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YEDITEPE UNIVERSITY

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DEPARTMENT OF MOLECULAR MEDICINE

Investigation of Global Genome Repair Genes Polymorphism in Patients with Ovarian Cancer in the Turkish Population

MASTER THESIS

SARA YASER BARHAM

ISTANBUL 2023

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THESIS APPROVAL FORM

Institute: Yeditepe University Institute of Health Sciences

Program: Molecular Medicine

Title of the Thesis: Investigation of Global Genome Repair Gene Polymorphism in Patients with Ovarian Cancer in the Turkish Population.

Owner of the Thesis: Sara Yaser Barham

Examination Date: 8.6.2023

This study has been approved as a Master Thesis regarding content and quality by the Jury.

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APPROVAL

This thesis has been deemed by the jury by the relevant articles of Yeditepe University Graduate Education and Examinations Regulation and has been approved by the Administrative Board of the Institute with a decision dated 8.6.2023

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DECLARATION

I declare that this thesis is entirely my own work and has not been submitted for a degree at any other institution. Any sources of information used in this study have been duly acknowledged. The views and opinions expressed in this thesis are solely those of the author and do not represent those of the institution or any other individuals or organizations. Furthermore, I affirm that the research presented in this thesis has been conducted in accordance with the ethical principles and guidelines outlined by the institution and the relevant regulatory bodies.

Sara Yaser Barham

DEDICATION

I would like to dedicate this thesis to my parents, who have been a constant source of support and encouragement throughout my academic journey. Without their unwavering belief in me and their guidance, this achievement would not have been possible.

I am also grateful to my family and friends, who have provided me with their love and understanding, even when I had to sacrifice time with them to complete this thesis. Their understanding and patience have been invaluable to me.

Finally, I would like to dedicate this thesis to all the individuals who have inspired me with their knowledge and insights, and who have paved the way for future generations of scholars. I hope that my work can contribute to their legacy and inspire others to continue their important work.

ACKNOWLEDGEMENTS

I would like to express my heartfelt gratitude to my father **Yaser**, and my mother **Wesal** for their unwavering support throughout my academic journey. Their encouragement and belief in me have been instrumental in helping me achieve this milestone.

I am also grateful to my sister **Aseel** and, my brother **Mohammed** for their love, support, and understanding. Their presence in my life has been a constant source of strength and motivation.

I would like to extend my gratitude to my friends **Sara, Shaimaa, Nadeen, Noor, Aysel** and **Dorcas** who have been with me through thick and thin, and who have provided me with their unwavering support and encouragement.

I would also like to acknowledge my **Prof. Dr. G. Seda GULEC YILMAZ** who has guided me and provided me with invaluable insights and knowledge that have helped shape my research. Her guidance and mentorship have been pivotal in my academic journey.

I am deeply grateful **Ph.D. Tuba AKDENIZ**, for her guidance, expertise, and mentorship. She has inspired me to pursue excellence and has instilled in me a love for learning that will last a lifetime.

Lastly, I would like to thank all the individuals who have contributed to my research in one way or another. Their assistance, guidance, and support have been invaluable in helping me complete this thesis.

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LIST OF SYMBOLS AND ABBREVIATIONS

OC:	Ovarian Cancer
PARP:	Poly ADP Ribose Polymerase
NER:	Nucleotide Excision Repair
DNA:	Deoxyribonucleic Acid
UV:	Ultraviolet
TCR:	Transcription-Coupled Repair
GGR:	Global Genomic Repair
XPC:	Xeroderma Pigmentosum Group C
DDB2:	DNA Damage-Binding Protein 2
WHO:	World Health Organization
HBV:	Hepatitis B Virus
HPV:	Human Papilloma Virus
HCV:	Hepatitis C Virus

HTLV-1:	Human T-cell Lymphotropic Virus type 1
HGSC:	High-Grade Serous Carcinomas
LGSC:	Low-Grade Serious Carcinomas
EOC:	Epithelial Ovarian Cancer
CCC:	Clear Cell Carcinoma
GCT:	Germ Cell Tumors
BRCA1:	Breast Cancer Gene 1
BRCA2:	Breast Cancer Gene 2
CA125:	The Cancer Antigen 125
HE4:	The Human Epididymis Protein 4
TVU:	Transvaginal Ultrasound
IP:	Intraperitoneal
DDB1:	DNA Damage-Binding Protein 1
XPG:	Xeroderma Pigmentosum Group G

XPA:	Xeroderma Pigmentosum Group A
ERCC1:	Excision Repair Protein 1
XPF:	Xeroderma Pigmentosum Group F
ATP	Adenosine Triphosphate
hHR23B	Human Rad23 Homolog
TFIIH	Transcription Factor IIH
UICC:	Union for International Cancer Control
TNM:	Tumor Node Metastasis
NSAIDs:	Nonsteroidal Anti-Inflammatory Drugs
SERMs:	Selective Estrogen Receptor Modulators
BC:	Breast Cancer
IV:	Intravenous
ssDNA:	Single Strand DNA
OD:	Optical Density

dsDNA:	Double Strand DNA
SNPs:	Single Nucleotide Polymorphisms
Tm:	Melting Temperature
OR:	Odds Ratios
CI:	Confidence Intervals

ABSTRACT

Barham, S. (2023). Investigation of Global Genome Repair Genes Polymorphism in Patients with Ovarian Cancer in the Turkish Population. Yeditepe University, Institute of Health Science, Department of Molecular Medicine. MSc thesis, Istanbul.

AIM: Investigate the relation between XPC rs2228001 and DDB2 rs830083 polymorphism with ovarian cancer (OC) susceptibility in the Turkish population.

MATERIAL and METHODS: Taqman^{R} SNP Genotyping Assays and BioScience (ABI) 7500 real-time PCR system will used to genotype the single nucleotide polymorphisms (SNPs) of the XPC and DDB2 genes. Statistical analysis will be performed using SPSS version 27.0. This study will involve a group of 103 OC patients and 104 healthy individuals.

RESULT: Through the XPC rs2228001 individuals with the homozygous TT genotype had a lower incidence of OC (OR 0.511, CI 95% 0.261 - 1.003) compared to individuals with the GG polymorphism had a greater risk of OC (OR 1.980, CI 95% 1.044 - 3.754). Also, the T allele was linked to a reduced incidence of OC with significant association (p-value = 0.035). While the DDB2 rs830083 homozygous GC genotype had a lower risk of OC (OR 0.521, CI 95% 0.282 - 0.961) compared to individuals with the CC polymorphism had a higher risk of OC (OR 1.895, CI 95% 1.033 - 3.476). While the G allele was linked to a lower incidence of OC with 2 fold.

CONCLUSION: It is the first study that investigating the relation between XPC rs2228001 and DDB2 rs830083 genes with OC susceptibility in Turkish populations. These findings give more insight into the genetic factors associated with OC susceptibility, focusing on the importance of DNA repair systems in diseases. Additional research is required to validate these findings in more diverse and larger populations, allowing for more accurate risk assessment and possibly directing particular treatment options for OC patients.

Keywords: Ovarian Cancer, Nucleotide Excision Repair, XPC rs2228001, DDB2 rs830083.

ÖZET

Barham, S. (2023). Türk Popülasyonunda Over Kanserli Hastalarda Global Genom Onarım Genleri Polimorfizminin Araştırılması. Yeditepe Üniversitesi Sağlık Bilimleri Enstitüsü Moleküler Tıp Anabilim Dalı. Yüksek lisans tezi, İstanbul.

AMAÇ: Türk popülasyonunda XPC rs2228001 ve DDB2 rs830083 polimorfizmi ile yumurtalık kanseri (YK) duyarlılığı arasındaki ilişkiyi araştırmak.

GEREÇ ve YÖNTEMLER: Taqman^{R} SNP Genotyping Assays and BioScience (ABI) 7500 gerçek zamanlı PCR sistemi, XPC ve DDB2 genlerinin tek nükleotid polimorfizmlerini (SNP'ler) genotiplemek için kullanılacaktır. İstatistiksel analiz SPSS versiyon 27.0 kullanılarak yapılacaktır. Bu çalışma 103 YK hastası ve 104 sağlıklı bireyden oluşan bir grubu içerecektir.

SONUÇ: XPC rs2228001 aracılığıyla, homozigot TT genotipine sahip bireyler daha düşük YK insidansına sahipti (OR 0,511, CI %95 0,261 - 1,003), GG polimorfizmi olan bireylere kıyasla daha yüksek YK riskine sahipti (OR 1,980, CI %95 1,044) - 3.754). Ayrıca, T aleli, anlamlı ilişki ile azalmış YK insidansı ile bağlantılıydı (p-değeri = 0.035). DDB2 rs830083 homozigot GC genotipinin YK riski daha düşükken (OR 0,521, CI %95 0,282 - 0,961), CC polimorfizmi olan bireylerde YK riski daha yüksekti (OR 1,895, CI %95 1,033 - 3,476). G aleli ise 2 kat ile daha düşük bir YK insidansı ile bağlantılıydı.

SONUÇ: Türk popülasyonunda XPC rs2228001 ve DDB2 rs830083 genleri ile YK duyarlılığı arasındaki ilişkiyi araştıran ilk çalışmadır. Bu bulgular, hastalıklarda DNA onarım sistemlerinin önemine odaklanarak, YK duyarlılığı ile ilişkili genetik faktörler hakkında daha fazla fikir vermektedir. Bu bulguları daha çeşitli ve daha büyük popülasyonlarda doğrulamak için daha doğru risk değerlendirmesine izin verecek ve muhtemelen YK hastaları için belirli tedavi seçeneklerini yönlendirecek ek araştırmalar gereklidir.

Anahtar Kelimeler: Yumurtalık Kanseri, Nükleotid Eksizyon Onarımı, XPC rs2228001, DDB2 rs830083.

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1. INTRODUCTION AND PURPOSE

Cancer is the most prevalent disease that leads to death in most regions of the world (1, 2).

Among reproductive cancers affecting women, ovarian cancer (OC) has the highest fatality rate (3). Furthermore, it is placed in the fifth position in terms of being a prevalent reason for death among women in general (4). Due to its minimal symptoms, OC is frequently known as the "silent killer" (5) for that 75% of females with OC have advanced disease with stages III and IV, and 47.4% of these patients can survive for 5 years (3, 6).

The general standard of care is operation followed then platinum-based chemotherapy. In the last decade, anti-angiogenic and poly ADP ribose polymerase inhibitors (PARP) become more prevalent in the treatment of this particular cancer. Anti-angiogenic like bevacizumab, which targets the formation of new blood vessels that feed tumors, and PARP, which blocks a specific enzyme involved in repairing damage to deoxyribonucleic acid (DNA) within cancer cells (4, 7).

Increased estrogen exposure, inflammatory diseases, hormone replacement therapy, smoking, metabolic abnormality, and obesity can all increase the risk of OC (8-10). Also, the most risk factors that cause this disease are genetic mutations and the history of the family (11).

Nucleotide excision repair (NER) has the capacity to identify and repair different types of DNA damage caused by factors such as radiation, as well as bulky DNA adducts generated by exposure to environmental mutagens or chemotherapy treatments (12). NER consists of sub-routes, which are global genomic repair (GGR) and transcription-coupled repair (TCR) (12, 13).

GGR contains different types of genes like xeroderma pigmentosum (XPC) and DNA damage binding protein 2 (DDB2) and those play a vital role in recognizing and identifying DNA damage that needs to be repaired (14).

XPC plays a vital role in GGR by recognizing the damage and initiating the repair mechanism to fix it (15).

DDB2, a significant DNA repair mechanism is recruited to the location of the damage and connects with other GGR proteins to start the repair process like correcting the ultraviolet radiation (UV) damage to stop the aggregation of mutations and the development of cancer (16).

This study aims to assess and analyze the relation between polymorphism genes in the GGR pathway and the risk of OC. The study focuses on two genes in this pathway, namely XPC rs2228001 and DDB2 rs830083.

2. LITERATURE REVIEW

2.1. Cancer

Cancer is a complicated condition that leads to change in cell structure. Other terms used are malignant tumors and neoplasms. The basic hallmark of cancer is abnormal cell proliferation (17). The primary factor that leads to death for most individuals with cancer is the invasion of tumor cells into adjacent tissues and their spread to other organs (18).

According to popular view, the prevalence of cancer spans all age groups, and it poses a growing threat to a significant number of individuals. Following cardiovascular disease, it is the second most common cause of death globally (19).

In 2020, the global number of individuals with cancer was 19.3 million, and the World Health Organization (WHO) has projected that the cancer incidence rate will increase to 21.6 million by 2025 see Figure 2.1. (20)

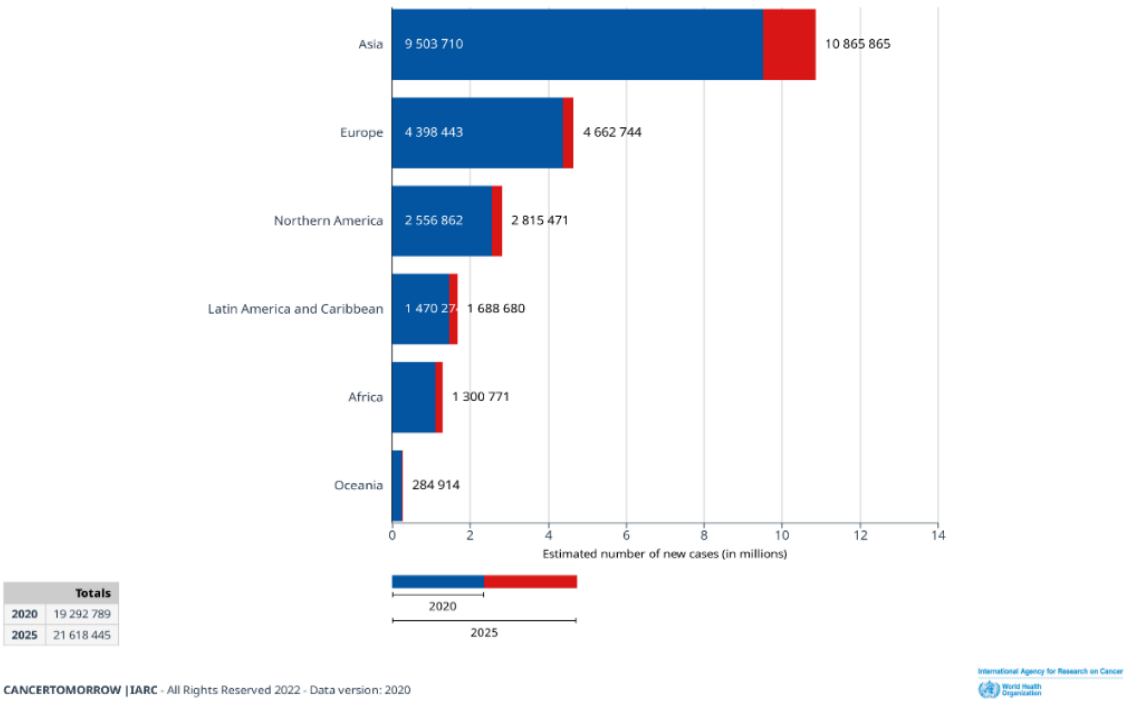

Figure 2.1. Projected amount of new instances between 2020 and 2025.

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2.1.1. Causes of Cancer

Cancer causes variables are divided into exogenous and endogenous categories (19). Exogenous factors consist of lifestyle factors including tobacco, drinks alcohol, and food preservative, as well as recent advancements in diagnostics and screening techniques and biological agents like viruses, bacteria, and other microorganisms (21).

Tumorigenic viruses are the most prevalent and well-known microbes that cause cancer. Other microorganisms, such as specific bacteria and parasites like *Helicobacter pylori* serve also as co-factors or cancer-causing agents. It is believed that 16% of carcinoma diagnosed cases are caused by pathogenic viruses (22).

Among DNA viruses that can lead to cancer, the most common are *hepatitis B virus* (HBV) and *human papillomavirus* (HPV), particularly HPV 16 or 18. These two viruses each have a unique involvement in the progression of cancer. HBV is believed to cause indirect mutagenesis by inducing chronic inflammation and producing reactive oxygen species (23) while, HPV-16 induces the viral genes E6 and E7, which are directly mutagenic (24).

RNA tumor viruses, such as Hepatitis C virus (HCV) that causes oxidative stress in infected cells and *human T-cell lymphotropic virus type 1* (HTLV-1) that causes mutations directly are recognized as the only retroviruses that can cause cancer in humans (25).

Endogenous influences include inflammatory and immune system damage with unknown etiologies, age, genetic change, endocrine balance, and physiological state and hereditary inheritance (19).

Genomic instability is a major contributor to genetic heterogeneity in cancer. Through a variety of ways, this instability may impact the creation of the cancer genome by accelerating the mutation rate (26). Changes in DNA repair genes, regulators of the cell cycle, and pathways related to cell death are impacted by mutations (27).

Families with a history of cancer may begin the growth of cancer at an early stage than other families, potentially as a result of inherited mutations (28).

2.1.2. Stages of Carcinogenesis

The term used to describe the process of cancer is carcinogenesis and it was initially presented in 1948 by Berenblum and Schubik (29). It involves several phases: initiation, promotion, and progression and it takes many years to complete (see Figure 2.1.2.) (30).

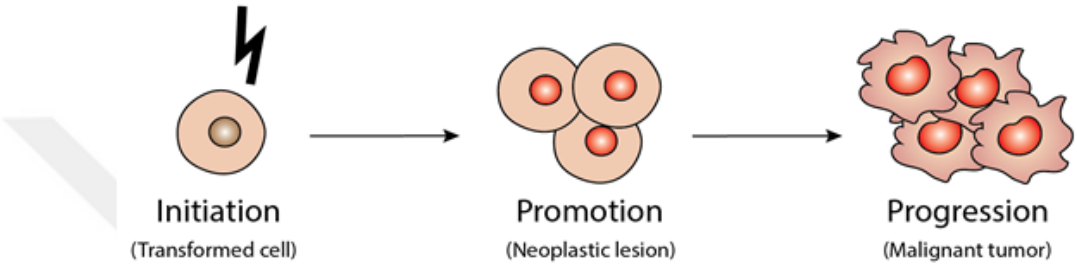

Figure 2.1.2. Carcinogenesis stages.

The initiation is the first stage of carcinogenesis, where a healthy cell undergoes a transformation into a cancerous cell. Exposure to substances that can cause cancer, known as carcinogens, such as chemicals, radiation, or viruses may be the cause of this transformation which damages the cell's DNA and it is irreversible (31).

The altered stem cell then divides in waves to create a clone of altered cells this procedure is referred to as promotion, in this stage, the cancerous cell begins to multiply and form a small cluster of abnormal cells, and this process is stimulated by factors such as hormones, growth factors, and chronic inflammation (32, 33).

Progression is when benign tumors transform into cancerous and aggressive lesions (32) the cancerous cells continue to grow and acquire additional genetic mutations, leading to increased aggressiveness and metastasis to other parts of the body (33).

2.1.3. Classification of Cancer

Each of these factors contributes to the identification and management of cancer: diagnosis of a tumor's malignancy, as well as the tumor's location of origination histotype, grade, and extent of spread throughout the body. These characteristics are specified in the classification

of malignant tumors created by the Union for International Cancer Control (UICC) and (WHO) (34).

Tumors have traditionally been classified based on four categories: (1) based on the organ, tissue, and system they originate from for example, OC or it can also be named based on the type of cells that make up the tumor like squamous cell carcinoma and melanoma, (2) based on their specific type, (3) based on their grade, and (4) based on the extent of their spread, using the Tumor Node Metastasis (TNM) system and it can be categorized as either benign (non-cancerous) or malignant (cancerous), that having the ability to invade nearby tissues and metastasize to other regions of the body. Finally, some cancers have specific genetic mutations that are associated with their development and progression. For example, breast cancer (BC) can be classified as Breast Cancer Gene type 1 or 2 (BRCA1 or 2) negative or positive based on whether the tumor has a mutation in the genes or not [34, 35].

2.1.4. Types of Cancer

More than 277 various forms of cancer diseases are included in the term cancer in its broadest sense (35).

Among men, the types of cancer with the highest proportions are prostate, lung, colon, rectal, and bladder cancer respectively. Breast, ovarian, bronchial, colon, rectal, and thyroid cancers are the most frequently occurring types of cancer in women. Blood cancer and malignancies of the brain and immune cells are cancers that affect children at the highest rates (36).

In 2022, BC and lung cancer were the most common types of cancer globally, representing 12.5% and 12.2% of all newly detected cases, in that order. With 1.9 million new cases in 2022, colorectal cancer was the third most prevalent malignancy (see Figure 2.1.4.) (20).

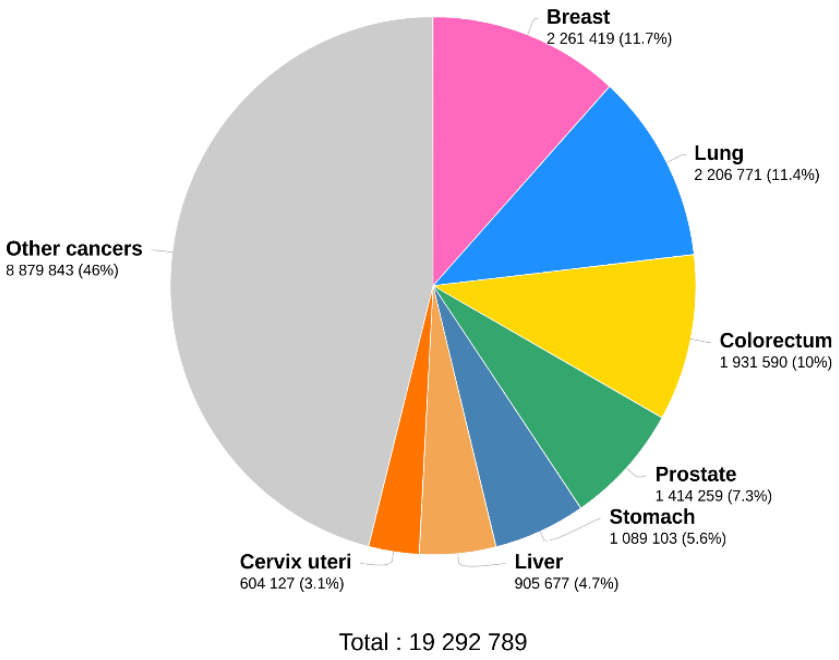

Figure 2.1.4. Estimated number of different cancer types 2020.

2.1.5. Treatment of Cancer

Over the last decade, there have been significant improvements in the treatment of cancer, resulting in better chances of survival, and recognition of cancer as a long-term health condition. In addition to modifications in outpatient and home medical care, abbreviated hospital stays, and surgical interventions (37). Accurate diagnosis is essential for effective cancer care because each type of cancer requires a tailored treatment plan. Treatments such as surgery, radiation, and systemic therapy (including chemotherapy, hormone therapy, and biological therapy) are commonly used to treat the disease (38). The choice of a treatment plan must take into account the patient as well as the malignancy. Achieving the anticipated therapeutic response depends on completing the treatment program within the allotted time frame (38). The treatments used against cancer are shown in Table 2.1.5. below and a brief explanation is given about them (39).

Table 2.1.5. Types of cancer treatment and their functions.

Type of Treatment	Explain of Use
Biomarker test	The term 'tumor markers' is used interchangeably with biomarkers to describe the identified gene, protein, or other components that provide information about cancer. Your doctor can choose cancer therapy with the aid of biomarker testing.
Chemotherapy drugs	Drugs are used in chemotherapy that works to destroy cancer cells
Hormonal therapy	Hormone treatment is a method of treating BC and prostate cancers that rely on hormones to grow, reduce, or stop their growth.
Overheating	Hyperthermia means when body tissue is heated to as much as 113°F to help injure and kill tumor cells with little to no injury to healthy tissue.
Immune cell therapy	Immunotherapy in order to assist your immune system defeat cancer.
Phototherapy	A medication that is triggered by light is used in photodynamic treatment to kill cancer cells and other aberrant cells.
Bone marrow transplant	Patients who have had their stem cells destroyed by aggressive chemotherapy or radiotherapy can get stem cell transplants to replace the ones that were lost.
Radiotherapy	Radiation is used to destroy cancer cells and reduce tumor size.
Operation	Operation is a procedure when a physician removed cancer from your body as part of a cancer treatment.
Target therapy	Target therapy can inhibit or slow down the progression of cancer by preventing the cells from continuing to divide, grow, and spread uncontrollably.

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2.2. Ovaries

Ovaries are female only reproductive glands. Its generate eggs and when it fertilized that settles in the uterus where it grows into a fetus after traveling from the ovary through the fallopian tubes. The primary sources of the female hormones progesterone and estrogen are also the ovaries. On either side of the uterus, there is one ovary (40).

Three different cell types made the majority of the ovaries, different types of tumors can arise from each type of cell: 1) Epithelial ovarian cancer (EOC) originates from the cells that form the outer layer of the ovary. 2) Germ cells that produce eggs are where germ cell tumors (GCT) originate (ova). 3) Stromal cells are the supportive cells that make up the bulk of the ovarian tissue and help to regulate ovarian function and it is the origin of stromal tumors (40).

2.3. Ovarian Cancer

Ovarian cancer (OC) encompasses a range of medical conditions that have their origin in the ovaries or in neighboring structures like the fallopian tubes (see Figure 2.3.) (41). For women over 40, especially in developed nations the occurrence of OC ranks second in frequency among all types of cancer, following BC (42). In women, OC is the fifth most common cause of cancer-related deaths. (4).

Despite increased knowledge of OC, trends in its cure and survival have remained relatively unchanged this is because it remains challenging to identify OC in its early stages which is due in part to a number of circumstances, including the absence of an accurate screening method and its' ambiguous symptoms because it’s are not foreign for most females such as changes in bowel movements, early satiety, stomach pain, frequent urination, or abdominal bloating (43) that may masquerade as other non-cancerous diseases (42).

As of 2022, the United States has reported more than 19,880 fresh instances of OC, and it has been responsible for causing 12,810 deaths (44).

OC can be split into various histological subtypes according to recognizable risk conditions, sources, molecular components, clinical features, and treatments (45).

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The majority of ovarian malignancies (90%) are EOC, which also includes serous, endometriosis, and clear cell carcinoma (CCC). Also, mucinous carcinomas. Sex cord-stromal tumors and GCT constitute approximately 10% of OC cases, these are examples of non-epithelial ovarian malignancies (43, 45). Serous tumors can be classified as either high-grade serous carcinomas (HGSC) or low-grade serous carcinomas (LGSC) (46). HGSCs made 70%, 80% of all EOC subtypes, while LGSCs made less than 5%. Cell subtypes are endometrioid, mucinous, and CCC 10%, 3%, and 10%, respectively (5).

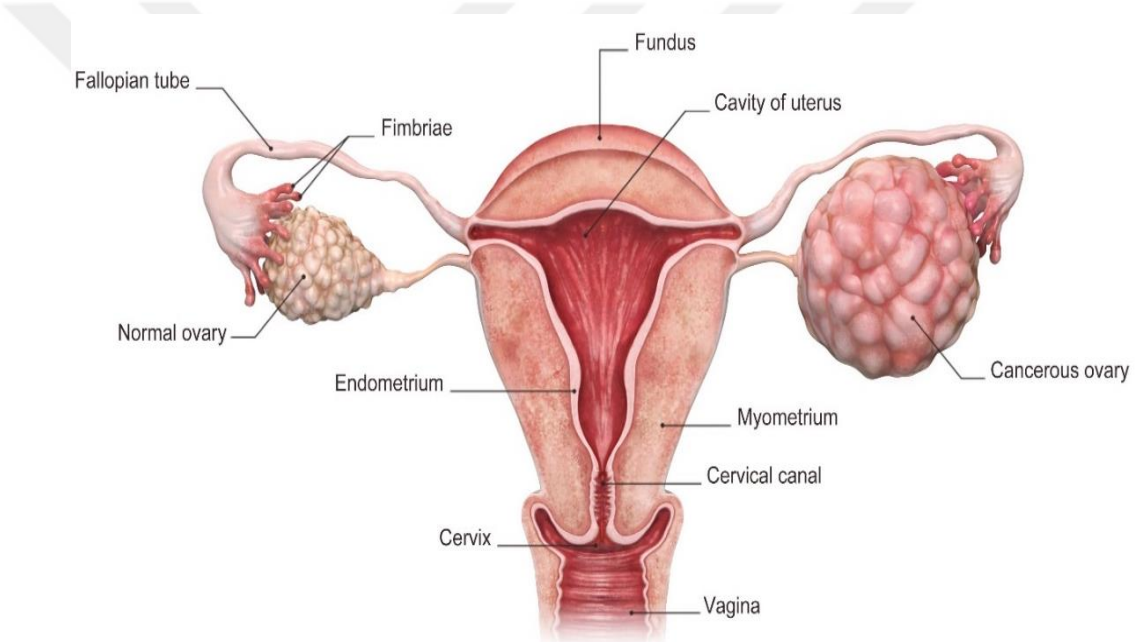

Figure 2.3. Ovarian Cancer.

2.3.1. Stages of Ovarian Cancer

Depending to Table 2.3.1. OC has four different stages. Each stage is different from the others in terms of disease and treatment. Only 25% of females had a localized early-stage diagnosis of OC (47). Recent research indicates that the rate of survival for OC patients is 47.4% after a span of 5 years (48).

Table 2.3.1. Stages of Ovarian Cancer.

Stage	Defined
Stage I	**Ovaries specific tumor.**
IA	There is cancer inside only one ovary.
IB	There is cancer inside both ovaries.
IC	The cancer reach surface (cancer that develops on the exterior surface of the ovaries).
Stage II	**Pelvic elongation.**
IIA	The cancer extends to the uterus or fallopian lobes or both.
IIB	Extension to further pelvic organs, such as colon, bladder, or rectum.
Stage III	**Extend out the pelvis including the intestine and lymph nodes.**
IIIA	There is cancer in your neighboring lymph nodes, and it could be spreading to nearby organs. This is typically found during surgery and is confirmed through biopsy.
IIIB	The cancer has metastasized to the lymph nodes located in the pelvis or abdomen and its measures less than 2 millimeters (cm) in diameter. This is typically detected during surgery and is confirmed through biopsy.
IIIC	Same IIIB, but the cancer growths are larger than 2 cm.
Stage IV	**The cancer can extend to some distant organs like lung, brain and skin.**

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2.3.2. Risk Factors of Ovarian Cancer

2.3.2.1. Ovulation

Ovulation and the risk of OC are directly related. Studies have revealed that a female chance of developing OC increases with the number of ovulatory cycles she completes. The pro-inflammatory reaction that occurs in the distant fallopian tubes at the time of ovulation may lead to a greater likelihood of malignant growths in the ovaries (49).

2.3.2.2. Menopausal hormones

It has been demonstrated that hormone replacement therapy raises postmenopausal female risk of getting OC; estrogen-only therapy increased risk by 22%, while combination estrogen and progesterone treatment increased risk by 10%. A meta-analysis has indicated that premenopausal women who use hormone replacement therapy are similarly prone to developing OC whether the therapy is comprised solely of estrogen or estrogen and progesterone in combination (50, 51).

2.3.2.3. Family History

Women who have a first-degree relative with OC have increased risk of approximately three times contracting the disease (52). Individuals with mutations in the BRCA1/2 genes are estimated to have a 44% and 17% of developing OC, respectively, by the age of 80. Other gene variants that influence OC risk in varied degrees, besides BRCA1 and BRCA2, are still being found (53).

BRCA1 interacting protein (BRIP1), MutS homolog 6 (MSH6), and RAD51 Paralog C (RAD51C) are a few gene mutations with a modest risk. There are also more widespread gene alterations that only marginally raise risk but, due to their abundance in the population, may be responsible for a significant proportion of cancer cases. These kinds of gene mutations continue to be better understood, discovered, and potentially useful in a therapeutic environment for risk prediction and cancer prevention (54).

Lynch syndrome is a hereditary condition that predisposes individuals to develop OC and other cancers, particularly colon cancer. It is caused by a genetic abnormality that is passed down in families (55).

2.3.3. Prevention of Ovarian Cancer

2.3.3.1. Pregnancy

Research has established that women who give birth to a child that has completed the entire gestational period and is born between the 37th and 42nd week of pregnancy experience a lower incidence of OC compared to those who have never given birth. For the first birth, the risk of OC is lowered by roughly 30%, and by 19% for each consecutive birth (56). According to several research, having a kid at an older age equal or more than 30 years also lowers the risk of OC (57, 58).

2.3.3.2. Hormonal Birth Control

It has been demonstrated that using oral contraceptives reduces OC risk in females with an average risk by 40% to 50% (51). The advantage of risk reduction increases with continued oral contraceptive use. It appears to be an effective and non-invasive way to lower the chance of developing OC (43).

2.3.3.3. Breastfeed

According to several research, women who breastfeed had a somewhat lower chance of developing OC. In general, breastfeeding for longer periods of time is linked with a lower risk of OC. This means that for each year a woman breastfeeds, there is about a 10% decrease in her risk of developing OC (59).

2.3.3.4. Pharmacologic Prophylaxis

Numerous drugs have been researched for their capacity to decrease the likelihood of getting OC, such as oral contraceptives, and nonsteroidal anti-inflammatory drugs (NSAIDs) (5, 60).

According to previous studies, that compare patients who do not take NSAIDs such as aspirin with those who take low-dose aspirin daily, the women that take aspirin daily have a low risk for OC (5).

2.3.4. Diagnosis and Screening of Ovarian Cancer

Women will be required to provide a complete medical history when OC is suspected (61), and they will go through a pelvic focused physical examination to look for an oversized ovaries or fluid in the abdomen (62). Some kinds of OC, mainly GCT, may be detected using blood tests (63). It is also possible to order imaging tests for the abdomen and pelvis, including transvaginal ultrasound (TVU), computerized tomography scans, or nuclear magnetic resonance imaging, but these imagines cannot definitively rule out cancer (64, 65).

Due to the OC symptoms' well-known lack of specificity and ambiguity, screening is challenging. In the past, the cancer antigen 125 (CA125) was commonly utilized for detecting OC, and some people used it as a screening for OC but the studies found this marker had low accuracy and precision. It was observed that CA125 was not elevated in up to 50% of females with OC in its early stages, despite the fact that it has been increased in benign situations and even during pregnancy. As a result, it is no longer advised to test for OC using the CA125 marker (64).

Although doctors have failed to create a reliable OC screening tool, a combination of many techniques can be at least partially reliable. TVU while helpful in detecting pelvic masses, is not employed to screen for OC, However, TVU may aid in early OC detection when combined with screening for CA125 or a newer protein marker referred to as the human epididymis 4 (HE4) (64).

If abdominal fluid is detected, a technique called paracentesis can be used to collect a sample and examine it for cancer cells (66).

A precise diagnosis of OC can be obtained through a tissue biopsy, which is a standard procedure for diagnosing cancer. During this procedure, tissue is aspirated and closely inspected to look for any signs of malignancy. TVU guided biopsies, which have a low risk of needle site

metastasis, have helped to lower the danger of abdominal wall metastasis that this previously carried (64).

Genetic screening is a possibility to find out one's risk status because genetic alterations can considerably raise one's risk for developing OC (64).

2.3.5. Treatment of Ovarian Cancer

There are several treatment options available if OC is discovered in a woman and prophylactic surgery is not a possibility. OC is treated with a combination of surgery and chemotherapy. Surgery may involve the removal of the tumor, as well as the surrounding tissue, and may be followed by chemotherapy to eliminate any remaining cancer cells (67).

2.3.5.1. Debulking surgery

Debulking is a common treatment for advanced OC. It is performed with the intention of removing the maximum amount of the tumor feasible to improve the effectiveness of chemotherapy and increase the patient's chances of recovery(68).

Two types of debulking surgery for OC are primary debulking surgery, which is performed before chemotherapy, and interval debulking surgery, which is performed after chemotherapy (69).

2.3.5.2. Chemotherapeutic Agents

Chemotherapy is frequently a systemic therapy, which means that the chemicals enter the blood and reach specific parts of the body [71]. Chemotherapy may be used to treat malignancies that have spread, to decrease extremely large tumors to facilitate surgery, or to eradicate very small cancer cell populations that may remain after surgery (70). Chemotherapy frequently makes use of medications that are either orally or through an intravenous (IV). In some circumstances, chemotherapy may also be administered directly into the abdomen using a catheter (a thin tube) and it is called intraperitoneally (IP) (71). This treatment involves making a small cut in the wall of the abdominal and inserting a catheter through the subcutaneous tissue into the peritoneal cavity (72).

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Combining multiple medications for chemotherapy appears to be more effective than using a single medication, but using a combination of more than 2 drugs does not lead to better results. Multiple randomized trials have demonstrated the third drug does not provide any extra advantages. Therefore, doublet chemotherapy is considered the best option (73). It is common to use a combination of a Taxane chemotherapy medication, like Taxotere (docetaxel) or Taxol (paclitaxel), and a platinum compounds chemotherapy drug, such as cisplatin or carboplatin (74).

PARP inhibitors are a relatively recent method of treating OC. PARP proteins aid cells in regenerating themselves after damage, which cancer cells also utilize to repair the damage caused by chemotherapy for OC treatment. Inhibiting these proteins obstructs the cancer cells' regeneration process, impeding their growth and the formation of bigger tumors (75). The addition of recently developed drugs in this category, such as olaparib and rucaparib have potential in treating OC (73). Ongoing research is being conducted to identify the most suitable medication based on the patient's condition, tumor type, and other relevant factors. Furthermore, despite being effective in the treatment of OC, these treatments are exceedingly expensive (see Table 2.3.5.) that is show common chemotherapy drugs that used in OC (76).

Table 2.3.5. Chemotherapy Drugs for Ovarian Cancer.

Medication	Route of Administration	Stage Treated of Ovarian Cancer
Paclitaxel with Carboplatin	IV	1
Docetaxel with Carboplatin	IV	1
Paclitaxel with Cisplatin	IV or IP	2,3,4
Dose-dense Paclitaxel with Carboplatin	IV	2,3,4
Carboplatin with Liposomal Doxorubicin	IV	2,3,4
Bevacizumab and Paclitaxel with Carboplatin	IV	2,3,4

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2.3.5.3. Vitamin D3

Low vitamin D3 levels raises your risk of developing OC. Combine active form of vitamin D3 (1,25 (OH)2D3) with other medications is another potential advancement in OC. Adipose cells, lymphocytes, microvascular cells, and fibroblasts all contribute to the development of a cancerous environment in this type of setting 1,25 (OH)2D3 has been demonstrated to greatly improve anticancer characteristics when combined with chemotherapy, particularly in the tumor cells (77).

2.4. DNA Damage

DNA damage refers to alterations in the chemical structure of DNA, and it is include numerous types of these damage, like apurinic/apyrimidinic regions (AP), single-strand breaks (SSB), double-strand breaks (DSB), DNA/protein cross-links, and insertion-deletion mismatches (78, 79).

Tens of thousands of DNA damage are affected daily to 10^{13} cells within the human body cells (80).

The DNA damage response, which is a complex signal transduction mechanism, identifies when DNA has sustained damage and triggers the cell to initiate responses to the injury (81).

DNA damage can occur via external (environmental factors) or endogenous sources. Endogenous sources such as cellular metabolic processes, oxidative, hydrolysis, and alkylation. Ionization radiation, UV, and other chemical agents are examples of external sources of DNA damage (82, 83).

If these damages are not repaired or are fixed wrongly, they can prevent the replication and transcription of the genome and it can lead to mutations or larger-scale genome abnormalities that jeopardize the viability of cells or organisms, and more significantly, the organisms are more likely to develop cancer, neurological problems, and immune deficiencies if its genomic integrity is lost (84).

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2.5. DNA Repair

Cells have therefore been forced to develop methods to repair DNA damage in order to retain the stability of their genomes. The primary categories of DNA repair methods include (I) the reversal of the chemical reaction that caused the lesions, (II) mismatch repair, (III) NER, (IV) base excision repair, (V) homologous recombination, or (VI) non-homologous end joining (85).

2.6. Nucleotide Excision Repair

The NER pathway is a multistep process that repairs different kinds of DNA damage, such as lesions brought on by UV, mutagenesis substances, or chemotherapy medicines that result in large DNA adducts. In mammalian cells, NER involves 30 main proteins. Numerous genetic variations in NER genes have been linked to serious human conditions include Xeroderma pigmentosum (XP) in addition to Cockayne syndrome (CS) (86, 87).

NER starts with the identification of the DNA damage, next involves making incisions at the locations that surround the damaged DNA site, and ultimately ends with the elimination of the oligonucleotide that contains the DNA damage site. The NER process is terminated through the binding of newly formed oligonucleotide that matches the existing strand (88). GGR and TCR are two different types of NER, Both GGR and TCR require multiple shared proteins and follow the same repair pathways, with the exception of when the DNA lesion is recognized. The XPC, Xeroderma Pigmentosum Group A (XPA), Xeroderma Pigmentosum Group G (XPG), DNA Damage-Binding Protein 1 (DDB1), and DDB2 proteins are involved in this recognition in the GGR, whereas the Cockayne syndrome group A ((CSA) excision repair 8 (ERCC8)) and Cockayne syndrome group B ((CSB) excision repair 6 proteins (ERCC6)) are involved in the TCR (89).

2.6.1. Global Genome Repair Pathway

The process of GGR is utilized by cells to fix DNA damage that results from a variety of external agents, such as chemical exposure, UV radiation, and other genotoxic stresses; Two key proteins involved in the GGR pathway are DDB2 and XPC (89).

DDB2 is a protein that recognizes and binds to DNA damage sites, which can be triggered by UV radiation, are a component of a more extensive complex called the UV-DDB complex, which also includes the protein DDB1 (90). Together, these proteins help to initiate the GGR pathway by attaching to the damaged DNA and enlisting additional proteins to the injury location (91).

XPC is a key protein involved in the GGR pathway. It is a constituent of the XPC complex, which is responsible for validating the existence of DNA damage and engaging other proteins to the lesion site. XPC identifies and attaches to diverse forms of DNA damage, such as those arising from UV radiation, chemical exposure, and other environmental stressors (92).

Once DDB2 and XPC have recruited other proteins to the lesion site of the DNA, the GGR pathway proceeds with excision of the damaged DNA segment and creation of a new DNA segment using the remaining, undamaged DNA as a template. TFIIH, XPA, and several other proteins are involved in the process of removing the damaged DNA segment and synthesizing a new one (14, 93).

2.6.1.1. Mechanism of Action for GGR

To initiate the GGR pathway, the UV-Damaged DNA-Binding (UV-DDB) complex made up of DDB1 and DDB2 proteins recognizes DNA damage, marking the first step of the process. DDB2 which has a strong attraction for pyrimidine dimers (CPDs) in addition to 6-4 photoproducts (6-4PP) caused by UV radiation, binds to the damaged DNA. This binding causes a structural change in the UV-DDB complex, allowing it to bring in other proteins to the damaged site including XPC (94).

XPC plays a critical role in verifying the existence of DNA damage and aiding in the recruitment of other proteins to the damaged site. XPC contains two subunits, XPC and a human Rad23 homolog (hHR23B), which together form a complex that binds to the DNA and scans for distortions in the double helix (13).

Once the DNA damage is verified, the XPC complex recruits additional proteins to the site of the damage, including the TFIIH complex and XPA. The TFIIH complex contains several

subunits, including XPB and XPD helicases, which use adenosine triphosphate (ATP) hydrolysis which is responsible for unwinding the DNA at the site of the lesion (95), and the XPA protein, which helps to stabilize the unwound DNA (13, 96).

After the damaged DNA is stabilized, the XPG and ERCC1-XPF endonucleases make incisions on both the upstream and downstream regions flanking the site of the DNA damage, generating a single-stranded DNA (ssDNA) gap (97). XPG creates an incision downstream of the lesion (at the 3' end), whereas ERCC1-XPF creates an incision upstream of the lesion (at the 5' end). The resulting gap contains the damaged DNA fragment and a short stretch of undamaged DNA on either side (13, 98).

Finally, DNA polymerase utilizes the intact DNA strand as a template to fill the gap at ssDNA. The polymerase extends the damaged DNA fragment until it reaches the incision made by the other endonuclease, at which point it dissociates. The break in the DNA strand is closed by a DNA ligase that connects the two separated strands (99).

2.6.1.2. GGR and Ovarian Cancer

The GGR pathway is significant in preserving the stability of the genetic material and preventing the accumulation of DNA damage. Defects in the GGR pathway elevated risk of developing cancer, including OC. Polymorphism in the genes responsible for the GGR pathway proteins have been associated with a higher likelihood of developing OC (100).

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3. MATERIAL AND METHOD

3.1. Sample Selection and Definition

The patient and control groups were composed entirely of individuals of Turkish descent (Caucasians) who hailed from the same geographical region in Turkey. The patient group comprised of 103 participants diagnosed with OC by Obstetrics and Gynecology, while the control group had 104 healthy. All participants were above the age of 18. Each participant underwent an interview where they were asked a structured questionnaire about their demographic details, cancer history, menopausal status, and number of pregnancies and childbirths. However, some participants chose not to answer all of the questions. After the interview, approximately 5 ml of venous blood was collected from each participant. The Ethics Committee of Yeditepe University has approved this study for the purpose of this thesis work.

3.2. Materials and Devices Used in the Experiment

3.2.1. Material used in DNA isolation

The venous blood samples were stored at a temperature of 4°C in tubes that had Ethylenediaminetetraacetic acid (EDTA) added to them to prevent clotting. To isolate DNA, the iPrep PureLink system from (Invitrogen and Thermo Fisher Scientific Inc) was used.

The mixture used for the isolation process included various substances such as Cell Lysis Solution, Proteinase K, RNase A, 100% Isopropanol, Elution Buffer, Wash Buffer, and iPrep PureLink gDNA Cartridge.

3.2.2. The Equipment Used in the Experiment

In this experiment, various instruments and equipment were employed, including the iPrep PureLink DNA Isolation Robot from (Invitrogen and Thermo Fisher Scientific Inc), the Nanodrop 2000 from (Thermofisher Scientific Inc), Real-Time PCR machines such as the LIGHT CYCLE 480 II Instrument from (Roche Diagnostics) and the Fast Real Time 7500 from (Applied Biosystems), a Plate Centrifuge from (Hettich), a Centrifuge from (Beckman Coulter), refrigerators at temperatures of +4°C, -80°C and -20°C from (Haier), Ultra-Pure Water obtained

from the (Pure Lab Option Q by Elga), a Vortex machine from (V.I. Plus Biosan), and a Pipette Kit provided by (Thermo Fisher Scientific Inc).

3.3. Methods

3.3.1. Genomic DNA Isolation from Blood

The patient and control groups' blood samples were collected in 5 mL tubes that contained EDTA. The samples were kept in a refrigerator at 4°C until DNA isolation was initiated. DNA extraction was performed using the iPrep DNA extraction robot. This system allows for the isolation of DNA from 350 µL of peripheral blood, enabling 13 blood samples to be processed at once. Each sample requires one cartridge, and the cartridges are agitated to ensure the magnetic beads bind properly to the DNA.

The iPrep PureLink DNA Isolation Kit utilizes magnetic bead technology to extract genomic DNA from whole blood. The magnetic beads have a strong affinity for DNA molecules and can selectively attach to the DNA in the sample, resulting in pure DNA isolation. These magnetic beads are made of superparamagnetic particles that have a silica coating, which is a stable and unreactive surface for DNA binding. The uniform size of the beads facilitates efficient DNA binding and separation. The DNA-silica coated magnetic bead interaction is facilitated by a binding buffer. Once the DNA is bound to the magnetic beads, the beads are separated from the sample using a magnetic field. The magnetic beads with the bound DNA are then easily removed by attracting them to the side of the tube. The beads are then washed to remove any impurities, and the purified DNA is eluted using an elution buffer.

Aqueous DNA samples were acquired and stored in the refrigerator at -20°C for short term or -80°C for long term.

3.3.2. DNA purity measurement

NanoDrop is a brand of UV spectrophotometer that is utilized for measuring the absorption of UV light by nucleic acids at a wavelength of 260 nm. To assess the purity of DNA, the optical density (OD) OD260/OD280 and OD260/OD230 ratios are calculated using

NanoDrop, while the concentration of DNA can also be determined with this instrument. For genotyping purposes, the optimal OD260/OD280 ratio falls within the range of 1.7 to 1.9.

Unlike other UV spectrophotometers, Nanodrop does not require the use of cuvettes or capillaries for sample measurement. This direct measurement approach minimizes the impact of external factors and results in more accurate and realistic outcomes.

The present thesis employed NanoDrop 2000 (Thermo Fisher Scientific Inc.) to measure the purity of DNA. 1µl of DNA sample from each participant in both the OC patient and control groups was measured using this instrument. In addition, distilled water was utilized as a blank sample, and after each sample quantification, the equipment was cleaned to provide a safe and clean zone for further experiments.

The following formula was used to calculate the concentration of DNA at 260 nm.

dsDNA concentration = OD260 × conversion factor (ng) × dilution factor (Ml)

The dilution factor is used if the DNA sample has been diluted before measurement to ensure that the OD260 reading falls within the linear range of the spectrophotometer. The conversion factor is the factor that relates OD260 readings to the concentration of double-stranded DNA (dsDNA) in µg/mL per OD unit. The conversion factor typically used is 50 µg/mL per OD unit for dsDNA.

3.3.3. Genotyping with real-time PCR

The genotyping analysis of the study was conducted using the 7500 Fast-Real-Time Polymerase Chain Reaction instrument from Applied Biosystems, which is a real-time PCR instrument. Fluorescent probes were used to detect SNP.

Taqman, the genotyping assay, is composed of two fluorescent probes, two primers (forward and reverse), and Taq polymerase. The fluorescent probes are used specifically in real-time PCR assays and can detect two different wavelengths corresponding to the mutant and wild type alleles. They contain either VIC or FAM reporter dyes which hybridize specifically to the target DNA sequence of interest. Furthermore, they contain a quencher molecule that is

positioned near the reporter dye, blocking fluorescence emission until the probe is cleaved by Taq polymerase during the PCR reaction. The cleavage releases the reporter dye from the quencher, allowing it to emit fluorescent light which is detected by a fluorescence detector. The amount of fluorescent light emitted is proportional to the amount of amplified target DNA and is detected by a fluorescence detector.

3.3.3.1. XPC rs2228001 and DDB2 rs830083

To genotype the XPC polymorphism, a Taqman assay was used with a real-time PCR procedure. The region of the XPC gene containing the polymorphism was amplified using

Forward primer: TGAAGAAATCCCGTGGTAACTGA

Reverse primer: GCTGCTTCACTAGCTGAAAGCTG

TaqMan probe 1: CCAGGGCTGAGGAT-VIC

TaqMan probe 2: CCAGGGTTGAGGAT-FAM

DDB2 rs830083 is an intron variant that could potentially impact gene expression through effects on splicing efficiency, mRNA stability, and gene regulation.

The Taqman assay primers and probe sequences for DDB2 rs830083 are

Forward primer: CACCTCAGCCTCCCAAGTG

Reverse primer: CAACGTGACAAAACCCCATCTTAAA

TaqMan probe 1: CCAGCTAATTTTTCTATTTT-VIC

TaqMan probe 2: CAGCTAATTTTTGTATTTT-FAM

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3.3.4. Real Time PCR Procedure

A volume of 5 µl of Master Mix, 0.25 µl of Taqman genotyping assay, 3.75 µl of DNase, RNase free water, and 1 µl of template DNA were utilized for the Real-Time PCR. The total volume of reagents and reaction mixtures can also be found in (Table 3.3.4.1.).

First, a mixture containing Master Mix, DNase, RNase free water, and TaqMan genotyping assay was prepared and added to each well of a 96-well plate. Then, the template DNA samples were added one by one to the mixture. The plate was carefully covered and subjected to centrifugation at 3000 rpm for 2 minutes to ensure homogeneity and precipitation of liquids to the bottom. The plate was then placed into the PCR device and the Real-Time PCR reaction was initiated.

Table 3.3.4.1. The mixtures of Real-Time PCR reaction

The Agent	Quantity of Agent
Free DNase and RNase Water	3,75 µL
TaqMan Fast Advanced Master Mix	5 µL
TaqMan Genotyping Assay	0,25 µL
Template DNA	1 µL

The PCR process consists of three main steps: denaturation, annealing, and extension.

Denaturation step involves heating the reaction mixture to a high temperature to denature the DNA strands, breaking the hydrogen bonds between the complementary base pairs. The temperature for denaturation is typically around 95°C, and the duration is typically 15-30 seconds.

Annealing step involves cooling the reaction mixture to a temperature that allows the primers to anneal to the complementary DNA strands. The temperature for annealing depends on the melting temperature (Tm) of the primers and typically ranges from 60-70°C. The duration is typically 15-30 seconds.

The Tm for the XPC rs2228001 primer was 70°C and for DDB2 rs830083 was 60°C. The Tm can be calculated by the below equation.

Tm = 4°C x (number of G's and C's in the primer) + 2°C x (number of A's and T's in the primer)

Extension step involves heating the reaction mixture to a temperature that allows the Taq polymerase to extend the primers and synthesize new DNA strands. The temperature for extension is typically around 72°C, and the duration depends on the length of the DNA sequence to be amplified. The extension time is typically 1 minute per kilo base of DNA.

As can be seen in the (Table 3.3.4.2.) denaturation, annealing and extension processes were applied as 40 cycles.

Table 3.3.4.2. Real-Time PCR Conditions

Stages	Temperature ° C	Duration / Period of Time
Denaturation	95°C	15-30 seconds
Annealing	60-70°C	15-30 seconds
Extension	72°C	1 minute

40 Cycles

3.3.4. Statistical analysis

In this thesis, the student's t-test was used to obtain numeric values, and the information obtained from genotyping was analyzed in SPSS 27.0 using Fisher's Exact Tests and Chi-square tests for statistical analysis. The analysis aimed to assess the distribution of genotypes and alleles within the groups, and a P-value of less than 0.05 was considered statistically significant. Also the study evaluated the connection between the occurrence of XPC and DDB2 gene variant genotypes and the risk of OC by determining the odds ratios (ORs) and 95% confidence intervals (CIs).

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4. RESULTS

4.1. Demographic Characteristics

The differences in the distribution of selected characteristics between OC patients and controls are summarized in (Table 4.1.1) and not all participants responded to all questions, and some of them seemed to feel uneasy when asked certain questions, resulting in incomplete or vague answers.

There was a significant difference in the distributions of smoking ($p < 0.0001$) and alcohol consumption ($p < 0.0005$). However, there was no significant difference between the mean age of patients and controls (p-value= 0.582) and history of cancer (p-value= 0.412)

Statistically significant factors included menopausal status (premenopausal and postmenopausal), pregnancy status (number of pregnancies ≤ 1 or number of pregnancies > 1), and parity (number of births ≤ 1 or number of births > 1).

The rate of postmenopausal women in the OC group was higher (79.5%) than the control group (17.4%). Furthermore, the controls with a number of births less than or equal to one (number of births ≤ 1) had a significantly higher percentage (56.5%) than the patient group (27.3%). Also, the control group had a higher percentage of pregnancy status (number of pregnancies ≤ 1) (56.5%) compared to the patient group (22.7%).

Table 4.1.1 Demographics of ovarian cancer and healthy participants

Characteristics		Ovarian Cancer Patients (n=103)	Control (n=104)	P-Value
Age $\bar{x}$± SD (years)		53.12 ± 12.48	46.62 ± 14.24	0.582 (NS)
Body Mass Index $\bar{x}$± SD (kg/m2)		30.11 ± 5.89	23.761 ± 4.30	0.043 (S)
Fasting Blood Glucose $\bar{x}$± SD (mg/dl)		109.12 ± 33.47	86.85 ± 7.809	< 0.0005 (S)
Alcohol consumption	Yes %	(8.7%)	(19.2%)	< 0.0005 (S)
	No %	(60.2%)	(25.0%)	
	I prefer not to say	(31.1%)	(55.8%)	
Smoking	Yes %	(82.2%)	(55.3%)	< 0.0001 (S)
	No %	(17.8%)	(44.7%)	
History of Cancer	Yes %	(35.8%)	(43.5%)	0.412 (NS)
	No %	(64.2%)	(56.5%)	
Menopause	Postmenopausal %	(79.5%)	(17.4%)	< 0.0001 (S)
	Premenopausal %	(20.5%)	(82.6%)	
Parity	≤ 1	(27.3%)	(56.5%)	0.05 (S)
	>1	(72.7%)	(43.5%)	
Pregnant State	≤ 1	(22.7%)	(56.5%)	0.01 (S)
	>1	(77.3%)	(43.5%)	

(n: number of sample, $\bar{x}$± SD: mean value ± standard deviation, *(S)= significantly different ($p< 0.05$), NS= non-significant ($p>0.05$)) .

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Based on (Table 4.1.2) 103 OC patients were examined in the study. They were split between (20.5%) premenopausal and (79.5%) postmenopausal. Also, (27.3%) of respondents had a parity of 1 or less, (72.7%) had a parity of more than 1. (22.7%) of women reported being pregnant with one child or less, (77.3%) reported being pregnant with many children.

Stage I ovarian cancer was present in (23.8%) of cases, whereas stage II was present in (21.4%), stage III was present in (40.5%), and stage IV was present in (14.3%). (76.1%) of the patient who responded had metastases, (45.7%) had relapsed, and (72.1%) had undergone adjuvant treatment.

Serous tumors were the most prevalent subtype of epithelial tumors among those who responded, accounting for (55%) of all cases. Serous tumors were then followed by mixed epithelial tumors (15%), and mucinous tumors (10%), and endometriosis tumor (7.5%). With only (5%) of cases for each, sex-cord stromal tumors, and germ cell tumors. Also, less frequent for clear cell tumors with (2.5%).

The tumor marker proteins CA125, CEA, CA19-9, and CA15-3 were present at 84.1%, 14.3%, 25.7%, and 64.5% respectively with more than the normal range for them.

Table 4.1.2 Clinical and Treatment Characteristics of patients.

Clinical and Treatment Characteristics			**Percentage (%) n=103**
Tumor Marker Proteins	CA125	> 35 (U/mL)	84.1%
	CEA	> 5 (ng/mL)	14.3%
	CA19-9	> 37 (U/mL)	25.7%
	CA15-3	> 30 (U/mL)	64.5%
Menopause	Postmenopausal		(79.5%)
	Premenopausal		(20.5%)
Parity	≤ 1		(27.3%)
	>1		(72.7%)
Pregnant State	≤ 1		(22.7%)
	>1		(77.3%)
Metastasis	Yes		(76.1%)
	No		(23.9%)
Relapse	Yes		(45.7%)
	No		(54.3%)
Adjuvant Chemotherapy	Yes		(72.1%)
	No		(27.9%)
Surgery	Staging		(25%)
	Debulking		(42.5%)
	Staging and Debulking		(32.5%)
Stage of Ovarian Cancer	Stage I		(23.8%)
	Stage II		(21.4%)
	Stage III		(40.5%)
	Stage IV		(14.3%)
Types of Ovarian Cancer	Epithelial tumors - Serous tumors - Mucinous tumors - Endometriosis tumors - Clear cell tumors - Mixed epithelial tumors		 (55%) (10%) (7.5%) (2.5%) (15%)
	Germ cell tumors		(5%)
	Sex-cord stromal tumors		(5%)

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4.2. Analysis of Genotype and Allele Related to the Patient and Control Groups

The genotype distributions of DDB2 rs830083 in the cases and the controls are shown in (Table 4.2.1). There was a significant association between the homozygote mutant genotype (CC) and heterozygote genotype (GC) with ovarian cancer risk (p=0,038) (p=0.036) respectively, but not for the homozygote wild type genotype (GG). In the patient group, the genotype frequencies of GG, GC, and CC genotypes were 1%, 22.3%, and 76.7%, respectively, while in the control group, they were 1%, 35.5%, and 63.5%. The G allele was found to be more frequent in the control group (19%) compared to the patient group (12.2%) and was significantly associated with OC risk (p=0.038), whereas the C allele did not show any significant differences between the groups (p=0.990).

Table 4.2.1. The distribution of genotypes and alleles for the DDB2 gene was compared between the patient and control groups.

DDB2 Genotypes	Patient Group (n=103)	Control Group (n=104)	P-Value	Odd Ratio (OR)	Confidence Interval 95% (CI)
GG	n=1 (1%)	n=1 (1%)	0.995 (NS)	1.010	0.062 -16.36
GC	n= 23 (22.3%)	n= 37 (35.5%)	0.036 (S)	0.521	0.282 - 0.961
CC	n= 79 (76.7%)	n= 66 (63.5%)	0.038 (S)	1.895	1.033 - 3.476
Alleles Distributions					
G Allele	n=25 (12.2%)	n=39 (19%)	0.038 (S)	0.528	0.288 - 0.968
C Allele	n= 181 (87.8%)	n=103 (81%)	0.995 (NS)	0.990	0.061 - 16.04

`

The XPC polymorphism was investigated in patients with OC and a healthy control group, and significant results were obtained between the two groups (p=0.042) as shown in (Table 4.2.2.). A clear correlation between the groups, with a calculated (p-value=0.035) for the homozygote mutant genotype, and (p-value=0.049) for the homozygote wild-type genotype. The frequencies of the homozygote wild type (TT), heterozygote type (GT), and homozygote mutant type (GG) were determined to be 27.9%, 52.9%, and 19.2% in the control group, and 16.5%, 51.5%, and 32% in the OC group, respectively. A comparison of the T allele between the two groups showed that it was lower in the patient group (n=87, 42%) than in the control group (n=113, 54.4%). In contrast, the G allele was higher in the patient group (n=119, 58%) than in the control group (n=95, 45.6%).

Table 4.2.2. The distribution of genotypes and alleles for the XPC gene was compared between the patient and control groups.

XPC Genotypes	**Patient Group (n=103)**	**Control Group (n=104)**	**P-Value**	**Odd Ratio (OR)**	**Confidence Interval 95% (CI)**
TT	n=17 (16.5%)	n=29 (27.9%)	0.049 (S)	0.511	0.261 - 1.003
GT	n=53 (51.5%)	n=55 (52.9%)	0.837 (NS)	0.944	0.547 - 1.629
GG	n=33 (32%)	n=20 (19.2%)	0.035 (S)	1.980	1.044 - 3.754
Alleles Distributions					
T Allele	n= 87 (42%)	n=113 (54.4%)	0.035 (S)	0.505	0.266 - 0.957
G Allele	n=119 (58%)	n=95 (45.6%)	0.049 (S)	1.956	0.997 - 3.838

The distribution of OR for various genotypes is illustrated in (Chart 4.2.) based on the data from (Table 4.2.1.) and (Table 4.2.2.) the OR for the DDB2 rs830083 CC and XPC rs2228001 GG genotypes were found to be 1.895 and 1.98, respectively, when comparing the control and patient groups. However, for individuals carrying both the DDB2 CC and XPC GG genotypes, the odds ratio was 0.389.

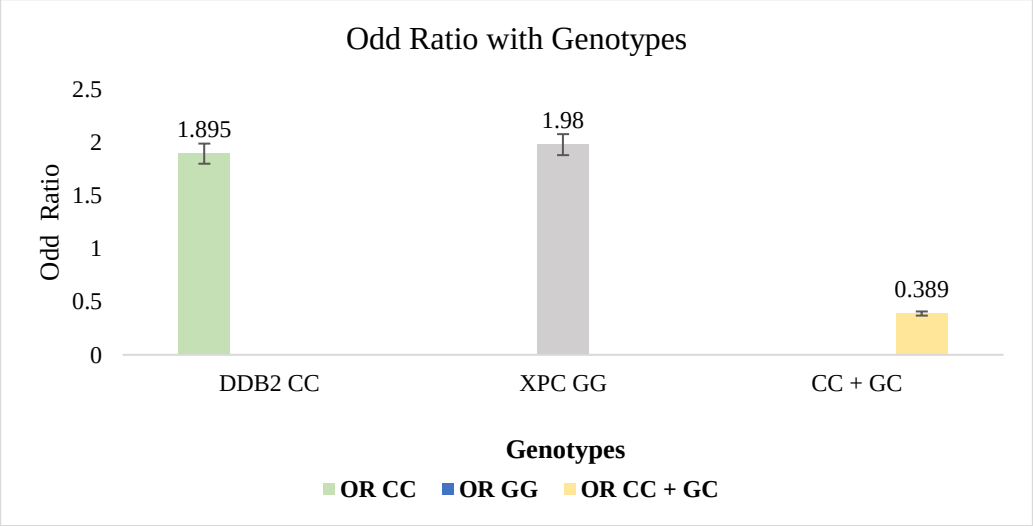

Chart 4.2. The distribution of odd ratios with different types of genotypes.

4.3. Distribution of genotype at patients with demographic data

Table 4.3.1 displays the distribution levels of various tumor markers, including CA125, CEA, CA19-9, and CA15-3 among individuals with different genotypes of the DDB2 and XPC genes.

The CA125, CEA, CA19-9, and CA15-3 levels were not significant association with p-value = 0.749, 0.162, 0.162, and 0.635 respectively for the DDB2 gene and p-value = 0.727, 0.783, 0.934, and 0.754 respectively for the XPC gene.

However, among individuals with the GC genotype of the DDB2 gene, there was a high level of the CA125 marker for OC, while the CEA marker was high among those with the same genotype at a rate of (33.3%). In contrast, the GG genotype was associated with high levels of the CA19-9 and CA15-3 markers at rates of (100%).

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The TT genotype of the XPC gene was associated with high levels of CEA and CA15-3 markers at rates of (20%) and (75%), respectively. Additionally, the GT genotype had a high percentage (87%) of the CA125 genotype, while the GG genotype had a high percentage (70%) of the CA15-3 marker for OC.

Table 4.3.1. The distribution levels of tumor marker proteins with different patient genotypes for the XPC and DDB2 gene.

			DDB2 rs830083			**P-Value**	**XPC rs2228001**			**P-Value**
Genotypes			GG	GC	CC		TT	GT	GG	
Tumor Marker Proteins	CA125	≤35 (U/mL)	0%	10 %	18.2 %	0.749 (NS)	25%	13%	15.4 %	0.727 (NS)
		>35 (U/mL)	100 %	90 %	81.8 %		75%	87%	84.6 %	
	CEA	≤5 (ng/mL)	100 %	66. 7%	92%	0.162 (NS)	80%	89.5 %	81.8 %	0.783 (NS)
		>5 (ng/mL)	0%	33. 3%	8%		20%	10.5 %	18.2 %	
	CA19-9	≤ 37 (U/mL)	0%	87. 5%	73.1 %	0.162 (NS)	75%	76.2 %	70%	0.934 (NS)
		> 37 (U/mL)	100 %	12. 5%	26.9 %		25%	23.8 %	30%	
	CA15-3	≤ 30 (U/mL)	0%	44. 4%	33.3 %	0.635 (NS)	25%	41.2 %	30%	0.754 (NS)
		> 30 (U/mL)	100 %	55. 6%	66.7 %		75%	58.8 %	70%	

Table 4.3.2 shows the distribution of metastasis and relapse among patients with various genotypes for the XPC and DDB2 genes. The findings suggest that there is no significant association between different genotypes with metastasis and relapse for XPC and DDB2. The p-values of metastasis and relapse for XPC were 0.565 and 0.332 and for DDB2 0.099 and 0.280 respectively. The GC genotype for the DDB2 gene had a high level of metastasis (90.9%)

and relapse (63.65), while the GT genotype of the XPC gene had (82.6%) and (56.5%) respectively.

Table 4.3.2. The distribution of metastasis and relapse with different patient genotypes for the XPC and DDB2 genes**.**

		DDB2 rs830083			**P-Value**	**XPC rs2228001**			**P-Value**
Genotypes		GG	GC	CC		TT	GT	GG	
Metastasis	Yes	0%	90.9%	73.5%	0.099 (NS)	66.7%	82.6%	71.4%	0.565 (NS)
	No	100%	9.1%	26.5%		33.3%	17.4%	28.6%	
Relapse	Yes	0%	63.6%	41.2%	0.280 (NS)	33.3%	56.5%	35.7%	0.332 (NS)
	No	100%	36.4%	58.8%		66.7%	43.5%	64.3%	

A comparison of XPC and DDB2 genotypes with the stages of ovarian cancer in the patient group is shown in (Table 4.3.3.).

The analysis reveals that there is no statistically significant association between XPC and DDB2 genotypes and stages of OC, with p-values of 0.972 and 0.658, respectively. Among the carriers of the TT genotype of the XPC gene, 37.5% were found to have stage I and III of OC. Also, the patient carrier with the GG genotype of the DDB2 gene was diagnosed with stage II OC.

Table 4.3.3. The percentage distributions of XPC and DDB2 genotypes in comparison with the stage I, II, III, and IV for ovarian cancer patients.

		DDB2 rs830083			**P-Value**	**XPC rs2228001**			**P-Value**
Genotypes		GG	GC	CC		TT	GT	GG	
Stages	Stage I	0%	30%	22.6%	0.658 (NS)	37.5%	19%	23.1%	0.972 (NS)
	Stage II	100%	20%	19.4%		12.5%	23.8%	23.1%	
	Stage III	0%	40%	41.9%		37.5%	42.9%	38.5%	
	Stage IV	0%	10%	16.1%		12.5%	14.3%	15.4%	

Table 4.3.4 shows a comparison between XPC and DDB2 genotypes and various ovarian cancer types within the patient group. There were no statistically significant findings with XPC and DDB2 genes (p=0.919, 0.08) respectively.

In serous tumors, the XPC homozygote wild type (TT), heterozygote (GT), and homozygote mutant type (GG) distributions were calculated respectively as 22.6%, 50%, and 58.3% while DDB2 homozygote wild type (GG), heterozygote (GC) and homozygote mutant type (CC) distributions were calculated respectively as 0%, 33.3%, and 63.3%. In mixed epithelial tumors with the XPC gene, the GG genotype had 8.3%, GT had 20% and TT had 12.5%. The GG with the DDB2 gene had germ cell tumors.

Table 4.3.4. The percentage distributions of XPC and DDB2 genotypes in comparison with ovarian cancer types in the patient group.

		DDB2 rs830083			**P-Value**	**XPC rs2228001**			**P-Value**
Genotypes		GG	GC	CC		TT	GT	GG	
Types of OC	Serous tumors	0%	33.3%	63.3%	0.08 (S)	22.6%	50%	58.3%	0.919 (NS)
	Mucinous tumors	0%	22.2%	6.7%		12.5%	5%	16.7%	
	Endometriosis tumors	0%	22.2%	3.3%		0%	10%	8.3%	
	Clear cell tumors	0%	0%	3.3%		0%	5%	0%	
	Mixed epithelial tumors	0%	22.2%	13.3%		12.5%	20%	8.3%	
	Germ cell tumors	100%	0%	3.3%		12.5%	5%	0%	
	Sex-cord stromal tumors	0%	0%	6.7%		0%	5%	8.3%	

The distribution of adjuvant chemotherapy among patients with different genotypes for the XPC and DDB2 genes is shown in (Table 4.3.5.). The results indicate that there is no significant association between DDB2 and XPC genotypes and adjuvant chemotherapy, with p-values of 0.645 and 0.839, respectively. Among XPC genotypes, the distribution of adjuvant chemotherapy for homozygous wild type (TT), heterozygous (GT), and homozygous mutant

type (GG) was found to be 75%, 68.2%, and 76.9%, respectively. Similarly, among DDB2 genotypes, the distribution of adjuvant chemotherapy for homozygous wild type (GG), heterozygous (GC), and homozygous mutant type (CC) was found to be 100%, 80%, and 68.8%, respectively.

Table 4.3.5. The distributions of adjuvant chemotherapy among the patient group based on their XPC and DDB2 genotypes.

		DDB2 rs830083			**P-Value**	**XPC rs2228001**			**P-Value**
Genotypes		GG	GC	CC		TT	GT	GG	
Adjuvant Chemotherapy	Yes	100%	80%	68.8%	0.645 (NS)	75%	68.2%	76.9%	0.839 (NS)
	No	0%	20%	31.3%		25%	31.8%	23.1%	

4.4. Statistical Evaluation of Real-Time PCR Results

The allelic discriminations in our study were automatically assessed using the software of the 7500 Fast-Real Time PCR Instrument. The fluorescence irradiation readings and interpretations were based on the dyes present in the probes. Specifically, the FAM dye showed as a blue color for both figures, while the VIC dye exhibited a green color. The ROX dye served as a reference color for comparing the FAM and VIC dyes. However, it is important to note that for certain samples, discrimination between alleles could not be achieved. In such cases, the Thermo Fisher Cloud platform was utilized to determine the undetermined samples. Our experiment was conducted multiple times for patients and control samples, (Figure 4.4.1. and Figure 4.4.2.) show some of the analyses of allelic discrimination through the examination and interpretation of radiance curves.

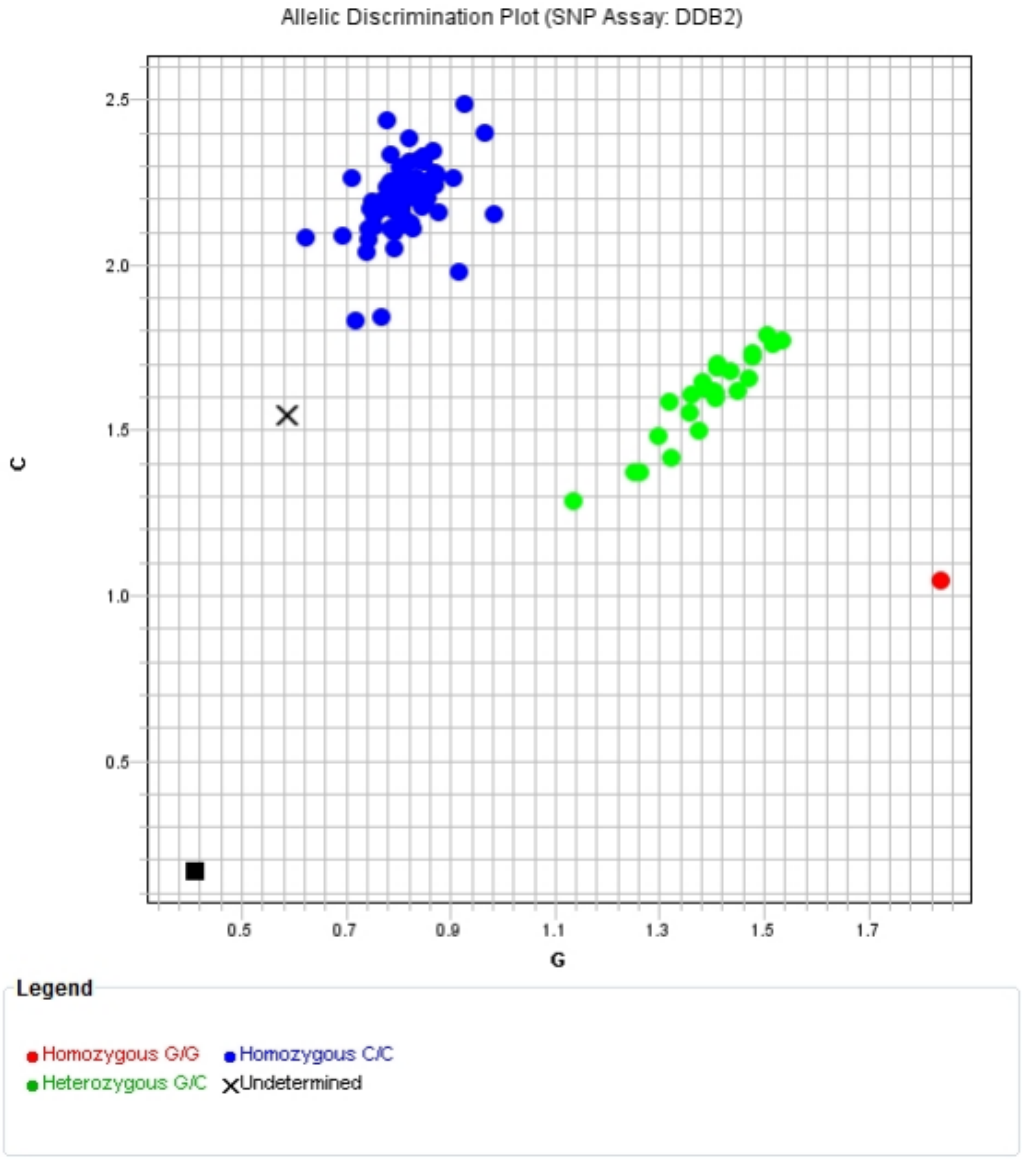

Figure 4.4.1. Allelic Discrimination Analysis of DDB2 genotypes (homozygote mutant genotype (CC), heterozygote genotype (GC) and homozygote wild type genotype (GG)).

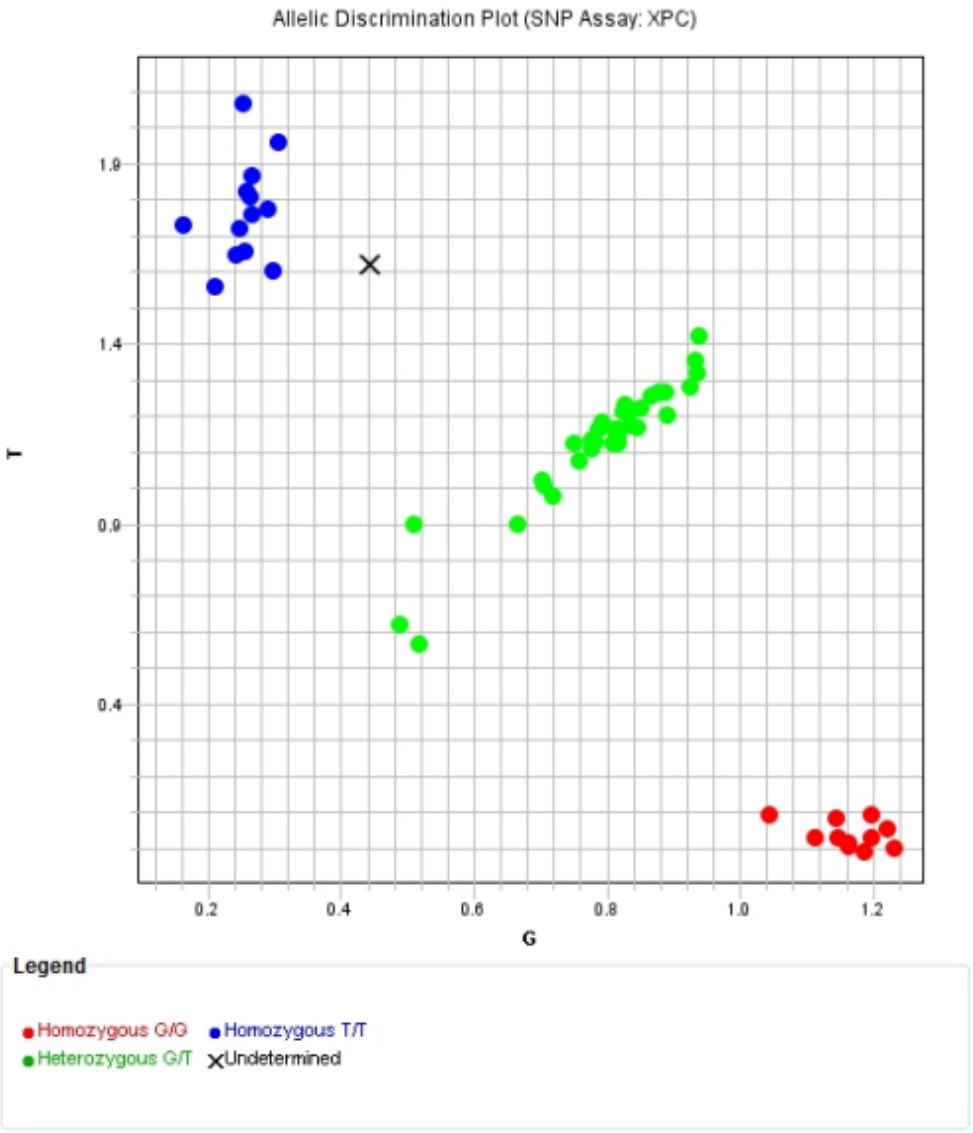

Figure 4.4.2. Allelic Discrimination Analysis of DDB2 genotypes (Homozygote wild type (TT), heterozygote type (GT), and homozygote mutant type (GG)).

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The y-axis of an amplification plot represents the level of fluorescence intensity or signal generated by a fluorescent dye, while the x-axis represents the number of PCR cycles. During the early cycles, the fluorescence signal is usually low or negligible. As the PCR progresses and the target DNA is amplified, the fluorescence signal increases.

(Figure 4.4.3.) Presents amplification plots depicting of the DDB2 gene with the C allele. The threshold value, represented by a gray line, is indicated as 0.084. Conversely, (Figure 4.4.4.) displays amplification plots of the G allele of the same gene, with the threshold value (0.021) denoted by a pink line.

Moving on to the XPC gene, (Figure 4.4.5.) exhibits the amplification plot of the G allele, and its corresponding threshold value is represented by a brown line at 0.014. On the other hand, (Figure 4.4.6.) showcases the amplification plot of the T allele for the XPC gene, with a yellow line denoting the threshold value at 0.059.

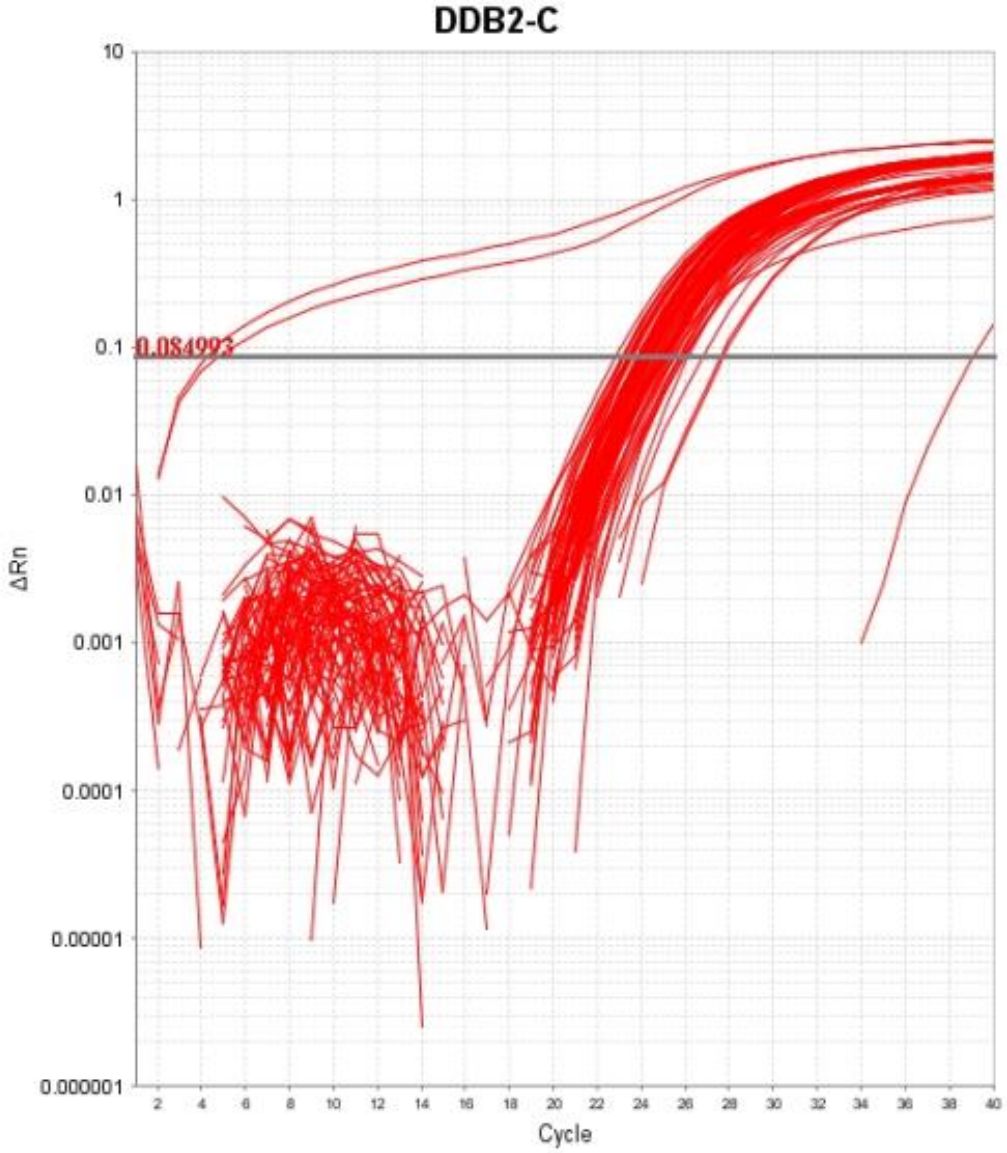

Figure 4.4.3. Amplification plot display of C allele with DDB2 gene.

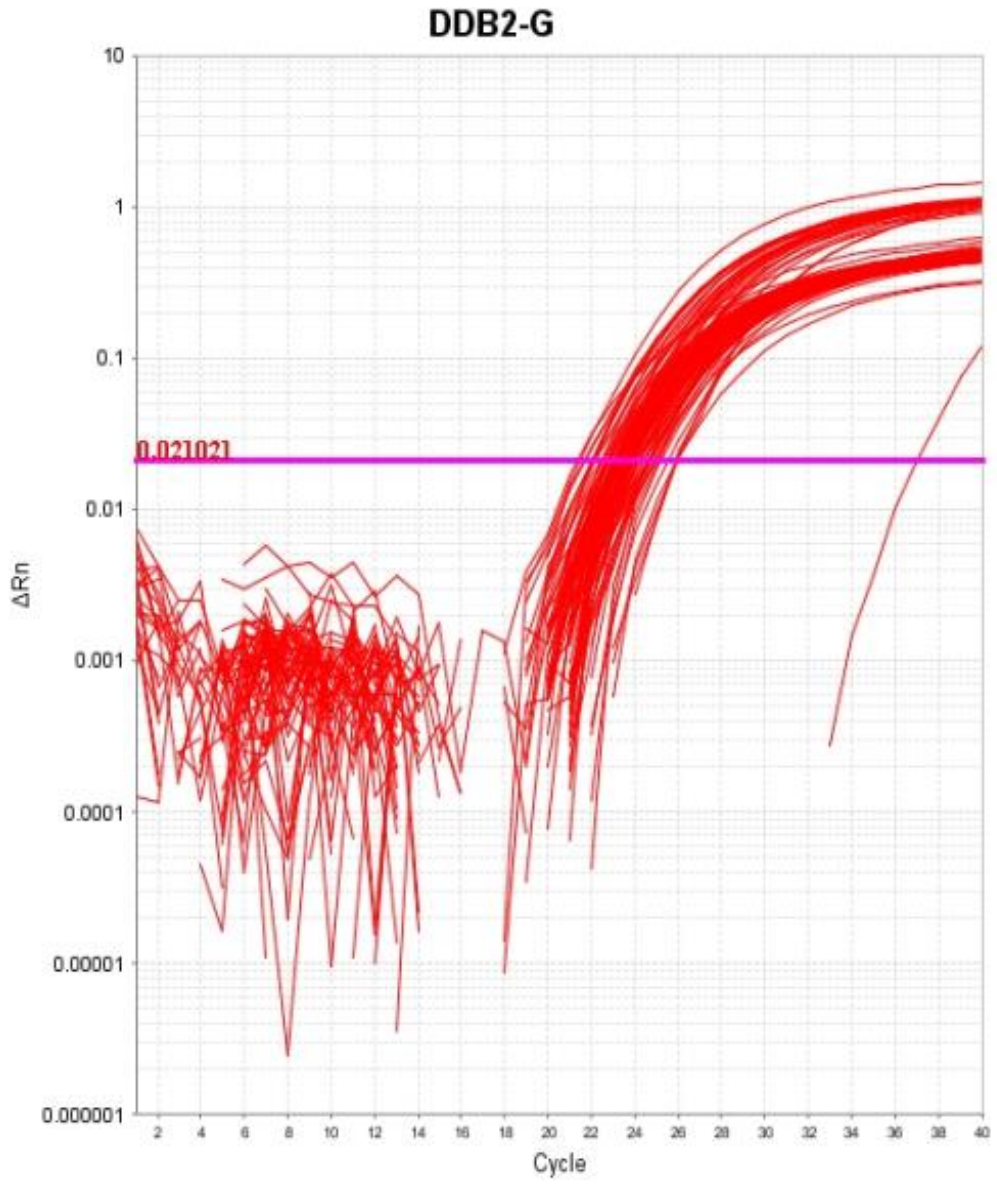

Figure 4.4.4. Amplification plot display of G allele with DDB2 gene.

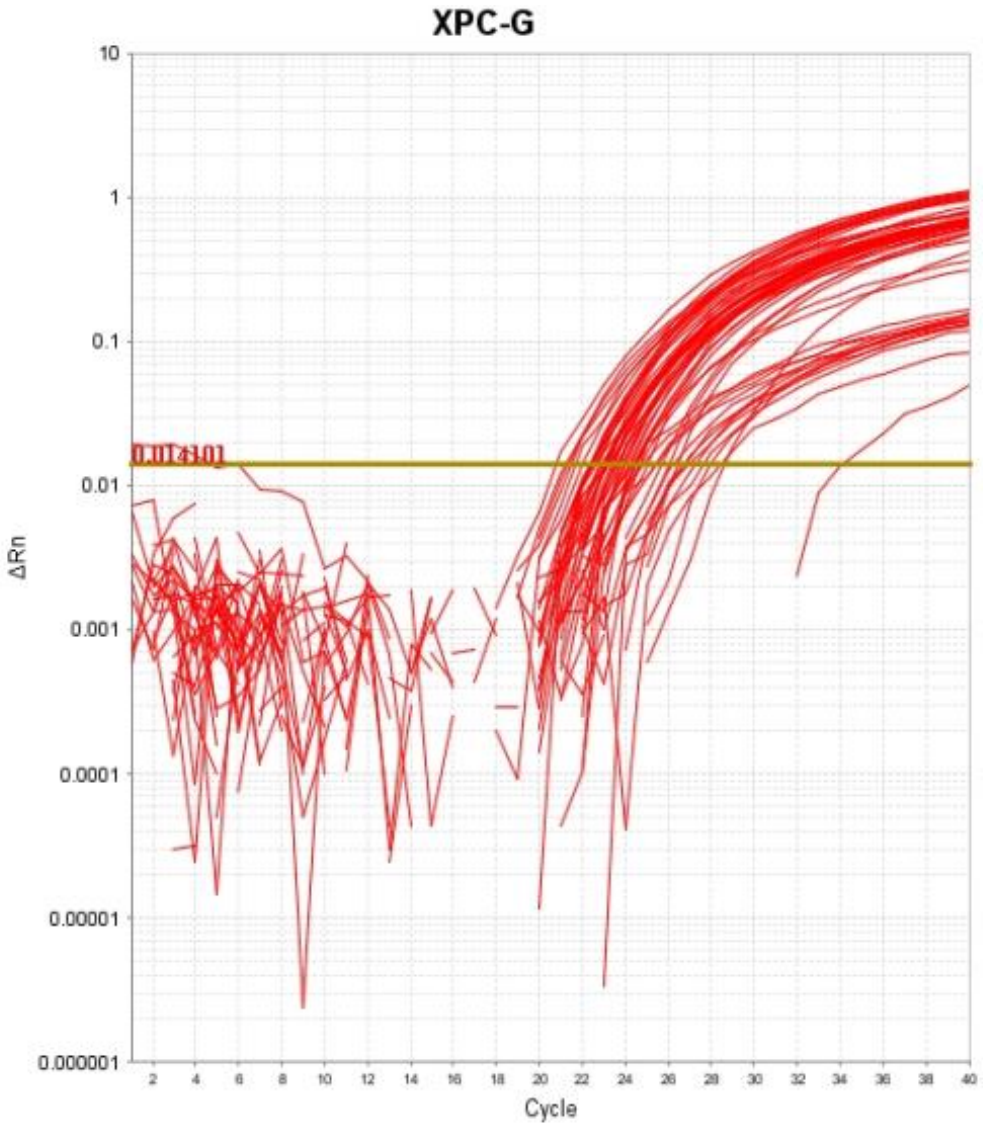

Figure 4.4.5. Amplification plot display of G allele with XPC gene.

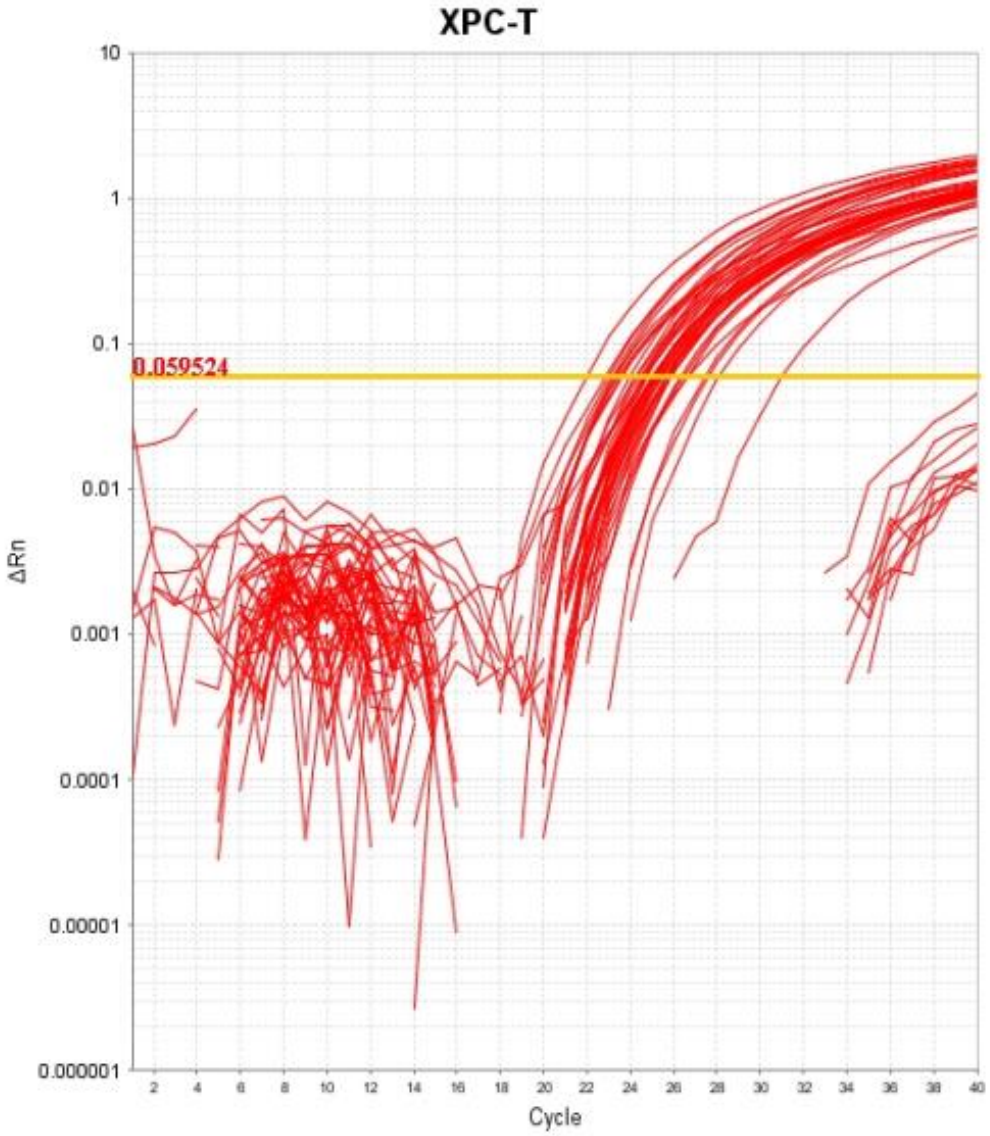

Figure 4.4.6. Amplification plot display of T allele with XPC gene.

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5. DISCUSSION

Ovarian cancer (OC) is the fifth most fatal disease among women, and it is considered the deadliest form of cancer affecting women (101).

Epithelial ovarian cancer is the most lethal cancer affecting the female reproductive system, particularly highly serous tumors (102). Our study revealed that (75%) of ovarian cancer patients had epithelial tumors, with a high percentage of these being serous tumors (55%), followed by mucinous tumors (10%), endometriosis tumors (7.5%), and mixed epithelial tumors (2.5%).

Protein markers such as CA125, CEA, CA19-9, and CA15-3 are used in the diagnosis of OC, but their diagnostic sensitivity and specificity are not considered high enough (103). Numerous studies have examined the serum CA125 levels in patients with OC and have found that approximately 80% of patients with advanced OC have elevated levels of CA125 in their blood (104). These results are similar to our result (84.1%) of OC patients who had a CA125 level of more than 35 (U/mL).

On the other hand, studies have also shown that CA125 levels can be elevated in individuals without OC. This decreases the diagnostic specificity of CA125 as a biomarker for ovarian cancer (103).

CEA was utilized as the initial biomarker for OC. However, it was rapidly replaced by CA125 because CEA displayed lower sensitivity and specificity in detecting OC using serum from patients, in contrast to CA125 (62). We found that in (84.1%) of patients with OC, CA125 levels were elevated, while only (14.3%) of those patients had elevated CEA levels. These findings suggest that CA125 is a much more effective marker for OC than CEA and it is low sensitivity in detecting OC.

Demographic considerations indicate that the average age of OC patients is (53.12) years, with a range of 18 to 85 years. The probability of OC rises with age, with the highest prevalence between the ages of 50 and 60 (105).

Smoking had an especially adverse effect on developing tumors in OC. Smoking was found to be statistically significant (p-value < 0.0001) in our study, and it is more prevalent among those with OC (82.2%) compared to the healthy group (55.3%). The results suggest that smoking may be a significant risk factor for OC (106).

In our study, (19.2%) of the healthy group consumed alcohol, whereas (8.7%) of the patients consumed alcohol, indicating that alcohol consumption may no effect on OC risk (107).

In our research, the majority of our patient participants, specifically (79.5%), were in the postmenopausal phase. In female who have reached the postmenopausal phase, higher levels of certain circulating androgens or hormones such as androstenedione, testosterone, and dehydroepiandrosterone (DHEA) have been linked to an increased risk of OC. Additionally, it is worth noting that many female after menopause undergo menopausal hormonal therapy, which has been associated with an elevated risk of developing OC (108).

A significant association was observed between the development of OC and individuals who had a familial history of the disease. In our thesis, the majority of patients (64.2%) had no cancer history in their family, while (35.8%) of our patients had cancer history in their family (109). While having a family history of OC raises the risk, a high percentage of OC cases occur in people without family history of the disease. Other risk factors that contribute to the development of OC include age, smoking, and menopausal hormones.

Each term of pregnancy has the ability to reduce the risk of OC around 19%, and each birth experienced by women has the potential to reduce the risk around 6%. However, our study found that the patient group (77.3%), (72.7%) had more multiple pregnancies and parity respectively than the control group (43.5%) for both. The disparity might be related to differences in the size and composition of the research sample (110).

Our study found that (54.8%) of patients with OC were diagnosed at an advanced stage (III or IV), which is consistent with previous research (111). This is likely due to the fact that the symptoms of OC are nonspecific and can be easily confused with symptoms that women experience regularly, such as abdominal bloating, pain, frequent urination, feeling full quickly, or changes in bowel movements (5).

Metastasis is a crucial factor in the progression of cancer and might make treatment more difficult. It frequently denotes an advanced stage of OC. The disease has metastasis to (76.1%) of our cases. The main course of therapy for advanced OC is debulking surgery (42.5%) with the aim to removal of all detectable tumors to be followed by chemotherapy (72.1%). Despite the fact that chemotherapy was the most commonly used treatment option relapses remain common in these patients (47.8%) (112, 113).

DNA repair activities are critical for the genome's integrity and stability. Polymorphisms in multiple DNA repair genes, most of which are represented by SNP, have the potential to modify individual DNA repair capabilities and increase the risk of cancer (114).

In this study, we investigated the genetic link between OC ability and two SNPs in genes implicated in the NER pathway (XPC and DDB2). These genetic variants have been genotyped in 103 patient and 104 controls.

XPC rs2228001 (Lys939Gln) at exon 16 has been linked to a variety of cancers. As a result, we investigate for the first time the relationship between XPC rs2228001 and OC in the Turkish population.

Individuals carrying the homozygous TT genotype at the XPC gene had a lower risk of OC (OR 0.511 CI 95% 0.261 - 1.003), whereas individuals carrying the GG polymorphism at the XPC gene had a higher risk of OC (OR 1.980 CI 95% 1.044 - 3.754) with p-value=0.035. Also, there is a significant association between the T allele and a lower risk of OC (p-value = 0.035), and it can reduce 2 times the risk of OC.

Regarded as published information focused on the significance of XPC variants in the modulation of an individual's risk of developing OC, the findings of Zhiguang Zhao's study on the Chinese population indicated that patients having rs2228001 CC/AC variant genotype had an increased chance of OC than those with those having AA variant genotype (adjusted OR = 1.72, 95% CI = 1.02-2.92, P=0.043). And this is identical to our results with a different allele type (G instead of C) (T instead of A) (100).

The XPC rs2228001 intron gene expression pattern differs between diseases. Several investigations have found that the XPC rs2228001 intron 11 splice acceptor site polymorphism is linked to an increase in exon 12 skipping, resulting in decreased DNA repair capacity with colorectal cancer [18]. Another study found that the XPC rs2228001 polymorphism causes a missense variant at position 939, specifically a glutamine to lysine change [19]. Furthermore, new evidence reveals that the XPC 939 alteration is associated with an increased frequency of p53 mutations with breast cancer [20]. Further research into the XPC rs2228001 intron and its effect on gene expression in the setting of OC may give more enlightening results for future studies and outcomes.

DDB2 rs830083 is an intron variant that has been linked to a variety of cancers. We investigated the relationship between DDB2 rs830083 and OC in the Turkish population for the first time. Also, there are no studies that suggest a direct link between DDB2 rs830083 variations and the risk of OC.

With a statistically significant p-value of 0.036, the presence of the homozygous GC genotype at the DDB2 gene is related with a decreased risk of OC (OR 0.521, CI 95% 0.282 - 0.961). On the other hand, Individuals with the CC polymorphism at the DDB2 gene had increased risk of OC (OR 1.895, CI 95% 1.033 - 3.476) with a p-value of 0.038. Furthermore, the G allele is associated with a decreased incidence of OC (p-value = 0.038), with 2 fold.

In a previous study focusing on gastric cancer, it was found that individuals with the DDB2 rs830083 GG genotype had a significantly higher risk of gastric cancer compared to those with the wild-type CC genotype (OR = 2.32, 95% CI = 1.75-3.08) (115). Another study from Zhibin Hu. that looked at DDB2 rs830083 and lung cancer found that the CG and GG genotypes had been linked with a considerably higher risk of lung cancer than the rs830083 CC genotype (116). And this is identical to our results with a different allele type (C instead of G) (G instead of C).

Previous study indicates that the mechanism linked to the intron DDB2 rs83008 variation has the ability to change alternative splicing patterns. This has major consequences for changing gene transcription regulation and, as a result, influencing the activity of certain proteins

implicated in the NER pathway. A change in NER capacity may affect the frequency of DNA mutations caused by unrepaired damaged DNA (117). Some study suggests that certain DDB2 variations, notably rs830083, may impact the association or function of p53, possibly impacting DNA repair pathways (118). Furthermore, DDB2 rs830083 has been found as a possible biomarker in several investigations. This means that if the rs830083 variant is closely connected to other neighboring variants, it is likely that they are inherited as a haplotype and cause gene expression (116).

Despite its potential significance, the specific molecular medicine mechanism behind DDB2 rs830083 actions is unclear. As a result, more research is needed, particularly in the context of OC, to acquire a better understanding of its functional consequences.

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6. CONCLUSION

In conclusion, ovarian cancer (OC) is a lethal disease that primarily affects women. Epithelial tumors have the most prevalent form. Protein markers like CA125 and CEA are commonly used to diagnose OC, but their accuracy and specificity are subpar. Age and tobacco have been linked to OC risk, but alcohol use is not shown to have a substantial effect. OC risk is also affected by family history, hormonal variables, and pregnancy history. The majority of OC cases are discovered at a late stage, and metastasis is common.

Our research sheds light on the genetic elements that contribute to OC. We investigated the association between two single nucleotide polymorphisms (SNPs) in genes implicated in NER pathway, XPC rs2228001 and DDB2 rs830083, and OC risk.

Individuals with the homozygous TT genotype exhibited a smaller chance of OC, whereas persons with the GG polymorphism showed a greater chance of developing it. The existence of the T allele was related with a lower risk of OC.

Concerning DDB2 rs830083, we discovered that persons who carried the homozygous GC genotype showed a lower risk of OC, whereas participants had the CC polymorphism had a higher risk. The existence of the G allele was linked to a reduced risk of OC.

The mechanisms by which these genetic variations affect OC risk are not clear. However, these variations can affect DNA repair ability, and gene expression, potentially influencing the frequency of DNA mutations generated by unrepaired damaged DNA.

It is important to note that our study only looked at one demographic, and more research on different populations is needed to corroborate our findings. Understanding the genetic components that contribute to OC risk can lead to better risk estimation, early detection, and individualized treatment approaches. Future studies should focus on elucidating the underlying molecular pathways linked to these genetic variations to gain a better understanding of OC growth and enhance clinical outcomes for those who are affected.

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8. APPENDIX

8.1. Raw Material

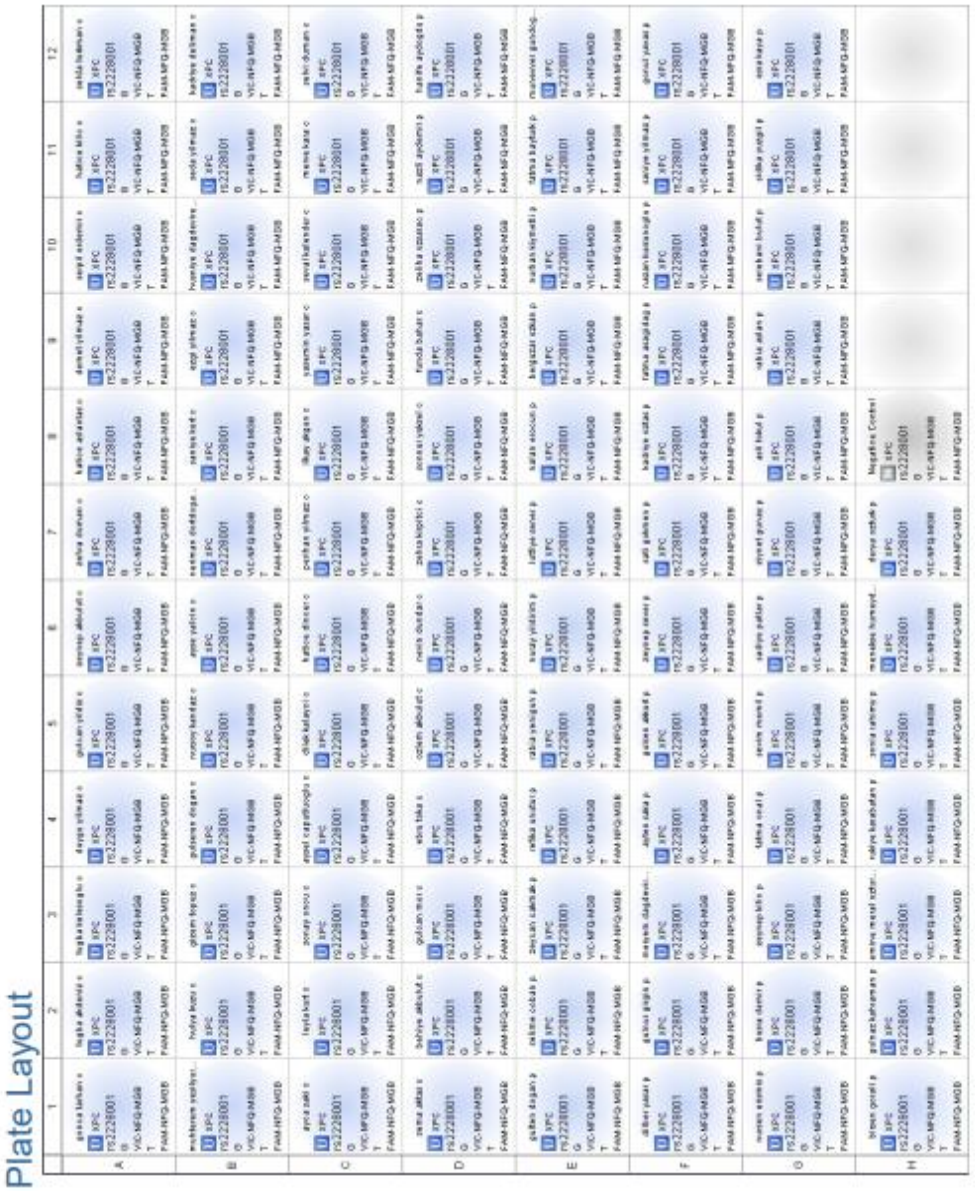
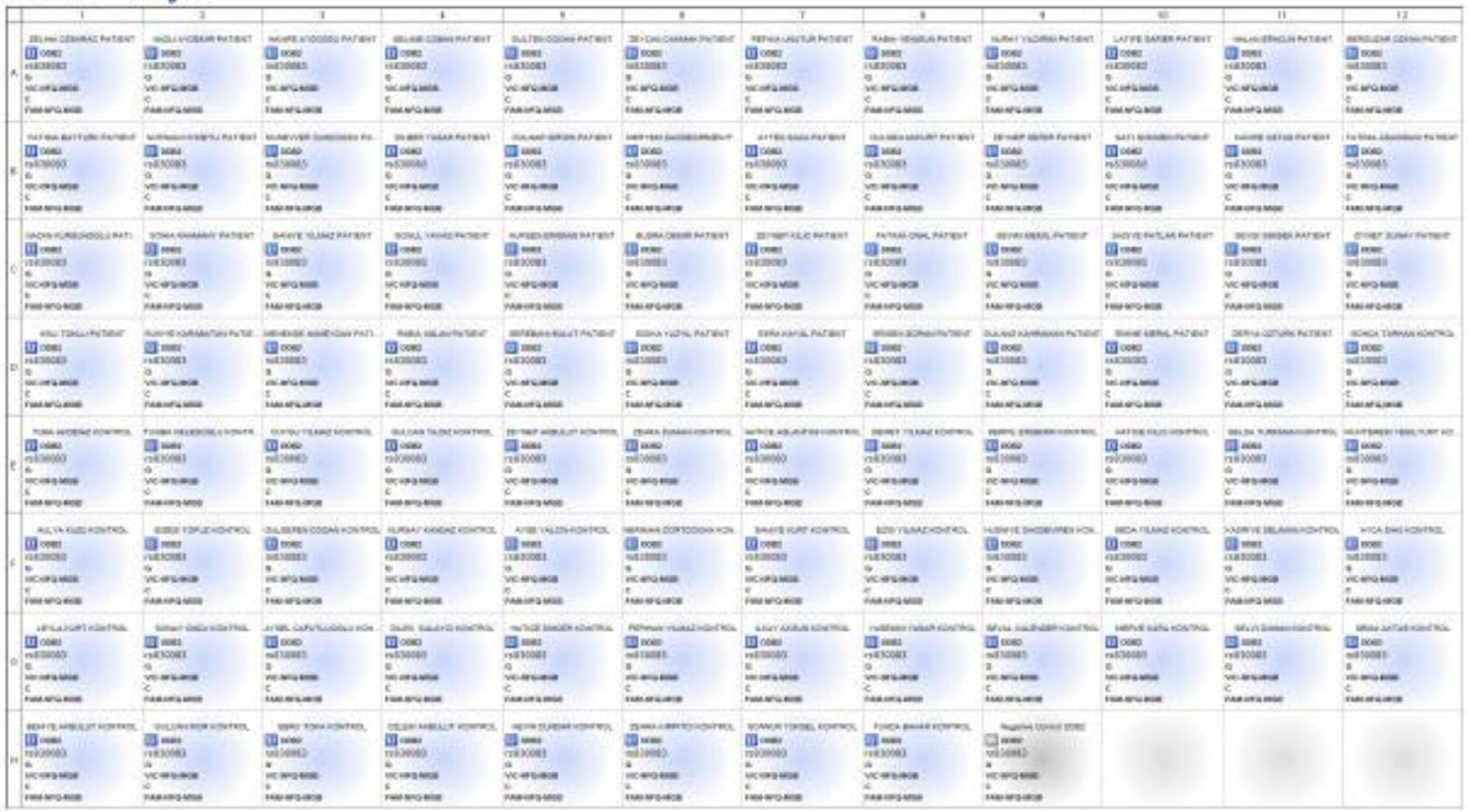


Plate Layout



Type * DDB2_rs830083

Crosstab

			DDB2_rs830083			
			CC	GC	GG	Total
Type	Control	Count	66	37	1	104
		% within Type	63.5%	35.6%	1.0%	100.0%
		% within DDB2_rs830083	45.5%	61.7%	50.0%	50.2%
		% of Total	31.9%	17.9%	0.5%	50.2%
	Patient	Count	79	23	1	103
		% within Type	76.7%	22.3%	1.0%	100.0%
		% within DDB2_rs830083	54.5%	38.3%	50.0%	49.8%
		% of Total	38.2%	11.1%	0.5%	49.8%
Total		Count	145	60	2	207
		% within Type	70.0%	29.0%	1.0%	100.0%
		% within DDB2_rs830083	100.0%	100.0%	100.0%	100.0%
		% of Total	70.0%	29.0%	1.0%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	4.427[a]	2	.109
Likelihood Ratio	4.459	2	.108
N of Valid Cases	207		

a. 2 cells (33.3%) have expected count less than 5. The minimum expected count is 1.00.

Type * GE2TYPE_GG

Crosstab

			GE2TYPE_GG		
			N	Y	Total
Type	Control	Count	103	1	104
		% within Type	99.0%	1.0%	100.0%
		% within GE2TYPE_GG	50.2%	50.0%	50.2%
		% of Total	49.8%	0.5%	50.2%
	Patient	Count	102	1	103
		% within Type	99.0%	1.0%	100.0%
		% within GE2TYPE_GG	49.8%	50.0%	49.8%
		% of Total	49.3%	0.5%	49.8%
Total		Count	205	2	207
		% within Type	99.0%	1.0%	100.0%
		% within GE2TYPE_GG	100.0%	100.0%	100.0%
		% of Total	99.0%	1.0%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.000[a]	1	.995		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.000	1	.995		
Fisher's Exact Test				1.000	.749
N of Valid Cases	207				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.00.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Type (Control / Patient)	1.010	.062	16.363
For cohort GE2TYPE_GG = N	1.000	.974	1.027
For cohort GE2TYPE_GG = Y	.990	.063	15.623
N of Valid Cases	207		

Type * GE2TYPE_CC

Crosstab

			GE2TYPE_CC		
			N	Y	Total
Type	Control	Count	38	66	104
		% within Type	36.5%	63.5%	100.0%
		% within GE2TYPE_CC	61.3%	45.5%	50.2%
		% of Total	18.4%	31.9%	50.2%
	Patient	Count	24	79	103
		% within Type	23.3%	76.7%	100.0%
		% within GE2TYPE_CC	38.7%	54.5%	49.8%
		% of Total	11.6%	38.2%	49.8%
Total		Count	62	145	207
		% within Type	30.0%	70.0%	100.0%
		% within GE2TYPE_CC	100.0%	100.0%	100.0%
		% of Total	30.0%	70.0%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.322[a]	1	.038		
Continuity Correction[b]	3.714	1	.054		
Likelihood Ratio	4.351	1	.037		
Fisher's Exact Test				.048	.027
N of Valid Cases	207				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 30.85.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Type (Control / Patient)	1.895	1.033	3.476
For cohort GE2TYPE_CC = N	1.568	1.018	2.416
For cohort GE2TYPE_CC = Y	.827	.691	.991
N of Valid Cases	207		

Type * GE2TYPE_GC

Crosstab

			GE2TYPE_GC		
			N	Y	Total
Type	Control	Count	67	37	104
		% within Type	64.4%	35.6%	100.0%
		% within GE2TYPE_GC	45.6%	61.7%	50.2%
		% of Total	32.4%	17.9%	50.2%
	Patient	Count	80	23	103
		% within Type	77.7%	22.3%	100.0%
		% within GE2TYPE_GC	54.4%	38.3%	49.8%
		% of Total	38.6%	11.1%	49.8%
Total		Count	147	60	207
		% within Type	71.0%	29.0%	100.0%
		% within GE2TYPE_GC	100.0%	100.0%	100.0%
		% of Total	71.0%	29.0%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.412[a]	1	.036		
Continuity Correction[b]	3.792	1	.052		
Likelihood Ratio	4.443	1	.035		
Fisher's Exact Test				.046	.025
N of Valid Cases	207				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 29.86.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Type (Control / Patient)	.521	.282	.961
For cohort GE2TYPE_GC = N	.829	.695	.989
For cohort GE2TYPE_GC = Y	1.593	1.023	2.482
N of Valid Cases	207		

Type * G_ALLELE

Crosstab

			G_ALLELE		
			N	Y	Total
Type	Control	Count	66	38	104
		% within Type	63.5%	36.5%	100.0%
		% within G_ALLELE	45.5%	61.3%	50.2%
		% of Total	31.9%	18.4%	50.2%
	Patient	Count	79	24	103
		% within Type	76.7%	23.3%	100.0%
		% within G_ALLELE	54.5%	38.7%	49.8%
		% of Total	38.2%	11.6%	49.8%
Total		Count	145	62	207
		% within Type	70.0%	30.0%	100.0%
		% within G_ALLELE	100.0%	100.0%	100.0%
		% of Total	70.0%	30.0%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.322[a]	1	.038		
Continuity Correction[b]	3.714	1	.054		
Likelihood Ratio	4.351	1	.037		
Fisher's Exact Test				.048	.027
N of Valid Cases	207				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 30.85.

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Type (Control / Patient)	.528	.288	.968
For cohort G_ALLELE = N	.827	.691	.991
For cohort G_ALLELE = Y	1.568	1.018	2.416
N of Valid Cases	207		

Type * C_ALLELE

Crosstab

			C_ALLELE		
			N	Y	Total
Type	Control	Count	1	103	104
		% within Type	1.0%	99.0%	100.0%
		% within C_ALLELE	50.0%	50.2%	50.2%
		% of Total	0.5%	49.8%	50.2%
	Patient	Count	1	102	103
		% within Type	1.0%	99.0%	100.0%
		% within C_ALLELE	50.0%	49.8%	49.8%
		% of Total	0.5%	49.3%	49.8%
Total		Count	2	205	207
		% within Type	1.0%	99.0%	100.0%
		% within C_ALLELE	100.0%	100.0%	100.0%
		% of Total	1.0%	99.0%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.000[a]	1	.995		
Continuity Correction[b]	.000	1	1.000		
Likelihood Ratio	.000	1	.995		
Fisher's Exact Test				1.000	.749
N of Valid Cases	207				

a. 2 cells (50.0%) have expected count less than 5. The minimum expected count is 1.00.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Type (Control / Patient)	.990	.061	16.047
For cohort C_ALLELE = N	.990	.063	15.623
For cohort C_ALLELE = Y	1.000	.974	1.027
N of Valid Cases	207		

Type * XPC_rs2228001

Crosstab

			XPC_rs2228001			
			GG	GT	TT	Total
Type	Control	Count	20	55	29	104
		% within Type	19.2%	52.9%	27.9%	100.0%
		% within XPC_rs2228001	37.7%	50.9%	63.0%	50.2%
		% of Total	9.7%	26.6%	14.0%	50.2%
	Patient	Count	33	53	17	103
		% within Type	32.0%	51.5%	16.5%	100.0%
		% within XPC_rs2228001	62.3%	49.1%	37.0%	49.8%
		% of Total	15.9%	25.6%	8.2%	49.8%
Total		Count	53	108	46	207
		% within Type	25.6%	52.2%	22.2%	100.0%
		% within XPC_rs2228001	100.0%	100.0%	100.0%	100.0%
		% of Total	25.6%	52.2%	22.2%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)
Pearson Chi-Square	6.351[a]	2	.042
Likelihood Ratio	6.421	2	.040
N of Valid Cases	207		

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 22.89.

Type * GE2TYPE_GG_2

Crosstab

			GE2TYPE_GG_2		
			N	Y	Total
Type	Control	Count	84	20	104
		% within Type	80.8%	19.2%	100.0%
		% within GE2TYPE_GG_2	54.5%	37.7%	50.2%
		% of Total	40.6%	9.7%	50.2%
	Patient	Count	70	33	103
		% within Type	68.0%	32.0%	100.0%
		% within GE2TYPE_GG_2	45.5%	62.3%	49.8%
		% of Total	33.8%	15.9%	49.8%
Total		Count	154	53	207
		% within Type	74.4%	25.6%	100.0%
		% within GE2TYPE_GG_2	100.0%	100.0%	100.0%
		% of Total	74.4%	25.6%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.457[a]	1	.035		
Continuity Correction[b]	3.810	1	.051		
Likelihood Ratio	4.491	1	.034		
Fisher's Exact Test				.039	.025
N of Valid Cases	207				

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Type (Control / Patient)	1.980	1.044	3.754
For cohort GE2TYPE_GG_2 = N	1.188	1.010	1.398
For cohort GE2TYPE_GG_2 = Y	.600	.370	.974
N of Valid Cases	207		

Type * GE2TYPE_TT

Crosstab

			GE2TYPE_TT		
			N	Y	Total
Type	Control	Count	75	29	104
		% within Type	72.1%	27.9%	100.0%
		% within GE2TYPE_TT	46.6%	63.0%	50.2%
		% of Total	36.2%	14.0%	50.2%
	Patient	Count	86	17	103
		% within Type	83.5%	16.5%	100.0%
		% within GE2TYPE_TT	53.4%	37.0%	49.8%
		% of Total	41.5%	8.2%	49.8%
Total		Count	161	46	207
		% within Type	77.8%	22.2%	100.0%
		% within GE2TYPE_TT	100.0%	100.0%	100.0%
		% of Total	77.8%	22.2%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.877[a]	1	.049		
Continuity Correction[b]	3.247	1	.072		
Likelihood Ratio	3.914	1	.048		
Fisher's Exact Test				.065	.035
N of Valid Cases	207				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 22.89.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Type (Control / Patient)	.511	.261	1.003
For cohort GE2TYPE_TT = N	.864	.746	1.001
For cohort GE2TYPE_TT = Y	1.689	.991	2.879
N of Valid Cases	207		

Type * GE2TYPE_GT

Crosstab

			GE2TYPE_GT		
			N	Y	Total
Type	Control	Count	49	55	104
		% within Type	47.1%	52.9%	100.0%
		% within GE2TYPE_GT	49.5%	50.9%	50.2%
		% of Total	23.7%	26.6%	50.2%
	Patient	Count	50	53	103
		% within Type	48.5%	51.5%	100.0%
		% within GE2TYPE_GT	50.5%	49.1%	49.8%
		% of Total	24.2%	25.6%	49.8%
Total		Count	99	108	207
		% within Type	47.8%	52.2%	100.0%
		% within GE2TYPE_GT	100.0%	100.0%	100.0%
		% of Total	47.8%	52.2%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	.042[a]	1	.837		
Continuity Correction[b]	.004	1	.947		
Likelihood Ratio	.042	1	.837		
Fisher's Exact Test				.890	.473
N of Valid Cases	207				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 49.26.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Type (Control / Patient)	.944	.547	1.629
For cohort GE2TYPE_GT = N	.971	.730	1.290
For cohort GE2TYPE_GT = Y	1.028	.792	1.334
N of Valid Cases	207		

Type * G_ALLELE_2

Crosstab

			G_ALLELE_2		
			N	Y	Total
Type	Control	Count	29	75	104
		% within Type	27.9%	72.1%	100.0%
		% within G_ALLELE_2	63.0%	46.6%	50.2%
		% of Total	14.0%	36.2%	50.2%
	Patient	Count	17	86	103
		% within Type	16.5%	83.5%	100.0%
		% within G_ALLELE_2	37.0%	53.4%	49.8%
		% of Total	8.2%	41.5%	49.8%
Total		Count	46	161	207
		% within Type	22.2%	77.8%	100.0%
		% within G_ALLELE_2	100.0%	100.0%	100.0%
		% of Total	22.2%	77.8%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	3.877[a]	1	.049		
Continuity Correction[b]	3.247	1	.072		
Likelihood Ratio	3.914	1	.048		
Fisher's Exact Test				.065	.035
N of Valid Cases	207				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 22.89.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Type (Control / Patient)	1.956	.997	3.838
For cohort G_ALLELE_2 = N	1.689	.991	2.879
For cohort G_ALLELE_2 = Y	.864	.746	1.001
N of Valid Cases	207		

Type * T_ALLELE

Crosstab

			T_ALLELE		
			N	Y	Total
Type	Control	Count	20	84	104
		% within Type	19.2%	80.8%	100.0%
		% within T_ALLELE	37.7%	54.5%	50.2%
		% of Total	9.7%	40.6%	50.2%
	Patient	Count	33	70	103
		% within Type	32.0%	68.0%	100.0%
		% within T_ALLELE	62.3%	45.5%	49.8%
		% of Total	15.9%	33.8%	49.8%
Total		Count	53	154	207
		% within Type	25.6%	74.4%	100.0%
		% within T_ALLELE	100.0%	100.0%	100.0%
		% of Total	25.6%	74.4%	100.0%

Chi-Square Tests

	Value	df	Asymptotic Significance (2-sided)	Exact Sig. (2-sided)	Exact Sig. (1-sided)
Pearson Chi-Square	4.457[a]	1	.035		
Continuity Correction[b]	3.810	1	.051		
Likelihood Ratio	4.491	1	.034		
Fisher's Exact Test				.039	.025
N of Valid Cases	207				

a. 0 cells (0.0%) have expected count less than 5. The minimum expected count is 26.37.

b. Computed only for a 2x2 table

Risk Estimate

	Value	95% Confidence Interval	
		Lower	Upper
Odds Ratio for Type (Control / Patient)	.505	.266	.957
For cohort T_ALLELE = N	.600	.370	.974
For cohort T_ALLELE = Y	1.188	1.010	1.398
N of Valid Cases	207		

8.2. Ethic Committee approval

BİLGİLENDİRİLMİŞ GÖNÜLLÜ OLUR FORMU

Araştırma Başlığı: Türk Popülasyonunda Over Kanserli Hastalarda Global Genom Onarım Gen Polimorfizmlerinin Araştırılması

Araştırmaya Katılımcı Sayısı: 125 hasta 125 kontrol toplam 250 katılımcı

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. En yüksek ölüm oranına sahip en yaygın jinekolojik kanser yumurtalık kanseridir. Karın ve pelvise uzanana kadar sıklıkla teşhis edilmez. OK önlemeye yardımcı olmak için en verimli risk değişkenleri tanımlanabilir. Yumurtalık kanseri oluşumunu ve yayılmasını anlamak için XPC ve DDB2 genlerinin etkisini araştırmak ve işlevini anlamak gerekir XPC polimorfizmleri, DNA onarım kapasitesini değiştirerek genetik kararsızlığa ve karsinojeneze yol açabilir. Bu sonuçlar, yumurtalık kanserinde XPC ve DBB2 genlerindeki polimorfizmlerin araştırılmasını gerektiğini işaret etmektedir.

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: 1621, tarih: 08.06.2022, dosya no: 2426, başlık: "İnterlökin -1 beta (IL1B) Gen Polimorfizmi ve Over Kanseri Arasındaki ilişkinin araştırılması") ve kan örneklerinden DNA izolasyonları yapılmış laboratuvarımızda hazır bulunan örneklerle PCR yapılması planlanmaktadır

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. Over kanserine sahip bireylerden ve kontrol gruplarından toplanan kantitatif parametreler student t-testi kullanılarak analiz edilecektir

Araştırma Sonunda Beklenen Fayda : Bu çalışma, GGR gene Polimorfizmi ve over kanseri Arasındaki İlişkinin belirlenmesi ve XPC ve DDB2 over kanseri gelisimindaki rolunun anlasilmasini sağlayabilir

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.

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

ARAŞTIRMA YÜRÜTÜCÜSÜ: Sara Barham
Yeditepe Üniversitesi Moleküler Tıp Anabilim Dalı,
sara.yasersalamehbarham@std.yeditepe.edu.tr, 0216 578 02 63

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Seda.gulec@yeditepe.edu.tr 0216 578 17 16

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8.3. Curriculum Vitae

Personal Information

Name	Sara Yaser Salameh Barham	**Surname**	Barham

Education

Degree	**Department**	**The name of the University**	**Graduation year**
Master	Molecular Medicine	Yeditepe University	2023
Bachelor	Pharmacy	Petra University	2021

Language

Language	**Grades**
English	79.8

Computer Skills

Program	**Level**
Operating systems (Windows and MacOS)	Average
Presentation software (PowerPoint)	Excellent
SPSS program	Intermediate

Voluntary Work

Research and Scientific Committee	RBCs Team
Translate Scientific articles from English into Arabic	Wikipedia

Team Member within a Volunteer Team Affiliated with the Jordanian Ministry of Youth
Team Member within a Volunteer Team Affiliated with the UNICEF

Others (Projects / Certificates / Rewards)

Infection Prevention and Control (IPC) for Novel Coronavirus (COVID-19)	World Health Organization
Let’s Break the Chain of COVID-19 Infections	MBRUNIVERSITY
Electronic Marketing and Pharmaceutical	Nahno Platform
Breast Cancer Health Awareness	Nahno Platform

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