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Investigation of Apurinic/Apyrimidinic Endonuclease 1 Expression Changes in Prostate Cancer

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What is already known on this topic?

- *Oxidative DNA damage and impaired base excision repair (BER) mechanisms contribute to prostate cancer development and progression.*
- *APE1 is a key enzyme in the BER pathway, and altered expression levels have been linked to various cancers, though its role in prostate cancer remains unclear.*

What this study adds on this topic?

- *This study is one of the few to directly assess APE1 gene expression in human prostate cancer tissues using quantitative real-time PCR.*
- *A significant correlation between PSA levels and APE1 expression is identified, suggesting a potential link between DNA repair activity and tumor biomarker expression.*

Abstract

Objective: Prostate cancer, a leading cause of cancer deaths in men, involves genetic alterations and DNA damage. Oxidative stress–induced DNA damage is crucial in its development, necessitating efficient DNA repair mechanisms. Base excision repair (BER), a key pathway, addresses oxidative DNA damage with enzymes like Apurinic/Apyrimidinic Endonuclease 1 (APE1). Recent findings show that altered APE1 expression disrupts BER balance, contributing to genomic instability and cancer progression. This study examines APE1 expression in prostate cancer tissues to clarify its role in cancer development and therapeutic implications. Assessing APE1 expression in prostate cancer may elucidate its role in tumor progression, therapeutic resistance, and genomic instability, offering deeper insights into the mechanistic relevance of the BER pathway in oncogenesis.

Methods: A total of 50 male patients diagnosed with prostate cancer were included in this study. Tumor and adjacent normal tissue samples were collected from consecutive male patients who underwent Tru-cut prostate biopsies due to clinical suspicion of prostate cancer, and gene expression levels were analyzed using real-time polymerase chain reaction.

Results: The results showed no significant difference in APE1 expression between tumor and normal tissues ($P > .05$). Clinical factors like smoking, age, diabetes, hypertension, PIRADS, and Gleason scores did not significantly correlate with APE1 expression. However, a statistically significant correlation was observed between PSA levels and APE1 expression (r: 0.287, $P = .04$).

Conclusion: The authors' findings suggest that while no substantial changes in APE1 expression were observed in prostate cancer tissues, the enzyme's role in DNA repair remains crucial. Abnormalities in APE1 expression and function can contribute to genomic instability and cancer progression. Future studies with larger sample sizes and standardized methodologies are necessary to better understand the potential role of APE1 as a biomarker and therapeutic target in prostate cancer.

Keywords: Prostate cancer, DNA repair, base excision repair, Apurinic/Apyrimidinic Endonuclease 1

Introduction

Prostate cancer remains a significant global health issue, with variations in incidence and mortality rates worldwide.[1] Although often indolent, it ranks as the third-leading cause of cancer-related deaths among men.[2] Cancer arises due to genetic alterations that lead to uncontrolled cell proliferation. The DNA damage response (DDR) plays a vital role in maintaining genomic stability, and defects in this system are strongly linked to cancer development and progression. These DDR networks encompass the DNA repair pathways themselves.[3,4]

Oxidative stress can result in DNA base lesions. Oxidative DNA base damage is predominantly repaired by the base excision repair (BER) pathway, which ensures genomic integrity by addressing various DNA lesions. Base excision repair is an evolutionarily conserved process that addresses oxidative DNA damage arising from cellular respiration, hydrolysis, and alkylation.[5] Mutations in

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BER-related genes, however, impair this repair process, leading to compromised genomic stability.[6] This pathway involves more than 30 proteins in humans and operates through 2 sub-pathways: short-patch BER (SP-BER), which removes a single damaged base, and long-patch BER (LP-BER), which synthesizes 2-8 nucleotides to replace the damaged region. The initial step in BER involves DNA glycosylases that identify and remove damaged bases.[7,8]

APE1 (Apurinic/Apyrimidinic Endonuclease 1) is located at 14q11.2, spans approximately 2.5-3 kb, and consists of 5 exons. The[9] Apurinic/Apyrimidinic Endonuclease 1 protein comprises 318 amino acids, with a molecular weight of around 35 kDa.[10] Due to post-translational modifications and proteolytic cleavage, APE1 exists in multiple cellular forms, notably the p37 and p33 isoforms under genotoxic stress.[11] These forms exhibit distinct enzymatic activities in DNA repair and redox regulation. Beyond its role in DNA repair, APE1 functions as a transcriptional coactivator for factors such as HIF-1α, p53, and NF-κB, making it a promising target for cancer therapy.[12] The protein is crucial for removing apurinic/apyrimidinic (AP) sites, which are lesions that block DNA and RNA polymerases.[13] As an endonuclease, APE1 also acts as a 3′-5′ exonuclease, 3′-phosphodiesterase, and participates in nucleotide incision repair.[14] Apurinic/Apyrimidinic Endonuclease 1 deficiency leads to cell inviability and increased sensitivity to alkylating agents and some chemotherapeutics. Apurinic/Apyrimidinic Endonuclease 1's dual roles in DNA repair and transcription regulation underline its significance in cellular stress responses, as well as cancer development and progression.[15]

The aim of this study is to investigate the gene expression levels of *APE1*, which plays a crucial role in the BER mechanism, in the tumor tissues of prostate cancer patients.

Methods

In this prospective study, prostate tissues were sampled from consecutive male patients who underwent Tru-cut prostate biopsies due to clinical suspicion of prostate cancer at the Urology Department of Istanbul Education and Research Hospital between 2023 and 2024. Informed consent was obtained from all cases included in the study. Ethics committee approval was received for this study from the ethics committee of Istanbul University Cerrahpaşa Cerrahpaşa Faculty of Medicine (Approval no: E-83045809-604.01.01-560514, Date: 12.12.2022). Following the histopathological confirmation of the patients' tumor and non-tumor (normal) prostate tissues, a total of 50 patients were included in the analysis. Pathological examinations of the collected tissues were performed at the Pathology Department of Istanbul Education and Research Hospital.

Reverse Transcription-Quantitative Polymerase Chain Reaction

Tissues were stored in sterile tubes containing RNA preservative (RNA later) at +4°C for 24 hours. After removing excess preservative, samples were stored at −80°C. Before analysis, tissues were thawed, treated with lysis buffer and β-mercaptoethanol, and homogenized in sterile tubes with ceramic beads using a cooled homogenizer for 5 minutes. RNA isolation was conducted from homogenized tumor and normal tissues to assess *APE1* gene expression levels, using the EXTRACT ME kit (Belirt, Poland). The quantity and purity of RNA samples isolated using the RNA extraction kit were assessed using a Thermofisher Scientific NanoDrop spectrophotometer. To synthesize complementary DNA (cDNA) from the isolated RNA, the ABScript III RT Mix kit (ABclonal) was used following the manufacturer's protocol. RNA concentrations were normalized across all samples based on the tissue with the lowest RNA concentration to ensure consistency. The synthesized cDNA was stored at −20°C for short-term use. After cDNA synthesis, changes in mRNA levels of the *APE1* gene were evaluated using real-time polymerase chain reaction (PCR), with beta-actin (ACTB) as the housekeeping gene (reference gene). Primer sequences for the genes (Suarge, Türkiye) of *APE1* and *ACTB* were used (Table 1). The reactions were performed using the ABclonal qPCR kit (Applied Biosystems) in a 20 µL total volume per well. *Apurinic/Apyrimidinic Endonuclease 1* expression levels were normalized to *ACTB* housekeeping gene expression. Messenger RNA (mRNA) levels of *APE1* in prostate cancer and normal tissues were calculated using the $2^{-\Delta\Delta Ct}$ method, based on the Ct values of target and reference genes. The CT values of *APE1* and *ACTB* were obtained for tumor and normal tissue samples from 50 patients. The ΔCT values were calculated by subtracting the reference gene CT from the target gene CT for both tumor and normal tissues. Using these ΔCT values, gene expression was determined for each patient. The ΔΔCT values were calculated by finding the difference between the ΔCT values of tumor and normal tissues.

Statistical Analysis

Gene expression values were presented as mean ± standard error (SE), while age-related data were reported as mean ± SD. Statistical comparisons between the 2 groups were performed using the Mann–Whitney *U*-test. The relationships between gene expression levels and other parameters were evaluated using Pearson's correlation test. All statistical analyses were conducted using IBM SPSS Statistics software (Version 21.0, Armonk, NY, USA). Statistical analysis results were considered significant when $P < .05$.

Results

Fifty patients diagnosed with prostate cancer who had not received any treatment were included in the study. The clinical data of the patients included in the study were obtained from their medical records. The demographic and clinical data of the patients can be seen in Table 2.

The gene expression values for *APE1* in tumor and normal tissue samples are shown in Table 3. According to the $2^{-\Delta CT}$ analysis, no

Table 1. Primer Target Regions and Fragment Lengths of Target and Control Genes

Gene Name	Ref Seq no. (qPCR target region)	Primer Sequence	Fragment Length (bp)
APE1	NM_001641.4 (947-1019)	Forward-GCCAAGGCTTCGGG GAATTA	73
	NM_080648.3 (881-953)	Reverse- GGTGTGTTGGGGTAG AGGTG	73
	NM_080649.3 (891-963)		73
	NM_001244249.2 (942-1014)		73
ACTB	NM_001101.5 (425-521)	Forward- CCAACCGCGAGAA GATGA Reverse- CCAGAGGCGTACA GGGATAG	97

ACTB, beta-actin; APE1, Apurinic/Apyrimidinic Endonuclease 1.

Table 2. Demographic and Clinical Data of Prostate Cancer Patients

Age (years)	66.3 ± 7.1		
PSA (Prostate-specific antigen)	14.6 ± 14.3		
Smoking	Non-smoker (–)	39 patients	78%
	Smoker (+)	11 patients	22%
Diabetes	–	38 patients	76%
	+	12 patients	24%
Hypertension	–	29 patients	58%
	+	21 patients	42%
Nodule	–	36 patients	72%
	+	14 patients	28%
Gleason score	<7	29 patients	58%
	>7	21 patients	42%
PIRADS (Prostate Imaging Reporting and Data System)	3	14 patients	28%
	4	17 patients	34%
	5	19 patients	38%

statistically significant difference was observed in the expression levels of the *APE1* gene between tumor tissues and normal tissues ($P > .05$).

When the $2^{-\Delta CT}$ values were converted to $2^{-\Delta\Delta CT}$ values to evaluate the fold change in gene expression levels, it was observed that *APE1* expression in tumor tissue was 1.76 times higher compared to normal tissue samples (Table 4).

The gene expression levels of *APE1* in tumor and normal tissue samples were analyzed based on smoking, age, diabetes, hypertension, nodule, Gleason, and PIRADS scores. No significant correlation was found between *APE1* expression levels and these clinical parameters.

We examined the correlation between PSA levels and gene expression levels in tumor and normal tissues in this study group. In normal tissues, no statistically significant correlation was found between PSA levels and gene expression. However, in tumor tissues, a statistically significant correlation was observed between PSA levels and *APE1* gene expression (r: 0.287, $P = .04$). As PSA levels increased, *APE1* gene expression also increased, as shown in Figure 1.

Table 3. Expression Level of Apurinic/Apyrimidinic Endonuclease 1 Gene in Tumor and Normal Tissue Samples

	Tumor Tissue	Normal Tissue	*P**
APE1	0.82 ± 0.21	0.72 ± 0.15	.27

The data are presented as mean ± SE.
*Mann–Whitney *U*-test.

Table 4. The Fold Change in Apurinic/Apyrimidinic Endonuclease 1 Expression Level in Tumor Tissue Compared to Normal Tissue

	ΔC_T (Avg)	$\Delta\Delta C_T$ (Avg)	$2^{-\Delta\Delta CT}$
Tumor tissue	2.06	−0.82	1.76
Normal tissue	2.88	1	1

The data are presented as mean ± SE.
Mann–Whitney *U*-test.

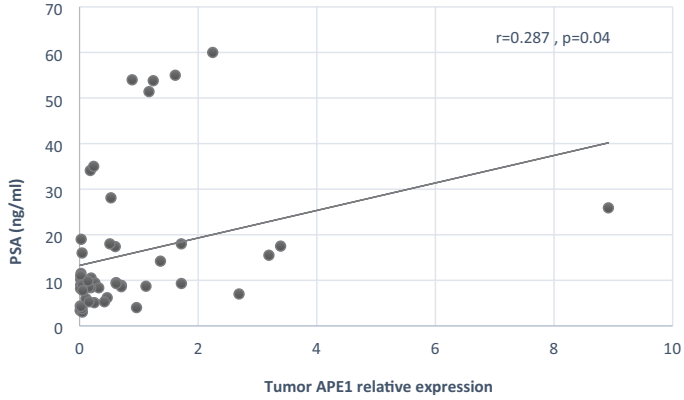

Figure 1. Correlation between PSA levels and APE1 gene expression in tumor tissue.

Discussion

Prostate cancer is the second most common cancer type in men. The Cancer Genome Atlas (TCGA) program has demonstrated that prostate tumors are characterized by gene fusions and mutations, highlighting the critical importance of these molecular changes in diagnosis and treatment strategies.[16] The TCGA study on prostate cancer revealed that alterations in DNA repair genes are relatively common in primary tumors, with nearly 20% of cases exhibiting mutations or deletions in genes such as *BRCA2*, *BRCA1*, *CDK12*, *ATM*, *FANCD2*, or *RAD51C*. In metastatic prostate cancer, changes in the DNA repair and PI3K pathways were observed more frequently, along with increased mutations or deletions in *TP53*, *RB1*, *KMT2C*, and *KMT2D*. Furthermore, the study identified several other clinically significant genes with lower mutation rates, including those involved in DNA repair, beta-catenin signaling, and major kinase pathways.[16] According to the GEO dataset, a significant proportion of prostate cancers (up to 74%) can be attributed to fusions in ETS family genes or mutations in genes such as *SPOP* (19%), *ATM* (7%), *TP53* (19%), or *FOXA1* (29%).[17] These datasets highlight the importance of the DNA repair mechanism in prostate cancers. Oxidative stress can damage DNA, proteins, and lipids, potentially leading to cancer development. The activation of DNA repair mechanisms may result from the increased DNA damage caused by oxidative stress in the early stages of carcinogenesis. Consequently, the expression of the *APE1* repair gene, associated with the BER mechanism, may vary in response to oxidative stress-induced DNA damage.[18,19] When comparing gene expression levels between tumor and normal tissues, no significant change was observed in the *APE1* gene.

Apurinic/Apyrimidinic Endonuclease 1/Ref-1 is a multifunctional protein that plays roles in both BER mechanisms and as a redox regulator for cancer-associated transcription factors, including NFκB, AP-1, HIF1α, and STAT3. These transcription factors are crucial in cancer initiation and progression. Apurinic/Apyrimidinic Endonuclease 1 contributes to cell proliferation and survival during stress by activating key transcription factors, including activator protein 1, NF-κB, hypoxia-inducible factor 1, and cAMP response element-binding protein 1.[20] By directly reducing their cysteine residues, APE1 activates the DNA-binding activity of numerous

redox-sensitive transcription factors. With its primary role as an antioxidant, p53 affects proteins such as sestrin, glutathione peroxidase, and aldehyde dehydrogenase, all of which participate in reducing oxidative stresses.[21] By modulating its DNA-binding ability and transcriptional activity, particularly through its redox regulatory function, APE1 influences NF-κB, a key regulator of inflammation and cell survival.[22] Inhibiting the redox activity of APE1 offers a potential therapeutic approach by simultaneously targeting these pathways.[23]

In a study by McIlwain et al, *APE1* gene expression levels were found to be elevated in human prostate tumor tissues and prostate cancer cell lines.[24] Furthermore, *APE1* inhibition was shown to reduce the expression of oncogenic transcriptional activators NFκB and STAT3, as well as the survivin protein. This inhibition also caused cell cycle arrest at the G1 phase without inducing cell death by significantly decreasing the levels of cell cycle proteins Cdc2 and Cyclin B1.[25] These findings suggest that *APE1*-targeted therapeutic strategies could be beneficial. The discrepancy between the authors' findings and McIlwain's results may be attributed to the limited sample size (only 12 prostate tumor samples) used in their study. Another study analyzing APE1 protein expression in prostate cancer patients reported elevated APE1 levels using immunohistochemical methods.[25] It was noted that high APE1 protein levels were independent of other prognostic markers. Similarly, a different study using immunohistochemistry also detected high APE1 protein expression in prostate cancer tissue samples but found no association between APE1 expression levels and PSA levels.[26] The findings of these last 2 studies indicate that APE1 levels are increased at the protein level in tumor samples derived from paraffin-embedded tissues.

One of the reasons for the discrepancy between the gene and protein expression results may be the materials used. While protein expression levels were mostly determined using paraffin-embedded tissue samples, the authors' gene expression results were obtained from fresh tru-cut biopsy samples. Furthermore, the reason for the difference between *APE1* gene expression results and protein expression results may be post-transcriptional and post-translational modifications. Post-translational modifications, such as ubiquitination, are chemical changes that occur after protein synthesis and play an important role in gene regulation. In a study conducted by Busso et al,[27] they demonstrated that ubiquitination of *APE1* is a mechanism that regulates its gene activity. Furthermore, by removing 3' phosphoryl groups from RNA decay products, *APE1* creates less stable 3' hydroxyl ends, thereby promoting their further breakdown. This again highlights APE's involvement in RNA metabolism.[28]

The findings of these 2 studies indicate that *APE1* levels in tumor tissue are increased at both the gene and protein levels.

To further investigate the significance of *APE1* in prostate cancer pathogenesis, several studies have focused on polymorphisms in the *APE1* gene.[29-32] A meta-analysis revealed that the *APE1* T1349G polymorphism is associated with an increased risk of prostate cancer, particularly in Caucasian populations.[33] Another study suggested that the *APE1* rs1760944 polymorphism might act as a protective factor against prostate cancer, while the *APE1* rs1130409 polymorphism could be a risk factor.[13]

Overexpression of *APE1* has been linked to increased cell proliferation and poor prognosis.[34] Additionally, inhibiting *APE1* has been shown to impair DNA repair, enhance apoptosis, and improve treatment sensitivity.[35] Studies indicate that *APE1* inhibitors have the potential to slow cancer progression.[36] In colorectal cancer, *APE1* overexpression has been associated with poor prognosis and therapy resistance.[15] Similarly, a study by Qing et al[37] in 2015 reported that *APE1* overexpression in gastric cancer was significantly associated with invasion, lymph node metastasis, and poor survival. A meta-analysis conducted by Yuan et al[38] in 2017 concluded that high *APE1* expression in solid tumors is linked to poor prognosis. This meta-analysis, which included various cancer types such as lung, esophageal, gastric, ovarian, hepatocellular, rectal, breast, glioma, and osteosarcoma, reported a correlation between high *APE1* expression and poor prognosis in 12 studies, while 3 studies associated it with better prognosis.[38]

Consistent with the authors' findings, studies on other cancer types have reported no significant differences in *APE1* gene expression. For example, Santos et al[39] observed no significant difference in *APE1* expression between normal and tumor tissues in colorectal cancer patients. Another study reported that the expression of the *APE2* gene, which shares similar activities with *APE1*, remained unchanged in prostate cancer tissues.[40]

The variation in findings across different cancer types may be due to genetic variations that cause differences in expression levels between individuals. The genetic makeup of populations may also influence these variations. Additionally, the carcinogenesis mechanisms associated with each cancer's pathogenesis are different, leading to changes in gene expression. Therefore, further research using standardized methods and large patient cohorts is needed to better understand the discrepancies in *APE1* expression across various cancer types.

The authors' study is limited by the fact that the authors did not confirm the authors' mRNA results using Western blot analysis. Additionally, the small sample size could diminish the statistical power of the authors' analyses. Consequently, additional studies with larger sample sizes are required to validate these findings.

The authors' findings suggest that while no substantial changes in *APE1* expression were observed in prostate cancer tissues, the enzyme's role in DNA repair remains crucial. Abnormalities in *APE1* expression and function can contribute to genomic instability and cancer progression. Future studies with larger sample sizes and standardized methodologies are necessary to better understand the potential role of *APE1* as a biomarker and therapeutic target in prostate cancer.

Data Availability Statement: The data that support the findings of this study are available on request from the corresponding author.

Ethics Committee Approval: Ethical committee approval was received for this study from the ethics committee of İstanbul University Cerrahpaşa Faculty of Medicine (Approval no: 560514, Date: December 12, 2022).

Informed Consent: Written informed consent was obtained from the patients who agreed to take part in the study.

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Declaration of Interests: The authors have no conflict of interest to declare.

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