# Does Oxidative Stress Promote The Effect of The Paraoxonase Enzyme Family (PON) On Cancer? A Review Study To Clarify This Relationship by PONs

## Oksidatif Stres Paraoksonaz Enzim Ailesinin (PON) Kanser Üzerindeki Etkisini Arttırır Mı? PON Ailesinin Oksidatif Stres ve Kanser İlişkisinin İncelenmesini Amaçlayan Bir Derleme

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**Öz**

Kanser gelişimi ve ilerlemesi oksidatif stres ile ilişkilidir. Yüksek seviyelerde reaktif oksijen türleri (ROS) ve serbest radikaller, fizyolojik bir durum olan oksidatif strese neden olmaktadır. Oksidatif strese karşı geliştirilen antioksidan metabolizması çok önemlidir. Antioksidan seviyelerindeki azalma, koroner kalp hastalıklarının risk faktörleri arasında sayılabilir. Paraoksonaz enzimi (PON), kan dolaşımındaki lipoproteinlerin yanı sıra hücre içindeki lipid peroksitlerini de parçalayarak antioksidan metabolizmanın devreye girmesine sebep olmakta ve düşük seviylerdeki antioksidanlar koroner kalp hastalığında etkili bir risk faktörü haline gelebilmektedir. Bu derleme, önemli bir antioksidan enzim olan PON'un; DNA hasarı, çeşitli kanser türlerinin progresyonu ve sinyal yolaklarındaki değişiklikler ve lipoproteinler ile ilişkisi üzerindeki rollerine odaklanmaktadır.

*Anahtar kelimeler* PON; kanser, antioksidan; oksidatif stres; hipoksi

**Abstract**

*Cancer development and progression are associated with oxidative stress. Oxidative stress can favor high concentrations of reactive oxygen species (ROS), and free radicals are associated with antioxidant metabolism. The human enzyme paraoxonase (PON) contributes to antioxidant metabolism and decreased antioxidant levels. This leads to a high-risk factor for coronary heart disease. This review focuses on specific changes that affect the DNA molecule, and signaling pathways, and regulate the various cancers through the attraction of PON, an enzyme for degrading lipid peroxides within the cell as well as lipoproteins in the bloodstream.*

*Keywords* *PON; cancer; antioxidant; oxidative stress; hypoxia*

## INTRODUCTION

### ROS and Cytochrome (CYP) P450

The cytochrome (CYP) P450 system is involved in the detoxification of xenobiotics, cellular metabolism, and homeostasis.[1]

Reactive oxygen species (ROS) acts a pivotal role in cancer cell viability and controls signal transduction pathways, paraoxonase (PON) 2 belongs to the PON gene family consisting of PON1, PON2, and PON3.[2]

### Paraoxonase enzyme Family (PON1, PON2, PON3)

Human paraoxonases (PON) are encoded by three, PON1, PON2, and PON3, different genes on chromosome 7. In mammals, the PON genes have a common sequence of 79-95% at the amino acid level and 81-95% homology at the nucleotide level between species. PON2 is the oldest member of the family, and PON3 and PON1 are responsible for gene duplication.[2]

The human body has biological redox systems to control the damage caused by increased oxidative stress during life. One of them is indicated with the PON enzymes. The well-known enzyme is PON1, which is associated with high-density lipoprotein (HDL) and has paraoxonase, arylesterase, and lactonase activities. Based on these properties, the PON1 enzyme has been associated with the development of neurodegenerative diseases. Here, we update the knowledge about the association of PON enzymes and their role in cancer.[3]

All three PONs have common properties such as PON1 is associated with HDL, and PON2 and PON3 are intracellular membrane proteins.[4,5]

Polymorphisms of PON have been related to a variety of diseases ranging from atherosclerotic diseases to a variety of cancers. Polymorphisms of the PON1 gene appear to be associated with a high risk of cancer-related to toxic materials and environmental chemicals.[6] The overexpression of PON2 and PON3 has been observed in cancer cells, and it has been proposed that both enzymes may be involved in tumor survival and stress resistance. Also, lower serum PON1 activity levels have been observed in cancer patients.[2]

ROS are also involved in the regulation of transcription factors such as activator protein 1 (AP-1), nuclear factor erythroid 2-related factor 2 (Nrf2), hypoxia-inducible transcription factor 1a (HIF-1a), p53, and nuclear factor κB (NF-κB). Alterations in enzyme activities involved in oxidative damage, such as superoxide dismutase (SOD) and catalase (CAT) in tumor cells, have recently been studied. Antioxidant enzymes include the PON family with PON1, PON2, and PON3. PON enzymes play a physical-pathological role that has been mainly studied in cardiovascular and neurodegenerative diseases. PON1 has been more extensively studied than PON2 and PON3. Alterations in PON status such as genotype, activity, and/or expression have been detected in cancer patients as well as in most cancer cells in vitro. Cells undergo neoplastic transformation through a series of different events, one of which is impaired regulation of the cell death program and resistance to apoptosis. Evidence suggests that the PON2 and PON3 enzymes act a crucial role in cancer cell survival due to the antioxidant and anti-apoptotic activities of these enzymes. Acting a pivotal role in drug resistance and cancer cell survival has also been attributed to PON2 and PON3.[2]

This review discusses aspects and issues related to the role of intracellular ROS formation and nutrition with its link to disease and its problematic therapeutic issues related to cancer and PON isoenzymes.

## PON1

ROS detoxification is mediated by scavengers such as vitamins C and E and various antioxidant enzymes that reflect ROS to reduce the harmless components. The PON1 enzyme is a hydrophilic esterase enzyme that plays a role in peroxidation products[6]. Regarding the physiological

role, Mackness et al[7] suggested that isolated PON1 and HDL-associated PON1 have a protective effect against lipid peroxidation of low-density lipoprotein (LDL). The oxidative status of LDL by ROS or cellular enzymes is indicated the atherogenesis that plays a role at the beginning of atherogenesis. PON1 also protects HDL and biological membranes from lipid peroxidation to some research articles in the literature. Mice deficient in PON1 are more susceptible to lipoprotein oxidation and inflammation, whereas mice overexpressing human PON1 are closest to inflammation and atherosclerosis.[2]

Higher oxidative stress is defined with low PON1 activity. Rosenblat et al[8] reported that the hydrolysis of oxidized lipids by PON1 is promoting the lactonizing formation and lactonase (lactone hydrolysis) activities of this enzyme. The antioxidant role of PON1 is also related to its peroxidase activity to prevent the neutralization of fatty acid, hydroperoxides, cholesteryl ester hydroperoxides, and hydrogen peroxide (H2O2). Oxidative stress and higher concentrations of lipid peroxidation products stimulate the synthesis of pro-inflammatory molecules. 4-Hydroxynonenal, which is formed by lipid peroxidation, is capable of oxidizing LDL (ox-LDL). This results in promoting the development of oxidative stress-induced cancers.[2]

## PON2

The PON2 isoform is highly expressed in different types of human cells and tissues, such as macrophages and hepatocytes, the lower respiratory tract of the lung, the brain, the heart, and the gastrointestinal system. It is found in association with the endoplasmic reticulum (ER) and mitochondria, particularly in association with the inner mitochondrial membrane complex III. PON2 deficiency contributes to mitochondrial function by decreasing mitochondrial complex I and III activity and total ATP levels and stimulating mitochondrial oxidative stress by increasing mitochondrial superoxide production, increasing lipid peroxidation, and decreasing levels of reduced glutathione[2]. PON2 is not found in plasma.[3]

PON2 has a calcium-dependent hydrolytic activity for lactones, esters, and aryl esters and also functions as an antioxidant enzyme. Overexpression of PON2 is also responsible for the oxidative state of cells such as preventing the cell-mediated oxidative modification of LDL and therefore blocks the ability of lightly oxidized LDL to induce monocyte chemotaxis. The redox function reduces the number of ROS and thus has an anti-apoptotic effect. However, the most important thing is to understand the effects of molecular damage to ROS and oxidative stress. This is an aspect that should be defined in the future.[9]

The PON2 isoform is highly expressed in various types of human cells and tissues, especially macrophages and hepatocytes, a lower respiratory tract of the lung, brain, heart, and gastrointestinal tract. It is found in association with the ER and mitochondria, particularly in association with the inner mitochondrial membrane complex III. PON2 deficiency alters mitochondrial function by decreasing mitochondrial complex I and III activity and total ATP levels and alters mitochondrial oxidative stress by increasing mitochondrial superoxide production, increasing lipid peroxidation, and decreasing levels of reduced glutathione. Studies in animal models have shown that increased PON2 expression can protect against atherosclerotic plaque formation by modulating intracellular oxidative stress.

PON2 deficiency is defined as atherosclerosis. Since the overexpression of PON2 is attached to a low level of intracellular oxidative stress caused by hydrogen peroxide. In brain tissue, PON2 is an antioxidant intracellular enzyme against oxidative stress. In the CNS, PON2 expression has been detected in the nucleus accumbens, striatum, and substantia nigra. The lack of PON2 expression in both cells negatively affects the cells' ability to prevent oxidative damage.[3]

## PON3

PON2 is a highly expressed intracellular protein that has

an interesting act bound to HDL and PON1. All of them have antioxidant properties.[10]

PON3 is acting as an antioxidant hydrolase enzyme that is synthesized in the liver. In plasma, PON3 is bound to HDL and apolipoprotein-AI and has potent antioxidant properties, but its concentration is about two orders of magnitude lower than that of PON1. PON3 is also expressed at low levels in the kidney. PON3 was the last enzyme of the PON family genetic cluster to be described.[3] Currently, very little is known about its function and physiological properties in humans. The PON3 and PON1 enzymes share some similarities in structure and hydrolase activity. Regarding structure, both enzymes have three highly conserved cysteine (Cys) residues at positions -41; -283, and -351 in the protein chain. In terms of enzyme activity, PON3 can rapidly hydrolyze cyclic carbonate esters and lactones, especially drugs such as statin-lactones. The arylesterase activity of PON3 is almost undetectable compared to PON1. PON3, like PONs 1 and 2, is involved in homeostasis to prevent oxidative stress. In vitro, PON3 hydrolyzes some oxidation products such as oxidized phospholipids and lipid (hydro)peroxides. A low level of PON3 has been found in HDL particles from patients with systemic lupus erythematosus and type 1 diabetes, which is associated with subclinical atherosclerosis. In addition, recent studies have described the increased expression of PON3 in various types of tumor cells. Currently, six SNPs have been described in the promoter region of the PON3 gene: C-567T, A-665G, C-746T, G-4105A, T-4970G, and A-4984G. These polymorphisms have little or no effect on PON3 levels.[3]

The physiological function of PON3 is not well-known. PON3 appears to be more effective than PON1 in protecting LDL from oxidative changes in vitro, although the serum PON3 concentration is about two orders of magnitude lower than that of PON111. Moreover, unlike PON1, PON3 expression in the liver is not affected by oxidized phospholipids (HepG2 cells) or by a high-fat diet (mouse liver). Circulating PON3 levels have been examined in a variety of human oxidative stress-related diseases to determine whether disease states are associated with changes in PON3 levels, as is the case with PON1. Indeed, significant increases in PON3 levels have been found in chronic liver disease, HIV infection, and coronary and peripheral artery disease. However, a recent study in patients with autoimmune diseases (systemic lupus erythematosus and type 1 diabetes) has shown a significant depletion of PON3 protein in the HDL of patients with autoimmune diseases and subclinical atherosclerosis. Of note, the technique used to measure PON3 was different in these studies (internal serum ELISA in the former studies versus HDL LC-MS /MS in the latter study). Interestingly, in the HIV study, the authors also investigated possible changes in the distribution of PON3 in lipoproteins in disease. Lipoproteins were fractionated by FPLC. They found that in uninfected participants, PON3 was detected exclusively in HDLs, whereas in HIV-infected individuals, a substantial amount of PON3 was measured in the smallest HDL and LDL particles. HDLs measured in patients with autoimmune diseases with and without subclinical atherosclerosis were separated by ultracentrifugation, and the presence of PON3 in LDLs was not examined. All in all, PON3 could be a useful analytical biomarker for oxidative stress-related diseases in humans.[11]

**Cell redox status of enzymes**

The cellular redox environment is so crucial to understanding the aspects of diseases in the metabolism. Several antioxidant enzymes have been investigated in vitro and/or in animal models to assess their potential therapeutic effects in the conditions linked to oxidative stress related to redox imbalance.[12,13]

Their results offer the importance of understanding the relationship between redox homeostasis and the status of ROS-related disease.

In human metabolism, redox balance is so crucial. Because the explanation of this balance is all about the defense sys-

tem to prevent effects not stimulate tumorigenesis. Prooxidant molecules modulate genes related to differentiation and cell growth and can cause structural DNA changes that trigger carcinogenic processes. Therefore, oxidants may play a critical role in both the development and progression of cancer. An important indicator of oxidative stress is malondialdehyde (MDA), the end product of lipid peroxidation.[14]

### Aging and PON

Aging is so open the organ dysfunction.9 And this process also maintains lipid peroxidation and tissue damage within the chronic inflammatory processes. The production of ROS and free radicals is stimulating this triple. All three PON proteins prevent oxidative stress.[9] The main objective of this section is to highlight the importance of the role of the PON2 enzyme in the aging process. Associated with high ROS stimulates cancer, cardiovascular disease, neurodegeneration, and diabetes. The highlighting of antioxidant control of ROS, mitochondria, and the ER are major sources of oxidative stress. The predominant localization of PON2 in these organelles supports its role in preventing oxidative damage at the mitochondrial level. Several studies have shown that PON2 protects cells and tissues from oxidative stress, human and rat intestine, human vascular endothelial cells, epithelial lung carcinoma cells, Caco-2/ cells, and mouse macrophages. In macrophages, PON2 is thought to protect against triglyceride accumulation and oxidative stress. In the gastrointestinal tract, PON2 defends oxidative and inflammatory processes. Among the three PON enzymes, PON2 is the only one expressed in nervous tissues. The high concentration of PON2 in the brain (about three times higher in women than in men) protects neurons and astrocytes from oxidative stress, toxicity, and lipid peroxidation. PON2 also protects against acute myocardial ischemia-reperfusion injury by reducing mitochondrial dysfunction and oxidative stress in cardiomyocytes via activation of the PI3K/Akt/GSK-3β pathway RISK.[9]

PON2 has attracted much attention in the last decade because it has been related such as atherosclerosis, cancer, insulin sensitivity, and neurodegeneration.[2]

This is consistent with previous but still current, studies showing that deregulated redox regulation in PON2 deficiency leads to vascular inflammation and blood coagulation abnormalities.[9]

### Oxidative stress and metabolic pathways

Tumor growth and metastasis depend on several factors, but at least one link between inflammation, oxidative stress, and cancer has been detailed.[9] Cancer cells stimulate specific metabolic pathways, alterations in mitochondrial and peroxisome functions, increased cellular receptor signaling, the eased function of inflammatory cytokines, and activation of oncogenes. In the initiation phase, ROS may contribute to oxidative changes and impairment of biomolecules such as DNA, polyunsaturated fatty acids of lipid membranes, and proteins. Oxidative changes in proteins can lead to loss of enzyme activity and make proteins more susceptible to proteolytic degradation. ROS can also contribute to abnormal gene expression, impaired intercellular communication, and alterations in signaling pathways. In particular, ROS activate stress-responsive survival pathways and can maintain cellular proliferation and differentiation. Several enzymes are detailed in signaling pathways activated by ROS, such as p38 mitogen-activated protein kinase (p38 MAPK), protein kinase C (PKC), extracellular signal-regulated kinase (ERK)1/2, Jun N-terminal kinase (JNK), and phosphoinositide 3-kinase/serine-threonine kinase (PI3K/Akt).[9]

### Cancer relation and PON enzyme family

An imbalance between oxidants and antioxidants is involved in the development of various diseases, including cardiovascular disease, liver disease, kidney disease, cancer, and diabetes mellitus.[15] Antioxidant enzymes play a key role in establishing a balance between oxidants and antioxidants.[15] Moreover, PON1 is an antioxidant enzyme

that associates with HDL in the bloodstream, and the antioxidant and antiatherogenic properties of this lipoprotein are closely related to PON1.[15]

The antioxidant and antiapoptotic activities of PON2 suggest a role in promoting cancer cell survival and resistance to chemotherapeutic agents. Despite the established and predominant role of PONs in cardiovascular disease and relevant parameters, recent studies have uncovered a novel link between PONs and cancer. Microarray studies have found overexpression of PON2 in some solid tumors such as hepatocellular carcinomas, and prostate carcinomas, and some others such as skin neoplasms, gastric cancer, and breast cancer.[9]

PON1 is an antioxidant enzyme bound to HDL in the membranes of most cells and also in the bloodstream.[16] The original function attributed to PON1 was that of a lactonase (LAC) since its primary substrates are lipophilic lactones.[17] This catalytic ability enables PON1 to degrade lipid peroxides both within the cell and in circulating lipoproteins.[18] In addition, PON1 possesses esterase activity that degrades organophosphate xenobiotics and nerve toxins.[16] PON1 is synthesized mainly in the liver and to a lesser extent in the kidney and colon and is subsequently transported into the bloodstream bound to HDL.[19] PON1 plays an important role in lipid metabolism as an antioxidant molecule for preventing inflammation. PON1 enzyme activity is affected by inflammatory processes and oxidized LDL levels. PON1 has been shown to protect against oxidative stress by hydrolyzing active oxidized phospholipids, destroying lipid hydroperoxides (carcinogenic lipid-soluble radicals from lipid peroxidation) and H2O2 (via its peroxidase-like activity), maintaining the integrity and function of HDL, and preventing LDL oxidation.[20]

Cancer is a disease characterized by cell mutation, proliferation, and abnormal cell growth and is usually defined by at least three stages-initiation, promotion, and progression-generally associated with oxidative stress. The first stage of cancer (initiation) is defined as a stable, heritable change. This stage is irreversible and results from a mutational event induced by physical agents, chemicals, and ROS. In addition, triggering agents result in genetic changes, including mutations, DNA damage, and structural changes. The second stage of carcinogenesis (promotion) is triggered by endogenous or exogenous stimuli of cell growth. ROS can alter gene expression in this stage and cause modification of second messenger systems, thereby increasing cell proliferation or inhibiting apoptosis and clonal expansion of initiated cells, resulting in a preneoplastic lesion. Finally, the third stage (progression) involves the transformation of benign preneoplastic lesions into neoplastic cancer. The role of antioxidant protective mechanisms based on enzymatic and non-enzymatic antioxidant molecules in the context of chronic inflammation and cancer is well established.[21]

In human cells, several genes and their products are involved in pro- and antioxidant functions to maintain a balance in the oxidative homeostasis of a cell. The most potent enzymatic antioxidants include SOD, CAT, GPx, and glutathione reductase (GRx). Recently, the antioxidant enzyme PON1 has attracted much interest as the protein responsible for most of the antioxidant properties of HDL. Studies have shown that PON1 prevents the formation of oxidized LDL and inactivates oxidized phospholipids from LDL once formed. In addition, PON1 also delays the oxidation of phospholipids into HDL. In addition, PON1 also scavenges carcinogenic lipid-soluble radicals. This antioxidant enzyme also maintains the balance between antioxidants and oxidants, which are generally believed to contribute to cancer development.[21]

Several studies have shown the link between oxidative stress and the development of human diseases, including cancers. Recently, many studies have focused on the relationship between PON1 and cancer. In this regard, some studies have reported low expression and activity of PON1 (PONase, AREase, LACase) in patients with various can-

cers, such as cancer blindness, gastrointestinal cancer, breast cancer, prostate cancer, lung cancer, non-Hodgkin's lymphoma, and central nervous system tumors. Using these results, Huang et al. demonstrated the variability of PON1 activity, which is very large. Low PON1 activity affects oxidative stress and leads to poorer prognosis in cancer patients. Huang et al[22] suggested that serum PON1 level could be used as a biomarker for microvascular invasion. They found that PON1 expression was inversely associated with the degree of vascular invasion in hepatocarcinoma cells.

From the studies, PON1 plays an important role in cancer. However, it is also important to consider cancer type, ethnicity, gene interactions, and various factors contributing to cancer development. In addition, the signal transduction pathways involved in the modulation of PON1 and the relationship between PKC and MAPK/ERK pathways activated by growth factors to regulate cell growth and differentiation, apoptosis, and angiogenesis are of great importance.[21]

PON1 is a glycoprotein composed of 355 amino acids and has a total weight of 43-45 kDa. It consists of six cylindrical β-propeller structures with four β-strands connected by a disulfide bridge, stabilizing the structure of the enzyme. PON1 contains three cysteine residues at positions 42, 284, and 353; the residue at position 284 has a free sulfhydryl group, which is thought to be responsible for the protective action of the enzyme. Apoprotein A-I is a protein that stabilizes PON1 in HDL molecules and selectively enhances the lactonase activity of this enzyme. Its effect on organophspatase and arylesterase activities is minimal. The presence of PON1 mRNA has been detected in organs such as the liver, lung, heart, brain, small intestine, and kidney. In humans, PON1 is mainly produced in the liver and then secreted into the blood, where it binds with HDL.[23]

The functions and regulations of the PON2 isoform are less well-known than those of PON1. It is known that PON2 is involved in the defense against inflammatory responses in the body; it also has antioxidant properties that may prevent the development of atherosclerosis. PON2 is not a plasma enzyme, nor is it associated with HDL or LDL molecules. However, it is localized intracellularly and bound to the plasma membrane. It has been detected in almost all human tissues, particularly in the liver, where it is produced, as well as in the lung, placenta, testis, and heart.[23]

PON3 exhibits antioxidant and antiatherosclerotic activities. It has been detected in small amounts in the kidney and liver, the site of its synthesis. It is excreted into the blood, where it binds to the HDL fraction. Some research supports the hypothesis that PON3 acts primarily intracellularly and is not physiologically excreted into the blood, and that its presence in serum is the result of pathological processes[23]. PON2 is possibly the oldest member of the family, followed by PON3 and PON1, which is most likely chromosome duplication. PON1 is better studied than PON2 and PON3. Expression of PON3 is markedly up-regulated in several different human cells, including cancer cells. PON3 is upregulated in lung adenocarcinomas and pancreatic carcinomas and downregulated clear cell sarcomas of the kidney, hepatocellular carcinomas, serous papillary carcinomas of the ovary, cervical carcinomas, papillary thyroid carcinomas, prostate carcinomas, and leukemias. PON3 is also reported to increase in early-stage cancer and decrease in late-stage cancer. PON3 is located at ER and predominantly in mitochondrial membranes, and increased PON3 expression leads to apoptotic resistance in tumor cells.[24]

PON1 is an extremely versatile enzyme that can hydrolyze a variety of substrates, including lactones, thiolactones, organophosphorus triester pesticides, and nerve gasses (paraoxon, diazoxon, sarin, and soman, to name a few), aryl esters, estrogen esters, cyclic carbamates, and glucuronide drugs. Because of these diverse enzymatic activities, the role of PON1 in the detoxification of organophosphate

compounds, drug metabolism, cardiovascular disease, and other diseases has been extensively studied. These activities may explain the diverse physiological functions of this enzyme. PON1 is closely related to the reduction of oxidative stress and inflammation, which may significantly influence the development of atherosclerotic plaques and cardiovascular events. Experiments using PON1 knockout mice have shown that the absence of PON1 leads to an increase in endothelial adhesion molecules and oxidative stress, confirming the role of this enzyme in preventing the occurrence of atherosclerosis.[25]

Detailed structure/function studies have revealed that the natural substrates for PON1 are lactones, with lipophilic lactones being the primary substrates. The aromatic nature of the amino acids in the active site of PON1 may explain why the enzyme prefers lipophilic substrates. PON1 is capable of hydrolyzing a wide range of lactones. The PON family shares this property as lactonases, albeit with different substrate specificities.[25]

In recent years, attention has focused on δ-lactone eicosanoids as PON substrates. These compounds are metabolites of arachidonic acid and mediate several metabolic processes in vivo. 5-Hydroxy-eicosatetraenoic acid-1,5-lactone (5 HL) is a substrate for all three PONs. PON1 has the greatest hydrolytic activity, followed by PON3, whereas PON2 has low activity toward this substrate. PON3 has by far the highest activity toward two other eicosanoids, cycloepoxycyclopentenone (cyclo- EC) and 5,6-dihydroxy-eicosatrienoic acid lactone (5,6-DHTL), again followed by PON1, while PON2 has little or no activity toward these substrates. Interestingly, this order of hydrolytic activity also applies to the hydrolysis of estrogen esters by the PON family. Lactonase activity in the endothelium may influence vasodilation.[26]

Genetic information provides a means of identifying people who have an increased risk of cancer, thus this knowledge of cancer genetics helps to identify the ability to characterize malignancies leading to the development of new therapeutic approaches. Because of this reason, Ozensoy et al investigated the role of human serum PON1 enzyme activity and phenotypic distribution in 32 breast cancer (BC) patients (age range 28–82) and 3 cancer-free (CF) control groups (age range 21–67).[27]

Another study is also designed by the same group of Ozensoy et al. to assess the activities of carbonic anhydrase (CA), CAT, PON1, and xanthine oxidase (XO) activities in 89 head and neck cancer (HNC) patients and 115 healthy volunteers. In this study, PON1 activity was found lower in HNC. So they confirmed PON1 levels could be a candidate as an oxidative marker in HNC patients.[28]

## CONCLUSIONS

ROS are important signaling molecules that play an important role in the progression of inflammatory diseases.[29] ROS generation is unfortunately poorly understood. ROS are generated as by-products of cellular metabolism through the electron transport chain (ETC) in mitochondria as well as via the cytochrome P450. To prevent the harmful effects of oxidants, cellular metabolism has antioxidant defense systems whose function is to remove ROS. The antioxidant enzymes SOD (dismutase of O2 to H2O2), CAT, GPx (converts H2O2 to H2O), peroxiredoxins, and Trxs are classified as ROS scavengers.

Although caspase activation and enhanced formation of ROS is central to the mechanism of apoptosis, there are reports of apoptosis, reports suggesting no significant role of ROS in the progression of apoptosis, and showing that reduced ROS generation stimulates apoptosis[30,31]. This is surprising, as the efficacy of pharmacological antioxidants such as GSH, NAC, deferoxamine, and antioxidant enzymes such as CAT or GPx in preventing apoptosis has been demonstrated by several groups. However, other studies have failed to demonstrate the role of antioxidants in preventing apoptosis.[30,31]

While it is clear that ROS plays an important role in the development of inflammation and tissue.[32] Cancers have a direct response to chronic tissue injury, where the resulting cell death increases the tumorigenic potential of neighboring cells. So the main problem is how tissue injury promotes tumorigenesis. There are so many key factors to clarify this situation by understanding the enzyme's chemical reactions.[33] But in fact, inflammation is associated with a decrease in extracellular pH. Therefore PON enzyme family is capable of detoxifying organophosphate compounds but their role in the physiological role is still so enigmatic for cancer. Further large-scale studies are needed for new clinical strategies for the prevention and treatment of cancer by the enzyme family PON.

Oxidative stress is so crucial and it is implicated in the development of inflammatory diseases including atherosclerosis and cancer, these recent studies on PON2 and PON3 proteins may provide a mechanism for the scores of epidemiological studies that show a link between PON genes and numerous inflammatory diseases.[34] Despite the role of PON proteins in important cellular functions and associated pathologies, the physiological substrates and molecular mechanisms by which PON proteins act as anti-inflammatory proteins are still largely unknown. Understanding such mechanisms will provide novel strategies in the treatment of diseases associated with pro-inflammatory oxidative stress where also cancer can have a place in this relation.

## Conflict of Interest

None

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