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YEDITEPE UNIVERSITY

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MASTER OF SCIENCE THESIS

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THESIS APPROVAL FORM

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Chair of the Jury:		
Supervisor:		
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APPROVAL

This thesis has been deemed by the jury in accordance with the relevant articles of Yeditepe University Graduate Education and Examinations Regulation and has been approved by the Administrative Board of Institute with decisions dated …….. and numbered .....

Title, Name-Surname

Director of Institute of Health Sciences

DECLARATION

I hereby declare that this thesis is my own work and that, to the best of my knowledge and belief, it contains no material previously published or written by another person nor material which has been accepted for an award of any other degree except where due acknowledgment has been made in the text.

Dorcas Pelumi Omotade

DEDICATION

I dedicate my thesis to my lovely family,

To God.

ACKNOWLEDGEMENTS

First and foremost, I want to thank **Turğay ISBIR, Prof. Dr.** for all of his assistance throughout my master's degree. He is undoubtedly one of the science community's most seasoned lecturers.

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The last word of gratitude goes out to my amazing family, including my Mother, Father, siblings, and friends both domestically and overseas, for their unwavering support.

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LIST OF SYMBOLS AND ABBREVIATIONS

µl	Microliter
EDTA	Ethylenediaminetetraacetic acid
DNA	Deoxyribonucleic acid
BMI	Body mass index
PSA	Prostate specific antigen
PCa	Prostate cancer
NER	Nucleotide Excision Repair
GG-NER	Global Genome Nucleotide Excision Repair
DDB2	DNA Damage Binding Protein 2
IGF-1	Insulin-like growth factor 1
TNM	Tumor, Nodes, Metastasis
MRI	Magnetic resonance imaging
CT	Computed Tomography
MP-MRI	Multiparametric MRI
FIGO	International Federation of Gynecology and Obstetrics
DRE	Digital rectal exam
BPH	Benign prostatic hyperplasia
TRUS	Transrectal ultrasound
TURP	Transurethral resection of prostate
HIFU	High-intensity focused ultrasound
HR23B	predictive biomarker for (HDAC inhibitor High Dose A ra -C**)**
UV-DDB	Ultraviolet-damaged DNA-binding protein
CPA	Cyproterone acetate
RPA	Recursive Partitioning Analysis

XPG	Xeroderma Pigmentosumcomplementation group G.
XPF	Xeroderma Pigmentosumcomplementation group F
ERCC1	Endonuclease Non-Catalytic Subunit ERCC Excision Repair 1
WD40	WD40 domain proteins
ADP	Adenosine diphosphate
CDP	Cyclobutane pyrimidine
CDK (P21WAF1/CIP1)	Cyclin-Dependent Kinase
PCR	Polymerase chain reaction
SNP	Single nucleotide polymorhism
ADT	Androgen deprivation therapy

ABSTRACT

Omotade D. O. (2022). Investigation of DNA damage binding protein 2 (DDB2) gene polymorhism in prostate cancer patients in the Turkish population. Yeditepe University, Institute of Health Science, Department of Molecular Medicine. MSc thesis, Istanbul.

AIM: To investigate in the Turkish population the gene variation of the DDB2 gene rs830083 polymorphism and prostate cancer (PC).

MATERIALS and METHODS: The SNPs of the DDB2 gene rs830083 will be genotyped using Taqman^{R} SNP Genotyping Assays and BioScience (ABI), real-time 7500 PCR system. The statistical analysis was carried out using SPSS version 26.0. This research project will be a case-control retrospective study comprising 93 patients with prostate cancer and a control group which consisted of 91 healthy individuals.

RESULTS: In this study, DDB2 gene (rs830083) polymorphism was analyzed in individuals with Prostate Cancer and control group. Although, there were no significant difference regarding genotype analysis (p=0.216), G allele frequency was significantly higher in the control group 46.2% (p = 0.037). In genotype distribution, of GC was significantly higher in the control group and CC genotype was significantly higher in the patient group, frequency was 26.9% and C 68.8% (p value = 0.048 and 0.037).

CONCLUSION: It is the first study investigating the relation between DDB2 gene variations (rs830083) with PC in Turkish populations. Our findings displayed that carrying G allele could be a risk reducing factor for PC susceptibility. Thus, new studies with larger populations should be conducted with the DDB2 polymorphism to show the effect of DDB2 on PC susceptibility.

Keywords: DNA Damage Binding Protein, Prostate cancer, (DDB2) gene (rs830083) polymorphism.

ÖZET

Omotade D. O. (2022). Türkiye popülasyonunda prostat kanseri hastalarında DNA hasar bağlayıcı protein 2 (DDB2) geminin polimorfizminin araştırılması. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü Moleküler Tıp Anabilim Dalı. Yüksek lisans tezi, İstanbul.

AMAÇ: Türk popülasyonunda DDB2 geni rs830083 polimorfizmi ve prostat kanseri (PC) gen varyasyonunun araştırılması.

GEREÇLER ve YÖNTEMLER: DDB2 geni rs830083'ün SNP'leri, TaqmanR SNP Genotyping Assays ve BioScience (ABI) 7500 gerçek zamanlı PCR sistemi kullanılarak genotiplendirilmiştir. İstatistiksel analizler SPSS versiyon 26.0 kullanılarak yapılmıştır. Bu araştırma projesi, prostat kanserli 94 hasta ve 91 sağlıklı kişiden oluşan kontrol grubunu içeren bir vaka-kontrol retrospektif çalışması olarak tasarlanmıştır.

BULGULAR: Bu çalışmada Prostat Kanserli bireylerde ve kontrol grubunda DDB2 geni (rs830083) polimorfizmi incelenmiştir. Genotip analizi açısından anlamlı bir fark olmamasına rağmen (p=0,216), G alel frekansı kontrol grubunda %46,2 ile anlamlı olarak daha yüksekti (p=0,037). Genotip dağılımında, kontrol grubunda GC ve hasta grubunda CC genotipi anlamlı olarak yüksekti, sıklık %26,9 ve C %68,8 idi (p değeri = 0,048 ve 0,037).

SONUÇ: Türk popülasyonunda DDB2 gen varyasyonları (rs830083) ile PC arasındaki ilişkiyi araştıran ilk çalışmadır. Bulgularımız, G aleli taşımanın PC duyarlılığı için risk azaltıcı bir faktör olabileceğini gösterdi. Bu nedenle, DDB2'nin PC duyarlılığı üzerindeki etkisini göstermek için DDB2 polimorfizmi ile daha büyük popülasyonlarla yeni çalışmalar yapılmalıdır.

Anahtar Kelimeler: DNA Hasar Bağlayıcı Protein, Prostat kanseri, (DDB2) geni (rs830083) polimorfizmi.

1. INTRODUCTION

Uncontrolled cell division and proliferation lead to cancer, a complicated illness that is impacted by both hereditary and environmental factors. The prevalence of cancer varies by country, region, and even by sub region within a country (1). The second most frequently discovered solid tumor in men is prostate cancer, also the reason why 10% of deaths in men from cancer. The multifactorial nature of the prostate disease, which is brought on by both hereditary and environmental causes, is well established (2, 3).

It is unknown what specifically causes prostate cancer. However, other etiologic variables, such as genetic makeup, steroid hormone metabolism, dietary habits, chronic inflammation, history of prostate cancer in family, and exposures to environmental factors are considered to play important roles. Individual differences with prostate cancer risk may be explained by variations in exposure to certain risk factors (4).

A key protection against the cancer-causing results of ultraviolet radiation out of the sun is Repair of Nucleotide Excision (NER) (6). Global genomic nucleotide excision repair (GG-NER) is a procedure, which involves numerous reactions of cells to UV-induced DNA injury, and is triggered by tumor suppressor protein p53 (7). The DDB2 gene is one of its products, and it is mutated in many human malignancies (8).

Only the nuclei of human cells contain the 48-kDa protein also known as DNA damage binding protein 2 (DDB2). In human cells, correction of widespread genomic nucleotide excision (GG-NER) is facilitated by DNA Damage Binding protein 2, which was initially a DNA damage detecting factor that has been identified. It contains the protein necessary for repairing UV-damaged DNA. Previous investigations have demonstrated that human prostate cancer tissues express less DDB2 than do non-neoplastic prostate tissues. (5).

The association between DDB2 rs830083 and prostate cancer risk will be examined in this thesis, as well as any potential clinical ramifications in Caucasians (Turkish). The DDB2 gene polymorphism may also have an impact on prostate cancer, similar to how it does in breast, skin, lung, and stomach cancers. Further investigation into the DDB2 gene and prostate cancer is also required as it is of these findings, since the association between DDB2 and PCa is yet

unknown. Previous investigations have shown that human DDB2 levels are lower and suggest that DDB2 expression in prostate cancer acts as a tumor suppressor.

2. LITERATURE REVIEW

2.1. The Prostate

The prostate is a walnut-sized gland that has been identified to be behind the bladder, below the penis, and ahead of the rectum. It encircles the urethra, the tube-like passageway in the penis that transports urine and sperm. Seminal fluid, which is the fluid found in semen which safeguards, maintains, and helps transport sperm, is produced mostly by the prostate. (9) (See Figure 1).

It's interesting to learn where the word "prostate" came from. It is derived from the Greek verb "prostates," meaning to face. Because it, in his opinion, sits before the testes, the anatomist Herophilus gave it the name prostate. The vasa deferentia transports sperm from the testes to the seminal vesicles (plural: Vasilis Deferens). The fluid that the seminal vesicles add to the semen during ejaculation. The prostate is actually made up of 30 to 50 glands, not just one, with a lot of tissue and bundles of smooth muscle in between (10).

THE PROSTATE

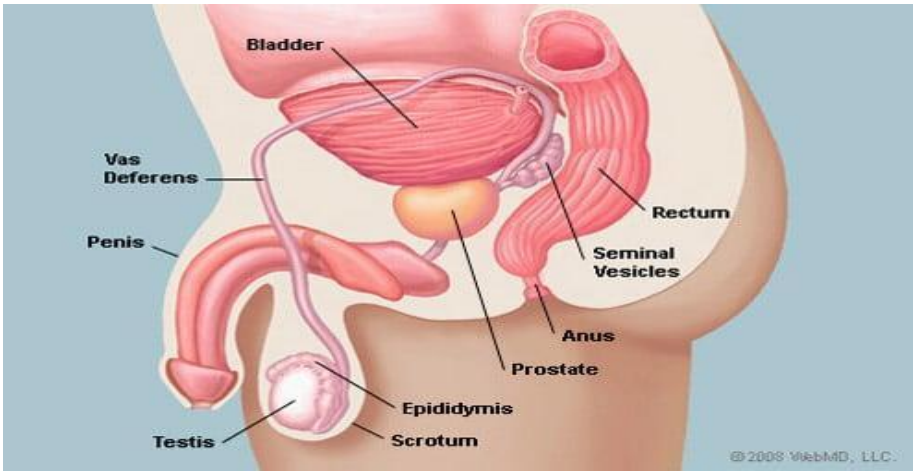

Figure 1: Side View of the Prostate (144).

2.2. Prostate cancer

A wide range of illnesses collectively known as cancer occur when some body cells develop defects and proliferate uncontrollably. These aberrant cells infect the tissues around

them, harming them, and eventually spread (metastasize) to other areas of the body, where they may cause more harm. These tumors have the potential to be fatal if the spread is unchecked. Tumors are not always invasive. Some are benign, which means they rarely pose a threat to one's life and do not spread to other bodily areas (11).

Prostate cancer, which affects one in nine men over 65, is the most prevalent illness identified. Adenocarcinomas, which make up the majority of prostate tumors, have a lot in common with other common epithelial malignancies including breast and colon cancer (12). Cancer of the prostate, it occurs second most often in males next to lung cancer, is a severe health problem on a global scale. Recent figures show that it is accounting for 7% of newly diagnosed malignancies in males worldwide (15% in developed regions). Annually, more than 1,200,000 fresh instances are identified, and even more 350,000 men die from prostate cancer worldwide (13).

The family history, age, and race/ethnicity are the only risk factors for prostate cancer that may be regarded as well-established. Prostate cancer risk starts to climb dramatically after age 55, and it reaches its peak between 70 and 74 before starting to modestly decline after that. Prostate cancer has a long induction period, according to autopsy studies, and many men develop early lesions in their 20s and 30s (14).

2.3. Incidence and etiology of Prostate cancer

2.3.1. Prostate cancer incidence

The second greatest cause of cancer-related mortality is prostate cancer (15). According to prior research, general prostate cancer incidence has been declining since the year 2000, but since 2010 the distant stage incidence of prostate cancer (i.e., cancer that has extend to areas of the body other than the initial tumor) has been rising (16, 17). Asia has a substantially lower incidence of prostate cancer due to the region's high soy intake (18).

The main problem is that cancer leads to death all over the world. To clarify, approximately 10 million patients will die in 2020. 2,260,000patients (breast cancer), 2,210,000 patients (lung cancer), 1,930,000 patients (rectum and colon cancer), 1,410,000 patients (prostate cancer), 1,200,000 patients (non-melanoma skin cancer), and 1,090,000 patients (stomach cancer) were death leads to most fatal cancer in 2020. Moreover, lung disease (1.8 million mortality), rectum and colon cancer (916 thousand mortality), liver tumor (830 thousand

mortality), gastric cancer (769 thousand mortality), likewise breast cancer (685 thousand mortality) are leading the most frequent cancer deaths in 2020. Addition to these, around 400 thousand children develop cancer (19).

Metabolic syndrome has a connection to a stronger correlation with more dangerous illness and biochemical recurrence in prostate cancer than it has with incidence of the illness (20). Additionally, the elevated prostate cancer incidence can be ascribed to the rising PSA screening rate, the aging population, and improved diagnostic tools (22)

2.3.2. Etiology of Prostate cancer

Several modifiable and non-modifiable risk factors are linked to the origin of prostate cancer, which is complex and yet extremely puzzling. Age, a favorable family history, and ethnicity are among proven risk factors (21). Aside from age and race, there are additional prostate cancer risk factors, although none have been definitively linked to the disease's etiology (22).

Prostate cancer risk is known to increase with age. Prostate cancer incidence rises with age. Below 40, there are very few cases of prostate cancer. The world over, in both industrialized and developing nations, there is an aging population trend (21). Males younger than 39 had a 0.005% likelihood of developing prostate cancer, compared by 2.2 percent between the ages of 60 and 79, there is a 13.7 percent risk between the years of 40 and 59 and a 40% chance. (23).

Prostate cancer has an increased heritability (24). More than 180 distinct SNPs (single nucleotide polymorphisms) that are connected to prostate cancer risk account for one-third of the heredity risk for families with the disease (25, 26).

It has been established that smoking and prostate cancer risk factors are related. Ex-smokers had a higher chance of developing Heavy smokers and prostate cancer risk was 24–30% higher danger of dying from prostate cancer (27).

Prostate cancer is all except one of the numerous malignancies diet and nutrition have been linked to. Contrarily, eating minimally or not at all processed meals is linked to a decreased danger of prostate cancer. Consuming high levels of processed food can raise the danger of prostate cancer (28).

Adiposity increases the occurrence of prostate cancer death, and obesity and an elevated body mass index have both been connected to several cancers, including this one (29). The sex

hormones adipokines, insulin-like growth factor 1 (IGF-1), and are three potential factors that link the risk of prostate cancer with obesity (30).

It seems that there is a considerable ethnic connection with prostate cancer (31). The frequency of prostate cancer varies by place and ethnicity. Black men from African increased levels of incidence rates, severity, and death (32).

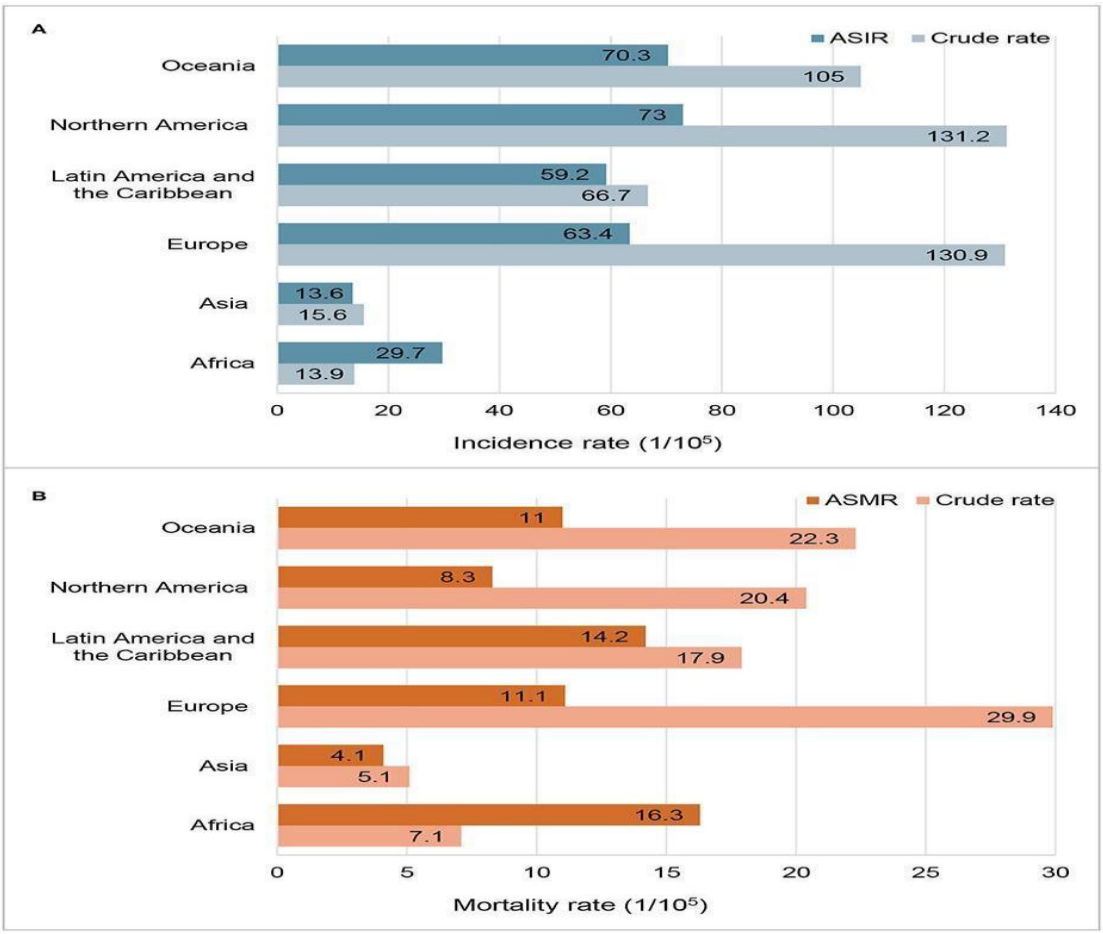

Figure 2: Incidence and mortality of prostate cancer in 2020 by continent. (A) Incidence rate; (B) Mortality rate; ASIR, age-standardized incidence rate; ASMR, age-standardized mortality rate (142).

2.4. Staging of prostate cancer

Identifying the stage is crucial to analyzing cancer of the prostate. The TNM (tumor/nodes/metastases) classification, which has three stages, is the staging scheme that is most frequently employed. The Gleason score (from a biopsy or surgical specimen), the PSA

level, the size and spread of a tumor, the existence of affected lymph glands, the Gleason score, and the existence of metastases are some of its constituent parts. The bones and lymph nodes are where cancer cells most frequently go when they move from the prostate to other regions of the body (33, 34).

T1 and T2 tumors are regarded as "localized" when they only affect the prostate. Although T3 cancer has migrated outside the prostatic capsule, the rectum or bladder have not been affected. Stage T3c, which is a concerning symptom, indicates that the cancer may have migrated to the seminal vesicles. Outside of the prostate, T4 tumors have metastasized to other regional tissues including the bladder. Their N (nodes) or M (metastasis) scores would indicate this if they spread to the liver, lymph nodes, or lungs. Only 29% of stage T4 prostate tumors with distant metastases survive for five years overall (35).

Stage I On a digital rectal exam, the tumor cannot be felt since it is tiny and only affects the prostate gland (T1a or T1b). There are no distant metastases or adjacent lymph nodes involved (36).

Stage II The tumor performing a digital rectal exam might be felt, but it is still only present in the prostate gland (T1c, T2a, or T2b). There are no nearby lymph nodes or distant metastases (37).

Stage III the bladder neck or seminal vesicles (T3a) may have been infiltrated by the tumor as it has developed outside of the prostate gland (T3b). There are no neighboring lymph nodes or distant metastases involved (38).

Stage IV N1 indicates that the tumor has migrated to adjacent lymph nodes; additional regions, such as the bones, liver, or lungs, are further away (M1). Stage IVA (spread to surrounding lymph nodes) or stage IVB are further classifications for this stage (spread to distant sites) (39).

2.4.1. Clinical staging

Clinical staging is crucial for determining a patient's risk of the illness and, consequently, for therapy recommendations (43). There are a number of clinical situations where primary staging of prostate cancer can be used, including the ones listed below (44). Finding suspicious lesions in individuals who have never had a biopsy but who have a clinical suspicion of having

prostate cancer (for example, increased blood amounts of a positive Prostate-specific antigen (PSA) or a digital rectal examination (45), finding cancer in patients despite persistent prostate cancer is clinically suspected despite negative biopsy findings (e.g. rising PSA) (46) or stage in individuals with prostate cancer who have undergone a biopsy (44).

To look for metastases and stage metastatic prostate cancer, a range of imaging methods are utilized, that is multiparametric MRI, computer tomography (CT) and bone scintigraphy to rule out metastatic spread (40, 41). Promising outcomes for prostate cancer detection, localization, risk stratification, staging, and potential therapy choices have been achieved with multiparametric magnetic resonance imaging (MP-MRI) (42).

Promising outcomes for prostate cancer detection, localization, risk stratification, staging, and potential therapy choices have been achieved with multiparametric magnetic resonance imaging (MP-MRI) (47).

2.4.2. Pathological staging

Pathological staging is a method utilized to evaluate severity spread of cancer based on the examination of tumor specimens obtained during surgery or biopsy. This staging system is important because it helps determine the appropriate treatment plan and prognosis for patients with cancer (48). Different staging systems are employed for various types of cancer, but some commonly used systems include:

For many different forms of cancer, the TNM staging approach is employed, including breast, lung, and prostate cancer. It uses three parameters to ascertain the cancer's stage. T (tumor invasion and size), N (lymph nodes are involved), M (spread to other bodily regions) (49).

Duke's staging system is used for colorectal cancer and divides the cancer into four stages depending on how widely they have spread through colon and lymph nodes (50).

The staging system in Ann Arbor is used for Hodgkin and non-Hodgkin lymphomas and divides the cancer into four stages based on the extent of spread to organs and lymph nodes (51).

The staging system of FIGO is used for gynecological cancers, such as cervical and ovarian cancer, and uses several factors to determine the stage including tumor size, extent of spread to other organs, and lymph nodes (52).

2.5. Classification of prostate cancer

Prostate cancer can be classified in several methods:

By stage is the most typical classification method for prostate cancer. TNM staging apparatus, which considers no matter if the disease has grown to surrounding lymph nodes (N), the size of the tumor (T), and if its metastatic spread (M) to far away parts of the body (53). TNM staging system. This system is updated periodically by the American Joint Cancer Committee (AJCC) and is utilized frequently in therapeutic practice (54).

By grade is another approach by which Prostate cancer is also categorized using the Gleason score, a grading scheme that assesses how aggressive the Observing cancer cells under a microscope. The higher the cancer's Gleason score, the more aggressive it is projected to be (55).

By risk group is in accordance with the patient's PSA level, Gleason score (56), and clinical stage biopsy results, prostate cancer can also be divided into low, intermediate, and high-risk categories. When making treatment decisions and giving patients prognosis information, this categorization is frequently employed. (57).

By molecular subtype, recent research has identified several molecular subtypes of prostate cancer, including luminal A, luminal B, basal, and neuroendocrine subtypes. These subtypes have different genetic characteristics and may respond differently to treatment (58).

By clinical presentation, some prostate cancers may be classified based on how they present clinically, such as a locally advanced form of prostate cancer (Prostate-specific) (extending beyond the prostate), or prostate cancer which has spread (the disease has spread to other bodily organs) (59).

Gleason score is a grading system that rates how aggressive the cancer cells appear as an image under a microscope. It runs from 6 to 10. The Gleason score is frequently utilized in clinical practice to direct treatment choices and give patients prognostic information. [60]. The Gleason score is widely used in clinical practice to guide treatment decisions and provide prognostic information to patients (60).

Gleason Grading of Prostate Carcinoma: When evaluating prostate cancer histopathologically, the Gleason grading method is frequently utilized. The system rates the two most notable tumor patterns seen under a microscope with a primary and secondary grade,

ranging from 1 to 5. The Gleason score, which aids in determining treatment options and forecasting disease outcomes, is created by adding these grades together. (61).

2.6. Diagnosis of prostate cancer

Early detection and accurate diagnosis are essential for successful treatment and improved outcomes. In this write-up, we will discuss the diagnosis of prostate cancer, including screening tests, diagnostic tests, and the current guidelines for prostate cancer diagnosis (62).

Digital rectal exam (DRE). This is a medical checkup where A medical professional puts a finger into the rectum while wearing gloves and lubricant to feel or examine the prostate gland for tumors or other anomalies (63).

Prostate-specific antigen test, or PSA test. This PSA, a protein produced by the prostate gland, is measured by blood tests. Higher amounts of PSA can reveal whether prostate cancer is present, but may be also due to additional ailments including inflammation or an enlarged prostate (64).

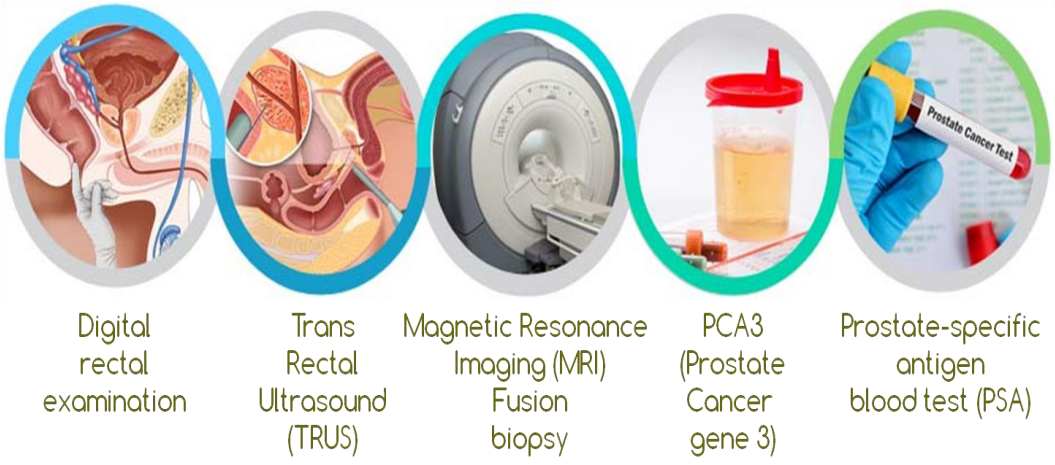

Figure 3: Different diagnostic methods of prostate cancer (142).

2.6.1 Biopsy technique

There is a tiny amount of prostate tissue removed during a biopsy and looked at with a microscope to look for signs of cancerous cells. Typically, biopsies with a needle inserted through the rectum or perineum are carried out under ultrasound guidance (65).scanning tests

Imaging tests: like MRIs, CTs, or bone scans can be used to figure out the extent and spread of prostatic cancer (66)

Genetic testing may be used to identify inherited genetic alterations that raise the possibility of developing prostate cancer (67).

2.6.2. Screening for prostate cancer

Two most commonly and frequently utilized screening procedures, PSA blood tests and digital rectal exams (DRE) are used to detect prostate cancer. (68). PSA testing detects the quantity of PSA, a PSA, or prostate-specific antigen protein, in the blood. Possible signs of prostate cancer include an increased level of PSA, but it can also be brought on by non-cancerous diseases such prostatitis or benign prostatic hyperplasia (BPH) (69). In DRE, the prostate gland is physically examined through the rectum to check for any anomalies (70).

2.6.3. Diagnostic test for prostate cancer

A biopsy may be advised if the PSA test or DRE suggests that prostate cancer may exist. Small tissue samples from the prostate gland are removed during a biopsy in order to be examined under a microscope for the presence of cancer cells (71). During the biopsy, transrectal ultrasonography (TRUS) may also be utilized to direct the needle to the proper region of the prostate gland (72).

2.7. Treatment of prostate cancer

When found in the beginning phases, prostate cancer is among the most curable cancers (73). Prostate cancer therapy is dependent on the individual's preferences, age, general wellbeing, and the cancer's grade and stage (74). Radiation therapy, systemic therapy, and surgery are the three main prostate cancer therapies. Depending on each circumstance, each one of these therapies may be administered alone or in combination (75).

2.7.1. Surgery

Surgery entails the prostate gland's removal, known to be prostatectomy. This is a typical remedy for localized prostatic cancer. Two main types of prostatectomy are (76).

Radical prostatectomy entails removing the prostate gland entirely along with part of the tissue around it, such as the seminal vesicles (77). This can be done through Open surgery or less invasive procedures like laparoscopic or robotic-assisted surgery can be used to accomplish this.

[78].

Transurethral resection of the prostate (TURP) a section of the prostate is removed during this less invasive treatment through the urethra using a resectoscope (79).

2.7.2. Radiation therapy

Radiation therapy involves the usage of powerful energy beams to eliminate malignant cells [80]. There are two different radiation treatment kinds for prostate cancer.

External beam radiation therapy In order to treat prostate gland treatment with radiation, a device outside of the body is used (81).

Brachytherapy, here seeds that are directly radioactive are inserted entering the prostate gland (82).

2.7.3. Systemic therapy

Drugs are used in systemic treatment to treat cancer cells throughout the body (83). There are two primary forms of systemic treatment for prostate cancer:

Hormone therapy: This includes inhibiting testosterone, which promotes the development of prostate cancer cells (84). Surgery to remove the testicles or prescription drugs are both options for hormone treatment (orchiectomy) (85).

Chemotherapy, this involves the use of medicines that destroy cancer cells anywhere in the body. Chemotherapy is usually used for prostate cancer that has spread to other progressed to other body areas (86).

In addition to these primary treatments, there are also several other therapies that can be used to manage symptoms and slow the progression of prostate cancer (87). These include

Active surveillance, the cancer is closely monitored with routine exams and imaging studies, and therapy is only initiated if the malignancy worsens or manifests symptoms (88).

Cryotherapy, this includes killing cancer cells by using extremely low temperatures.

High-intensity focused ultrasound (HIFU), this includes heating and eliminating cancer cells using high-frequency sound waves (89).

Immunotherapy entails taking medications that support the body's defense mechanism in fighting cancer (90).

Palliative care, symptoms as well as living quality for people having metastatic or advanced prostate cancer are managed in this (91).

It's critical to remember that prostate cancer therapy is extremely customized and should be addressed with a healthcare professional (92).

2.8. Nucleotide Excision Repair

The damage-recognition issue has now been addressed by a wide variety of DNA repair mechanisms. A significantly broader and more flexible nucleotide excision-repair (NER) identification capability (93). In NER, a protein that is not catalytically active but serves as a binding site or anchor for catalytically active proteins to concentrate on participates in the recognition event (94).

Nucleotide excision repair, or NER, is a highly conserved system for recognizing and removing a number of DNA damages, including large chemical UV-induced pyrimidine dimers, adducts, and other helix-distorting lesions (95). The complicated process of NER includes many proteins and may be separated into transcription-coupled repair (TCR) and global genome repair (GGR) (96).

While TCR particularly targets DNA damage that prevents RNA polymerase from performing transcription, GGR is in charge of identifying and mending DNA lesions throughout the genome (97). The first action in both sub pathways involves the identification of damage complicated by proteins made up of the proteins XPC, HR23B, and UV-DDB. This complex looks at the DNA and detects lesions that change the helix structure (98).

After damage recognition, the NER machinery assembles around the lesion to form a pre-incision complex that includes several proteins, such as XPF-ERCC1, XPA, RPA, TFIIH, XPG, and XPA. This complex then unwinds and excises a short segment of damaged DNA, creating a single-stranded gap (99). The opening is closed by DNA polymerases, and the just created strand is connected back to the initial strand by DNA ligase (100). There are also several accessory factors involved in NER, including chromatin remodelers, histone modifiers, and ubiquitin ligases, which help to regulate the accessibility of the DNA and coordinate the assembly and disassembly of the repair machinery (101).

Many genetic disorders have been associated with defects in NER, including the extremely sensitive conditions trichothiodystrophy, Cockayne syndrome, and xeroderma pigmentosum to UV radiation, neurological abnormalities, and premature aging (102).

Additionally, defects in NER have been connected to higher chances of acquiring certain forms of cancer, including skin and lung cancer (103).

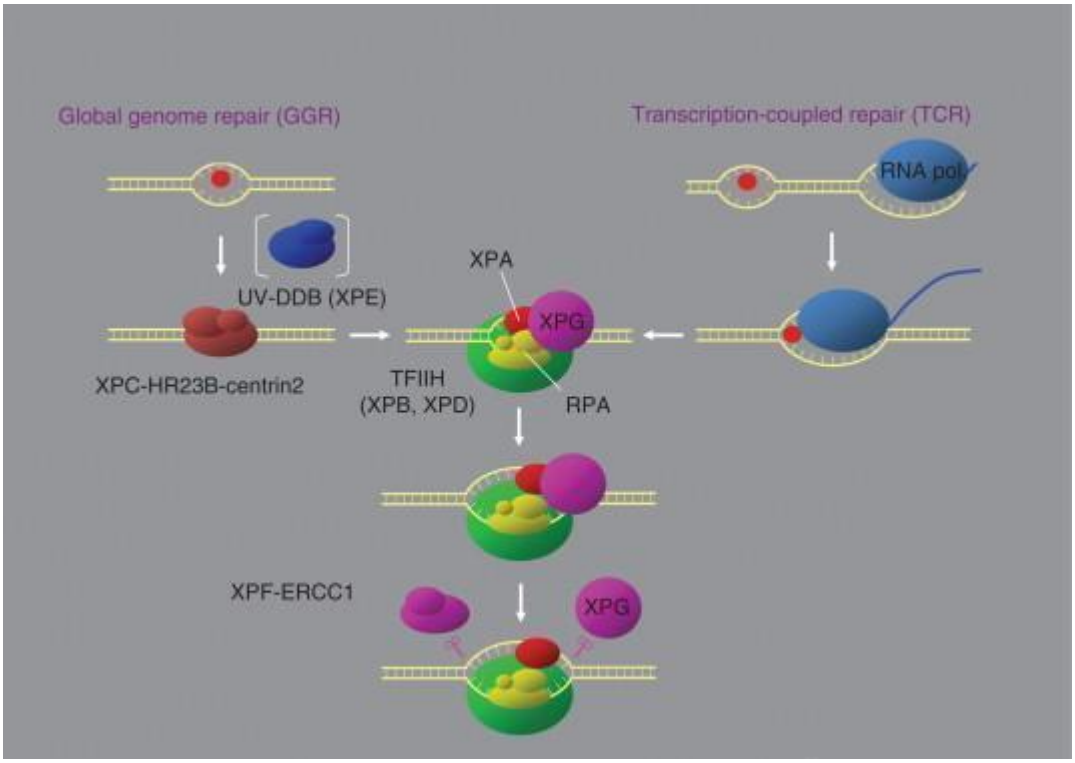

Figure 4: Two distinct pathways for mammalian NER (143).

2.9. DNA damage binding protein

48-kDa protein DDB2 also known as p48 subunit that is only found within mammalian cells' nuclei. It's a damage-specific DNA-binding protein. Human tissues all contain DDB2, albeit it is expressed differently in each tissue. Large amounts of DDB2 expression have been found in the kidney, liver, thymus, and testes, however, low levels have been found in the mind, lung, skin, heart, and muscles (104). DDB2 is made up of a Helix-loop-helix motif at the end and seven repeat domains for WD40. Locally, DDB2 detects locations of DNA harm and initiates the excision repair procedure for the entire genome (GG-NER) (105). DDB2 appears to be crucial for the repair of the latter kind of UV-damaged DNA lesion, which includes dimers of cyclobutane pyrimidine (CDPs) and (6-4) pyrimidine-pyrimidone photoproducts (6-4PPs) (106). DDB2 does this task by enlisting Polymerases of poly (ADP-ribose (PARP), which add multiple ribose ADP units to histones (proteins) (107). DDB2, one of the NER system's components, helps to repair large DNA adducts in addition to those caused by UV. DDB2, for

illustration, has been demonstrated to identify a variety of DNA damage types, such as those brought on by single-stranded DNA, goods made from platin, nitrogen mustard, and psoralen, and a basic site (108). DDB2 helps maintain low CDK inhibitor levels p21Waf1/Cip1 by assisting in the degradation of the p53 protein. (109).

DNA damage binding proteins (DDBPs) are protein groupings that play an essential role in identifying and repairing damaged DNA. Below are a few examples of DDBPs with references to support their roles in DNA damage repair.

2.9.1. Ku (Ku autoantigen)

Ku is a protein that is heterodimeric and has the components Ku70 and Ku80, and is engaged in end-joining that is not homologous pathway repair of DNA. Ku recognizes broken double-strands in DNA and seeks out other repair factors at the location of the break to facilitate repair. Defects in Ku have been linked to various human diseases, including cancer and immune system deficiencies (110).

2.9.2. XPC (Xeroderma Pigmentosum Complementation Group C Protein)

The XPC, also a DDBP involved in the beginning identification of DNA damage in the Repair of nucleotide excision pathway. It connects with damaged DNA sites as well as hires additional proteins to the lesion location for repair. XPC is currently demonstrated to play a crucial role in protecting cells against DNA damage brought on by UV radiation (111).

2.9.3. BRCA1 (Breast Cancer Susceptibility Gene 1)

BRCA1 a DDBP engaged in the DNA repair process known as homologous recombination. It plays an essential part in mending DNA splits in two strands and maintaining genome stability. BRCA1 mutations are linked to an increased risk of breast cancer and ovarian cancer (112).

2.9.4. ATM (Ataxia Telangiectasia Mutated Protein)

A crucial component of the DNA damage reaction system is the kinase ATM. In order to start the repair process, it recognizes DNA double-strand breaks and phosphorylates downstream targets. Ataxia Telangiectasia, a rare genetic condition caused by defects in ATM, is characterized by a high vulnerability to malignancy and neurodegeneration (113).

2.9.5. Ultra-Violet DNA Damage Binding Protein (UV-DDB)

The UV-sensitive DNA-binding protein damage. This protein, which is made up of the two subunits DDB1 and DDB2, is essential for identifying and repairing DNA damage brought on by UV radiation (114).

2.9.6. DNA Damage Binding Protein (DDB2)

DNA damage-binding protein 2. A part of this protein is a UV-DDB complex and is essential for identifying and repairing UV-induced DNA damage (115).

2.9.7. DNA Damage Binding Protein (DDB1)

Repairing protein for DNA damage 1. In the UV-DDB complex, this protein functions as a component and aids in the restoration of DNA damage brought on by UV radiation (116).

2.9.8. RAD23

This protein, which is a part of the NER machinery, assists in identifying and repairing various kinds of DNA damage (117).

2.10. DDB2 Gene as Tumor Suppressors

The discovery that the DDB2 gene is mutated caused a deficiency in both DDB2-DNA and DDB2-DDB1 contacts and associated NER engagement abnormalities prompted the initial consideration of DDB2 to serve as a new tumor suppressant (105). Such defects are seen in subgroups of genetic disease called Xeroderma pigmentosum (Xeroderoma pigmentosum group E, XP-E), which exhibits incredibly high susceptibility to skin malignancies and UV radiation [107]. Numerous studies identified that DDB2 expression is different, relative non-cancerous tissues, in various types of malignancies (118) consisting of prostate, (119) colorectal, (120, 121) skin, (122) neck and head (123) and ovarian cancers (124).

DDB2 is necessary for DNA triggered by UV harm repair. DDB2 is hired at locations of UV-induced DNA harm and is required for efficient removal of the damaged DNA. In cells lacking DDB2, repair of DNA damage caused by UV radiation is severely impaired (125).

DDB2 mutations are associated with human diseases. Mutations in DDB2 have been linked to a rare genetic disorder called xeroderma pigmentosum complementation group E (XP-E). XP-E is distinguished by a high UV sensitivity radiation and a higher chance of getting skin cancer (126).

DDB2 is a factor in the control of gene expression. DDB2 has been shown to work in conjunction with transcription factors and function to control genes that are activated in response to DNA damage. DDB2 can serve as a co-activator for transcription for certain genes that regulate cell cycle and apoptosis (127).

DDB2 contributes to genome maintenance integrity. DDB2 contributes to identifying and fixing DNA damage caused by various genotoxic agents, including UV radiation, ionizing radiation, and chemotherapeutic drugs. DDB2-deficient cells show increased genomic instability and are more susceptible to cell death brought on by DNA damage (128).

2.11. DNA Damage Binding Protein 2 and cancer

Numerous investigations have demonstrated an association between low levels of DDB2 expression and a higher danger of developing cancer. In a research that was published in the journal Cancer Research, for instance, it was discovered, the expression of DDB2 was much dropped in lung cancer tissue comparisons to healthy lung organ. Low DDB2 expression had a connection to a poor prognosis in bladder cancer patients, according to a different investigation that was published in the journal Oncogene (129).

According to research, DDB2 can decrease tumor growth by encouraging repair of DNA damage, as well as limiting the occurrence mutation with cancer-causing genes. For instance, a study indicated that DDB2 deficiency raised levels of DNA damage and genomic instability, which increased the risk of cancer formation (130).

An investigation on the relationship within the DDB2 rs830083 risk of polymorphism and prostate cancer in a Turkish population was published in the journal Oncology Letters. According to the study, people with the CC genotype had a noticeably lower danger of developing prostate cancer than those with the TT genotype. When accounting for age, smoking habits, and cancer in the family, this link was still shown to be significant (131).

According to research, DDB2 may influence how well cancer patients respond to both radiation and chemotherapy. Patients with breast cancer, DDB2 expression was linked with a good response to treatment. According to research, DDB2 may influence how well cancer patients respond to radiation treatment and chemotherapy among those with breast cancer, DDB2 expression was linked with a good response to treatment (132).

By preserving genome stability and encouraging DNA repair, research indicates that DDB2 is crucial in avoiding the onset of cancer. Current research is looking into its potential as a therapeutic target for cancer treatment (133).

Overall, the data points to a possible link between the DDB2 rs830083 polymorphism and the chance of developing prostate cancer, however the findings vary depending on the community. Further research is required to verify these results and explore the underlying mechanisms (134).

3. MATERIALS AND METHOD

3.1. Sample Selection and Definition

Both PCa patients (n=93) and healthy persons serving as a control group (n=91) are included in this study. Patients diagnosed by the department of pulmonary medicine make up the patient group, whereas individuals in the control group are in good health.

3.1.1. Patient group

All Yeditepe University Hospital patients with prostate cancer whose ages range from 42 to 83 were included in this study.

3.1.2. Control group

Healthy individuals who have not yet received a diagnosis make up the control group. The age range of the control group is also 45 to 86.

3.2. Materials and Devices Used in Experiment

3.2.1. Materials used in DNA isolation.

Blood samples via the periphery were used to isolate DNA. Before usage, the samples of blood were kept in tubes containing EDTA at -4 °C. Because it prevents coagulation, EDTA is utilized. Additionally, the (iPrep pure link, Invitrogen, and Thermo Fisher Scientific Inc.) DNA Isolation Robot technology was employed to create the DNA isolation. The DNA isolation mixture contained 1.12 mg/ml Proteinase K, cell lysis solution, RNAse A, 100% Isopropanol, Elution Buffer, Wah Buffer and iPrep PureLink gDNA Cartridge.

3.2.2. Equipment used in experiment

Real-time PCR (Fast Real Time 7500, Applied Biosystems), 7500 Fast Real-Time PCR Instrument, Plate Centrifuge (Hettich), Centrifuge (Centrifuge 22R-Beckman Coulter), Nanodrop 2000 (Thermo Fisher Scientific Inc.), DNA Isolation Robot (iPrep Purelink, Invitrogen, Thermo Fisher Scientific Inc.), -20°C Refrigerator, -4°C Refrigerator (Haier).

3.3. Methods

3.3.1. Genomic DNA Isolation from blood

Each blood sample from the individuals with prostate cancer and the healthy group was collected in 5mL EDTA-containing tubes. All blood samples were kept in refrigerators at a temperature of -4°C until the isolation process began. Isolation of DNA was done using an iPrep DNA extraction robot and an iPrep genomic DNA isolation kit from Invitrogen. This technology enables the processing of 13 blood samples simultaneously since 350 L of peripheral blood may be used to isolate DNA. Each sample is placed into its own cartridge, which has been agitated for a bit to make sure the magnetic beads and DNA are properly bound together.

The iPrep robot functions as a calibrated extraction technique using ChargeSwitch® (CST®) technology. This process has the benefit of isolating significant amounts of genomic DNA from the samples. In this method, paramagnetic particles are used to extract significant volumes of pure genomic DNA from materials. These specks are enclosed by a surface that binds DNA. When compared to conventional extraction techniques, such as silica-based DNA extraction, the ChargeSwitch® (CST®) extraction approach is truly unique. The pH of the buffering particles that surround the beads affects their charge. The DNA backbone is negatively charged at low pH levels, where it attaches to positive ions in beads. Those charged beams the use of a low salt buffer neutralizes with a greater pH for DNA elution. The molecule of nucleic acid has entered.

3.3.2. DNA purity measurement

A UV spectrophotometer known as Nanodrop is used to measure the UV (ultraviolet) light absorption of nucleic acids at 260 nm. To determine DNA purity, the OD260/OD230 and OD260/OD280 ratios are evaluated. Nanodrop also measures DNA concentration. When opposed to conventional UV spectrometers, Nanodrop does not have a cuvette or capillaries, thus materials are analyzed directly, free from other effects. As a consequence, more accurate findings are achieved.

ThermoFisher Scientific Inc.'s Nanodrop 2000 was used in this experiment to evaluate DNA purity. Each person's 1 l of DNA, which was known to both the control group and prostate cancer patients, was utilized. Additionally, distilled water was utilized as a control sample.

Distilled water was utilized to clean the sample placing stage after every 15-20 measurements. Following the completion of all sample measurements, distilled water was used to clean the Nanodrop 2000.

3.3.3. Genotyping with real-time PCR

In this study, genotyping analysis was performed with Applied Biosystems' 7500 Fast Real-Time Polymerase Chain Reaction known as a Real-Time PCR device. Detection of single nucleotide polymorphisms (SNPs) was detected using fluorescent dyes of probes. Detection of fluorescent signals is clearly visible. In the Real-time PCR method, fluorescent dye probes are used and they have two different wavelengths specific to the alleles called mutant and wild type. There were two different TaqMan probes used to detect. One of them was FAM and the other one was VIC. FAM can detect wild type variants of alleles. VIC can also detect mutant variants of alleles. The fluorescent dye-linked probes of each allele attach with the amplified region. Taq polymerase enzyme is performed to hydrolyze the probes.

The primer was designed depending on the sequence of DDB2 in humans. Determination of DDB2 gene (rs830083) TaqMan Genotyping Assay and TaqMan Genotyping Master Mix (TaqMan Reagents, Applied Biosystems, Foster City, CA, USA) were used to perform polymorphism on the Applied Biosystems 7500 Fast Real-Time PCR apparatus. Based on this procedure, the polymorphism-contained region was amplified by using 5'AACCCCATCTTAAAAAAAAAAAATA**[G/C]**AAAAATTAGCTGGGCATGGTGGCAC 3'.
Due to the Minor allele frequency (MAF) analysis, allele frequencies considered as G wild type and C mutant form for the DDB2 gene.

3.3.3.1. Real-time PCR protocol

3.75µl of DNase, RNase free water, 5µl of TaqMan genotyping assay [probe], 0.2 µl of primer [DDB2 rs830083] and 1 µl of template DNA were used. The total volume of reagents used in reaction mixtures and real-time PCR are also shown in Table 1. First, mixture was prepared with primer, DNase, RNase free water and TaqMan genotyping assay and then mixture separated to each well of 96-well. After that, each template DNA samples were added onto the mixture one by one. Later, 96-well plates were covered carefully. Centrifuge was performed 2 min at 3750 rpm to make the solution more homogeneous and to precipitate all

liquids to the bottom. Then the plate is carefully placed in the PCR device and Real-Time PCR is started.

Table 1: The Mixtures of Real Time PCR Reaction

THE AGENT	QUANTITY OF AGENT
DNase, RNase free water	3.75µl
TaqMan genotyping assay	5µl
Primer [DDB2, rs830083]	0.25µl
Template DNA	1µl

Real-Time PCR stages were designed. First there were 10 minutes waiting time at 95 °C, then the denaturation process was continued for 15 seconds per cycle at 92 °C and last stage were elongation to 1 minute for each cycle at 60 °C. As it is shown in Table 2, denaturation and annealing/extension processes were applied as 40 cycles.

Table 2: Real-time PCR protocol

STAGES	TEMPERATURE [°C]	DURATİON/PERIOD OF TIME
HOLD	95	10MINS
DENATURATION	92	15SECS
ANNEALING/ELONGATION	60	1MIN

3.3.4. Statistical Analysis

In this research, a student's t-test was used to get numerical values. When PCR experiments were done and allelic discrimination data were obtained, all data were entered in the SPSS 26.0 program. Moreover, the other clinical parameters were already collected and entered in the SPSS document. Clinical parameters are shown in Table 3 and 4. Then, the

information was analyzed in SPSS 26.0 by using Fisher's Exact Tests, Mann-Whittney U test and Chi-square tests. Chi-square and Fisher's Exact Tests were applied to statistically analyze the genotype distribution and alleles in the groups; while Mann-Whittney U test was used to compare means and for standard deviation. P values less than or equals to 0.05 are considered statistically significant, so possible risk factors for PCa can be identified and assessed by the analysis.

4. RESULTS

4.1. Demographic Characteristics

Demographic data of PCa patients (n=93) and healthy controls (n=91), which constitute the groups of our thesis study, are given in Table 3 comparatively.

Table 3: Demographic and biochemical characteristics of patient and control

		Prostate cancer N = 93	Control group N = 91	P=value
Age (years) mean ± SD		67.3881 ± 73.3600	60.3333 ± 13.80757	0.89623 NS
Smoking		30.56 ± 18.696	27.64 ± 17.682	0.636 NS
BMI mean ± SD		27.1194 ± 3.71125	26. 7567 ± 2.95790	0.45194 NS
Kilo mean ± SD		78.1343 ± 11.52322	79.3077 ± 9.87062	0.596 NS
Cigarette use mean ± SD		1.2090 ± 0.40963	1.1250 ± 0.34157	0.5004 NS
PSA mean ± SD		81.0656 ± 141.87826	2.3938 ± 1.62910	0.0001 S
Cancer Family History	Yes%	75%	25%	0.050 S
	No%	56.1%	43.9%	

N = Number of samples, chi-square test has been used to show the difference of genotype and Allele distribution between two groups. **S** = statistically significant (p value< 0.05). **NS** = no significance (p value>0.05).

As shown in Table 3, demographic data in the patient and healthy control groups were analyzed statistically. As a result of the analysis, as can be seen in the table, there was no statistically significant difference in the mean Age, the BMI, Cigarette use and Kilo in the cancer patient group compared to the control group, but there is a statistical difference in the cancer family history of p value = 0.05 and PSA with $p<0.05$ ($p = 0.0001$) with higher values in the prostate cancer group. This was calculated using the Mann-Whitney Test.

Table 4: Clinical and Treatment Characteristics of the group of patients with prostate cancer.

Clinical and Treatment Characteristics		Percentage (%)
Stage of prostate cancer	stage 2	70.1%
	stage 3	29.9%
Primary gleason	3	35.8%
	4	55.2%
	5	9.0%
Secondary gleason	3	22.4%
	4	58.2%
	5	19.4%
Treatment	ADT	29.9%
	curative radiotherapy	14.9%
	radical prostatectomy	55.2%
Metastasis	Yes	13.4%
	No	86.6%

Pathological T-Stage	pT2a	11.9%
	pT2b	14.9%
	pT2c	43.3%
	pT3a	14.9%
	pT3b	14.9%
Clinical T-Stage	cT1c	38.8%
	cT2	49.3%
	cT3	11.9%

Table 4 demonstrates the clinical and therapeutic characteristics of the group of prostate cancer patients. Stage 2 of prostate cancer accounts for 70.1% of cases, whereas stage 3 accounts for 29.9%. Also found were main gleason at 3, 4, and 5 (35.8%, 55.2%, and 9.0%, respectively), secondary gleason at 3, 4, and 5 (22.4%, 58.2%, and 19.4%, respectively), and Treatment with Radical prostatectomy was performed in 55.2% of cases, with ADT was 29.9%, curative radiation was used in 14.9%, metastatic disease was present in 13.4% of cases, but was absent in 86.6 % of cases. Pathological T-Stage pT2a, pT2b, pT2c, pT3a, pT3b was (11.9%, 14.9%, 43.3%, 14.9%, 14.9%), Clinical T-Stage cT1c, cT2, cT3 (38.8%, 49.3%, 11.9%).

4.2. Statistical analysis of Real-Time PCR Results.

Table 5 displays the genotype distributions of DDB2 rs830083 in prostate cancer and the controls. The homozygous mutant genotype (CC) and the heterozygous genotype (GC) shown a significant association with (p=0.037), (p=0.048) respectively. While the homozygous wild-type (GG) (p=0.707) had non-significant association with prostate cancer. The genotype frequencies of the GG, GC, and CC genotypes were 4.3%, 26.9%, and 68.8%, respectively, in the prostate patient group while they were 5.5%, 40.7%, and 35.8% in the

control group. The G allele exhibited notable variations between the groups (p=0.037), however the C allele did not have any significant association with prostate cancer (p=0.773) as shown in table 6.

Table 5: The assessment between Prostate cancer patients and control groups according to genotype.

GENOTYPE DDB2	CONTROL GROUP N = 91	PATIENT GROUP N = 93	P-VALUE	ODD RATIO (OR)	CONFIDENCE INTERVAL 95%
DDB2 rs830083	GG (N = 5) 5.5% GC (N = 37) 40.7% CC (N = 49) 53.8%	GG (N = 4) 4.3% GC (N = 25) 40.3% CC (N = 64) 68.8%	0.111 NS		
GG	N=5 5.5%	N =4 4.3%	0.707 NS	1.294	0.336 – 4.979
GC	N = 37 40.7%	N = 25 26.9%	0.048 S	1.864	1.002 – 3.466
CC	N = 49 53.8%	N = 64 68.8%	0.037 S	0.529	0.290 – 0.965
ALLELIC DISTRIBUTION					
G ALLELE	42 46.2%	29 31.2%	0.037 S	1.892	1.036 – 3.454
C ALLELE	69 94.5%	89 95.7%	0.707 S	0.773	0.271 – 2.975

N = Number of samples, chi-square test has been used to show the difference of genotype and Allele distribution between two groups. **S** = statistically significant (p value< 0.05). **NS** = no significance (p value>0.05).

Table 6: The assessment of allelic distribution between carriers and non-carriers in control and patients.

ALLELIC DISTRIBUTION	CONTROL GROUP (%)	PATIENT GROUP (%)	P-VALUE
G ALLELE CARRIERS	42 (%)	29 (16%)	0.037
G ALLELE NON-CARRIERS	49 (27%)	64 (34%)	
C ALLELE CARRIERS	86 (47%)	89 (48%)	0.707
C ALLELE NON CARRIERS	5 (3%)	4 (2%)	

As a result, after the experiment of DDB2 rs830083 polymorphism, about 93 sample of PCa patients and 91 healthy control groups samples in this study, there is no statistically significant difference among the two groups in the genotyping, but a statistically significant difference in the allelic distribution. The statistical analysis was done using Chi square (χ^2) and Fisher's Exact test as shown in Table 5.

4.3. Analysis of Genotype and Allele Related to the Patient Groups

In patients with different genotypes for the DDB2 genes, Table 6 displays the distribution of metastasis, cancer stage, treatment, primary and secondary Gleason, and cancer family history. According to the results, there is no correlation between different genotypes and cancer family history with DDB2, treatment, primary and secondary Gleason, or metastasis stage of cancer.

The p-values for cancer treatment, primary and secondary Gleason, family history of cancer, and metastatic stage were 0.391, 0.404, 0.258, 0.883, 0.143, and 0.112, respectively.

Table 7: The distribution levels of tumor marker proteins with different patient genotypes for the DDB2 gene.

		DDB2 rs830083			P value
Genotype		GG	GC	CC	
stage of cancer	2	6.4%	31.9%	61.7%	0.391
	3	0.0%	25.0%	75.0%	
Primary Gleason	3	4.2%	16.7%	79.2%	0.404
	4	5.4%	35.1%	59.5%	
	5	0.0%	50.0%	50.0%	
Treatment	ADT	5.0%	25.0%	70.0%	0.258
	curative radiotherapy	0.0%	60.0%	40.0%	
	radical prostatectomy	5.4%	24.3%	65.7%	
Metastasis	Yes	0.0%	25.0%	75.0%	0.883
	No	5.2%	31.0%	63.8%	
Secondary Gleason	3	0.0%	53.3%	46.7%	0.143
	4	7.7%	23.1%	68.2%	
	5	0.0%	23.1%	76.9%	
Cancer Family History	Yes	7.5%	25.0%	67.5%	0.112
	No	3.0%	43.9%	53.0%	

N = Number of samples, chi-square test has been used to show the difference of genotype and Allele distribution between two groups. **S** = statistically significant (p value< 0.05). **NS** = no significance (p value>0.05).

4.4. Statistical Evaluation of Real-Time PCR Results

Additionally, using the 7500 Fast-Real Time PCR, the allele types of each person were investigated in the sick and control groups. The allelic discrimination plot produced by this tool

is displayed below, and the allelic discriminations were generated by the tool's software automatically.

Expression and readings of fluorescent radiation with the contribution of dyes in the probes. However, some samples could not be distinguished and interpreted. In this study, two different dyes corresponding to the FAM color blue and the VIC color green were used. ROX corresponds to a standard hue for contrasting FAM and VIC dyes. Allelic prejudice was evaluated by looking at and analyzing radiance curves.

According to Figure 5, there is allelic discrimination shown. GG which is seen as red dots is homozygous wild type, GC which is seen as green dots is heterozygote and CC which is seen as blue dots is heterozygous mutant type.

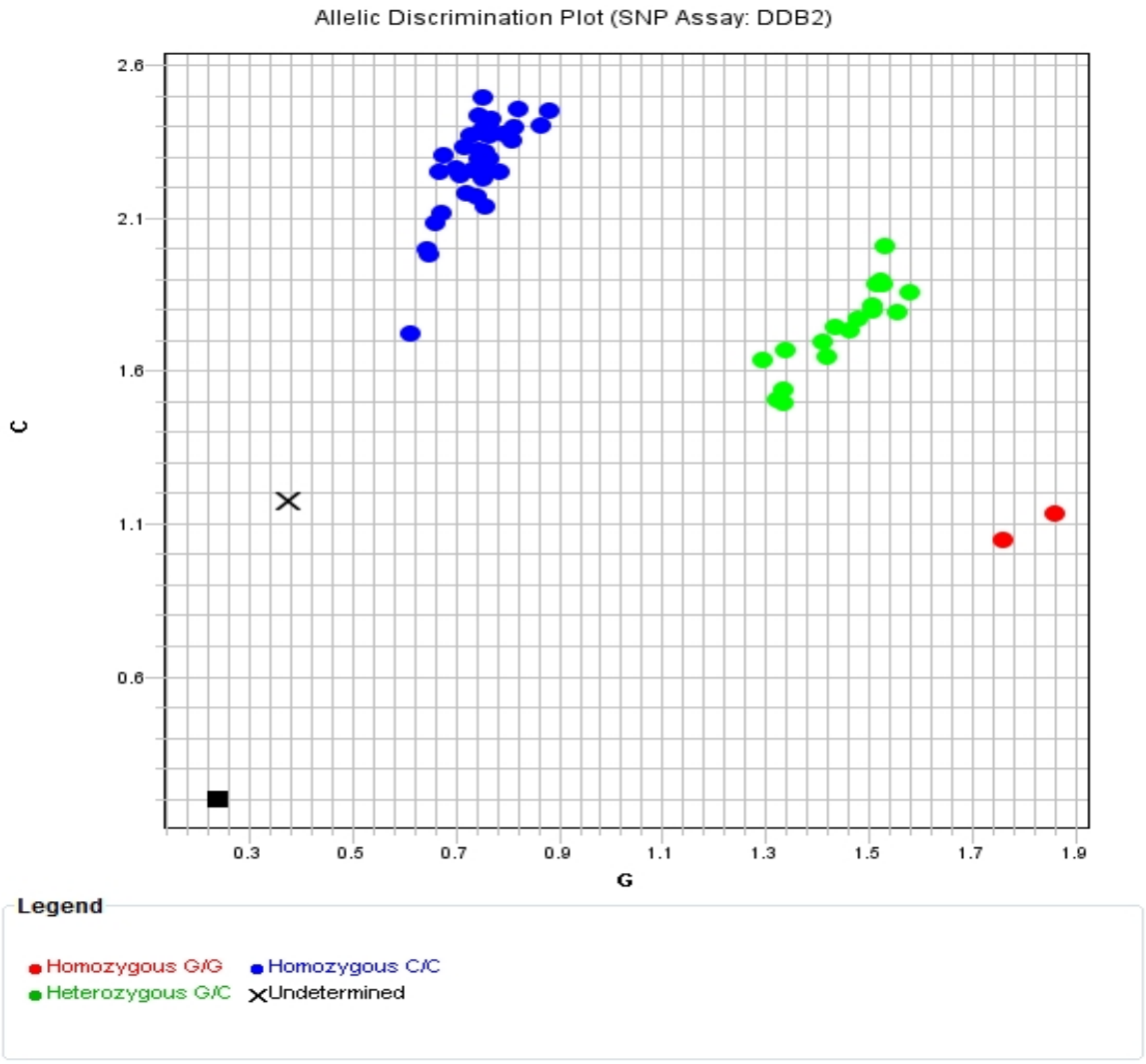

Figure 5: Allelic Discrimination Analysis of DDB2 genotypes (homozygous mutant genotype (CC), heterozygous genotype (GC) and homozygous wild type genotype (GG)).

A plot of amplification has an a y-axis for the fluorescence and an x-axis for the number of PCR cycles intensity or signal produced by a fluorescent dye. The fluorescence signal is typically modest or nonexistent in the early cycles. The fluorescence signal grows as the PCR goes along and the target DNA is amplified

Amplification plots of the DDB2 gene with the C allele are shown in Figure 6. The gray line indicating the threshold value shows it to be 0.084. In contrast, Figure 4.7 shows

amplification plots for the G allele of the same gene, with a pink line designating the threshold value (0.021).

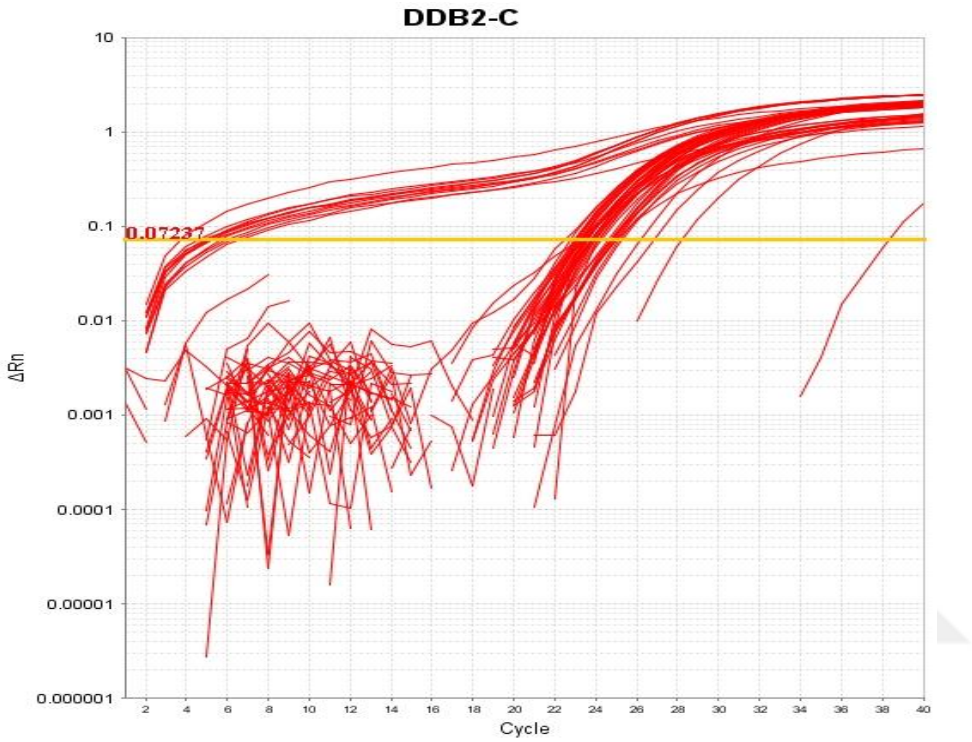

Figure 6: Amplification plot display of C allele with DDB2 gene.

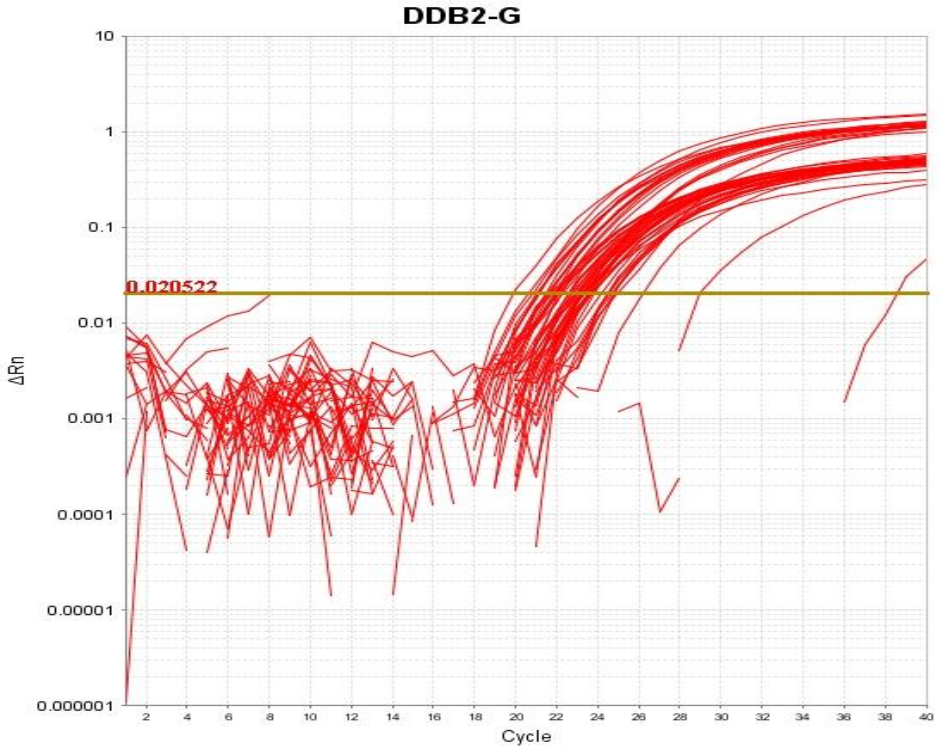

Figure 7: Amplification plot display of G allele with DDB2 gene.

5. DISCUSSION

The second-most prevalent cancer diagnosis in men and the fifth-leading cause of death worldwide is prostate cancer, is also diagnosed in these patients. Prostate cancer has recently placed first in terms of death rates, and regardless of whether the cancer is inherited or not, its etiology is unknown. Early prostate cancer often has no symptoms and spreads slowly, necessitating only treatment under careful observation (135).

Early-stage prostate cancer frequently progresses slowly and without symptoms, thus treatment options may be limited or nonexistent. Numerous cases of prostate cancer are found based on high plasmatic levels of prostate-specific antigen (PSA > 4 ng/mL), a glycoprotein typically produced by prostate tissue. A tissue biopsy is the standard of care to rule out cancer, however this is because men without cancer have also been observed to have increased PSA levels (136-137).

Cancer is split into two categories: malignant malignancies and benign tumors based on the types of cells present. Malignant tumors spread throughout the body through a process known as metastasis. Malignant tumors can invade and spread, whereas benign tumors cannot (138). Cancers of the lung, prostate, liver, and cervix are malignant. The location, progression, and size of a tumor all affect the symptoms of cancer cells. The diagnosis and management of cancer varies. MRI, CT, biomarkers, and imaging are frequently used to diagnose malignancies. Patients with early-stage cancer have a better chance of surviving. Numerous studies have been conducted on prostate cancer, which is still mostly unknown when compared to other frequent malignancies. Prostate cancer risk factors include advanced age, ethnicity, genetic factors, and family history. (139).

DDB1 (damage-specific DNA-binding protein 1, also known as p127 subunit) and DDB2 were first discovered as parts of the UV-DDB human damage-specific DNA-binding heterodimeric complex. DDB2 was originally based on the findings, is a new tumor suppressor finding that mutations in the ddb2 gene impair the DDB2-DNA or DDB2-DDB1 interaction, resulting in defective NER activity. DDB2 recognizes sites of DNA damage locally and initiates the global genomic nucleotide excision repair process (GG-NER). (140).

The rs830083 polymorphism was found to be a minor polymorphism in the Turkish population. The GG homozygous wildtype genotype was very low in both the control and patient groups, with 5.5% and 4.3%, respectively. There was no significant association between this genotype and prostate cancer risk. The GC heterozygous genotype was higher in the control group, with 40.7%. This genotype was found to be significantly associated with a lower risk of prostate cancer, with a p-value of 0.048. The CC genotype was higher in the patient group, with 68.8%. This genotype was found to be significantly associated with an increased risk of prostate cancer, with a p-value of 0.037. This means that people with the CC genotype are twice as likely to develop prostate cancer as people with the GG genotype.

Table 6 shows that there is a statistically significant difference between the two groups in terms of the percentage of G alleles. The percentage of G alleles is significantly higher in the control group than in the patient group. This suggests that the G allele may be protective against prostate cancer. These findings suggest that the rs830083 polymorphism may play a role in prostate cancer risk. However, more research is needed to confirm these findings and to better understand the mechanism by which this polymorphism affects prostate cancer risk.

The DDB2 polymorphism (rs830083) can be used to determine if the GG genotype prevents prostate cancer and whether the CC genotype causes it. According to this finding, the DDB2 polymorphism (rs830083) does not significantly differ between the control and sick groups. However, in this study, The CC and GC genotypes were found to be significant in this study, with p-values of 0.037 and 0.048, respectively. This suggests that having one or two C alleles may be a risk factor for cancer, while the G allele is a more significant risk reducing factor with a p-value of 0.037. The p-value for the G allele is lower than the p-value for the CC and GC genotypes. This means that the evidence for an association between the G allele and cancer risk is lesser than the evidence for an association between the CC and GC genotypes and cancer risk. It is important to note that these results are based on a relatively small study, and more research is needed to confirm these findings. However, the findings of this study suggest that the G allele may be a significant risk factor for cancer.

According to Hu, Z., Shao, M., Yuan, J., Xu, L., Wang, F., Wang, Y.,... & Shen, H., individuals with the heterozygous rs830083 CG genotype had a significantly 1.31-fold elevated risk of lung cancer (95% confidence interval (CI) 1.08-1.60) and those with the homozygous rs830083GG genotype had a non-significant (146).

Turkish prostate cancer patients' DDB2 gene variant (rs830083) has not been investigated. Low levels of this gene might possibly impact the likelihood of prostate cancer, according to this journal (131). The risk of prostate cancer was not shown to be substantially correlated with the C allele. This indicates that individuals with one or two C alleles have the risk of developing prostate cancer. A decreased risk of prostate cancer was discovered to be strongly related with the G allele. This indicates that individuals with one or two G alleles have a risk reducing factor of prostate cancer than individuals without any G alleles. Prostate cancer risk was shown to be considerably higher in men with the CC genotype. Accordingly, those who have two C alleles are twice as likely to have prostate cancer as those who do not. Prostate cancer risk was shown to be considerably lower in men with the GC genotype. This indicates that individuals with one C allele and one G allele have a lower risk of prostate cancer than individuals without any C alleles.

The conclusion is that the C allele is not a significant risk factor for prostate cancer, but the G allele is a significant protective factor. The CC genotype is significantly associated with an increased risk of prostate cancer, while the GC genotype is significantly associated with a lower risk of prostate cancer. These findings suggest that the rs830083 polymorphism may play a role in prostate cancer risk, but the mechanism by which it does so is not yet understood.

Based on the aforementioned findings, DDB2 gene expression and variation vary depending on the population and the person. Additional research on the functional analyses of DDB2 polymorphisms and the identification of associated prostate cancer risk in bigger molecular epidemiological studies with varied ethnic populations and many DDB2 SNPs are required to support the findings.

6. REFERENCES

1) Balkan, E., Bilici, M., Gundogdu, B., Aksungur, N., Kara, A., Yasar, E., ... & Ozturk, G. (2020). ERCC2 Lys751Gln rs13181 and XRCC2 Arg188His rs3218536 gene polymorphisms contribute to susceptibility of colon, gastric, liver, lung and prostate cancer. *Journal Of Buon*, *25*(1), 574-81.
2) International Agency for Research on Cancer. (2020). Globocan 2020 (2020). Prostate Cancer Incidence, Mortality and Prevalence Worldwide in 2008. Retrieved from http://globocan.iarc.fr/factsheet.asp
3) Yang, B., Chen, W. H., Wen, X. F., Liu, H., & Liu, F. (2013). Role of DNA repair-related gene polymorphisms in susceptibility to risk of prostate cancer. *Asian Pacific journal of cancer prevention*, *14*(10), 5839-5842.
4) Park, J. Y., Huang, Y., & Sellers, T. A. (2009). Single nucleotide polymorphisms in DNA repair genes and prostate cancer risk. *Cancer Epidemiology*, 361-385.
5) Gilson, P., Drouot, G., Witz, A., Merlin, J. L., Becuwe, P., & Harlé, A. (2019). Emerging roles of DDB2 in cancer. *International Journal of Molecular Sciences*, *20*(20), 5168.
6) Wood, R. D. (1997). Nucleotide excision repair in mammalian cells. *Journal of Biological Chemistry*, *272*(38), 23465-23468.
7) Fitch, M. E., Cross, I. V., Turner, S. J., Adimoolam, S., Lin, C. X., Williams, K. G., & Ford, J. M. (2003). The DDB2 nucleotide excision repair gene product p48 enhances global genomic repair in p53 deficient human fibroblasts. *DNA repair*, *2*(7), 819-826.
8) Amundson, S. A., Patterson, A., Do, K. T., & Fornace, Jr, A. J. (2002). A nucleotide excision repair master-switch: p53 regulated coordinate introduction of global genomic repair genes. *Cancer biology & therapy*, *1*(2), 145-149.
9) Marchant, N. (1995). *Diseases of the prostate*. Office of Health Economics.
10) Netter, F. H. (2018). *Atlas of Human Anatomy: Latin Terminology E-Book: English and Latin Edition*. Elsevier Health Sciences.
11) AIHW, A. (2012). Cancer in Australia: an overview 2012. *Canberra: AIHW*.
12) Abate-Shen, C., & Shen, M. M. (2000). Molecular genetics of prostate cancer. *Genes & development*, *14*(19), 2410-2434.
13) Rebello, R. J., Oing, C., Knudsen, K. E., Loeb, S., Johnson, D. C., Reiter, R. E., ... Bristow, R. G. (2021). Prostate cancer. Nature Reviews Disease Primers, 7(1).

14) Gann, P. H. (2002). Risk factors for prostate cancer. *Reviews in urology*, *4*(Suppl 5), S3.
15) Cronin, K. A., Lake, A. J., Scott, S., Sherman, R. L., Noone, A. M., Howlader, N., ... & Jemal, A. (2018). Annual Report to the Nation on the Status of Cancer, part I: National cancer statistics. *Cancer*, *124*(13), 2785-2800.
16) Negoita, S., Feuer, E. J., Mariotto, A., Cronin, K. A., Petkov, V. I., Hussey, S. K., ... & Penberthy, L. (2018). Annual report to the nation on the status of cancer, part II: recent changes in prostate cancer trends and disease characteristics. *Cancer*, *124*(13), 2801-2814.
17) Lehrer, S., & Rheinstein, P. H. (2020). Re: Prostate Cancer Incidence 5 Years After US Preventive Services Task Force Recommendations Against Screening. *JNCI: Journal of the National Cancer Institute*, *112*(10), 1067-1068.
18) Applegate, C. C., Rowles 3rd, J. L., Ranard, K. M., Jeon, S., & Erdman, J. W. Soy consumption and the risk of prostate cancer: an updated systematic review and meta-analysis. Nutrients 2018; 10: 40.
19) Cruz, C. S. D., Tanoue, L. T., & Matthay, R. A. (2011). Lung cancer: epidemiology, etiology, and prevention. *Clinics in chest medicine*, *32*(4), 605-644.
20) Gacci, M., Russo, G. I., De Nunzio, C., Sebastianelli, A., Salvi, M., Vignozzi, L., ... & Serni, S. (2017). Meta-analysis of metabolic syndrome and prostate cancer. *Prostate cancer and prostatic diseases*, *20*(2), 146-155.
21) Jacques Ferlay, I. S., Dikshit, R., Eser, S., Mathers, C., Rebelo, M., Parkin, D. M., ... & Bray, F. (2014). Cancer incidence and mortality worldwide: sources, methods and major patterns in GLOBOCAN 2012. *Int J Cancer*, *136*, 29.
22) Ng, K. L. (2021). The etiology of prostate cancer. *Exon Publications*, 17-27.
23) Newcomer, L. M., Stanford, J. L., Blumenstein, B. A., & Brawer, M. K. (1997). Temporal trends in rates of prostate cancer: declining incidence of advanced stage disease, 1974 to 1994. *The Journal of urology*, *158*(4), 1427-1430.
24) Moqaddem, Z. M. (2019). EPIDEMIOLOGICAL AND GENETICAL PROFILE OF PROSTATE CANCER CASES IN TLEMCEN, WEST ALGERIA: Array. *ActaHealthMedica*, *4*(2), 279-283.
25) Amin Al Olama, A., Dadaev, T., Hazelett, D. J., Li, Q., Leongamornlert, D., Saunders, E. J., ... & Meyer, J. (2015). Multiple novel prostate cancer susceptibility signals

identified by fine-mapping of known risk loci among Europeans. *Human molecular genetics*, *24*(19), 5589-5602.

26) Hooker, S., Hernandez, W., Chen, H., Robbins, C., Torres, J. B., Ahaghotu, C., ... & Kittles, R. A. (2010). Replication of prostate cancer risk loci on 8q24, 11q13, 17q12, 19q33, and Xp11 in African Americans. *The Prostate*, *70*(3), 270-275.

27) Huncharek, M., Haddock, K. S., Reid, R., & Kupelnick, B. (2010). Smoking as a risk factor for prostate cancer: a meta-analysis of 24 prospective cohort studies. *American journal of public health*, *100*(4), 693-701.

28) Trudeau, K., Rousseau, M. C., & Parent, M. É. (2020). Extent of food processing and risk of prostate cancer: The PROtEuS Study in Montreal, Canada. *Nutrients*, *12*(3), 637.

29) Ma, J., Li, H., Giovannucci, E., Mucci, L., Qiu, W., Nguyen, P. L., ... & Stampfer, M. J. (2008). Prediagnostic body-mass index, plasma C-peptide concentration, and prostate cancer-specific mortality in men with prostate cancer: a long-term survival analysis. *The lancet oncology*, *9*(11), 1039-1047.

30) Smith, L. A., O'Flanagan, C. H., Bowers, L. W., Allott, E. H., & Hursting, S. D. (2018). Translating mechanism-based strategies to break the obesity− cancer link: a narrative review. Journal of the Academy of Nutrition and Dietetics, 118(4), 652-667.

31) DeSantis, C. E., Siegel, R. L., Sauer, A. G., Miller, K. D., Fedewa, S. A., Alcaraz, K. I., & Jemal, A. (2016). Cancer statistics for African Americans, 2016: Progress and opportunities in reducing racial disparities. *CA: a cancer journal for clinicians*, *66*(4), 290-308.

32) Burks, D. A., & Littleton, R. H. (1992). The epidemiology of prostate cancer in black men. *Henry Ford Hospital Medical Journal*, *40*(1), 89-92.

33) Herden, J., Heidenreich, A., & Weißbach, L. (2016). TNM-Classification of localized prostate cancer: The clinical T-category does not correspond to the required demands. *Der Urologe*, *55*, 1564-1572.

34) Grignon, D. J., & Sakr, W. A. (1996). Pathologic staging of prostate carcinoma: What are the issues?. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *78*(2), 337-340.

35) Bonekamp, D., Jacobs, M. A., El-Khouli, R., Stoianovici, D., & Macura, K. J. (2011). Advancements in MR imaging of the prostate: from diagnosis to interventions. *Radiographics*, *31*(3), 677-703.

36) Amin, M. B., Greene, F. L., Edge, S. B., Compton, C. C., Gershenwald, J. E., Brookland, R. K., ... & Winchester, D. P. (2017). The eighth edition AJCC cancer staging manual: continuing to build a bridge from a population-based to a more "personalized" approach to cancer staging. *CA: a cancer journal for clinicians*, *67*(2), 93-99.

37) Byrd, D. R., Brookland, R. K., Washington, M. K., Gershenwald, J. E., Compton, C. C., Hess, K. R., ... & Meyer, L. R. (2017). *AJCC cancer staging manual* (Vol. 1024). M. B. Amin, S. B. Edge, & F. L. Greene (Eds.). New York: springer.

38) Mohler, J. L., Antonarakis, E. S., Armstrong, A. J., D'Amico, A. V., Davis, B. J., Dorff, T., ... & Freedman-Cass, D. A. (2019). Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, *17*(5), 479-505.

39) Byrd, D. R., Brookland, R. K., Washington, M. K., Gershenwald, J. E., Compton, C. C., Hess, K. R., ... & Meyer, L. R. (2017). *AJCC cancer staging manual* (Vol. 1024). M. B. Amin, S. B. Edge, & F. L. Greene (Eds.). New York: springer.

40) Shamsudeen, S., & Leslie, S. W. (2022). Prostate Cancer Tissue-Based Biomarkers.

41) American Urological Association. (2017). Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. *Guías clínicas de urología. USA: American Urological Association, American Urological Association*.

42) Pierorazio, P.M.; Walsh, P.C.; Partin, A.W.; Epstein, J.I. Prognostic Gleason grade grouping: Data based on the modified Gleason scoring system. *BJU Int.* **2013**, *111*, 753–760.

43) Partin, A. W., Mangold, L. A., Lamm, D. M., Walsh, P. C., Epstein, J. I., & Pearson, J. D. (2001). Contemporary update of prostate cancer staging nomograms (Partin Tables) for the new millennium. *Urology*, *58*(6), 843-848.

44) Turkbey, B., Brown, A. M., Sankineni, S., Wood, B. J., Pinto, P. A., & Choyke, P. L. (2016). Multiparametric prostate magnetic resonance imaging in the evaluation of prostate cancer. *CA: a cancer journal for clinicians*, *66*(4), 326-336.

45) Powell, I. J., Bock, C. H., Ruterbusch, J. J., & Sakr, W. (2010). Evidence supports a faster growth rate and/or earlier transformation to clinically significant prostate cancer in black than in white American men, and influences racial progression and mortality disparity. *The Journal of urology*, *183*(5), 1792-1797.

46) Woo, S., Suh, C. H., Kim, S. Y., Cho, J. Y., & Kim, S. H. (2017). Shear-wave elastography for detection of prostate cancer: a systematic review and diagnostic meta-analysis. *AJR Am J Roentgenol*, *209*(4), 806-814.

47) Rifkin, M. D., Zerhouni, E. A., Gatsonis, C. A., Quint, L. E., Paushter, D. M., Epstein, J. I., ... & McNeil, B. J. (1990). Comparison of magnetic resonance imaging and ultrasonography in staging early prostate cancer: results of a multi-institutional cooperative trial. *New England Journal of Medicine*, *323*(10), 621-626.

48) Hamilton, S. R., & Aaltonen, L. A. (Eds.). (2000). *Pathology and genetics of tumours of the digestive system* (Vol. 2). Lyon:: IARC press.

49) Komuro, A., Yashiro, M., Iwata, C., Morishita, Y., Johansson, E., Matsumoto, Y., ... & Miyazono, K. (2009). Diffuse-type gastric carcinoma: progression, angiogenesis, and transforming growth factor β signaling. *Journal of the National Cancer Institute*, *101*(8), 592-604.

50) Dienstmann, R., Mason, M. J., Sinicrope, F. A., Phipps, A. I., Tejpar, S., Nesbakken, A., ... & Guinney, J. (2017). Prediction of overall survival in stage II and III colon cancer beyond TNM system: a retrospective, pooled biomarker study. *Annals of Oncology*, *28*(5), 1023-1031.

51) Cheson, B. D., Fisher, R. I., Barrington, S. F., Cavalli, F., Schwartz, L. H., Zucca, E., & Lister, T. A. (2014). Recommendations for initial evaluation, staging, and response assessment of Hodgkin and non-Hodgkin lymphoma: the Lugano classification. *Journal of clinical oncology*, *32*(27), 3059.

52) Cibula, D., Pötter, R., Planchamp, F., Avall-Lundqvist, E., Fischerova, D., Haie-Meder, C., ... & Raspollini, M. R. (2018). The European Society of Gynaecological Oncology/European Society for Radiotherapy and Oncology/European Society of Pathology guidelines for the management of patients with cervical cancer. *Virchows Archiv*, *472*, 919-936.

53) Prat, J., Olawaiye, A. B., Bermudez, A., Chen, L., Copeland, L. J., Gibb, R. K., ... & Mutch, D. G. (2017). Ovary, fallopian tube, and primary peritoneal carcinoma. *AJCC cancer staging manual*, *8*, 681-690.

54) Butler, S. S., Muralidhar, V., Zhao, S. G., Sanford, N. N., Franco, I., Fullerton, Z. H., ... & Mahal, B. A. (2020). Prostate cancer incidence across stage, NCCN risk groups, and age before and after USPSTF Grade D recommendations against prostate-specific antigen screening in 2012. *Cancer*, *126*(4), 717-724.

55) Ludwig, W. W., & Matlaga, B. R. (2018). Urinary stone disease: diagnosis, medical therapy, and surgical management. *Medical Clinics*, *102*(2), 265-277.

56) Robinson, D., Van Allen, E. M., Wu, Y. M., Schultz, N., Lonigro, R. J., Mosquera, J. M., ... & Chinnaiyan, A. M. (2015). Integrative clinical genomics of advanced prostate cancer. *Cell*, *161*(5), 1215-1228.

57) Chen, R. C., Rumble, B., Loblaw, A., Finelli, A., Ehdaie, B., Cooperberg, M. R., ... & Jain, S. (2016). Active surveillance for the management of localized prostate cancer (Cancer Care Ontario Guideline): American Society of Clinical Oncology clinical practice guideline endorsement. *Journal of Clinical Oncology*, *34*(18).

58) Mottet, N., Bellmunt, J., Bolla, M., Briers, E., Cumberbatch, M. G., De Santis, M., ... & Cornford, P. (2017). EAU-ESTRO-SIOG guidelines on prostate cancer. Part 1: screening, diagnosis, and local treatment with curative intent. *European urology*, *71*(4), 618-629.

59) Egevad, L., Delahunt, B., Srigley, J. R., & Samaratunga, H. (2016). International Society of Urological Pathology (ISUP) grading of prostate cancer–An ISUP consensus on contemporary grading. *Apmis*, *124*(6), 433-435.

60) Donat, S. M., Diaz, M., Bishoff, J. T., Coleman, J. A., Dahm, P., Derweesh, I. H., ... & Chang, S. S. (2013). Follow-up for clinically localized renal neoplasms: AUA guideline. *The Journal of urology*, *190*(2), 407-416.

61) Epstein, J. I., Egevad, L., Amin, M. B., Delahunt, B., Srigley, J. R., & Humphrey, P. A. (2016). The 2014 International Society of Urological Pathology (ISUP) consensus conference on Gleason grading of prostatic carcinoma. *The American journal of surgical pathology*, *40*(2), 244-252.

62) Moyer, V. A., & US Preventive Services Task Force*. (2014). Screening for oral cancer: US Preventive Services Task Force recommendation statement. *Annals of internal medicine*, *160*(1), 55-60.

63) US Preventive Services Task Force*. (2008). Screening for prostate cancer: US Preventive Services Task Force recommendation statement. *Annals of internal medicine*, *149*(3), 185-191.

64) Barentsz, J. O., Richenberg, J., Clements, R., Choyke, P., Verma, S., Villeirs, G., ... & Fütterer, J. J. (2012). ESUR prostate MR guidelines 2012. *European radiology*, *22*, 746-757.

65) Fowler Jr, F. J. (2000). McNaughton Collins M, Albertsen PC, Zietman A, Elliott DB, Barry MJ. Comparison of recommendations by urologists and radiation oncologists for treatment of clinically localized prostate cancer. *Jama*, *283*, 3217-22.

66) Mydlo, J. H., & Godec, C. J. (Eds.). (2015). *Prostate cancer: science and clinical practice*. Academic Press.

67) Moyer, V. A., & US Preventive Services Task Force*. (2014). Screening for oral cancer: US Preventive Services Task Force recommendation statement. *Annals of internal medicine*, *160*(1), 55-60.

68) Mydlo, J. H., & Godec, C. J. (Eds.). (2015). *Prostate cancer: science and clinical practice*. Academic Press.

69) Drake, T., Grivas, N., Dabestani, S., Knoll, T., Lamm, T. B., Maclennan, S., ... & Sarica, K. (2017). What are the benefits and harms of ureteroscopy (URS) compared with shock-wave lithotripsy (SWL) in the treatment of upper ureteral stones: A systematic review. *European Urology Supplements*, *3*(16), e746-e747.

70) Schiavetti, A., & Ventriglia, F. (2014). Contrast echocardiography test for intrapleural extravasation by central venous catheter. *Imaging in Medicine*, *6*(1), 21.

71) Sanda, M. G., Cadeddu, J. A., Kirkby, E., Chen, R. C., Crispino, T., Fontanarosa, J., ... & Treadwell, J. R. (2018). Clinically localized prostate cancer: AUA/ASTRO/SUO guideline. Part I: risk stratification, shared decision making, and care options. *The Journal of urology*, *199*(3), 683-690.

72) Mohler, J. L., Antonarakis, E. S., Armstrong, A. J., D'Amico, A. V., Davis, B. J., Dorff, T., ... & Freedman-Cass, D. A. (2019). Prostate cancer, version 2.2019, NCCN clinical

practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, *17*(5), 479-505.

73) Network, N. C. C. (2018). NCCN clinical practice guidelines in oncology. *Older adult oncology. Version 1*, 2018.

74) Novara, G., Ficarra, V., Rosen, R. C., Artibani, W., Costello, A., Eastham, J. A., ... & Wilson, T. G. (2012). Systematic review and meta-analysis of perioperative outcomes and complications after robot-assisted radical prostatectomy. *European urology*, *62*(3), 431-452.

75) Cooperberg, M. R., Carroll, P. R., & Klotz, L. (2011). Active surveillance for prostate cancer: progress and promise. *Journal of clinical oncology: official journal of the American Society of Clinical Oncology*, *29*(27), 3669-3676.

76) McDougal, W. S., Wein, A. J., Kavoussi, L. R., Partin, A. W., & Peters, C. A. (2015). *Campbell-Walsh urology 11th Edition review e-book*. Elsevier Health Sciences.

77) Su, H. J., Castro, C. E., Marras, A. E., & Hudoba, M. (2012). Design and fabrication of DNA origami mechanisms and machines. In *Advances in Reconfigurable Mechanisms and Robots I* (pp. 487-500). Springer London.

78) Partin, A. W., Wein, A. J., Kavoussi, L. R., Peters, C. A., & Dmochowski, R. R. (2020). *Campbell Walsh Wein Urology, E-Book*. Elsevier Health Sciences.

79) McAninch, J. W., & Lue, T. F. (2020). *Smith and Tanagho's general urology*. McGraw Hill Professional.

80) Hristov, B., Christodouleas, J. P., & Lin, S. H. (Eds.). (2010). *Radiation oncology: a question-based review*. Lippincott Williams & Wilkins.

81) Sweeney, C. J., Chen, Y. H., Carducci, M., Liu, G., Jarrard, D. F., Eisenberger, M., ... & DiPaola, R. S. (2015). Chemohormonal therapy in metastatic hormone-sensitive prostate cancer. *New England Journal of Medicine*, *373*(8), 737-746.

82) Mohler, J. L., Antonarakis, E. S., Armstrong, A. J., D'Amico, A. V., Davis, B. J., Dorff, T., ... & Freedman-Cass, D. A. (2019). Prostate cancer, version 2.2019, NCCN clinical practice guidelines in oncology. *Journal of the National Comprehensive Cancer Network*, *17*(5), 479-505.

83) Chabner, B. A., & Longo, D. L. (2011). *Cancer chemotherapy and biotherapy: principles and practice*. Lippincott Williams & Wilkins.

84) Cattrini, C., Castro, E., Lozano, R., Zanardi, E., Rubagotti, A., Boccardo, F., & Olmos, D. (2019). Current treatment options for metastatic hormone-sensitive prostate cancer. *Cancers*, *11*(9), 1355.

85) Skolarus, T. A., Wolf, A. M., Erb, N. L., Brooks, D. D., Rivers, B. M., Underwood III, W., ... & Cowens-Alvarado, R. L. (2014). American Cancer Society prostate cancer survivorship care guidelines. *CA: a cancer journal for clinicians*, *64*(4), 225-249.

86) Cooperberg, M. R., & Carroll, P. R. (2015). Trends in management for patients with localized prostate cancer, 1990-2013. *Jama*, *314*(1), 80-82.

87) Gillessen, S., Attard, G., Beer, T. M., Beltran, H., Bossi, A., Bristow, R., ... & Omlin, A. (2018). Management of patients with advanced prostate cancer: the report of the Advanced Prostate Cancer Consensus Conference APCCC 2017. *European urology*, *73*(2), 178-211.

88) Kinsella, N., Helleman, J., Bruinsma, S., Carlsson, S., Cahill, D., Brown, C., & Van Hemelrijck, M. (2018). Active surveillance for prostate cancer: a systematic review of contemporary worldwide practices. *Translational andrology and urology*, *7*(1), 83.

89) Mehta, A. K., & Smith, T. J. (2020). Palliative care for patients with cancer in the COVID-19 era. *JAMA oncology*, *6*(10), 1527-1528.

90) Zelefsky, M. J., Eastham, J. A., Cronin, A. M., Fuks, Z., Zhang, Z., Yamada, Y., ... & Scardino, P. T. (2010). Metastasis after radical prostatectomy or external beam radiotherapy for patients with clinically localized prostate cancer: a comparison of clinical cohorts adjusted for case mix. *Journal of clinical oncology*, *28*(9), 1508.

91) Friedberg, E. C. (2001). How nucleotide excision repair protects against cancer. *Nature Reviews Cancer*, *1*(1), 22-33.

92) Jan, H. (2001). HJ Genome maintenance mechanisms for preventing cancer. *Nature*, *411*(6835), 366-374.

93) Sugasawa, K., Ng, J. M., Masutani, C., Iwai, S., van der Spek, P. J., Eker, A. P., ... & Hoeijmakers, J. H. (1998). Xeroderma pigmentosum group C protein complex is the initiator of global genome nucleotide excision repair. *Molecular cell*, *2*(2), 223-232.

94) Marteijn, J. A., Lans, H., Vermeulen, W., & Hoeijmakers, J. H. (2014). Understanding nucleotide excision repair and its roles in cancer and aging. *Nature reviews Molecular cell biology*, *15*(7), 465-481.

95) Marteijn, J. A., Lans, H., Vermeulen, W., & Hoeijmakers, J. H. (2014). Understanding nucleotide excision repair and its roles in cancer and aging. *Nature reviews Molecular cell biology*, *15*(7), 465-481.

96) Fousteri, M., & Mullenders, L. H. (2008). Transcription-coupled nucleotide excision repair in mammalian cells: molecular mechanisms and biological effects. *Cell research*, *18*(1), 73-84.

97) Vesely, P. (2004). Molecular biology of the cell. By Bruce Alberts, Alexander Johnson, Julian Lewis, Martin Raff, Keith Roberts and Peter Walter. ISBN 0-8153-3218-1; hardback; 1,616 pages; $110.00 Garland Science Inc., New York, 2002.

98) Sugasawa, K. (2009). XPC: its product and biological roles. *Molecular Mechanisms of Xeroderma Pigmentosum*, 47-56.

99) Polo, S. E., & Almouzni, G. (2015). Chromatin dynamics after DNA damage: the legacy of the access–repair–restore model. *DNA repair*, *36*, 114-121.

100) Itin, P. H., Sarasin, A., & Pittelkow, M. R. (2001). Trichothiodystrophy: update on the sulfur-deficient brittle hair syndromes. *Journal of the American Academy of Dermatology*, *44*(6), 891-924.

101) Sugasawa, K. (2016). Molecular mechanisms of DNA damage recognition for mammalian nucleotide excision repair. *DNA repair*, *44*, 110-117.

102) Tan, T., & Chu, G. (2002). p53 Binds and activates the xeroderma pigmentosum DDB2 gene in humans but not mice. *Molecular and cellular biology*, *22*(10), 3247-3254.

103) Scrima, A., Koníčková, R., Czyzewski, B. K., Kawasaki, Y., Jeffrey, P. D., Groisman, R., ... & Thomä, N. H. (2008). Structural basis of UV DNA-damage recognition by the DDB1–DDB2 complex. *Cell*, *135*(7), 1213-1223.

104) Scrima, A., Fischer, E. S., Lingaraju, G. M., Böhm, K., Cavadini, S., & Thomä, N. H. (2011). Detecting UV-lesions in the genome: The modular CRL4 ubiquitin ligase does it best!. *FEBS letters*, *585*(18), 2818-2825.

105) Luijsterburg, M. S., Lindh, M., Acs, K., Vrouwe, M. G., Pines, A., van Attikum, H., ... & Dantuma, N. P. (2012). DDB2 promotes chromatin decondensation at UV-induced DNA damage. *Journal of Cell Biology*, *197*(2), 267-281.

106) Tang, J., & Chu, G. (2002). Xeroderma pigmentosum complementation group E and UV-damaged DNA-binding protein. *DNA repair*, *1*(8), 601-616.

107) Sharma, P., & Nag, A. (2014). CUL4A ubiquitin ligase: a promising drug target for cancer and other human diseases. *Open biology*, *4*(2), 130217.

108) Fell, V. L., & Schild-Poulter, C. (2015). The Ku heterodimer: function in DNA repair and beyond. *Mutation Research/Reviews in Mutation Research*, *763*, 15-29.

109) Sugasawa, K. (2009). XPC: its product and biological roles. *Molecular Mechanisms of Xeroderma Pigmentosum*, 47-56.

110) Lord, C. J., & Ashworth, A. (2012). The DNA damage response and cancer therapy. *Nature*, *481*(7381), 287-294.

111) Shiloh, Y. (2003). ATM and related protein kinases: safeguarding genome integrity. *Nature reviews cancer*, *3*(3), 155-168.

112) Cancer Genome Atlas Research Network. (2011). Integrated genomic analyses of ovarian carcinoma. *Nature*, *474*(7353), 609.

113) Lavin, M. F. (2008). Ataxia-telangiectasia: from a rare disorder to a paradigm for cell signaling and cancer. *Nature reviews Molecular cell biology*, *9*(10), 759-769.

114) Luijsterburg, M. S., Lindh, M., Acs, K., Vrouwe, M. G., Pines, A., van Attikum, H., ... & Dantuma, N. P. (2012). DDB2 promotes chromatin decondensation at UV-induced DNA damage. *Journal of Cell Biology*, *197*(2), 267-281.

115) Friedberg, E. C., Walker, G. C., Siede, W., & Wood, R. D. (Eds.). (2005). *DNA repair and mutagenesis*. American Society for Microbiology Press.

116) Bagchi, S., & Raychaudhuri, P. (2010). Damaged-DNA binding protein-2 drives apoptosis following DNA damage. *Cell division*, *5*, 1-5.

117) Chen, H. H., Fan, P., Chang, S. W., Tsao, Y. P., Huang, H. P., & Chen, S. L. (2017). NRIP/DCAF6 stabilizes the androgen receptor protein by displacing DDB2 from the CUL4A-DDB1 E3 ligase complex in prostate cancer. *Oncotarget*, *8*(13), 21501.

118) Yang, H., Liu, J., Jing, J., Wang, Z., Li, Y., Gou, K., ... & Xing, C. (2018). Expression of DDB2 protein in the initiation, progression, and prognosis of colorectal cancer. *Digestive Diseases and Sciences*, *63*, 2959-2968.

119) Liu, J., Li, H., Sun, L., Feng, X., Wang, Z., Yuan, Y., & Xing, C. (2018). The differential expression of core genes in nucleotide excision repair pathway indicates colorectal carcinogenesis and prognosis. *BioMed research international*, *2018*.

120) Stoyanova, T., Roy, N., Bhattacharjee, S., Kopanja, D., Valli, T., Bagchi, S., & Raychaudhuri, P. (2012). p21 cooperates with DDB2 protein in suppression of ultraviolet ray-induced skin malignancies. *Journal of Biological Chemistry*, *287*(5), 3019-3028.

121) Bommi, P. V., Ravindran, S., Raychaudhuri, P., & Bagchi, S. (2018). DDB2 regulates epithelial-to-mesenchymal transition (EMT) in oral/head and neck squamous cell carcinoma. *Oncotarget*, *9*(78), 34708.

122) Han, C., Zhao, R., Liu, X., Srivastava, A., Gong, L., Mao, H., ... & Wang, Q. E. (2014). DDB2 Suppresses Tumorigenicity by Limiting the Cancer Stem Cell Population in Ovarian CancerDDB2 Limits Ovarian Cancer Stem Cell Population. *Molecular Cancer Research*, *12*(5), 784-794.

123) Stoyanova, T., Yoon, T., Kopanja, D., Mokyr, M. B., & Raychaudhuri, P. (2008). The xeroderma pigmentosum group E gene product DDB2 activates nucleotide excision repair by regulating the level of p21Waf1/Cip1. *Molecular and Cellular Biology*, *28*(1), 177-187.

124) De Laat, W. L., Jaspers, N. G., Hoeijmakers, J. H., Weeda, G., & Vermeulen, W. (1999). Mutations in the xeroderma pigmentosum group D DNA damage recognition gene in individuals with sun sensitivity due to trichothiodystrophy. Human Molecular Genetics, 8(5), 989-996.

125) Lim, K. H., Song, M. H., & Baek, K. H. (2016). Decision for cell fate: deubiquitinating enzymes in cell cycle checkpoint. *Cellular and Molecular Life Sciences*, *73*, 1439-1455.

126) Lehman, A. R., Kirk-Bell, S., Arlett, C. F., Paterson, M. C., Lohman, P. H., de Weerd-Kastelein, E. A., & Bootsma, D. (1975). Xeroderma pigmentosum cells with normal levels of excision repair have a defect in DNA synthesis after UV-irradiation. *Proceedings of the National Academy of Sciences*, *72*(1), 219-223.

127) Stoyanova, T., Roy, N., Kopanja, D., Bagchi, S., & Raychaudhuri, P. (2009). DDB2 decides cell fate following DNA damage. *Proceedings of the National Academy of Sciences*, *106*(26), 10690-10695.

128) Wang, H., Zhai, L., Xu, J., Joo, H. Y., Jackson, S., Erdjument-Bromage, H., ... & Zhang, Y. (2006). Histone H3 and H4 ubiquitylation by the CUL4-DDB-ROC1

ubiquitin ligase facilitates cellular response to DNA damage. *Molecular cell*, *22*(3), 383-394.

129) Gunes, S., Arslan, A., Kaya, M., et al. (2017). Association of DNA repair gene polymorphisms with prostate cancer risk in Turkish population. Oncology Letters, 14(6), 7833-7842.

130) Li, X., Zheng, L., Liu, J., Zhang, L., Jia, L., Liu, Z., Zhang, J., Li, C., Shan, H., & Zhang, J. (2017). DDB2 enhances the sensitivity of bladder cancer cells to chemotherapy by up-regulating miR-149-3p. American Journal of Translational Research, 9(10), 4638-4646.

131) Gunes S, Arslan A, Kaya M, et al. Association of DNA repair gene polymorphisms with prostate cancer risk in Turkish population. Oncol Lett. 2017;14(6):7833-7842.

132) Li, X., Li, C., Li, J., et al. (2018). DDB2 regulates cell cycle and apoptosis in colorectal cancer via miR-486-5p/MACC1 axis. Journal of Cell Biochemistry, 119(7), 5489-5499.

133) Zhang, J., Zhou, Y., Zhang, H., et al. (2013). Association of the DDB2 rs830083 polymorphism with cancer susceptibility: a meta-analysis. Molecular Biology Reports, 40(10), 5977-5986.

134) Gao, M., Wei, W., & Li, M. M. (2021). Role of DDB2 in the sensitivity of cancer cells to chemotherapy and ionizing radiation and its potential as a therapeutic target. Oncology Letters, 21(4), 296.

135) Bray, F., Ferlay, J., Soerjomataram, I., Siegel, R. L., Torre, L. A., & Jemal, A. (2018). Global cancer statistics 2018: GLOBOCAN estimates of incidence and mortality worldwide for 36 cancers in 185 countries. CA: A Cancer Journal for Clinicians, 68(6), 394-424.

136) Chan, J. M., Gann, P. H., & Giovannucci, E. L. (2005). Role of diet in prostate cancer development and progression. *Journal of Clinical Oncology*, *23*(32), 8152-8160.

137) Platz, E. A., Leitzmann, M. F., Michaud, D. S., Willett, W. C., & Giovannucci, E. (2003). Interrelation of energy intake, body size, and physical activity with prostate cancer in a large prospective cohort study. *Cancer research*, *63*(23), 8542-8548.

138) Autier, P., Boniol, M., Pizot, C., & Mullie, P. (2014). Vitamin D status and ill health: a systematic review. *The lancet Diabetes & endocrinology*, *2*(1), 76-89.

139) Bostwick, D. G., Burke, H. B., Djakiew, D., Euling, S., Ho, S. M., Landolph, J., ... & Timms, B. (2004). Human prostate cancer risk factors. *Cancer: Interdisciplinary International Journal of the American Cancer Society*, *101*(S10), 2371-2490.

140) Scrima, A., Koníčková, R., Czyzewski, B. K., Kawasaki, Y., Jeffrey, P. D., Groisman, R., ... & Thomä, N. H. (2008). Structural basis of UV DNA-damage recognition by the DDB1–DDB2 complex. *Cell*, *135*(7), 1213-1223.

141) Dr. Reeja Tharu. (2022, February 21). *Prostate Cancer | Cancer of Prostate - Incidence, Prevention, Causes, Symptoms & Treatment*. Medindia. Retrieved on May 25, 2023 from https://www.medindia.net/patientinfo/prostate-cancer.htm.

142) Wang, L., Lu, B., He, M., Wang, Y., Wang, Z., & Du, L. (2022). Prostate cancer incidence and mortality: global status and temporal trends in 89 countries from 2000 to 2019. *Frontiers in Public Health*, *10*, 811044.

143) Hanaoka, F. (2013). Xeroderma Pigmentosum. In R. C. Myers (Ed.), Brenner's Encyclopedia of Genetics (2nd ed., pp. 359-362).

144) Image Source: WebMD. (2009). Prostate Picture. Retrieved from https://www.emedicinehealth.com/image-gallery/prostate_picture/images.htmText Reference: National Cancer Institute. (n.d.). Anatomy of the Prostate

145) Hu, Z., Shao, M., Yuan, J., Xu, L., Wang, F., Wang, Y., ... & Shen, H. (2006). Polymorphisms in DNA damage binding protein 2 (DDB2) and susceptibility of primary lung cancer in the Chinese: a case–control study. *Carcinogenesis*, *27*(7), 1475-1480

7. APPENDICES

7.1. Raw Data

Case Processing Summary

	Cases					
	Valid		Missing		Total	
	N	Percent	N	Percent	N	Percent
tanım * DDB2_rs830083	184	100,0%	0	0,0%	184	100,0%
tanım * DDB2_GG	184	100,0%	0	0,0%	184	100,0%
tanım * DDB2_GC	184	100,0%	0	0,0%	184	100,0%
tanım * DDB2_CC	184	100,0%	0	0,0%	184	100,0%
tanım * G_ALLEL	184	100,0%	0	0,0%	184	100,0%
tanım * C_ALLEL	184	100,0%	0	0,0%	184	100,0%

tanım * DDB2_rs830083

Crosstab

			DDB2_rs830083			
			GC	GG	CC	Total
tanım	hasta	Count	25	4	64	93
		% within tanım	26,9%	4,3%	68,8%	100,0%
		% within DDB2_rs830083	40,3%	44,4%	56,6%	50,5%
		% of Total	13,6%	2,2%	34,8%	50,5%
	kontrol	Count	37	5	49	91
		% within tanım	40,7%	5,5%	53,8%	100,0%
		% within DDB2_rs830083	59,7%	55,6%	43,4%	49,5%
		% of Total	20,1%	2,7%	26,6%	49,5%
Total		Count	62	9	113	184
		% within tanım	33,7%	4,9%	61,4%	100,0%
		% within DDB2_rs830083	100,0%	100,0%	100,0%	100,0%
		% of Total	33,7%	4,9%	61,4%	100,0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	4,404[a]	2	,111
Likelihood Ratio	4,424	2	,109
N of Valid Cases	184		

a. 2 cells (33,3%) have expected count less than 5. The minimum expected count is 4,45.

tanım * DDB2_GG

Crosstab

			DDB2_GG		
			YOK	VAR	Total
tanım	hasta	Count	89	4	93
		% within tanım	95,7%	4,3%	100,0%
		% within DDB2_GG	50,9%	44,4%	50,5%
		% of Total	48,4%	2,2%	50,5%
	kontrol	Count	86	5	91
		% within tanım	94,5%	5,5%	100,0%
		% within DDB2_GG	49,1%	55,6%	49,5%
		% of Total	46,7%	2,7%	49,5%
Total		Count	175	9	184
		% within tanım	95,1%	4,9%	100,0%
		% within DDB2_GG	100,0%	100,0%	100,0%
		% of Total	95,1%	4,9%	100,0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	,141[a]	1	,707		
Continuity Correction[b]	,001	1	,973		
Likelihood Ratio	,141	1	,707		
Fisher's Exact Test				,746	,486
N of Valid Cases	184				

a. 2 cells (50,0%) have expected count less than 5. The minimum expected count is 4,45.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for tanım (hasta / kontrol)	1,294	,336	4,979
For cohort DDB2_GG = YOK	1,013	,948	1,081
For cohort DDB2_GG = VAR	,783	,217	2,823
N of Valid Cases	184		

tanım * DDB2_GC

Crosstab

			DDB2_GC		
			YOK	VAR	Total
tanım	hasta	Count	68	25	93
		% within tanım	73,1%	26,9%	100,0%
		% within DDB2_GC	55,7%	40,3%	50,5%
		% of Total	37,0%	13,6%	50,5%
	kontrol	Count	54	37	91
		% within tanım	59,3%	40,7%	100,0%
		% within DDB2_GC	44,3%	59,7%	49,5%
		% of Total	29,3%	20,1%	49,5%
Total		Count	122	62	184
		% within tanım	66,3%	33,7%	100,0%
		% within DDB2_GC	100,0%	100,0%	100,0%
		% of Total	66,3%	33,7%	100,0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3,908[a]	1	,048		
Continuity Correction[b]	3,316	1	,069		
Likelihood Ratio	3,926	1	,048		
Fisher's Exact Test				,061	,034
N of Valid Cases	184				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 30,66.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval Lower	Upper
Odds Ratio for tanım (hasta / kontrol)	1,864	1,002	3,466
For cohort DDB2_GC = YOK	1,232	,999	1,520
For cohort DDB2_GC = VAR	,661	,436	1,003
N of Valid Cases	184		

tanım * DDB2_CC

Crosstab

			DDB2_CC YOK	VAR	Total
tanım	hasta	Count	29	64	93
		% within tanım	31,2%	68,8%	100,0%
		% within DDB2_CC	40,8%	56,6%	50,5%
		% of Total	15,8%	34,8%	50,5%
	kontrol	Count	42	49	91
		% within tanım	46,2%	53,8%	100,0%
		% within DDB2_CC	59,2%	43,4%	49,5%
		% of Total	22,8%	26,6%	49,5%
Total		Count	71	113	184
		% within tanım	38,6%	61,4%	100,0%
		% within DDB2_CC	100,0%	100,0%	100,0%
		% of Total	38,6%	61,4%	100,0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4,350[a]	1	,037		
Continuity Correction[b]	3,741	1	,053		
Likelihood Ratio	4,369	1	,037		
Fisher's Exact Test				,049	,026
N of Valid Cases	184				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 35,11.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval Lower	Upper
Odds Ratio for tanım (hasta / kontrol)	,529	,290	,965
For cohort DDB2_CC = YOK	,676	,464	,983
For cohort DDB2_CC = VAR	1,278	1,011	1,615
N of Valid Cases	184		

tanım * G_ALLEL

Crosstab

			G_ALLEL		
			YOK	VAR	Total
tanım	hasta	Count	64	29	93
		% within tanım	68,8%	31,2%	100,0%
		% within G_ALLEL	56,6%	40,8%	50,5%
		% of Total	34,8%	15,8%	50,5%
	kontrol	Count	49	42	91
		% within tanım	53,8%	46,2%	100,0%
		% within G_ALLEL	43,4%	59,2%	49,5%
		% of Total	26,6%	22,8%	49,5%
Total		Count	113	71	184
		% within tanım	61,4%	38,6%	100,0%
		% within G_ALLEL	100,0%	100,0%	100,0%
		% of Total	61,4%	38,6%	100,0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4,350[a]	1	,037		
Continuity Correction[b]	3,741	1	,053		
Likelihood Ratio	4,369	1	,037		
Fisher's Exact Test				,049	,026
N of Valid Cases	184				

a. 0 cells (0,0%) have expected count less than 5. The minimum expected count is 35,11.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval Lower	Upper
Odds Ratio for tanım (hasta / kontrol)	1,892	1,036	3,454
For cohort G_ALLEL = YOK	1,278	1,011	1,615
For cohort G_ALLEL = VAR	,676	,464	,983
N of Valid Cases	184		

tanım * C_ALLEL

Crosstab

			C_ALLEL YOK	VAR	Total
tanım	hasta	Count	4	89	93
		% within tanım	4,3%	95,7%	100,0%
		% within C_ALLEL	44,4%	50,9%	50,5%
		% of Total	2,2%	48,4%	50,5%
	kontrol	Count	5	86	91
		% within tanım	5,5%	94,5%	100,0%
		% within C_ALLEL	55,6%	49,1%	49,5%
		% of Total	2,7%	46,7%	49,5%
Total		Count	9	175	184
		% within tanım	4,9%	95,1%	100,0%
		% within C_ALLEL	100,0%	100,0%	100,0%
		% of Total	4,9%	95,1%	100,0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	,141[a]	1	,707		
Continuity Correction[b]	,001	1	,973		
Likelihood Ratio	,141	1	,707		
Fisher's Exact Test				,746	,486
N of Valid Cases	184				

a. 2 cells (50,0%) have expected count less than 5. The minimum expected count is 4,45.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval Lower	95% Confidence Interval Upper
Odds Ratio for tanım (hasta / kontrol)	,773	,201	2,975
For cohort C_ALLEL = YOK	,783	,217	2,823
For cohort C_ALLEL = VAR	1,013	,948	1,081
N of Valid Cases	184		

Means

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
kiloo * tanım	106	57,3%	79	42,7%	185	100,0%

Report

kiloo

tanım	Mean	N	Std. Deviation	% of Total Sum	% of Total N
hasta	78,1343	67	11,52322	62,9%	63,2%
control	79,3077	39	9,87062	37,1%	36,8%
Total	78,5660	106	10,91091	100,0%	100,0%

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
bmii * tanım	106	57,3%	79	42,7%	185	100,0%

Report

bmii

tanım	Mean	N	Std. Deviation	% of Total Sum	% of Total N
hasta	27,1194	67	3,71125	63,5%	63,2%
control	26,7567	39	2,95790	36,5%	36,8%
Total	26,9859	106	3,44308	100,0%	100,0%

Case Processing Summary

	Cases					
	Included		Excluded		Total	
	N	Percent	N	Percent	N	Percent
tanıyaş * tanım	133	71,9%	52	28,1%	185	100,0%

Report

tanıyaş

tanım	Mean	N	Std. Deviation	% of Total Sum	% of Total N
hasta	66,1170	94	7,54322	72,5%	70,7%
control	60,3333	39	13,80757	27,5%	29,3%
Total	64,4211	133	10,09741	100,0%	100,0%

Hasta * patolojikevre

Crosstab

			patolojikevre					
			pT2a	pT2b	pT2c	pT3a	pT3b	Total
hasta	hasta	Count	8	10	29	10	10	67
		% within hasta	11,9%	14,9%	43,3%	14,9%	14,9%	100,0%
		% within patolojikevre	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%
		% of Total	11,9%	14,9%	43,3%	14,9%	14,9%	100,0%
Total		Count	8	10	29	10	10	67
		% within hasta	11,9%	14,9%	43,3%	14,9%	14,9%	100,0%
		% within patolojikevre	100,0%	100,0%	100,0%	100,0%	100,0%	100,0%
		% of Total	11,9%	14,9%	43,3%	14,9%	14,9%	100,0%

7.2. Ethical Committee Approval

T.C.
YEDİTEPE ÜNİVERSİTESİ REKTÖRLÜĞÜ
Girişimsel Olmayan Klinik Araştırmalar Etik Kurulu

Sayı : E.83321821-805.02.03-204
Konu : Non Interventional Clinical Research Ethics Board Decision

Sayın Doç. Dr. Gülsüm Seda Güleç Yılmaz

Yeditepe University Non-Interventional Clinical Research Ethics Board has reviewed the research proposal placed upon ethical approval for the project as the research title, the researchers, the application number, the ethics board meeting details, and the provided documents have been outlined below. This research proposal has been evaluated by the members of the ethics board and full ethical **APPROVAL** has been granted.

Research Title:	INVESTIGATION OF DNA DAMAGE BINDING PROTEIN2 (DDB2) AND XPC (XERODERMA PİGMENTOSUM COMPLEMENTATION GROUP C PROTEIN)GENE IN PROSTATE CANCER PATIENT IN TURKISH POPULATION
Researchers:	Omotade Dorcas PELUMİ,Assoc. Prof. Dr. G. Seda GÜLEÇ YILMAZ
Application Number:	202305Y0406

ETHICS BOARD MEETING DETAILS			
Meeting Date:	12 May 2023	**Meeting Place:**	Online (Google Meet)

PROVIDED DOCUMENTS
Wet signed application file, file uploaded to a CD or USB media, and electronic submission
Title of research and the names of the researchers
Letter of application
Application Form
Nature of the Research;
• Type
• Significance and distinctive value
• Aims and objectives
• Method
• Management of the research
• Widespread impact
• Pertinence of the budget and reason (if applicable)
• Timeframe and convenience

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• References
Informed consent form (uniquely prepared for the research)
Letter of Undertaking-1 A commitment to undertake the responsibility of obtaining institutions permission from where the data collection will be made
Letter of Undertaking-2 A commitment to read the latest version of the World Medical Association Declaration of Helsinki and all relevant guidelines of the Ministry of Health
Letter of Undertaking-3 A commitment on whether there are previous ethical board applications
Letter of Undertaking-4 A commitment that no action will be taken during the research that is not included in the research budget and that will bring additional burden to the volunteer or the Social Security Institution
Letter of Undertaking-5 A commitment to reading the circular on treatment approaches and scientific research in COVID-19 patients
Letter of Undertaking-6 A commitment to reading the document of Research Application Permissions that is published by Ministry of Education
'Resume Forms' filled separately by all the researchers and signed
Additional documents (Scale permissions used, if any, etc.)

Prof. Dr. Didem ÖZDEMİR ÖZENEN
Chair

Assoc. Prof. Dr. Gökhan ERTAŞ
Deputy Chair

Assoc. Prof. Dr. Elif SUNGURTEKİN EKÇİ
Reporter

Prof. Dr. Feryal SUBAŞI
Member

Assoc. Prof. Dr. Binnur OKAN BAKIR
Member

Assist. Prof. Dr. Emine Nur ÖZDAMAR
Member

Assist. Prof. Dr. Sevim ŞEN OLGAY
Member

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7.3. Case Report Form

YEDİTEPE ÜNİVERSİTESİ GİRİŞİMSEL OLMAYAN KLİNİK ARAŞTIRMALAR ETİK KURULU

BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU

Araştırma Başlığı:

Türk Toplumunda Prostat Kanseri Hastasında DNA Hasarı Bağlayıcı Protein 2 (DDB2) Gen Polimorfizminin İncelenmesi

Örnek Sayısı: Önceden alınmış 125 erişkin hasta DNA örneği, 125 erişkin sağlıklı kişi DNA örneği

Bu araştırmanın Amacı: Genomik DNA, hem endojen hem de harici kaynaklardan gelen çok çeşitli maddeler tarafından sürekli olarak zarar görmektedir. Nükleotid eksizyon onarımı (NER) adı verilen önemli bir DNA onarım sistemi, çoğunlukla ultraviyole ışık (UV) ışıması ve büyük kimyasal bileşikler gibi çevresel mutajenlerin neden olduğu çeşitli sarmalı bozan DNA lezyonlarını ortadan kaldırabilir. Prostat Kanseri (PCa): Erkek üreme organı olan prostatın dokularında kötü huylu (kanser) hücrelerin gelişmesi durumudur. Erkekler için ikinci en tipik kanser teşhisi ve dünya çapında altıncı en yaygın öldürücüdür. DDB2 polimorfizmleri, DNA onarım kapasitesini değiştirerek genetik kararsızlığa ve karsinojeneze yol açabilir.

Araştırmanın Süresi: 1 Yıl veya daha az

İzlenecek Yöntem/Yöntemler: Bu çalışmada daha önce etik kurul onayı alınmış (Yeditepe Ünivesitesi Klinik Araştırmalar Etik Kurulu karar no: 1660, tarih 05.10.2022, başlık "Vitamin d Reseptör Polimorfizmi ve Prostat Kanseri Arasındaki ilişkinin araştırılması") ve kan örneklerinden DNA izolasyonları yapılmış laboratuvarımızda bulunan örneklerle PCR yapılması planlanmaktadır. Real Time PCR ile gen polimorfizm analizi yapılacaktır.

Çalışmanın istatistiksel analizi için IBM SPSS Statistics version 24 (IBM Corp., Armonk, NY, USA) paket programı kullanılacaktır. İstatistiksel anlamlılık $p<0.05$ olarak kabul edilir. Chi-Kare analizi verilerini değerlendirmede kullanılacaktır. Prostat kanserine sahip bireylerden ve kontrol gruplarından toplanan kantitatif parametreler student t-testi kullanılarak analiz edilecektir

Araştırma Sonunda Beklenen Fayda : Bu çalışmanın amacı, Türk populasyonunda prostat kanseri ile DDB2 geninin rs830083 polimorfizminin araştırılmasıdır. DDB2 gen polimorfizmi meme, deri, akciğer ve mide kanserlerinde olduğu gibi prostat kanserinde de etkili olabilir.

ONAM (RIZA)

Bilgilendirilmiş Gönüllü Olur Formundaki tüm açıklamaları okudum. Bana, yukarıda konusu ve amacı belirtilen araştırma ile ilgili yazılı ve sözlü açıklama aşağıda adı belirtilen araştırmacı tarafından yapıldı. Araştırmaya gönüllü olarak katıldığımı, istediğim zaman gerekçeli veya gerekçesiz olarak araştırmadan ayrılabileceğimi ve kendi isteğime bakılmaksızın araştırmacı tarafından araştırma dışı bırakılabileceğimi biliyorum. Bu araştırmaya katılırken zorlama, maddi çıkar ve ast üst ilişkisine dayalı herhangi bir baskı olmaksızın bu çalışmaya katıldığımı beyan ederim. Bu bilimsel çalışmanın devamı esnasındaki süreçle ilgili olarak ayrıca eklenen çalışma protokolü ile bilgilendirildim. Bu bilgiler bana aşağıda iletişim bilgileri verilen **Araştırma Yürütücüsü Dorcas Pelumi Omotade** tarafından yapılmıştır.

Söz konusu araştırmaya, hiçbir baskı ve zorlama olmaksızın kendi rızamla katılmayı kabul ediyorum.

Gönüllünün:
Adı Soyadı:
İmzası:
Tarih:

Tanık Olan Kişinin:
Adı Soyadı:
İmzası:
Tarih:

ARAŞTIRMA YÜRÜTÜCÜSÜ:
Adı Soyadı: Dorcas Pelumi Omotade,
İmzası:
Tarih:
Adres: Yeditepe Üniversitesi Moleküler Tıp Anabilim Dalı, 26 Ağustos Yerleşkesi Kayışdağı
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SORUMLU ARAŞTIRMACI :
Adı Soyadı: Doç Dr. Seda Güleç Yılmaz,
İmzası:
Tarih:
Adres: Yeditepe Üniversitesi Moleküler Tıp Anabilim Dalı, 26 Ağustos Yerleşkesi Kayışdağı
E-posta: Seda.gulec@yeditepe.edu.tr
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7.4. Curriculum Vitae

Personal Information

Name	Dorcas Pelumi	Surname	Omotade

Education

Degree	**Department**	**The name of institution graduated from**	**Graduation year**
Doctorate			
Master			
University	Microbiology	Crawford University	2018
High school	Science	Command Day Secondary School Oshodi	2014

Languages	**Grades**
English (TOEFL)	79
Turkish	B1

[#] All the grades must be listed if there is more than one (KPDS, ÜDS, TOEFL; IELTS vs),

Computer Skills

Program Level	
MS Programs	Basic
SPSS	Average

***Excellent, good, average or basic**
Scientific works