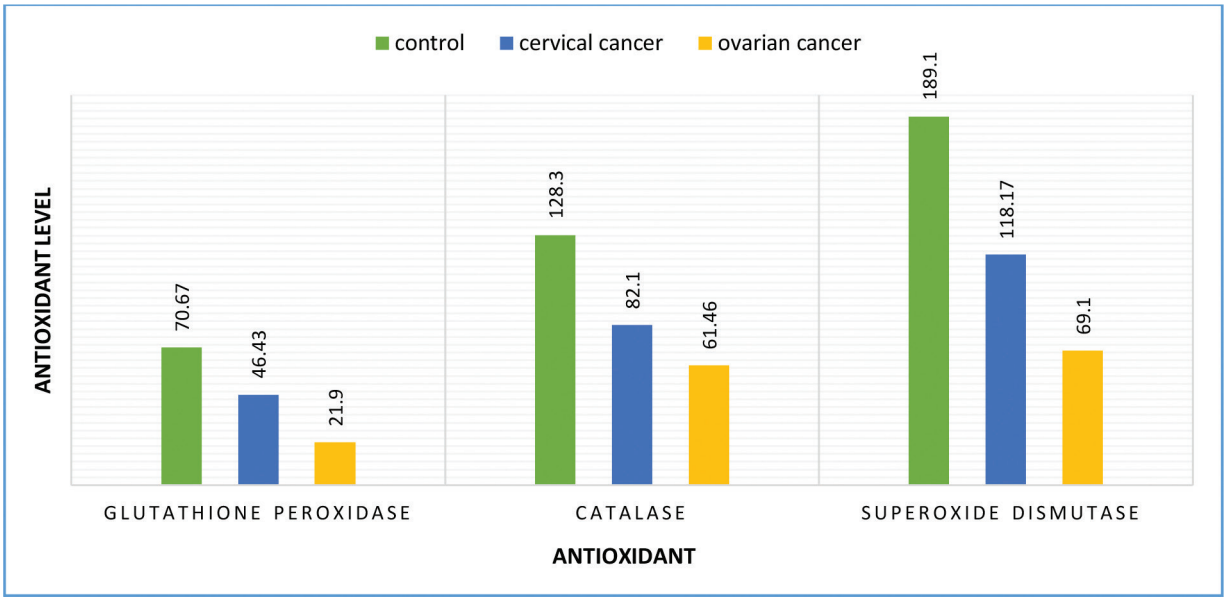

Fig. 2 **Comparison of control, cervical, and ovarian cancer serum antioxidant concentrations.**

Discussion

This study is designed to explore the correlation between the incidence of specific types of gynecological cancer, including cervical and ovarian cancer, among Iraqi patients. It also sought to identify the impact of reduced serum endogenous antioxidant levels on the incidence of these cancers. Study results demonstrated a significant correlation between the decline in serum enzymatic antioxidant levels and cervical and ovarian cancer incidence. With an elevation in the incidence of cervical cancer compared to ovarian cancer.

Several studies were performed on the same topic of our research. One was demonstrated that the serum of patients with cervical cancer was combined with impairment in the antioxidant systems, either enzymatic or cellular.[26,27] A study proved that stimulating cellular antioxidant enzymes triggers cell repair processes and promotes moderate apoptosis.[28,29] Furthermore, Natural antioxidants can influence cellular signaling pathways by stimulating or inhibiting redox-sensitive transcription factors, demonstrating potential employment as anticancer therapy. They may impede each phase of carcinogenesis—initiation, promotion, and progression—to inhibit cancer growth.[30]

Conversely, the results of our study demonstrated a reduction in antioxidants associated with the incidence of ovarian cancer. Along similar lines, numerous studies have been performed to explore the oxidative stress and antioxidant levels in the circulation of patients with ovarian cancer, performing significantly lowered levels of superoxide dismutase and catalase observed in ovarian cancer patients compared with healthy females.[31] Another study suggested that a substantial decline in the activity of GP_X and SOD activities was observed in women with ovarian cancer corresponded to healthy women.[32]

Several mechanisms can clarify the role of endogenous antioxidants in preventing the incidence of cervical cancer

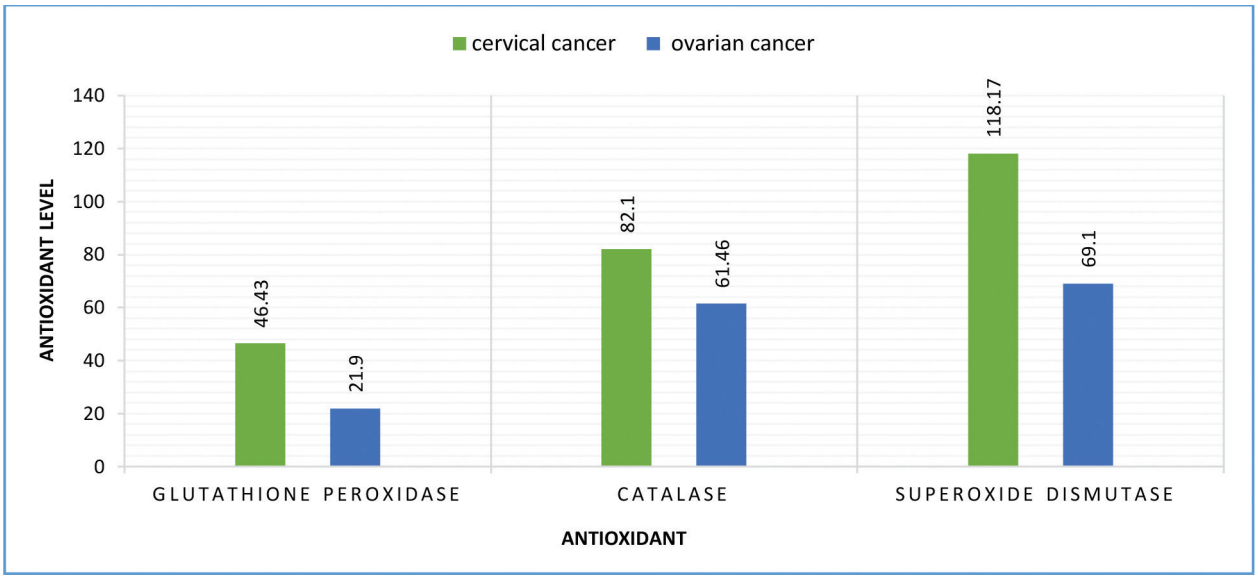

Fig. 3 **Comparison of serum antioxidant concentration across cervical cancer cases versus those with ovarian cancer.**

and ovarian cancer. One suggestion implies that a decline in mutagenic risk could originate from the induction of several phase 2 detoxifying and antioxidant enzymes, like glutathione-S-transferase, NAD(P)H quinone reductase, and heme oxygenase. The process involves the antioxidant response element (ARE), located in the promoter region of genes that are significantly regulated in response to oxidative stress. This element is essential for cell survival and involves specific redox-sensitive transcription factors, including Nrf2, NF-κB, AP-1, and MAPKs.[33–35] Regulating activity in genes influences cellular redox status and gene expression responses to oxidative stress, probably via sulfhydryl alteration of critical cysteine residues on these proteins and other upstream redox-sensitive molecular targets.[36] For example, decreased oxidant levels stimulate the AP-1 transcription factor, leading to AP-1/DNA binding and enhanced gene expression. Activation of AP-1 induces JNK gene activity, leading to the phosphorylation of the c-Jun transactivation domain.[37]

The proactive role of antioxidants in cancer can be summarised as follows: Superoxide dismutase (SOD) and catalase (CAT), antioxidant enzymes present in all cells, are found in substantial amounts in erythrocytes.[38] By converting the very harmful superoxide anion to O_2 and a less reactive molecule, H_2O_2, SOD shields cells against O_2 _S.[39] CAT safeguards the cell against H_2O_2 produced by several processes.[40,41] Further studies found reduced levels of SOD and CAT in individuals with ovarian cancer. The observed spike in circulating lipid peroxides in ovarian cancer patients is linked with a decline in SOD and CAT activities. This can contribute to the formation of superoxide anion, a highly diffusible and strong oxidizing radical that may penetrate membranes, inflicting detrimental effects at locations far from the tumor.[42] Elevated lipid peroxidation product malondialdehyde levels may reduce CAT activity, which can create cross-links that inactivate various membrane-bound enzymes.[43,44]

Our study's findings indicated that the influence of endogenous antioxidants on the incidence of ovarian cancer was minimal, similar to the observations made in cervical cancer. The decline in endogenous antioxidant levels increases reactive oxygen species, facilitating HPV-induced cervical carcinogenesis by regulating viral oncoproteins E6 and E7.[45] Conversely, there exists a tenuous correlation between HPV infection and the probability of developing ovarian cancer.[46]

Many studies have looked at how oxidative stress relates to human papillomavirus infection, which is a significant risk factor for cervical cancer. Although there are over 200 different kinds of HPV, The most prevalent high-risk cervical cancer types are eighteen and sixteen.[47] The viral genome integrates into the host's DNA, resulting in the overexpression of oncogenes. It also promotes cellular transformation by inhibiting the actions of the tumor suppressors p53 and pRb, consequently.[47,48] HPV integration is a pivotal stage in HPV-induced carcinogenesis and may be promoted by inflammation and oxidative stress.[49,50] The activation of inflammatory responses serves as a defense mechanism initiated by HPV infection. It leads to the activation of leukocytes and the release of various cytokines and chemokines into circulation.[50] The inflammation caused by HPV can lead to an increased generation of (ROS) via polymorphonuclear neutrophils and macrophages. (ROS) Inducing DNA damage and increasing the frequency of (DNA double-strand breaks) is essential for integrating viral DNA into the cellular genome and initiating carcinogenesis.[50] These mechanisms clarify the outcomes of our study and explain why cervical cancer incidence is high as compared with ovarian cancer in patients with low serum endogenous antioxidant levels.

Study limitations encompassed the selection of cervical and ovarian cancer to assess the impact of lowered antioxidant levels on incidence. These cancers represent the deadliest gynecological cancers and share comparable characteristics, as both are mainly epithelial cancers.

Conclusion

Study results indicate that reducing serum enzymatic antioxidant levels below the normal range could raise the incidence of gynecological cancers, particularly cervical and ovarian cancer, with a higher potential prevalence of cervical cancer compared to ovarian cancer in patients with dropped antioxidant levels. Conducting a higher vulnerability of cervical cancer to lowered antioxidant levels in contrast to ovarian cancer.

The findings of this study indicate that the serum level of endogenous antioxidants may serve as a marker for predicting the incidence of cervical cancer, particularly associated with human papillomavirus infection, with a lesser association with ovarian cancer.

Author Contributions

Design and development: Azal Hamoody, Kawakeb N. A. Abdullah
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Statistical analysis and comprehension: Azal Hamoody, Montadher Ali Mahdi
Composition of the article: Kawakeb N. A. Abdullah, Azal Hamoody
Reviewing the essay critically for key conceptual points: Sura Basil Findakly,
Proficiency in statistical analysis: Azal Hamoody, Montadher Ali Mahdi
Ultimate endorsement and guarantee of the article: Azal Hamoody, Montadher Ali Mahdi

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Conflicts of Interest

No conflicts of interest were present.

Declaration of Generative AI and AI-assisted technologies in the Writing Process

The authors assert that this study does not utilize generative artificial intelligence (AI) or AI-assisted technologies.

Abbreviations

LSD: least significant difference
SPSS: Statistical Package for the Social Sciences
GP_X: Glutathione peroxidase
CAT: Catalase
SOD: Super oxide dismutase
HPV: human papilloma virus
ROS: reactive oxygen species

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