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Genetic predisposition for ovarian cancer development

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Abstract

Ovarian cancer is a leading malignancy in the female reproductive system and is responsible for more deaths than any other type of cancer affecting this system. Ovarian cancers can be hereditary or sporadic. Anatomic, cellular, microenvironmental and molecular features of ovarian cancers show a high degree of heterogeneity. Numerous genes implicated in the pathogenesis and progression of ovarian cancers have been identified to date. The majority of these genes act as tumour suppressor genes, oncogenes, or are involved in mismatch repair and double-strand break repair mechanisms. The identification of mutations in cancer susceptibility genes could be a major step forward towards earlier diagnosis, personalized therapy approaches and outcome monitoring. In healthy women, detecting a specific mutated gene can provide a rationale for personalized surveillance, chemopreventive strategies, and prophylactic surgery. Next-generation sequencing offers comprehensive genome analysis, which enables profound understanding and identification of cancer susceptibility genes, and new molecular diagnostic markers and therapeutic targets.

Key words: ovarian cancer, genetic predisposition, *BRCA, p53*

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Introduction

Ovarian cancer is a leading malignancy in the female reproductive system and is responsible for more deaths than any other type of cancer affecting this system (1–4). It ranks as the eighth most commonly diagnosed cancer worldwide, with roughly 220,000 new cases reported annually (1–4). According to the Globocan 2022 projections, the number of women diagnosed with ovarian cancer globally is expected to increase by over 55% by 2050 (3). In Serbia, the situation is similar to that in other developing nations, with an average of 820 new diagnoses and 420 deaths from ovarian cancer each year (5).

Ovarian cancer is often aggressive and frequently lethal, and the drivers of high mortality rates in this tumour are various (6). Most patients are unfortunately typically diagnosed with advanced-stage disease upon presentation (7), as a consequence of the subtle nature of initial symptoms and absence of reliable early screening techniques (8). The likelihood of survival over five years and the risk of recurrence are closely linked to the stage of cancer at the time of diagnosis (7).

Ovarian carcinoma is a not a single disease entity, and exhibits significant heterogeneity across molecular, microenvironmental, immunological, and anatomical aspects (6). While treatment strategies are gradually evolving, there is still a lack of personalized treatment approaches, resulting in high rates of ineffectiveness and drug resistance in therapy (6). Ovarian cancers are classified based on their tissue of origin: epithelial, germ cell, and sex cord–stromal, each of which can be further subdivided. Epithelial tumours account for 90% of malignant ovarian cancers, while germ cell tumours make up about 5%, and sex cord–stromal tumours 3–5% (7). Ovarian cancers are also categorized into two types by grade and morphology: Type I includes low-grade serous, mucinous, endometrioid, clear cell, and transitional tumours, while Type II includes high-grade serous ovarian cancers, carcinosarcomas, and undifferentiated carcinomas (9). Advanced-stage aggressive epithelial tumours make up 70% of Type II ovarian cancers (10).

Ovarian cancer detection has traditionally relied on transvaginal sonography and the measurement of the CA125 tumour marker (Cancer Antigen 125), a large glycoprotein found on the surface of ovarian cancer cells. However, CA125 lacks both sensitivity for early detection and specificity, since it is elevated in only 50% of early-stage ovarian cancers (11) and 80% of healthy women in routine screening have elevated levels but do not have ovarian cancer, resulting in a high false-positive rate (12). In contrast, about 92% of advanced-stage ovarian cancers show elevated CA125 levels. Recently, new potential biomarkers have been identified using tandem mass spectrometry with data-independent acquisition, but these require further validation before they can be widely applied (13).

Ovarian cancer can be hereditary or sporadic, with more than 20% of cases linked to hereditary susceptibility (26). The development of hereditary ovarian cancer is currently linked to at least 16 genes and their mutations, although many of them have still not been revealed (26, 27, 28). The risk of ovarian cancer is 2.4 times higher in the absence of a known genetic mutation for individuals with a first-degree relative diagnosed

with the disease (27, 28). In addition to genetic factors, environmental and lifestyle factors play a significant role in ovarian cancer risk. The use of postmenopausal hormone therapy (HT) has been associated with a higher risk (14), while hormonal contraceptives have been shown to reduce ovarian cancer risk in both average and high-risk women (15–19). A 2021 meta-analysis found a decreased risk of ovarian cancer in women using intrauterine devices (20), although another study found no significant difference in cancer risk between users and non-users of the levonorgestrel intrauterine system (21). Other factors such as obesity, lifestyle, and exposure to talcum powder or asbestos have also been linked to a higher risk of ovarian cancer (22).

Ovarian cancer is mostly a "later-age" cancer, most commonly diagnosed in women over 45 (23). A later onset of menarche, an earlier age at menopause, and breastfeeding have been found to decrease the risk of ovarian cancer (24, 25).

In the following sections, we will highlight the basics of hereditary ovarian cancer and the main genes involved in its development and progression.

Hereditary ovarian cancer and genetic mutations

In hereditary ovarian cancer, many genes have been found to be mutated. Most of them function either as tumour suppressor genes, oncogenes, implicated in the mismatch repair (MMR) process or associated with the repair of double-strand breaks (10, 29).

On a molecular level, type I tumours are generally genetically stable and most commonly feature mutations in *KRAS*, *BRAF*, *ERBB2*, *PTEN*, *PIK3CA*, b-catenin gene (*CTNNB1*), *ARID1A*, and *PPP2R1A* genes (10). Type II ovarian cancers exhibit high genomic instability at the time of presentation, and the most frequently mutated gene is *TP53* (up to 95% of patients with type II ovarian carcinomas (mostly high-grade serous ovarian carcinomas – HGSOC)), but patients can also be carriers of *BRCA1* and *BRCA2* mutations (10, 30). Patients with type I ovarian tumours experience slower disease progression and better survival rates compared to those with type II tumours.

Genes related to type I ovarian cancer

The DNA repair mechanisms responsible for removing single-strand breaks include the mismatch repair (MMR) system, as well as the base excision repair (BER) and nucleic acid excision repair (NER) systems. Germline mutations in MMR genes, such as *MLH1*, *MSH2, MSH6, MLH3*, and *PMS2*, result in the loss of function of one of the MMR proteins in the repair system, which leads to microsatellite instability. Several oncogenes and tumour suppressor genes, including *TGFβR2, IGFIIR, BAX*, and *RAD50*, contain microsatellites; consequently, impairments in the mismatch repair (MMR) system can lead to mutations in these genes, contributing to tumorigenesis. For carriers of *MSH2* and *MLH1* mutations, the cumulative lifetime risk of ovarian cancer is estimated to be 6–10%. Cancers with these mutations are typically endometrioid or clear cell types, which are diagnosed at earlier stages, and associated with higher stage-specific survival rates (10).

The MAPK (mitogen-activated protein kinase) pathway is a critical regulator of cell growth, differentiation, apoptosis, and response to cellular stress. This pathway is activated through two types of surface receptors: tyrosine-kinase receptors and G protein-coupled receptors, which interact with various growth factors and cytokines. As a result, this pathway has considerable oncogenic potential, and mutations in genes such as *KRAS* (Kirsten rat sarcoma virus) and *BRAF*, which are key components of the pathway, are frequently found in mucinous ovarian carcinomas (31).

PTEN (phosphatase and tensin homolog) is a critical tumour suppressor gene that helps regulate cell growth, division, and apoptosis by inhibiting the PI3K-AKT pathway. PTEN protein can exerts lipid phosphatase activity, essential for blocking cell-cycle progression from cell growth to DNA replication, and protein phosphatase activity, which suppresses focal adhesion, cell migration, and spreading. By dephosphorylating phosphatidylinositol (3,4,5)-trisphosphate (PIP3), PTEN reduces AKT activation and inhibits the MAPK signalling pathway (32). Therefore, the loss of PTEN protein function, caused by mutations or epigenetic silencing, can lead to uncontrolled cell growth and survival (32).

Genes related to type II ovarian cancer

The TP53 gene

The tumour protein *TP53* gene (or *p53*), located on chromosome 17 (17p13.1), is a pivotal tumour suppressor gene, “the guardian of the genome”, a vital nuclear transcriptional regulator for maintaining genomic integrity. Its expression is triggered by oncogene activation, hypoxia, and DNA damage, leading to cell cycle arrest, senescence, differentiation, apoptosis, and ferroptosis (33). Structurally, the p53 protein contains four functional domains: N-terminal ubiquitin ligase (MDM2) binding site, amino-terminal transactivation domains TAD1 and TAD2, a proline-rich domain (PRD), a DNA-binding domain (DBD), a linker region (LR), a tetramerization domain (TD), and a carboxyl terminal domain (CTD) (34). *P53* is the most frequently mutated gene in various cancers, and its mutations can result either in loss of function or in acquisition of oncogenic activity. In advanced HGSOC, *p53* is mutated in more than 90% of cases, with both loss-of-function and gain-of-function mutations. Loss-of-function mutations impair cell cycle arrest, apoptosis, and senescent growth arrest, while also causing chromosomal instability and defective DNA base excision repair. In contrast, gain-of-function mutations in p53 promote accelerated tumour metastasis, altered gene transcription, resistance to apoptosis, and increased chemotherapy resistance (35). In type II HGSOC, 82% of p53 mutations are missense mutations in the DNA-binding domain (DBD), causing a structural alteration that leads to greater rigidity of the p53 protein. This change disrupts the DNA-binding ability and function of the p53 protein, leading to an enhanced stress response and tumour growth due to the lack of apoptosis. Another type of p53 mutations leads to an exposure of a “sticky” sequence and results in protein aggregation in the cytosol in HGSOC, affecting the functionality of p53 (36). But p53 function can be impaired in the absence of any p53 mutations. In the absence of any p53 mutations, p53 protein can be

downregulated by upregulated MDM2 and MDM4 in cancers, which act as ubiquitin ligases, and target p53 for proteasomal degradation (37). The PI3K (phosphatidylinositol 3-kinase) pathway is upregulated in 40–70% of ovarian cancer cases, which leads to a deprivation of p53 action, leading to uncontrolled tumour cell proliferation (38). Overall, p53 function can be altered directly by a mutation of the *p53* gene, or affected by several interconnected pathways, illustrating the complexity of p53 regulation in cancers.

BRCA1 and BRCA2 genes and pathway

The genetic abnormality in 10–15% of all cases, and in more than half to four-fifths of hereditary cases, is a germline mutation in the *BRCA* genes *(*BReast CAncer gene: *BRCA1* and *BRCA2)* (26, 39, 40). Both genes act as tumour suppressors and are involved in the pathway responsible for repairing double-strand DNA breaks (10). A female with a *BRCA1* mutation faces a lifetime risk of 39–58%, while a *BRCA2* mutation carries a lifetime risk of 13–29% (41). *BRCA* mutations are inherited in an autosomal dominant pattern (22), with carriers facing a heightened risk of ovarian, breast, pancreatic, and prostate cancers (42–46). *BRCA1* and *BRCA2* are tumour suppressor genes involved in the homologous recombination repair (HRR) pathway, the primary mechanism for repairing double-strand DNA breaks (47).

Located on chromosome 17q21, the *BRCA1* gene encodes a large protein made up of 1,863 amino acids. Mutations in this gene, including frameshift insertions or deletions, nonsynonymous truncations, and splice site disruptions (48), are most commonly found in regions corresponding to the N-terminal end, the RING (Really Interesting New Gene) domain, the BARD1 (BRCA1 Associated RING Domain protein 1) domain, and exons 11–13, which encode nuclear localization signals (NLS) in the central region of the protein. These mutations lead to the production of a non-functional protein (49, 50).

The *BRCA2* gene, located on chromosome 13q12.3, encodes a protein of 3418 amino acids. This protein features two DNA-binding domains: a central region with BRC repeats that binds to RAD51, and a C-terminal region containing two nuclear localization signals (NLS) as well as an additional RAD51 interaction site (51). Mutations, such as frameshift insertions, deletions, and nonsense mutations, lead to premature truncation or the production of a non-functional protein (22). The most frequently mutated region is exon 11, which encodes the BRC repeats (52).

BRCA1 and *BRCA2* proteins are expressed in various tissues during the replicative phase and G2 phases of the cell cycle. This signalling pathway also involves other proteins encoded by genes such as *ATM, ATR, BLM, CHEK2, CHEK1, ERCC1, MLH1*, *PALB2*, *RAD50*, and *PTEN* (10).

The *PALB2* (partner and localizer of BRCA2) gene plays a significant role in DNA repair, particularly in the process of HRR by interacting with the BRCA1 and BRCA2 proteins (22, 53). Located on chromosome 16p12.2, mutations in this gene can lead to increased risks for breast and ovarian cancer in individuals who are heterozygous carriers of pathogenic variants. In cases of homozygosity for mutations in *PALB2*, individuals may develop Fanconi anaemia (22, 53).

The *RAD51* gene, located on chromosome 15q15.1, plays a role in HR and DNA repair by interacting with the single-strand DNA-binding protein RPA, RAD52, BRCA1 and BRCA2 (54). Mutations in the *RAD51* gene can lead to genomic instability and have been linked to a higher risk of certain cancers, notably breast and ovarian cancer (40).

The *CHEK2* (checkpoint kinase 2) gene is situated on chromosome 22q12.1. The protein coded by this gene is a tumour suppressor nuclear Ser/Thr kinase. In response to DNA double-strand breaks, the CHEK2 protein becomes phosphorylated, ultimately preventing entry into mitosis (55). Additionally, CHEK2 phosphorylates the p53 tumour suppressor protein, stabilizing it and preventing its degradation, which leads to cell cycle arrest in the G1 cell cycle stage; however, it can also initiate apoptosis through pathways that do not rely on p53. The missense variant of *CHEK2* has been identified in ovarian cystadenomas, borderline ovarian tumours, and low-grade invasive cancers, but it is not commonly found in high-grade ovarian cancer (55, 56).

DICER1 encodes an RNase III endonuclease that converts precursor microRNAs into active forms. Most tumours related to the *DICER1* syndrome have one allele with a mutation causing total loss of function, and the other with a missense mutation in the RNase IIIb domain. Such mutations disrupt the cleavage of 5p miRNAs, resulting in an abnormal miRNA ratio that affects downstream mRNA expression. The International Ovarian and Testicular Stromal Tumor Registry shows that nearly half of SLCT cases have germline *DICER1* mutations (57).

The advent of next-generation sequencing methods has facilitated high-throughput and comprehensive genome analysis. In recent years, several additional cancer susceptibility genes have been identified as associated with various types of ovarian carcinomas (7). However, the major issue for translation of these findings into clinical settings is the question of penetrance of the proposed genes. Therefore, further research should be focused on identifying true candidate genes for ovarian cancer diagnosis and also for prognosis, since mutations can be indicative of patient outcome and response to therapy (7, 10).

Although screening is not recommended for asymptomatic, low-risk individuals, for women at high risk, such as those with a family history of ovarian or breast cancer, or both, genetic counselling is recommended by several organizations, including the American College of Obstetricians and Gynaecologists (ACOG), the National Comprehensive Cancer Network (NCCN), the National Institute for Health and Care Excellence, and the Society of Obstetricians and Gynaecologists of Canada (7). The NCCN currently recognizes several genes associated with moderate or high risk for ovarian cancer, including *ATM, BRCA1, BRCA2, BRIP1, DICER1, EPCAM, MLH1, MSH2, MSH6, PALB2, PMS2, RAD51C*, and *RAD51D* (41).

Knowledge of genetic predispositions can play a crucial role in shaping treatment decisions for ovarian cancer patients by guiding personalized therapies for treatment plans, such as PARP inhibitors, which exploit DNA repair deficiencies in cancer cells, causing fewer side effects compared to traditional chemotherapy. Furthermore, knowledge of genetic risks can influence the extent of surgical intervention, such as

prophylactic surgeries for patients with BRCA mutations, and also guide closer postoperative monitoring, helping to assess recurrence risks more effectively. Overall, understanding genetic predispositions allows for more personalized treatment strategies in ovarian cancer, improving outcomes and patient management (7, 8, 10).

Conclusion

The diversity of ovarian cancers is evidenced by the molecular variation in mutations found in cancer susceptibility genes. Identifying these mutations in affected genes is a significant advancement for developing specific and sensitive diagnostic and treatment options for ovarian tumours. For healthy women, detecting a specific mutated gene may warrant more intensive personalized surveillance, chemopreventive strategies, and/or prophylactic surgery that would not typically be justified based solely on family history. Additionally, identifying a mutation in patients who already have the disease can offer crucial insights into the tumours' pathogenesis, potentially guiding targeted therapies, enhancing treatment responses, and improving patient outcomes (7, 10).

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Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Author contributions

IJ: conceptualization; data curation; formal analysis; investigation; supervision; visualization; writing - original draft & review; UPZ: conceptualization; data curation; writing - original draft & review; AN: conceptualization; data curation; writing - original draft; TR: conceptualization; data curation; writing - original draft; Jelena Munjas: conceptualization; data curation; funding acquisition; investigation; methodology; project administration; supervision; visualization; writing - original draft, review & editing.

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Genetska predispozicija za razvoj karcinoma jajnika

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Kratak sadržaj

Rak jajnika je malignitet ženskog reproduktivnog sistema koji je, uzimajući u obzir visok stepen agresivnosti i otkrivanje u kasnijim stadijumima, uzrok najvećeg broja smrtnih slučajeva u poređenju sa bilo kojim drugim malignim tumorom ženskog reproduktivnog sistema. Rak jajnika može biti nasledan ili stečen. Anatomske, ćelijske i molekularne karakteristike karcinoma jajnika pokazuju visok stepen heterogenosti. Do sada su identifikovani mnogi geni uključeni u patogenezu i napredovanje karcinoma jajnika. Većina ovih gena funkcionišu ili kao tumor supresorski geni, onkogeni, geni uključeni u popravku pogrešno sparenih baza u DNK ili dvolančanih prekida u DNK molekulu. Identifikacija specifičnih mutacija u genima koji mogu biti uzročnici raka jajnika predstavlja napredak koji bi omogućio pravovremenu dijagnozu, individualni pristup terapiji i preciznije praćenje ishoda pacijenata. Kod zdravih žena, identifikovanje mutacije u genima koji mogu doprineti nastanku kancera ovarijuma bi omogućilo intenzivnije usmeravanje ka pojačanom nadzoru tih žena, ili bi pružilo indikaciju za hemopreventivne pristupe i profilaktičku hirurgiju. Sekvenciranje sledeće generacije nudi sveobuhvatnu analizu genoma, koja omogućava duboko razumevanje i identifikaciju gena koji mogu biti u osnovi patogeneze raka jajnika, kao i nove molekularne dijagnostičke markere i terapijske ciljeve.

Ključne reči: tumor jajnika, genetska predispozicija, *BRCA*, *p53*