**Open Access** **Baghdad Science Journal** **P-ISSN: 2078-8665**
**Published Online First: July 2022** **2023, 20(1): 82-89** **E-ISSN: 2411-7986**

DOI: https://dx.doi.org/10.21123/bsj.2022.6778

# Potential Role of 8-Hydroxyguanosine and some Pro Inflammatory Cytokines as Biomarkers in Colorectal Cancer Iraqi Patients

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Received 22/11/2021, Revised 16/1/2022, Accepted 18/1/2022, Published Online First 20/7/2022, Published 1/2/2023



## Abstract:

8-hydroxyguanosine (8-OHdG) is considered as an indicator of the oxidative stress. Pro inflammatory cytokines are critical parts of the pathophysiological processes to which treatment can be applied. The aim of this study was to evaluate 8-OHdG and pro inflammatory cytokines concentration in colon carcinoma patients. Blood samples were taken before treatment from 50 incident cases with colon cancer (stage III) admitted for health examination at the Nanakali Hospital in Erbil city with 45 healthy samples of controls with age range between 38-69 years for both groups. All studied parameters were estimated by ELISA. Participants at this study were 95 Participants ranged in age from 38 to 69 years, 50 Participants had been newly diagnosed with colorectal cancer (without treatment) with 45 individuals were healthy used as controls. The data showed a non-significant elevation by comparing the normal participants with colorectal cancer cases for (8-OHdG) by *P*-value 0.054 and a significant elevation for Tumor necrosis factor alpha (TNF-α) by *P*-value 0.019 and interleukin-6 (IL6) by *P*-value <0.0001. While the data showed a significant depletion by *P*-value <0.0001 for SOD and POX .The findings of the current study reveal that 8-OHdG refers to the local oxidative stress in colorectal cancer and TNF-α is accountable for increasing the concentrations of IL6, which is linked with inflammation process in the surrounding of cancer cell.

**Keywords:** Colon cancer, 8-Hydroxy-2′-deoxyguanosine, Interleukin-6, Tumor necrosis factor alpha

## Introduction:

According to the world health organization (WHO), cancer is a leading cause of death worldwide[1]. Moreover, colorectal cancer is considered to be one of the main causes of death all around the world. Various methods and strategies have been used to treat such kind and others of cancer[2].

Moreover, untimely identification of colon cancer patients at high level perilous of progression spread of tumor in colon cancer is critical for early interfering to ameliorate colon cancer consequence. Current therapy for colon cancer patients comprised, medicament, immunotherapy, goal remedy and surgical resection[3]. Elevated concentration of oxygen radicals has been identified in approximately all cancers, which attribute to their role as a best-identifiable constituent in malignancy. Though oxygen radicals act as a vital molecule in cancers, the rate of high rate of reactive oxygen species can be accurately assessed by evaluating stable metabolites of radical interactions due to its high unreliability. One of the important outcome of free radical damage is 8-OHdG, this compound is considered as a helpful indicator for evaluating reactive oxygen oxidative damage in DNA and has been a characteristic of oncogenesis in various studies[4]. However, few researches have examined whether 8-OHdG gathering in colon cancer cell is correlated with colon carcinoma development[5].

Pro-inflammatory cytokine tumor necrosis factor-alpha acts as a vital mediator of inflammation linked with cancer and its generation by cancer cell has been revealed to be linked with a weak prediction. Tumor necrosis factor-alpha cannot be identified in blood of healthy individuals but can be identified in people suffering from cancer, particularly in advanced grade. In other words, prediction the stage of colon cancer and its prognosis can be examined by TNF-α[6]. Previous studies confirmed that serum concentration of TNF-α in colon cancer patients were remarkably increased, and patients with declined concentration

of TNF-α had preferable prediction compared with elevated concentration of TNF-α[7]. Modification of immune system by Interleukins (ILs) depends on their capacity to interact with different kinds of cell, in addition (ILs) have ability to influence on a broad spectrum of cancers[8]. The IL-6 acts as both a pro-inflammatory cytokine and an anti-inflammatory myokine, is as well regarded as a vital species for cancerous cells due to their role as stimulating cell proliferation, wound healing, and occasionally cellular differentiation.

Tumor-infiltrating immune cells as well as cancer cells themselves act as major generator of Interleukin-6[9].

Previous studies recorded that IL-6 linked with colon cancer development. IL-6 is contributed to progression grades of cancer cell and weak survival rate of colon cancer patients also stimulate the locomotion of colon cancer cells[10]. Oxygen radicals are accountable for the processes of carcinogenesis in which elevated concentrations of intracellular oxygen radicals and an abnormal controlling of Oxygen radicals contribute into various pathological situations such as cancer and the formation of new blood vessel. One of these oxygen radicals is superoxide anion ($O^{2-}$) that stimulate oncogenesis and has a remarkable negative influence that causes mutations in tumor suppressor genes which contribute in DNA damage molecules. Superoxide dismutase-1 (SOD1) generated by human defense system inhibits the process of oncogenesis. Elevation of circulating concentration of SOD1 is associated to the raise in the severity degree of colon oncogenesis as demonstrated in tumour cells in comparison to healthy cells[11].

Peroxiredoxins (PRDXs) following to GPx are described as the potent peroxide that belong to oxidoreductase class of enzymes in vegetal cells and they function as a second line antioxidant defense mechanism that preserving cellular normal redox status. The peroxidases (POX) activity principally denotes thiol-dependent peroxidases (GPx and PRDXs) enzyme activities which act together at similar action levels and critically protect cellular components from oxidative damage[12]. This research was achieved to better examine the relationship among studies parameters (8-OHdG, TNF-α, IL-6, SOD and POX) and the colon carcinoma risk.

## Materials and Methods:

In this study 95 samples were included with age range (38-69) years. Two groups of samples were included in this study. Group (1) contained people with colon cancer (n=50), they were compared to a apparently healthy individual group of (n=45) control (group2) who matched in age and gender. Patients were clinically and histologically diagnosed with colorectal cancer (stage III). The samples were collected from Nanakali hospital for Blood diseases and Cancer & Rizgary hospital (Oncology Unit) in Erbil City. Patients were assessed by full medical history in order to exclude any existing systemic disease or taking any treatment that may influence biochemical the parameters to be measured.

### Collection of Blood Samples

About 5mL of venous blood was taken from each individual, collected in gold-top serum separator tubes (SST), allowed standing for 15 minutes, separation of serum from blood cell was performed by centrifugation at (3000 rpm) for 15 minutes. The obtained serum was transferred immediately to pre-labeled and coded Eppendorf tubes. These samples were frozen at –20°C for upcoming investigation.

### Biochemical Assays

The concentrations of (8-OHdG), TNF-α, IL-6, total SOD and POX (Thiol-dependent peroxidases) in serum were determined by sandwich enzyme-linked immunosorbent assay (ELISA) technique using the kits manufactured by Bio Vision company.

### Statistical Analysis

SPSS version 21 and GraphPad prism version 8 computer programs were utilized for statistical data analysis. Statistical test results and Bar graphs were expressed as Mean±SE. Unpaired T-test (Man-Whitney U) test and ROC curve was used for comparing the study parameter means between patients group and healthy control groups.

## Results:

### Circulating concentration of 8-OHdG

Figure. 1 revealed a non-significant elevation (P=0.054) in circulating concentration of 8-OHdG in patients (1.34±0.18 pg/mL) as compared to controls (0.77±0.04 pg/mL).

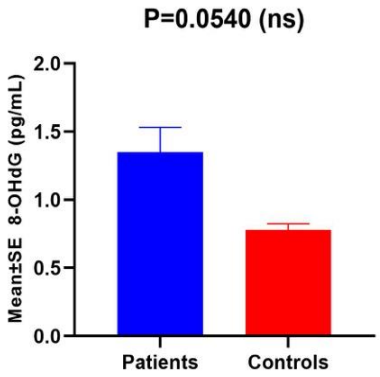



**Figure 1. 8-OHdG in sera of the two studied groups**

**Circulating concentration of TNF-α and IL-6**

Figure 2 revealed a remarkable elevate (P=0.019) in serum level of TNF-α in patients (3.24±2.25 ng/mL) as compared to controls (3.12±1.36 ng/mL). Fig. 3 also showed a remarkable elevation (P<0.0001) in serum level of interlukine-6 in patients (16.48±2.64 ng/mL) as compared to controls (2.33±0.35 ng/mL)

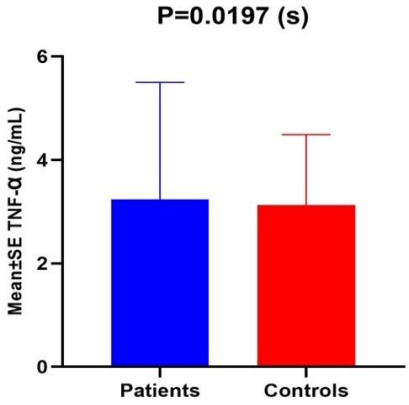



**Figure 2. TNF-α in sera of the two studied groups**

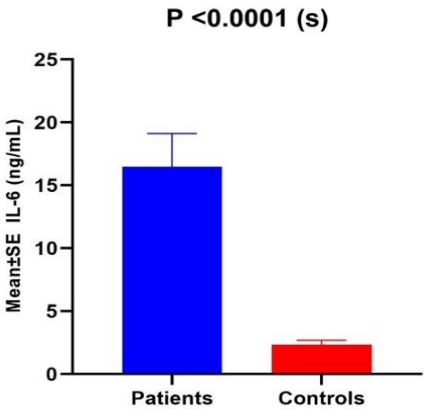



**Figure 3. IL-6 in sera of the two studied groups**

**Serum levels of SOD and POX**

The results in Figs. (4 & 5) also showed that there were remarkable decline (P<0.0001) in circulating concentration of SOD and POX in patients (0.23±0.03 IU/mL and 0.54±0.05 IU/mL) respectively as compared to controls (16.73±3.57 IU/mL and 6.71±1.16 IU/mL), respectively.

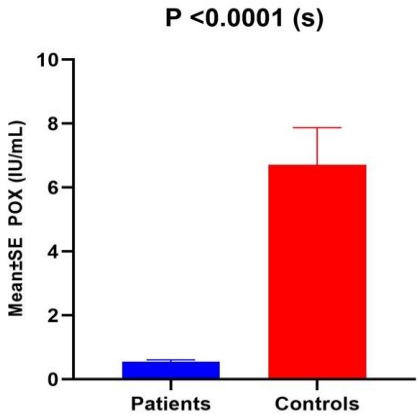



**Figure 4. POX in sera of the two studied groups**

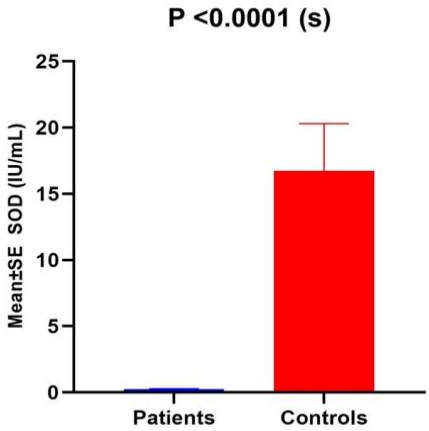



**Figure 5. SOD in sera of the two studied groups**

**Correlations among studies biochemical parameters**

The relationship between 8-OHdG level and measured biochemical parameters is presented in Fig. 6. The results demonstrated that there were none remarkable positive association between serum 8-OHdG level TNF-α, IL-6, SOD and POX which are (r=0.206; *P*=0.565), (r=0.123; *P*=0.565), (r=0.094; *P*=0.793) and (r=0.409; *P*=0.239), respectively.

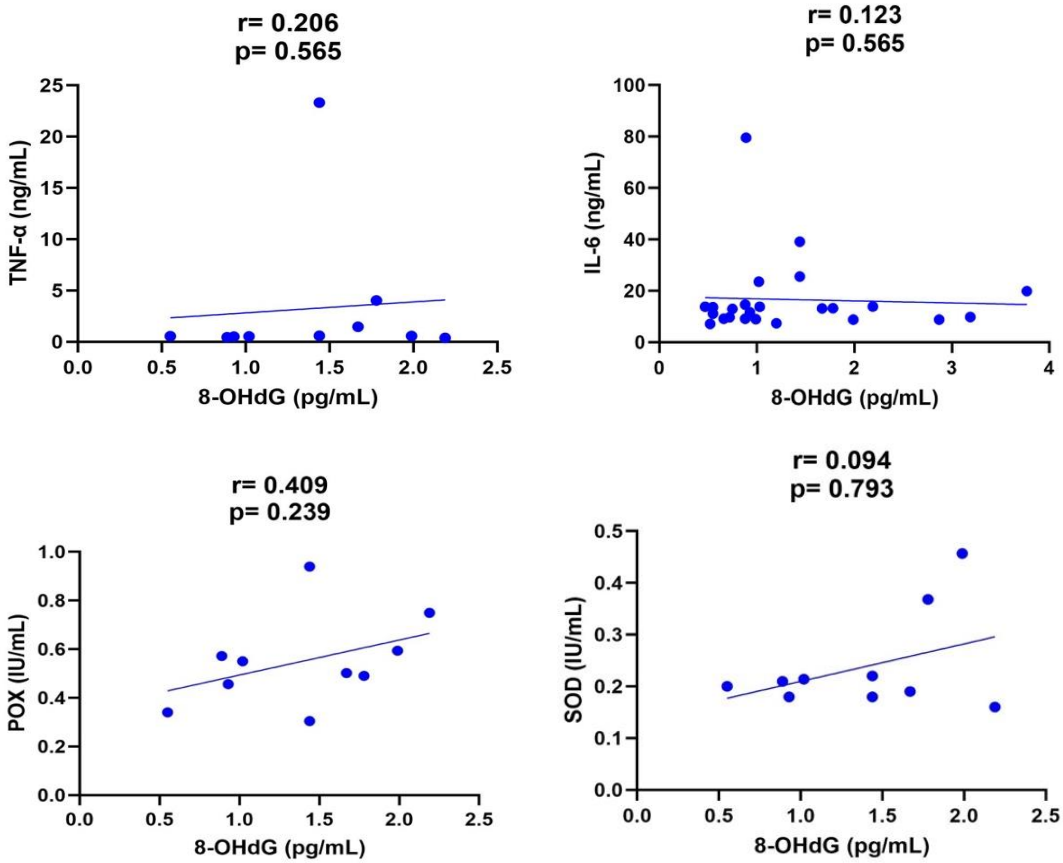
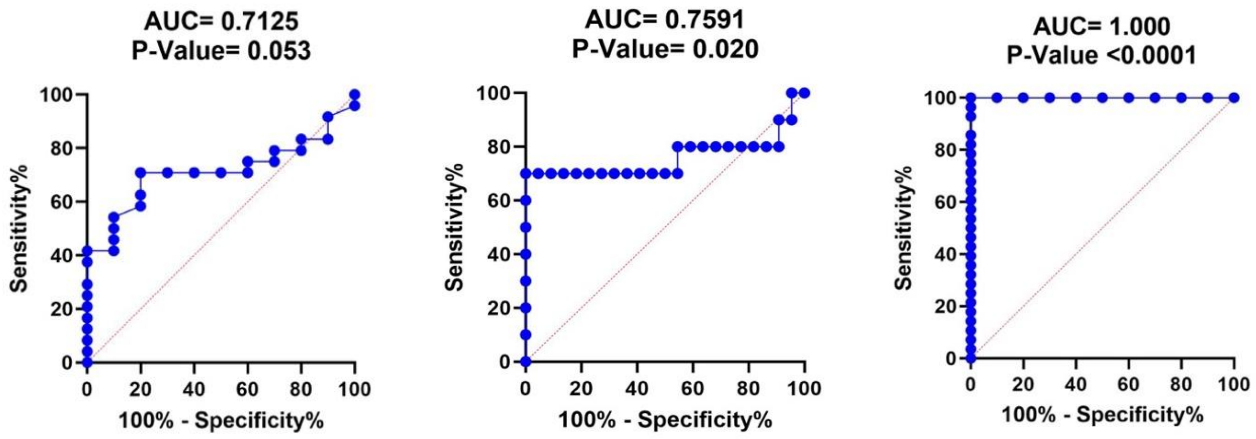



**Figure 6. Correlation of 8-OHdG with TNF-α, IL-6, SOD and POX**

**ROC curve analysis**

Depending on the (Receiver Operating Characteristic) ROC curve, the area under the curve (AUC) of 8-OHdG, TNF-α and IL-6 was (0.7125), (0.7591 and 1.000), respectively, Fig. 7.




**(a)** **(b)** **(c)**

**Figure 7. ROC curves of (a) 8-OHdG, (b) TNF-alpha and (c) IL-6**

## Discussion:

The mean of 8-OHdG concentration of colorectal cancer patients was remarkably higher than that of control subjects as shown in Fig. 7. 8-OHdG, a typical indicator of excess amount free radicals that causes oxidative stress, which generates from oxidation of nitrogen base in DNA molecule mainly guanine[13]. Elevated concentrations of 8-OHdG in tumors, serum or urine have been found in several cancers. 8-OHdG has been utilized in various researches as a biological marker for the determination of oxidative damage in DNA species, and as a vital risk for cancer[14]. High circulating concentration of 8-OHdG in malignant cells in

comparison to non- malignant controls has been recorded, but oxygen radicals, generated by cancer cell or via inflammatory reactions, contribute in DNA damage in normal cells[15].

Hence 8-OHdG as a vital biomarker of oxidative damage of DNA could be a helpful indicator, but its role as a diagnostic factor in colon cancer seems to be restricted[16]. Cancer-dependent amassing of 8-OHdG in DNA enhances tumor development in colon cancer. Mutations of G: C to T: A due to accumulation of 8-OHdG may stimulate genes linked to cancer metastasis. Since 8-OHdG gathering in DNA consequence from oxygen radical promote oxidative nucleic acid damage, excessive oxygen radical production may elevate colon cancer attach and spread of tumour by stimulating signal transduction molecules in patients suffering from high 8-OHdG ratios in DNA[5].

The possible sources of the raised serum 8-OHdG in patients suffering from colon tumors have been supposed. Another possible source of 8-OHdG is general oxidative stress occur by excessive generation of oxygen radical in this connection, it has been revealed that metabolic syndrome is extremely linked with the prevalence of colon tumors. Elevation in 8-OHdG has been examined in nonsmall-cell lung cancer, in squamous cell cancer, and in prostate cancer cells. An elevating in oxygen radical can enhance cell differentiation and proliferation, whereas excessive level of oxygen radical can contribute in oxidative DNA damage[17].

The obtained results showed a remarkable elevate in serum concentration IL-6 and TNF-α in colon cancer patients in comparison to healthy individuals. The inflammation in cancer is guided by chemokines, cytokines and soluble factors. These chemicals are released by tumor cells. Cytokines stimulate growth of tumor cell, differentiation, and survival. Most of the cytokines play a vital role in metastasis, angiogenesis, invasion, proliferation through processes of apoptosis. Cytokines activate cancer-linked fibroblasts to release growth factors[18]. Many studies point to the involvement of IL-6 and TNF-α proteins in the progressing of a cancer cell. Vital role played by Cytokines at all stages of oncogenesis, comprising: alterations the microenvironment of cancer cell permitting its further progression, and they control the reactivity of immune system. On the one hand, many researchers have demonstrated the remarkable action of cytokines in blocking tumour, its stimulation and distribution[19]. A developing disorder for synthesis of cytokines takes place during the progression of cancer. Various cytokines that released by the elements cancer contribute in the autocrine growth of cancer cells and progression of cancer functioning of immune cells, e.g. by promoting release of pro-inflammatory cytokines (IL-6 and TNF-α), angiogenic cytokines, and, consequence of this the further progression of cancer may occur. The researchers propose that enhancement of tumor growth attribute to an increasing of inflammatory cytokines[19].

Multivariate previous statistical analysis reveals that the increased circulating concentration of IL-6 is an independent health risk for development to liver metastasis. An increased concentration of IL-6 did not associate with shorter period time of maintenance[20]. It has been recorded that high expression of IL-6 can promote the migration of breast cancer cells by promoting cell–cell adhesion of epithelial[21]. The TNF-α is generated early in the subsequent process of the inflammation. It is responsible for the stimulation of enhancers of immune response; macrophages, lymphocytes and neutrophils. The antitumor influence of TNF-α is mainly attributing to the stimulation of cell death program. TNF-α is participated in several stages of cancer neoplastic transformation[22]. It plays a vital action in the production of a cancer influence on the progression of blood vessels and promotes remodeling of tissue. Facilitation in the process of metastasis depends on operation of cytokines that allows movement of cancer cells via the walls of blood vessels and lymphatic vessels. TNF-α by promoting the expression of proteases participated in breakdown of the barrier to tumour cell metastasis. Higher levels were recorded in clinical stage IV oral cancer. Apart from elevated level of TNF-α and Interleukin -6 were also observed in saliva of patients with oral carcinoma when compared to the control group[23, 24].

The present result showed a remarkable decline in serum concentration of SOD and GPx in colon cancer patients in comparison to healthy individuals. These results suppose that changes in human defenses system by the action of antioxidant compound, which protect biological molecules from the action of oxygen radicals, it is realizable that the carcinogenesis itself contributes in the obtained disturbance of the antioxidant function. Oxygen radicals are involved in the mechanism of tissue injury in various human disorders. Alteration of the pro-oxidant/antioxidant balance due to elevated oxygen-radical formation, inactivation of antioxidant enzyme, and increased consumption of antioxidant, is critical factor in oxidative DNA damage. The oxygen radicals contribute in chain reaction that alters permeability of cell, precipitate proteins, alters enzymic activity; reduce of

neurotransmitter transmission, resulting in damage of DNA, and break down of proteins structure. Thus, oxygen radicals species are directly contribute in the mutations in genetic species and oncogenesis. The body has various mechanisms of defense system against oxygen radical which mediated tissue damage. It has been proposed that oxygen radicals produce their cytotoxic influence by proteins carbonylation, resulting in the lack of physiological function of protein. Disturbance in protein action is believed to be an extensive indicator of severe oxidative damage. Increased antioxidant enzymatic activities such as catalase and peroxidase were also recorded in response to oxidative stress as an adjustable mechanism in many tumour cells[25].

Peroxidase is counteracting oxidative stress with its capacity to inhibit oxidative damage of DNA, and generation of prostaglandins and leukotrienes as proinflammatory mediators. Thus, peroxidase 1 may inhibit oncogenesis at least in the beginning phase. The lack of peroxidase in initial stages of oncogenesis may causes cancer commencement, whereas it may stimulate cell growth and division reactions in final phase of cancer. Potentially, the action of peroxidase in healthy cells is the inhibition of oxidative pathway in the immunological reactions, while in metamorphose cells, almost same roles inhibit oxidative pathway in the commencement of cell death program and elevate cell growing. As opposed to increase peroxidase may inhibit oxidative stress including DNA oxidation and inflammation reactions, but may also inhibit process of programmed cell death. Apoptotic cell death, causing increase surviving of metamorphotic cells. Thus, peroxidase has a complex influence on the cancer development because of double role of peroxyls and its function as an intracellular modulating for reactive oxygen species[26].

In the present study, a non-remarkable positive relationship between plasma 8-OHdG level and proinflammatory biomarkers (IL-6 & TNF-α) was observed, which means that with the increasing proinflammatory cytokines level, 8-OHdG serum levels are also increased. Based on the graph it can be suggested that proinflammatory mediators secreted in the tumor microenvironment by macrophages and epithelial cells along with other cytokines could enhance oxidative stress and are partially involved in invigorating nuclear oxidative DNA damages. These correlations confirms the idea that oxidative stress and systemic inflammation were strongly interrelated processes during colorectal carcinogenesis. Regarding the correlation between 8-OHdG levels and antioxidant enzymes non-significant correlations were observed with each of SOD and POX. increased oxidative stress and underlying oxidative damages employed by ROS could be largely caused by defected or significantly reduced enzymatic antioxidants activities (SOD & POX) which actually tolerate the dominant oxidative damages into vital cell components (specifically vulnerable DNA structure). Thus, diminished SOD and POX catalytic activity in CRC patients permit ongoing (active) oxidative stress condition to release more ROS, which in turn, it induces an increased release of 8-OHdG into the bloodstream of patients.

The diagnostic tool of 8-OHdG, L-6 and TNF- were measured by means of a graphical plot of receiver operating characteristic (ROC). The overall attainment was explained in terms of area under ROC curve (AUC) with 95% CI and *P*-value statistics for difference between calculated AUC and AUC 5 0.5. A cut-off value associated with the elevated reliability was determined along with the related sensitivities and specificities. Oxidative damage is not disorder-selective due to its contribution in the mechanism of human disorders causing cancer non-selectivity that changes in the concentrations of indicators of oxidative stress restricting their effectiveness as a screening utility. As current study reveals, there is an elevated oxidative damage in colon cancer and the metastasis stage, size of tumor, and lymph node contribute in the elevation concentration of oxidatively modified species with, status, hence, these biological indicators can be used as preferential markers for the detecting the existence of cancer cell.

## Conclusions:

The data of current research revealed that the increased serum 8-OHdG is correlated with an elevated risk of colon cancer and early cancer. The present result support the theory that colon carcinogenesis is associated with excessive oxidative stress and an improve explaining of inflammation processes and the participation of cytokines in it assist to demonstrate undetermined pathophysiological and clinical features of colon cancer. Significant decline in serum POX and SOD levels, as an important antioxidant component may be a causative factor in the progression of colon cancer.

## Author's declaration:

- Conflicts of Interest: None.
- I hereby confirm that all the Figures and Tables in the manuscript are mine. Besides, the Figures and images, which are not mine, have been given

the permission for re-publication attached with the manuscript.
- The author has signed an animal welfare statement.
- Author sign on ethical consideration's approval
- The project was approved by faculty council (Faculty of Science/ Soran University) and the Deanery of Faculty of Science/ Soran University

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**Open Access** **Baghdad Science Journal** **P-ISSN: 2078-8665**
**Published Online First: July 2022** **2023, 20(1): 82-89** **E-ISSN: 2411-7986**

# الدور المحتمل لـ 8-هيدروكسي غوانوسين وبعض السيتوكينات المنشطة للالتهابات كمؤشرات حيوية في مرضى عراقيين بسرطان القولون المستقيم

**هژار محمد حمدامين**

قسم الكيمياء، كلية العلوم، جامعة سوران، اربيل، العراق

**الخلاصة:**

يعتبر 8-هيدروكسي غوانوسين مؤشرا على الإجهاد التأكسدي. السيتوكينات المنشطة للالتهابات هي جزء مهم من العمليات الفيزيولوجية المرضية التي يمكن تطبيق العلاج عليها هدف الدراسة هو تقييم تركيز 8- هيدروكسي غوانوسين والسيتوكينات المسببة للالتهابات في مرضى سرطان القولون. حيث تم أخذ عينات الدم قبل العلاج من 50 حالة مصابة بسرطان القولون (المرحلة الثالثة) تم إدخالها للفحص الصحي في مستشفى نانەکەلي في مدينة أربيل مع 45 عينة صحية من الضوابط تتراوح أعمارهم بين 38-69 سنة لكلا المجموعتين . تم تقدير تركيز -هيدروكسي غوانوسين، السيتوكين الالتهابي مثل عامل نخر الورم ألفا وإنترلوكين 6 بواسطة تقنية إليزا. تم تحليل التراكيز المتداولة لمستويات سوبر اوكساید دسميوتيز و بيروكديز أيضًا باستخدام تقنية إليزا أيضًا. كان المشاركون في هذه الدراسة 95 شخصا تراوحت أعمارهم من 38 إلى 69 عامًا، 50 حالة مصابة بسرطان القولون المستقيم و تم تشخيصها حديثًا (بدون علاج) مع 45 فردًا تم استخدامهم كمجموعة ضابطة. أظهرت البيانات ارتفاع غير معنوي من خلال مقارنة اشخاص الاصحاء مع حالات سرطان القولون المستقيم لـ-هيدروكسي غوانوسين بقيمة (0.054) وارتفاع معنوي لـ عامل نخر الورم ألفا بقيمة (0.019) و وإنترلوكين 6 بقيمة (0.0001>) بينما أظهرت البيانات إنخفاض معنوي بقيمة (0.0001>) لمستويات سوبر اوكساید دسميوتيز و بيروكديز. تشير نتائج الدراسة الحالية أن 8-هيدروكسي غوانوسين عامل الإجهاد التأكسدي في سرطان القولون المستقيم وأن عامل نخر الورم ألفا مسؤول عن زيادة تراكيز إنترلوكين 6، والتي ترتبط بعملية الالتهاب في محيط الخلية السرطانية.

**الكلمات المفتاحية**: سرطان القولون، 8-هيدروكسي غوانوسين، إنترلوكين ٦، عامل نخر الورم ألفا