Association of paraoxonase (PON1) polymorphisms and activity with colorectal cancer predisposition

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ABSTRACT
Paraoxonase 1 (PON1) is a well recognised member of human endogeneous free radical scavenging systems and its polymorphism and enzyme activity are attributed to various different cancer formations. We aimed to study the Paraoxonase 1 (PON1) polymorphism and enzyme activity in colorectal cancer patients. Peripheral blood samples for DNA extraction were collected from 54 colorectal cancer patients and 85 healthy individuals. Polymerase chain reaction (PCR) and restriction fragment length polymorphism (RFLP) techniques were used for determination of the PON1192 polymorphism. The frequency of AA genotype was greater than BB and AB genotypes in all groups (n:65 with 46.8%; n:15 with 10.8% and n:59 with 42.4%, respectively). In both tumor groups, PON activities were significantly lower than the control group (p<0.05).

The AA genotype was significantly more frequent than the AB and BB genotypes in colorectal cancer patients. Although the rectum cancer patients’ number is low in our study, we hypothesise that decreased enzyme activity of PON 1 related to 192 gene polymorphisms might have a role in the formation of an oxidative microenvironment for cancerous DNA damage which may tend to increase distally in the colon. Further studies considering the location and the stage of the colorectal tumors with more patients may put a broadly wider view on this polymorphism and enzyme activity with respect to cancer formation.

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Introduction
The third common cause of all cancer diagnoses in the world is colorectal cancer (CRC). Of all cancer-related deaths, CRC are also the second common cause [1]. About 90% of CRC cases are sporadic, and the rest 10% have a hereditary background with high penetrance. The path from benign polyps to the formation of cancer has attribution to lifestyle-related factors such as diet, low physical activity, alcohol consumption and smoking [2,3]. Although the majority of CRC cases are sporadic, it seems probable to have some underlying genetic predispositions for malignant transformations [4,5]. The DNA damage related to the loss of antioxidant defense mechanisms for DNA protection may provoke triggering mutation cascades. Different studies report that superoxide producing Enterococcus faecalis causes DNA damage in colonic epithelial cells [6] and colon mucosa is more prone to oxidative stress due to lower antioxidant mechanisms despite increased oxidative stress compared to intestines [7]. Paraoxonase is an antioxidant enzyme associated with high-density lipoprotein (HDL) playing a role in the detoxification of organophosphates and products of lipid peroxidation [8]. Polymorphisms of Paraoxonase are related to a wide range of pathologies ranging from atherosclerotic diseases to a variety of cancers [9,10].

The PON1 gene is a gene on the 7th chromosome. It is on the short arm at the q21–q22 locus [11]. The most frequently investigated single nucleotide polymorphisms (SNP) of the PON1 gene are Q192R and L55M. The Q192R polymorphism (substitution of Glutamine-Arginine) changes the affinity of the enzyme towards various organophosphates. The molecular basis of the polymorphism is an amino acid shift at the 192nd position. The A allele with a lower affinity to paraxone has Glutamine, and the B allele of higher has Arginine at 192nd position [11,12]. Another
polymorphism of locus 55 is related to a leucine-to-methionine shift and is thought to be less relevant to enzyme activity [12]. However, Garin et al. demonstrated that the PON55 polymorphism exhibits substantial differences in the activity of enzyme via modulating concentrations of PON1 protein in non-insulin dependent diabetes mellitus (NIDDM) [13]. PON1-192 B allele, which is assumed to be associated with coronary heart disease, has less effectivity on the hydrolysis of lipid peroxides than the A allele [14].

Paraoxonase gene (PON1) polymorphisms seem to be associated with increased cancer risk related to various toxic agents and environmental chemicals [8,15,16]. Akçay et al. reported lower serum PON levels in gastric and pancreatic cancer patients concerning age and gender-matched control groups [17,18]. Marchesani et al. showed increased prostate cancer risk related to carriers of PON1-I102V polymorphism [19]. The studies on PON1 and colorectal cancer associations are controversial. Ahmed et al. reported significantly lower PON1 activity in CRC patients compared to controls [20]. Van der Logt et al. evaluated the PON1 polymorphism without pairing with enzyme activity in 365 CRC patients’ DNA samples and found no association between PON polymorphisms and CRC [3].

We studied the paraoxonase activity and polymorphisms in a CRC patient cohort and evaluated the risk of genetic or acquired CRC predisposition related to this unique antioxidant enzyme.

**Subjects and methods**

This study included 54 colorectal cancer patients (mean age of 56 years, ranging between 33 and 74 years; and 1:1 male/female ratio, 28 male and 26 female) and 85 healthy individuals (mean age 52, ranging between 29 and 71 years; and 1:1 male/female ratio, 43 male and 42 female).

Inclusion criteria were pathologically verified adenocancer of colon and rectum, no presence of prior cancer history, no presence of synchronous primary cancer of other organs. The exclusion criteria were absence of pathological verification, presence of prior cancer history, presence of synchronous primary cancer of other organs.

**Ethics statement**

The study was conducted in accordance with the 1964 Helsinki Declaration and its later amendments. All participants provided written informed consent forms for participation in the study.

**Blood sampling**

EDTA tubes were used to collect 10 mL of peripheral blood and were stored at room temperature to use within 24 h. Blood samples of three groups of colon cancer, rectal cancer patients and healthy individuals were collected in dry tubes and centrifuged at 3000 g for 10 min for serum extraction. Serum samples were conserved at −20 °C until the genetic analysis was conducted. All DNA samples were purified from peripheral whole blood according to a salting-out technique. All samples were analyzed using NanoDrop spectrophotometer (NanoDrop Technologies, Maestrogen Nano, Taiwan) to accurately assess DNA quality and quantity.

**Genotyping of paraoxonase 192 polymorphism**

DNA was extracted from the leukocyte pellets. This procedure included sodium dodecyl sulphate lysis, ammonium acetate extraction and ethanol precipitation [21]. PON1 genotypes were determined by PCR as described by previous protocols [11,12]. Sense primer 5’- TAT TGT TGC TGT GGG ACC TGA G-3’ and antisense primer 5’-CAC GCT AAA CCC AAA TACATCTC-3’ were used to encompass the polymorphic regions in the human PON1 gene. The ingredients of the PCR reaction mixture were 100 ng DNA template, 50 pmol of each primer, 1.5 mmol/L MgCl2, 200 mmol/L dNTPs (4 dNTPs mixture), and 1 U Taq DNA polymerase (MBI Fermentas). The amplification cycle included: DNA denaturation for 5 min at 94 °C, followed by 35 cycles of 1 min denaturation at 95 °C, 1 min annealing at 60 °C and 1 min extension at 72 °C-, and a final extension of 5 min at 72 °C. Then, 8 U BspI restriction endonuclease (MBI Fermentas, Lithuania) was used to digest the 99 bp PCR product at 55 °C overnight. The fragments were separated by electrophoresis in a 4% MetaPhorTM agarose gel. Ethidium bromide was used for visualisation.

The unique BspI restriction site on B-genotype (Arginine) generates two different products of 66 and 33 base-pairs. Since the A-genotype lacks this restriction site, no products of restriction can be achieved, allowing the PON1 192 genotype to be determined [12].

**Paraoxonase activity measurement**

Furlong et al. defined the quantification method of paraxonase activity previously [22]. The assay buffer consisted of 0.132 mol/L Tris HCl (pH 8.5), 1.32 mmol/L
CaCl$_2$ and 2.63 mmol/L NaCl. The initiation of the assay started with addition of 200 mL of 6 mmol/L freshly prepared paraoxon (0,0-diethyl-0-p-nitrophenyl phosphate; Sigma, Poole, UK) and 40 mL of serum. A continuously recording spectrophotometer at 405 nm and at 37°C was used to determine the rate of generation of p-nitrophenol. A molar extinction coefficient of 18.05 × 10$^3$ was used for calculation using paraoxon as a substrate. One unit of paraoxonase activity was defined as the amount of enzyme that hydrolyzes 1 mmol of paraoxon per minute.

**Statistical analyses**

SPSS software package, version 10.0 was used for statistical analyses and the clinical laboratory data were expressed as mean values with standard deviation (± SD). The comparison of the mean values of PON activities between cases and control groups was done by the unpaired Student’s t-test. Differences in the distribution of PON genotypes or alleles between cases and controls were assessed using the Chi-square statistic, respectively. PON allele frequencies were estimated by gene counting methods. Values were considered statistically significant at the level of $p < 0.05$.

**Results and discussion**

**PON 192 genotypes and PON1 activity**

PON 192 genotypes and allele frequencies were analysed in 16 rectum cancer, 38 colon cancer patients and 85 non-tumoral healthy individuals. PON1 activities were studied in only 67 samples (21 controls, 30 colon and 16 rectum cancer patients) due to technical insufficiency in the laboratory. The frequency of PON 192 genotypes is shown in Table 1 for all case and control groups. In the whole study group of 139 individuals, the frequency of the AA genotype was greater than that of the BB and AB genotypes (n:65 with 46.8%; n:15 with 10.8% and n:59 with 42.4%, respectively). This predominance of the AA frequency was more pronounced in the rectum cancer group compared to BB and AB genotypes, respectively (n:11 with 68.8%; n:2 with 12.5% and n:3 with 18.8%, respectively).

**PON1 activity**

The PON1 activities are shown in Table 2. In both tumor groups, the PON activities were significantly lower than those in the control group ($p < 0.05$). For both PON AA and AB genotypes, the PON activities in the colon groups were significantly lower than the control groups ($p < 0.01$ for both). In AA genotype samples, the rectum cancer group had also significantly lower paraoxonase activity than the control group ($p < 0.05$). The number of samples in the rectum cancer group (n:3) was very low to evaluate statistically. Also, the BB genotype group consisted of five cases, and no statistical analyses were able to be conducted for this group. The AA and AB genotype groups’ activities are shown in Tables 3 and 4, respectively.

The paraoxonase activities in the cancer patients (both colon and rectum cancer groups) were significantly lower than those in the control groups in the PON192 A allele groups of AA and AB when taken as a sum ($p < 0.01$ and $p < 0.05$, respectively, for colon and rectum cancer patients). The paraoxonase activities in the PON192 A allele groups of AA and AB are shown in Table 5. The PON192 B allele carriers also showed comparable results. The PON1 enzymatic function of cancer patients was significantly lower than that in the control groups in PON192 B allele carriers ($p < 0.01$ for both cancer groups). In the B allele group, the rectum cancer patients’ paraoxonase activities were lower than those in the colon cancer patients ($p = 0.05$). The PON 192B allele activities are given in Table 6.
having a multifactorial etiology, CRC also is associated with environmental factors. In a geographically Middle Eastern region susceptible to severe exposure to pesticides, CRC patients had increased blood pesticide levels and decreased PON1 arylesterase enzyme activity, which was significantly relevant with cancer formation [34]. The decreased PON1 activity is generally thought to be related to cancer initiation [20,33,35]. We also observed a statistically significant relation of decreased activity and colorectal cancer. Bulbuler et al. showed significantly lower PON1 activity in lung, breast and colorectal cancer patients’ blood samples compared to healthy controls. Also, not in breast and lung cancer groups, but in colorectal cancer patients, metastatic disease was significantly associated with lower PON1 activity when compared to the non-metastatic state [35]. In a cohort of hepatocellular carcinoma patients, PON1 was significantly associated with invasiveness of tumor and metastases and also local recurrence. PON1 activity downregulation has been found to be related to poor prognosis and severe course of the disease [36]. This observation may lead to a new hypothesis of an association of PON1 activity to predict the metastatic disease for CRC also. However, current studies on PON1 association with CRC, including ours, lack a sufficient number of patients to have significant results. Moreover, some recent studies report controversial results, as an association of increased PON1 and arylesterase (ARE) activities with CRC [37]. Bulbuler et al. evaluated PON1 enzyme activity, total thiol levels and total antioxidant status of 40 CRC patients in 2013 and showed statistically significant relation of low PON1 activity with colorectal cancer [38]. PON1 polymorphisms were not investigated in the study [38]. Ellidag et al. [3] (from the same team with Bulbuler [38]) published results of 40 colorectal, 40 multiple myeloma and 40 bladder cancer patients who were investigated on PON1 polymorphism and the activity of PON1 and arylesterase in 2014. This second study also confirmed the association of lower enzyme activity and colorectal cancer; however, no correlation was found between colorectal cancer and genetic polymorphisms [33]. These results are in correlation with Van Der Logt et al.’s study [3]. Van Der Logt et al. [3] found no

### Table 4. PON activity in PON AB genotype in the control group and the groups of patients.

| Sample size | PON activity (U/mL) (Mean ± SE) |
|-------------|--------------------------------|
| 15          | 329.29 ± 33.08                  |
| 7           | 109.99 ± 31.17                  |
| 1           | 35.87 ± 0                       |

### Table 5. PON activity in PON A allele carriers in the control group and the groups of patients.

| Sample size | PON activity (U/mL) (Mean ± SE) |
|-------------|--------------------------------|
| 38          | 304.69 ± 29.18                  |
| 13          | 83.55 ± 18.67                   |
| 5           | 92.65 ± 46.68                   |

### Table 6. PON activity in PON B allele carriers in the control group and the groups of patients.

| Sample size | PON activity (U/mL) (Mean ± SE) |
|-------------|--------------------------------|
| 21          | 396.94 ± 39.14                  |
| 9           | 94.76 ± 25.87                   |
| 3           | 36.42 ± 6.32                    |

Reactive oxygen species (ROS) generated during oxidative stress trigger carcinogenesis by oxidation of the DNA bases, leading to mutagenic formations and disruptions [23–25]. In an experimental skin model, oxygen radicals converted benign papillomas to cancer [26]. A study on melanomas and non-melanoma skin cancers reported that oxygen radicals that originate naturally or due to inflammation play significant roles in the formation of these diseases [27]. The oxidative stress in mouse liver, if prolonged enough, causes DNA damage due to abnormally high DNA synthesis and rapid replication without leading to cell death. The neoplastic cell lines that initiate from these unrepaird damaged sites, form further immortal cancer cell groups by selective clonal expansion of the initiated cell population [28].

The effects of increased exposure of the gastrointestinal tract and especially the colonic mucosa to endogenous and exogenous oxidative stress and ROS are known [29]. ROS detoxification is an antioxidative process which is mediated by scavengers like vitamin C and E and various antioxidant enzymes that degrade ROS to harmless subcomponents [30]. The human serum paraoxonase 1 enzyme is a hydrophilic esterase that plays a role in the neutralization of lipid peroxidation products [11].

The association of decreased serum levels and activity with polymorphisms of the enzyme was first reported in 1976 [31] and association with various cancer predispositions parallel to decreased antioxidant effects were also shown [9,23]. A recent study associated PON1 192R polymorphism with uterine leiomyoma, but the enzyme activity was not measured to confirm clinical implication [32]. A few studies have evaluated the relation of PON1 polymorphisms and/or enzyme activity with colorectal cancers and two of them found no correlation between genetic polymorphisms and CRC [3,33].
significant relation with PON polymorphism and colorectal cancer after analyzing the blood samples of 365 patients with sporadic colorectal cancer. Again controversially, another study from Iran reported significant relevance with PON1 polymorphism and breast cancer formation in a larger cohort of 150 patients and 150 controls [39]. In 2014, Ahmed et al. [20] from Egypt evaluated PON1 enzyme activity and polymorphisms of 50 newly diagnosed colorectal patients and found both activity and polymorphisms were associated statistically with colorectal cancer.

In our study, the most frequent genotype was AA in the cancer group and AB in the control group. Our results were in correlation with the Egypt group [20]. Ahmed et al. [20] also found the homozygote QQ genotype, which is the same as AA, as the most frequent genotype in colorectal cancer patients. The most frequent genotype in the control group was the heterozygote QR genotype, the same as AB [20]. In our study, the PON activity was significantly lower in the cancer patients \( p < 0.05 \). When the AA carrier groups were considered, the PON activities of the cancer groups were significantly lower than the control group [colon \( p < 0.01 \) and rectum \( p < 0.05 \) groups, respectively]. The comparison of colon and rectum cancer patients with AA genotype showed that the PON activity of the colon cancer patients had a lower level. Still, the difference was not statistically significant, which could be due to the small number of rectum patients in our cohort. Still, a focus of interest may be present for investigation of a further association of PON1 polymorphism and especially colon cancer rather than rectum. The sample size of the BB genotype was insufficient to compare statistically (control 6, cancer 4 samples). Only one patient in the rectum cancer group had the AB genotype, and so no statistical analyses were conducted. In the colon cancer group with AB genotype, the PON activity was significantly lower than the control group \( p < 0.01 \). These findings may suggest a correlation between A allele carriers (AA and AB) and colon cancer. The analyses on the A allele carriers also supported this hypothesis. The PON activity was significantly lower in the cancer group as compared to the controls [for colon \( p < 0.01 \) and rectum \( p < 0.05 \) cancer, respectively] with a further decrease in the colon cancer group; although no statistically significant difference was present in the two cancer groups. The rectum patients in the AB group were only three and their number was again insufficient to analyze statistically. The B allele carrier cancer patients also had significantly lower enzyme activity compared to the control group \( p < 0.01 \). However, the B allele group rectum cancer patients had a slightly more pronounced decrease in PON1 activity when compared to the colon cancer patients.

**Limitations**

This study has some limitations. Although our cancer sample size was comparable with other studies on colorectal cancer patients, we had technical problems analyzing the PON activity in all study groups. We could only study 15 colon cancer and 8 rectum cancer patients’ blood samples for PON activity. This might have affected our results. We found a correlation between A allele carriers and colon cancer. Also, B allele carriers were shown to be correlated with rectum cancer. Although we can assume that there might be an association between PON activity and cancer formation, we know that there may be factors other than polymorphism that affect the serum levels and activity of the PON1 enzyme, too. Ahmed et al. [20] showed in newly diagnosed colorectal cancer patients that the decreased PON1 activity was restored after surgical resection with an accompanying decrease in carcinoembryonic antigen (CEA) and alpha-fetoprotein (AFP), which reflects control of the disease. This observation brings the hypothesis that the alterations of PON1 activity and serum levels may be not solely due to genetic predisposition, but due to the decrease of cancer-related oxidative stress after resection. As it is well-known that cancer which derives from increased exposure of the colon mucosa to ROS [29] further increases the oxidative stress in the colon itself. The resection of the tumor might decrease the oxidative stress on the gastrointestinal mucosa. Supporting this hypothesis, Balci et al. emphasized that PON1 activity loss might be a consequence rather than the reason for cancer [35].

It can be hypothesized that oxidative stress may increase proximally to distally in the colon and rectum. Although Van Der Logt et al. [3] found no correlation between genetic polymorphism of PON and colorectal cancer grossly, they emphasize a slightly increased risk of rectum cancer in PON1-55M allele carriers. However, within the limitations of our study, our results are contradictory to Van Der Logt’s paper. Except for only the BB genotype carriers, in the whole cancer group, colon cancer patients had lower PON activities compared to rectum cancer patients in our study.

None of the four papers except Balci et al. [35] evaluated metastatic disease and PON relation. Balci et al. [35] reported statistically significant lower levels
of PON activity in metastatic disease. Likely Ahmed et al. [20] also shared the distribution according to stages; however, they did not analyze the difference between stages and so the metastatic state or location through the colorectal path.

Conclusions

In this study, except for only the BB genotype carriers, in the whole cancer group, colon cancer patients had lower PON activities compared to rectum cancer patients. Although insufficient to state a definite connection between PON and colorectal cancers, there are plenty of significant findings to point out an association in these specific points of investigation. Both genetic predisposition and environmental factors seem to affect the PON activity at the end, which tends to provoke an oxidative microenvironment for cancerous DNA damage. According to our point of view, further studies should be planned to investigate the relation of PON polymorphisms and different anatomical locations of colorectal cancers with regards to metastatic disease presence and preoperative and postoperative states in larger cohorts.

Disclosure statement

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

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Data availability

Non-digital data supporting this study are curated at Department of Molecular Medicine, Institute of Experimental Medicine, Istanbul University, Istanbul, Turkey.

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