DOI: https://doi.org/10.2298/SARH240502036S
UDC: 618.11-006:575.113

REVIEW OF LITERATURE / ПРЕГЛЕД ЛИТЕРАТУРЕ

Association of common glutathione transferase polymorphisms with ovarian cancer risk and chemoresistance

Petar Simić[1], Marija Plješa-Ercegovac[2,3,4]

[1]Narodni Front Clinic for Gynecology and Obstetrics, Belgrade, Serbia;
[2]University of Belgrade, Faculty of Medicine, Belgrade, Serbia;
[3]Institute of Medical and Clinical Biochemistry, Belgrade, Serbia;
[4]Center of Excellence for Redox Medicine, Belgrade, Serbia

SUMMARY
Ovarian cancer is regarded as the most lethal gynecological cancer with a five-year survival below 45%. It represents the seventh most common cancer among women. Due to the limited availability of biomarkers and reliable screening methods for early diagnosis of ovarian cancer, much research is being conducted to explore and understand the factors that may increase the risk of developing this kind of cancer. When surgery and chemotherapy treatments have been fully utilized, the development of chemoresistance becomes a critical factor in the progression of the disease. Glutathione transferases (GSTs) are a group of enzymes that play a role in the process of detoxification. Genes that code for GSTs proteins exhibit polymorphism, which can lead to either total or partial loss of enzymatic function. Cytosolic GST activity is composed of many different isoenzymes that facilitate interactions between glutathione and hazardous chemicals, including cancerogenes, anticancer drugs, and byproducts of oxidative stress. The scope of this review is to clarify the association of common GST polymorphisms with ovarian cancer risk and chemoresistance.
Keywords: glutathione transferases; ovarian cancer; polymorphisms; risk; chemoresistance

OVERVIEW OF OVARIAN CANCER

Ovarian cancer is regarded as the most lethal gynecological cancer with a five-year survival below 45%. Around 290,000 women worldwide are diagnosed with ovarian cancer and 180,000 die every year, which represents the seventh most common cancer among women [1, 2, 3]. Ovarian cancer can originate from any of the histologic components of the ovary, such as epithelium, stroma, or germ cells. The most prevalent among them is high-grade serous ovarian carcinoma (HGSOC) originating from the ovarian epithelium [4]. However, pathogenesis of ovarian cancer has evolved from the hypothesis that HGSOC develops from ovarian epithelium to the theory that it starts as a precursor lesion in the epithelium of distal fallopian tube as a serous tubal intra epithelial carcinoma [5, 6]. Almost 15–20% of HGSOC have germline *BRCA* ½ mutations with cumulative risk of epithelial ovarian cancer estimated to be 44% and 17% for *BRCA1* and in *BRCA2* mutation carriers, respectively [7].

Over the course of time, several distinct risk factors have been discovered for ovarian cancer. As an example, La Vecchia [8] examined the connection between the age at which menstruation begins, the age at which menopause occurs, the regularity of ovulation cycles, and the specific locations of ovarian cancer. Researchers determined that women with irregular menstrual cycles had a nearly 42% greater likelihood of developing ovarian cancer during the postmenopausal phase of life [8]. This may also be observed from the perspective of polycystic ovarian syndrome, which is considered the most common cause of irregular menstrual periods in women of reproductive age [9].

From the pathology standpoint of view, HGSOC has a diverse development pattern characterized by the presence of huge papillae, glandular structures, solid areas, and occasional micropapillary formations, sometimes accompanied by necrosis [10]. It is distinguished by the presence of high-grade nuclei, and a high mitotic index. The immunohistochemistry stain usually shows aberrant expression of p53, diffuse expression of p16, and high expression of Ki67. Other markers associated with HGSOC are ER, PR, WT-1, and PAX8 [11].

Since, HGSOC is regarded as chromosomally unstable with frequent DNA gains and losses, there is a great deal of potential for acquiring chemoresistance [12]. Molecular abnormalities are defined by ubiquitous inactivating mutations in TP53, copy number alterations and whole genome duplications [11]. From a molecular perspective, high grade ovarian cancer can be classified into four distinct subtypes: mesenchymal, immunological, differentiated, and proliferative [13, 14]. Research done by Cheng et al. [15] discovered seven copy-number signatures that are associated with the prognosis of ovarian cancer.

Received • Примљено: May 2, 2024
Revised • Ревизија: May 15, 2024
Accepted • Прихваћено: May 16, 2024
Online first: May 21, 2024

Correspondence to:
Petar SIMIĆ
Narodni front Clinic for Gynecology and Obstetrics
Kraljice Natalije 62
11000 Belgrade
Serbia
simicp93@gmail.com

EPIDEMIOLOGY AND INCIDENCE

The average lifetime risk of developing ovarian cancer is 1.3%, the equivalent of 1 in 78 women [16]. The overall ovarian cancer incidence rate in the US was 11.5 per 100,000 women during 2010–2014. More than 90% of ovarian malignancies are of epithelial origin. Epithelial ovarian carcinomas are classified by tumor cell histology as serous, endometrioid, mucinous, or clear cell, with one-quarter being more rare subtypes or unspecified.

At the moment, there is no officially endorsed screening test for ovarian cancer. However, there are extensive randomized clinical trials aimed at identifying viable screening methods. In fact, the Prostate, Lung, Colorectal, and Ovarian Cancer Screening Trial evaluated the effectiveness of transvaginal ultrasound and detection threshold (≥ 35 U/mL) in the tumor marker CA125 for detecting ovarian cancer at an early stage. But the study did not find any decrease in ovarian cancer-related deaths even after a follow-up period of up to 19 years [17].

CHALLENGES IN DIAGNOSIS AND TREATMENT

Nonspecific symptoms such as abdominal bloating, early satiety, nausea, and abdominal distension are associated with ovarian cancer. Changes in bowel function, urinary symptoms, fatigue, and weightloss usually manifest many months before the diagnosis is made. The majority of patients are diagnosed in an advanced stage of illness. Due to the extended period of asymptomatic nature of the disease, signs of ovarian cancer are demonstrated by the pattern of cancer tissue spreading throughout the abdominal cavity.

The classic treatment method of ovarian cancer is characterized by an initial debulking surgery followed by chemotherapy [18]. The most crucial factor for survival is the complete elimination of any visible illness in the abdomen [19]. Poor prognosis and inferior survival rates are associated with suboptimal surgical treatment that fails to completely eradicate the tumor burden.

ROLE OF GLUTATHIONE TRANSFERASES IN CANCER

Cytosolic GST is made up of several different forms of enzymes that facilitate interactions between glutathione and lipophilic molecules containing electrophilic centers. GSTs are recognized as important enzymes in cell detoxification processes, playing a critical role in the metabolism of both external substances (such as chemical carcinogens, environmental contaminants, and even anticancer drugs) and internal electrophilic chemicals [20]. Regarding the substrates of GSTs, it is important to mention that GSTM1, GSTP1 and GSTT1 are involved in the inactivation of substances that can cause cancer, produced during the breakdown of polycyclic aromatic hydrocarbons and arylamines [21]. GST family members also possess antioxidant activity [22, 23].

GST enzymes have been categorized into seven classes: alpha, mu, pi, theta, zeta, omega, and sigma. The most extensively investigated glutathione transferase genetic polymorphisms are GSTA1, *GSTM1*, GSTP1, and GSTT1 and to some less extent GSTO1 [24]. Most of the variations found in genes that code for cytosolic GSTs are single nucleotide polymorphisms (SNPs). The substitution of isoleucine (Ile) with valine (Val) resulting from SNP alters the catalytic and regulatory characteristics of the GSTP1 enzyme [25, 26]. On the other hand, the GSTA1 polymorphism is characterized by three SNPs, namely -567TOG, -69COT, and -52GOA, which appear to be connected. The changes mentioned lead to differential expression, with the variant GSTA1*B allele (-567G, -69T, -52A) having reduced transcriptional activation compared to the common GSTA1*A allele (-567T, -69C, -52G) [27]. The substitution of the amino acid Alanine (Ala) with Aspartic acid (Asp) at position 140, caused by SNP where C is replaced by A, in exon 4 of the GSTO1 gene (GSTO1*Ala140Asp), alters the deglutathionylase and thioltransferase activity of the gene [28, 29, 30]. The GSTO2 rs156697 polymorphism involves a SNP where the nucleotide A is replaced by G. This substitution results in the amino acid Asparagine being replaced by Aspartic acid at position 142 (GSTO2*Asn142Asp) [31, 32]. This genetic variation may be associated with changes in the levels of the GSTO2 protein.

The functional importance of GST SNPs has been emphasized by Hollman et al. [33], who proposed a categorization of disorders strongly associated with SNPs discovered in GSTs, including malignancies. Conversely, deletion polymorphisms of genes that encode for human cytosolic GSTM1 and GSTT1 are rather prevalent in human populations. Roughly 50% of the population does not have GSTM1 enzyme activity because they have a homozygous deletion of the *GSTM1* gene. In the case of GSTT1, about 20% of Caucasians have a gene homozygous deletion, resulting in a lack of GSTT1 enzyme activity [34, 35].

GST polymorphisms have been associated with an increased risk for a variety of other types of cancer, such as breast, gastric, renal, lung and colorectal [36]. Meta-analysis conducted by Chinese authors on total of 17 studies, involving 5323 breast cancer cases and 7196 controls, found a significant association between the null *GSTM1* and breast cancer risk [37]. This study exclusively recruited individuals of Chinese ethnicity, which limits the ability to apply the findings on general population due to the well-established variations in the distribution of *GSTM1* among other racial populations. The frequency of GSTT1 null genotype varies from 20% in Caucasians to 60% in Asians, whereas around 50% of the global population (varying from 22% in Africa to 62% in Europe) have the *GSTM1* null genotype [21].

A study carried out by Coric et al. [38] examined the impact of GST gene variations on the likelihood of developing renal cell carcinoma (RCC) and the postoperative prognosis in patients with clear cell RCC. It has been shown that individuals with *GSTM1*-null and GSTP1-variant genotypes have a higher risk of developing RCC. In contrast, the absence of the GSTM1 protein due to *GSTM1* null genotype is linked to a positive postoperative outcome in clear cell RCC [38]. Matic et al. [39] investigated

the correlation between genetic variations in the GSTA1, *GSTM1*, GSTP1, and GSTT1 genes with the risk of bladder cancer. They further assessed whether this correlation was influenced by smoking. The presence of null or low-activity genotypes of the GSTA1, *GSTM1*, GSTT1, and GSTP1 genes did not have a separate impact on the likelihood of developing bladder cancer in our patients. Nevertheless, the combination of low activity GSTA1 and *GSTM1*-null genotype enhances an individual's vulnerability to bladder cancer when associated with smoking [39].

In addition to its typical function as a phase II detoxifying enzyme, glutathione transferases may also directly inactivate several standard anti-cancer medications (such as chlorambucil, cyclophosphamide, melphalan, cisplatin, thiotepa, and others] through GST-dependent conjugation reactions, as they are also substrates for GSTs [40, 41]. GSTs also appears to interact with efflux transporters, hence enhancing the efflux of anticancer drugs from the cell. Additionally, GSTs interact with other signaling molecules that are involved in the control of apoptosis. This specifically applies to the GSTP1, since it can bind to both small and large molecules. It acts as a suppressor of kinase-dependent apoptotic signaling pathways by forming protein-protein complexes with regulatory mitogen-activated kinases like JNK1 (c-Jun NH2-terminal kinase). Additionally, GSTP1 plays a role in detoxifying potentially cancer-causing substances. Furthermore, it can enhance the removal of drugs from cells, thereby contributing to chemoresistance. Also, GSTP1 demonstrates a synergistic impact on the development of chemoresistance to ethacrynic acid, chlorambucil, vincristine, and etoposide via interacting with MRP-1 [42].Thus, the catalytic and regulatory activities of GSTs may be regarded as significant components that contribute to at least several key pathways of chemoresistance [20]. Obviously, GSTs may have a role in chemoresistance, even for drugs that are not typically metabolized by GSTs. Therefore, GSTs appear to be well-suited for the creation of new drugs, particularly because each type of cancer cells possess a distinct GST signature. This allows for precise targeting and selectivity when designing inhibitors and pro-drugs specific to each isoenzyme [43, 44]. Ishikawa et al. [45] carried out research on the expression of ATP-dependent glutathione S-conjugate export pump (GSX-Pump) and the capacity of tumor cells to eliminate a potentially cytotoxic glutathione-platinum complex, thereby modulating glutathione (GSH)-associated resistance to cisplatin. It was discovered that human promyelocytic leukemia HL-60 (HL-60/R-CP) cells had functionally overexpressed GSX-Pump [45]. Horton et al. [46] performed a study on ovarian cancer cells that were isolated after subjecting the parent cells to increasing doses of alkylating agent over time. The study demonstrated that the resistant cell line exhibited nearly a five-fold increase in GST activity compared to the original cell line. Additionally, they demonstrated that the resistant cell line exhibited a minimum of 11 times greater GSTM activity compared to the parental cells, in which this isoform was hardly detectable. The results have shown a close and direct relationship between resistance to the alkylating drug chlorambucil and the increased expression of mu-class GSTs. These findings imply that this increased expression may be partially responsible for the acquired resistance of ovarian cancer cells [46].

GLUTATHIONE TRANSFERASE POLYMORPHISMS AND OVARIAN CANCER RISK

Due to the difficulty in the early-stage diagnosis of ovarian cancer, extensive research has been dedicated to understanding the factors that increase an individual's vulnerability to this malignant illness. Currently, there are no recommendations regarding population-wide screening procedures that have demonstrated sufficient effectiveness to be implemented in routine practice. SNPs are the predominant type of genetic variation in humans and might potentially influence an individual's susceptibility to cancer. It seems reasonable to assume that glutathione transferases play a role in metabolizing different carcinogens that could potentially contribute to the development of ovarian cancer, providing a strong biological basis for the study of associations of GST polymorphisms with risk of ovarian cancer. Several large-scale meta-analyses have been undertaken in recent decades to investigate the correlation between GST polymorphisms with the likelihood of developing ovarian cancer. Significantly, most of them focused on specific GST polymorphisms, including the GSTM, GSTT, and GSTP gene families. Economopoulos et al. [21] conducted a large and thorough meta-analysis. They analyzed eight studies that investigated the *GSTM1* null polymorphism status, with a total of 2357 cases and 3044 controls. They also analyzed six studies on the GSTT1 null polymorphism, with 1923 cases and 2759 controls. Additionally, three studies on the GSTP1 Ile105Val were included in the meta-analysis. The investigated *GSTM1*, GSTT1, and GSTP1 genetic polymorphisms do not appear to provide any extra proof of susceptibility to ovarian cancer [21]. In a study carried out by Jin et al. [47], they utilized literature data to examine the association between *GSTM1* polymorphism and GSTT1 polymorphism in ovarian cancer. They identified a total of eight studies, which included 2397 cases and 2910 controls for *GSTM1* polymorphism, and 2049 cases and 2668 controls for *GSTT1* polymorphism. The comprehensive data indicated that individuals with the *GSTM1* null genotype did not exhibit a substantially higher risk of ovarian cancer compared to those with the *GSTM1* active genotype. In both the overall analysis and the subgroup of Caucasian subjects, no association was found between *GSTT1* polymorphism and the investigated model [47]. Although current studies have not yet provided conclusive evidence of a link between GST polymorphisms and epithelial ovarian cancer risk, recent study on the role of GST omega class polymorphisms has shown that that *GSTO* locus variants may confer ovarian cancer risk. Preferably, *GSTO2* should be primarily sequenced for variants that may influence the disease risk [48, 49].

Nevertheless, investigations done on other cancers of the urogenital system indicate a correlation between

GSTs and the development of cancer. Matic et al. [39] investigated the correlation between genetic variations in the *GSTA1, GSTM1, GSTP1*, and *GSTT1* genes with the incidence of bladder cancer. Additionally, they assessed whether these variations were influenced by smoking. None of the analyzed polymorphisms exhibited a statistically significant independent connection with bladder cancer risk. However, when combined with smoking, both the low activity *GSTA1* and *GSTM1*-null genotype contribute to an increased vulnerability to bladder cancer [39]. These findings indicate that GSTs polymorphisms have a role in carcinogenesis, and lifestyle factors can also impact the outcome. Since this aspect was not included in the previous research on the risk of ovarian cancer, the study of gene-environmental interactions in ovarian cancer risk might be an appropriate direction for future investigations. Besides, polymorphisms of GST members should also be examined in correlation with the degree of oxidative stress which may be one of contributing factors that initiate ovarian cancerogenesis [22, 23, 50].

GLUTATHIONE TRANSFERASE POLYMORPHISMS AND OVARIAN CANCER CHEMORESISTANCE

The conventional treatment for ovarian cancer patients involves cytoreductive surgery followed by the administration of chemotherapeutic drugs, specifically platinum-based compounds with taxans. However, a significant number of patients who experience a relapse develop resistance to platinum-based chemotherapy due to repeated treatment cycles. As a result, resistance to chemotherapy, whether inherent or acquired, is a prevalent issue in the management of ovarian cancer patients. The precise mechanisms of chemoresistance have not yet been completely understood. Presently, about 90% of patients acquire a kind of chemoresistance that ultimately proves fatal. The primary factors contributing to chemoresistance are:

1. the fact that there are heterogeneous tumor cells;
2. the presence of cancer stem cells;
3. the particular features of the tumor microenvironment [51].

As previously mentioned, the majority of polymorphisms found in genes that encode cytosolic GSTs belong to SNPs. Furthermore, the alterations in amino acids caused by SNPs lead to variations in the expression of GST variants, resulting in reduced transcriptional activity or functional change due to altered protein structure [43]. In addition to their role in promoting chemoresistance through their conjugating activity, GSTs also appear to interact with efflux transporters, therefore enhancing the efflux of anti-cancer drugs from the cell. This is another mechanism that is related to the development of chemoresistance [42].

Zhang et al. [52] examined the molecular and cellular factors behind chemoresistance in ovarian cancer, focusing on determining the expression of genes that encode glutathione transferase T1 in ovarian cancer cell cultures. The study demonstrated a significant increase in the expression of GSTT1 genes in serous ovarian cancer cell lines that are resistant to paclitaxel and carboplatin [52]. In addition, the study done by Liblab et al. [53] examined the correlation between genetic variations in ERCC1, XRCC1, and GSTP1, which have a role in platinum metabolism. The study showed that individuals with the GSTP1 A/G genotype exhibited a greater incidence of grade 2 anemia. This finding suggests that grade 2 anemia might potentially serve as a valuable indicator for predicting the clinical effectiveness of platinum-based chemotherapy [53]. These conclusions display the intricate function that glutathione S transferase can play in oncological therapy. Both polymorphisms and gene expression can impact the outcome. In addition, it has been revealed that GST can also impact the rate of complications, which are classified based on the grade or severity of multiple organ systems as a secondary effect of chemotherapy.

Kolwijck et al. [54] assessed the correlation between GSTP1-1 levels in ovarian cyst fluid, collected prior to chemotherapy during surgery, and the clinical outcomes of patients with epithelial ovarian cancer. The study included a total of 56 patients diagnosed with epithelial ovarian cancer and 109 patients without disease, who served as controls. The outcome was assessed by comparing the duration of progression-free survival and overall survival. It was discovered that patients with malignant illness and advanced FIGO stage exhibited elevated levels of GSTP1. Also, patients who received chemotherapy and had elevated levels of GSTP1 have worse progression-free survival and overall survival rates. Therefore, it may be concluded that cancer cells increase their ability to metabolize and remove anti-cancer drugs in GSTP1 dependent manner [54]. Nagle et al. [55] examined the impact of glutathione-S-transferase polymorphisms on the survival of women diagnosed with ovarian cancer. The researchers examined Australian women who were diagnosed with ovarian cancer between 1985 and 1997. They used DNA isolated from peripheral blood and uninvolved (normal) tissues for their analysis. They found that women with non-functional GST polymorphism, specifically the GSTP1 Ile105Val GG/GA genotype, experienced a significantly improved survival. This can be attributed to the enhanced ability of functional GST enzymes to efficiently detoxify anti-cancer drugs, leading to quicker elimination and reduced impact on tumor cells [55]. The study undertaken by O'Brien et al. [56] examined the impact of coordinated overexpression of glutathione phase II detoxification gene products on drug resistance. Specifically, glutathione, glutathione transferases, and the multidrug resistance-associated protein 1 have been individually examined for their roles in drug resistance. Upon combining all three, there was a notable increase in resistance levels for doxorubicin and etoposide. These findings validate the idea that the simultaneous improvement of detoxification pathways leads to a more effective defensive characteristic, leading to enhanced survival of tumor cells [56].

Khrunin et al. [57] analyzed 21 variations in 10 genes that encode the proteins responsible for cisplatin metabolism. A study was conducted to examine the relationship between the effectiveness and harmful effects of the

cisplatin-cyclophosphamide treatment in 104 patients with ovarian cancer. The association between the *GSTP1* Ile105Val polymorphism and progression-free survival was shown to be significant. The allelic status of the *GSTA1* C > T polymorphism was shown to be associated with better overall survival. Despite this, there were no observed associations between genotypes and complete tumor responses [57]. Furthermore, Kim et al. [58] conducted an analysis on several genes, including *GSTP1, GSTM1,* and *GSTT1* polymorphisms, to investigate their relationship with drug toxicity and their potential as a predictive factor. Data was collected for the medical records of 118 patients. The study demonstrated that having an active (non-null) genotype in the *GSTT1* was associated with a lower likelihood of overall response to chemotherapy. Additionally, those with an *A/A* genotype in the *GSTP1* Ile105Val polymorphism had a significantly higher chance of experiencing grade 3 or 4 hematological complications. Both of these two studies highlight the significance of *GST* polymorphisms in the prognosis, responsiveness, and complication rate associated with ovarian cancer [58].

Nonetheless, several compounds that can inhibit GSTs have been produced, and certain natural inhibitors have also been identified and studied. This is because blocking GSTs can help reverse drug resistance. The synthesis of GST inhibitors and the investigation of natural inhibitors have been extensively documented. Most of these compounds are either GST substrates or GSH analogs or mechanism-based inhibitors, resulting in enzyme inhibition through various mechanisms. The efficient accumulation and/or activation of anti-cancer drugs within cancer cells can be achieved by exploiting the overexpression of certain GSTs in distinct types of malignancies. Therefore, GSTs are appropriate as biomarkers for combination therapy including specific GST inhibitors and for the creation of new anti-cancer medications with focused selectivity [43, 59]. Molecules with the ability to inhibit GSTs may play a role in the series of actions that can be taken to combat drug resistance. Specifically, a substantial quantity of GST inhibitors has previously been developed, while there has been long-standing evidence of natural inhibitors. The primary mechanisms underlying the reversal of drug resistance involve the creation or utilization of molecules that act as either GST substrates or GSH analogues, therefore leading to enzyme inhibition in many ways.

Collectively, the previously cited research papers suggest a strong association between GSTs polymorphisms and clinical response, specifically in terms of overall survival and prognosis of chemotherapy toxicities. Insufficient activity in GST enzymes seems to result in an improved response to therapy [60].

CONCLUSION – CLINICAL IMPLICATIONS AND FUTURE DIRECTIONS

Glutathione transferases are essential for the detoxification of several conventional chemotherapeutic agents. Additionally, they are involved in the regulation of cellular proliferation and apoptosis. Conventional cancer treatment faces a significant obstacle in the form of inadequate capability to target cancer cells specifically while minimizing adverse effects and resistance to anticancer medications. Addressing the issue of multidrug resistance to chemotherapeutic agents is a significant concern in the field of ovarian cancer treatment as well. Similarly, considerable research effort is being devoted to discovering novel and inventive approaches to overcome this challenge. Likewise, chemoresistance is an exceedingly complex and multifaceted phenomenon that encompasses a multitude of underlying mechanisms. Introduction of new technology in conjunction with innovative GST targeted drugs offers innovative approaches to combating the growing trend of chemoresistance in ovarian cancer.

Ethics: The authors declare that the article was written according to ethical standards of the Serbian Archives of Medicine as well as ethical standards of institutions for each author involved

Conflict of interest: None declared.

REFERENCES

1. Webb PM, Jordan SJ. Epidemiology of epithelial ovarian cancer. Best Pract Res Clin Obstet Gynaecol. 2017;41:3–14. [DOI: 10.1016/j.bpobgyn.2016.08.006] [PMID: 27743768]
2. Doherty JA, Peres LC, Wang C, Way GP, Greene CS, Schildkraut JM. Challenges and Opportunities in Studying the Epidemiology of Ovarian Cancer Subtypes. Curr Epidemiol Rep. 2017;4(3):211–20. [DOI: 10.1007/s40471-017-0115-y] [PMID: 29226065]
3. Sung H, Ferlay J, Siegel RL, Laversanne M, Soerjomataram I, Jemal A, et al. Global Cancer Statistics 2020: GLOBOCAN Estimates of Incidence and Mortality Worldwide for 36 Cancers in 185 Countries. CA Cancer J Clin. 2021;71(3):209–49. [DOI: 10.3322/caac.21660] [PMID: 33538338]
4. O'Shea AS. Clinical Staging of Ovarian Cancer. Methods Mol Biol. 2022;2424:3–10. [DOI: 10.1007/978-1-0716-1956-8_1] [PMID: 34918284]
5. Labidi-Galy SI, Rodrigues M, Sandoval JL, Kurtz JE, Heitz F, Mosconi AM, et al. Association of location of BRCA1 and BRCA2 mutations with benefit from olaparib and bevacizumab maintenance in high-grade ovarian cancer: phase III PAOLA-1/ENGOT-ov25 trial subgroup exploratory analysis. Ann Oncol. 2023;34(2):152–62. [DOI: 10.1016/j.annonc.2022.11.003] [PMID: 36564284]
6. Ducie J, Dao F, Considine M, Olvera N, Shaw PA, Kurman RJ, et al. Molecular analysis of high-grade serous ovarian carcinoma with and without associated serous tubal intra-epithelial carcinoma. Nat Commun. 2017;8(1):990. [DOI: 10.1038/s41467-017-01217-9] [PMID: 29042553]
7. Kuchenbaecker KB, Hopper JL, Barnes DR, Phillips KA, Mooij TM, Roos-Blom MJ, et al. Risks of Breast, Ovarian, and Contralateral Breast Cancer for BRCA1 and BRCA2 Mutation Carriers. JAMA. 2017;317(23):2402–16. [DOI: 10.1001/jama.2017.7112] [PMID: 28632866]
8. La Vecchia C. Ovarian cancer: epidemiology and risk factors. Eur J Cancer Prev. 2017;26(1):55–62. [DOI: 10.1097/CEJ.0000000000000217] [PMID: 26731563]
9. Mažibrada I, Djukić T, Perović S, Plješa-Ercegovac M, Plavšić L, Bojanin D, et al. The association of hs-CRP and fibrinogen with

anthropometric and lipid parameters in non-obese adolescent girls with polycystic ovary syndrome. J Pediatr Endocrinol Metab. 2018;31(11):1213–20. [DOI: 10.1515/jpem-2017-0511] [PMID: 30335612]
10. Lheureux S, Braunstein M, Oza AM. Epithelial ovarian cancer: Evolution of management in the era of precision medicine. CA Cancer J Clin. 2019;69(4):280–304. [DOI: 10.3322/caac.21559] [PMID: 31099893]
11. Vang R, Shih IM. Serous tubal intra-epithelial carcinoma: what do we really know at this point? Histopathology. 2022;81(5):542–55. [DOI: 10.1111/his.14722] [PMID: 35859323]
12. Patch AM, Christie EL, Etemadmoghadam D, Garsed DW, George J, Fereday S, et al. Whole-genome characterization of chemoresistant ovarian cancer. Nature. 2015;521(7553):489–94. [DOI: 10.1038/nature14410]. Erratum in: Nature. 2015 Nov 19;527(7578):398. [DOI: 10.1038/nature15716] [PMID: 26017449]
13. Konecny GE, Wang C, Hamidi H, Winterhoff B, Kalli KR, Dering J, et al. Prognostic and therapeutic relevance of molecular subtypes in high-grade serous ovarian cancer. J Natl Cancer Inst. 2014;106(10):dju249. [DOI: 10.1093/jnci/dju249] [PMID: 25269487]
14. Tothill RW, Tinker AV, George J, Brown R, Fox SB, Lade S, et al. Novel molecular subtypes of serous and endometrioid ovarian cancer linked to clinical outcome. Clin Cancer Res. 2008;14(16):5198–208. [DOI: 10.1158/1078-0432.CCR-08-0196] [PMID: 18698038]
15. Cheng Z, Mirza H, Ennis DP, Smith P, Morrill Gavarró L, Sokota C, et al. The Genomic Landscape of Early-Stage Ovarian High-Grade Serous Carcinoma. Clin Cancer Res. 2022;28(13):2911–22. [DOI: 10.1158/1078-0432.CCR-21-1643] [PMID: 35398881]
16. Torre LA, Trabert B, DeSantis CE, Miller KD, Samimi G, Runowicz CD, et al. Ovarian cancer statistics, 2018. CA Cancer J Clin. 2018;68(4):284–96. [DOI: 10.3322/caac.21456] [PMID: 29809280]
17. Pinsky PF, Yu K, Kramer BS, Black A, Buys SS, Partridge E, et al. Extended mortality results for ovarian cancer screening in the PLCO trial with median 15 years follow-up. Gynecol Oncol. 2016;143(2):270–5. [DOI: 10.1016/j.ygyno.2016.08.334] [PMID: 27615399]
18. Griffiths CT, Fuller AF. Intensive surgical and chemotherapeutic management of advanced ovarian cancer. Surg Clin North Am. 1978;58(1):131–42. [DOI: 10.1016/s0039-6109(16)41440-4] [PMID: 417410]
19. du Bois A, Reuss A, Pujade-Lauraine E, Harter P, Ray-Coquard I, Pfisterer J. Role of surgical outcome as prognostic factor in advanced epithelial ovarian cancer: a combined exploratory analysis of 3 prospectively randomized phase 3 multicenter trials: by the Arbeitsgemeinschaft Gynaekologische Onkologie Studiengruppe Ovarialkarzinom (AGO-OVAR) and the Groupe d'Investigateurs Nationaux Pour les Etudes des Cancers de l'Ovaire (GINECO). Cancer. 2009;115(6):1234–44. [DOI: 10.1002/cncr.24149] [PMID: 19189349]
20. Pljesa-Ercegovac M, Savic-Radojevic A, Coric V, Radic T, Simic T. Glutathione transferase genotypes may serve as determinants of risk and prognosis in renal cell carcinoma. Biofactors. 2020;46(2):229–38. [DOI: 10.1002/biof.1560] [PMID: 31483924]
21. Economopoulos KP, Sergentanis TN, Vlahos NF. Glutathione S-transferase M1, T1, and P1 polymorphisms and ovarian cancer risk: a meta-analysis. Int J Gynecol Cancer. 2010;20(5):732–7. [DOI: 10.1111/IGC.0b013e3181dedeb5] [PMID: 20966642]
22. Cotton SC, Sharp L, Little J, Brockton N. Glutathione S-transferase polymorphisms and colorectal cancer: a HuGE review. Am J Epidemiol. 2000;151(1):7–32. [DOI: 10.1093/oxfordjournals.aje.a010124] [PMID: 10625170]
23. Coughlin SS, Hall IJ. Glutathione S-transferase polymorphisms and risk of ovarian cancer: a HuGE review. Genet Med. 2002;4(4):250–7. [DOI: 10.1097/00125817-200207000-00003] [PMID: 12172391]
24. Rebbeck TR. Molecular epidemiology of the human glutathione S-transferase genotypes GSTM1 and GSTT1 in cancer susceptibility. Cancer Epidemiol Biomarkers Prev. 1997;6(9):733–43. [PMID: 9298582]
25. Kellen E, Hemelt M, Broberg K, Golka K, Kristensen VN, Hung RJ, et al. Pooled analysis and meta-analysis of the glutathione S-transferase P1 Ile 105Val polymorphism and bladder cancer: a HuGE-GSEC review. Am J Epidemiol. 2007;165(11):1221–30. [DOI: 10.1093/aje/kwm003] [PMID: 17404387]
26. Dusinská M, Ficek A, Horská A, Raslová K, Petrovská H, Vallová B, et al. Glutathione S-transferase polymorphisms influence the level of oxidative DNA damage and antioxidant protection in humans. Mutat Res. 2001;482(1–2):47–55. [DOI: 10.1016/s0027-5107(01)00209-3] [PMID: 11535248]
27. Coles BF, Kadlubar FF. Human alpha class glutathione S-transferases: genetic polymorphism, expression, and susceptibility to disease. Methods Enzymol. 2005;401:9–42. [DOI: 10.1016/S0076-6879(05)01002-5] [PMID: 16399377]
28. Tanaka-Kagawa T, Jinno H, Hasegawa T, Makino Y, Seko Y, Hanioka N, et al. Functional characterization of two variant human GSTO 1-1s (Ala140Asp and Thr217Asn). Biochem Biophys Res Commun. 2003;301(2):516–20. [DOI: 10.1016/s0006-291x(02)03066-8] [PMID: 12565892]
29. Whitbread AK, Masoumi A, Tetlow N, Schmuck E, Coggan M, Board PG. Characterization of the omega class of glutathione transferases. Methods Enzymol. 2005;401:78–99. [DOI: 10.1016/S0076-6879(05)01005-0] [PMID: 16399380]
30. Menon D, Board PG. A role for glutathione transferase Omega 1 (GSTO1-1) in the glutathionylation cycle. J Biol Chem. 2013;288(36):25769–79. [DOI: 10.1074/jbc.M113.487785] [PMID: 23888047]
31. Mukherjee B, Salavaggione OE, Pelleymounter LL, Moon I, Eckloff BW, Schaid DJ, et al. Glutathione S-transferase omega 1 and omega 2 pharmacogenomics. Drug Metab Dispos. 2006;34(7):1237–46. [DOI: 10.1124/dmd.106.009613] Erratum in: Drug Metab Dispos. 2006;34(9):1666. [PMID: 16638819]
32. Allen M, Zou F, Chai HS, Younkin CS, Miles R, Nair AA, et al. Glutathione S-transferase omega genes in Alzheimer and Parkinson disease risk, age-at-diagnosis and brain gene expression: an association study with mechanistic implications. Mol Neurodegener. 2012;7:13. [DOI: 10.1186/1750-1326-7-13] [PMID: 22494505]
33. Hollman AL, Tchounwou PB, Huang HC. The Association between Gene-Environment Interactions and Diseases Involving the Human GST Superfamily with SNP Variants. Int J Environ Res Public Health. 2016;13(4):379. [DOI: 10.3390/ijerph13040379] [PMID: 27043589]
34. B Board P, Coggan M, Johnston P, Ross V, Suzuki T, Webb G. Genetic heterogeneity of the human glutathione transferases: a complex of gene families. Pharmacol Ther. 1990;48(3):357–69. [DOI: 10.1016/0163-7258(90)90054-6] [PMID: 2084706]
35. Wiencke JK, Pemble S, Ketterer B, Kelsey KT. Gene deletion of glutathione S-transferase theta: correlation with induced genetic damage and potential role in endogenous mutagenesis. Cancer Epidemiol Biomarkers Prev. 1995;4(3):253–9. [PMID: 7606200]
36. Bumbasirevic U, Bojanic N, Pljesa-Ercegovac M, Zivkovic M, Djukic T, Zekovic M, et al. The Polymorphisms of Genes Encoding Catalytic Antioxidant Proteins Modulate the Susceptibility and Progression of Testicular Germ Cell Tumor. Cancers (Basel). 2022;14(4):1068. [DOI: 10.3390/cancers14041068] [PMID: 35205816]
37. Xue CX, He XM, Zou DH. Glutathione S-transferase M1 Polymorphism and Breast Cancer Risk: a Meta-Analysis in the Chinese Population. Clin Lab. 2016;62(11):2277–84. [DOI: 10.7754/Clin.Lab.2016.160333] [PMID: 28164656]
38. Coric VM, Simic TP, Pekmezovic TD, Basta-Jovanovic GM, Savic-Radojevic AR, Radojevic-Skodric SM, et al. GSTM1 genotype is an independent prognostic factor in clear cell renal cell carcinoma. Urol Oncol. 2017;35(6):409–17. [DOI: 10.1016/j.urolonc.2017.02.005] [PMID: 28284893]
39. Matic M, Pekmezovic T, Djukic T, Mimic-Oka J, Dragicevic D, Krivic B, et al. GSTA1, GSTM1, GSTP1, and GSTT1 polymorphisms and susceptibility to smoking-related bladder cancer: a case-control study. Urol Oncol. 2013;31(7):1184–92. [DOI: 10.1016/j.urolonc.2011.08.005] [PMID: 24075358]
40. Singh S. Cytoprotective and regulatory functions of glutathione S-transferases in cancer cell proliferation and cell death. Cancer Chemother Pharmacol. 2015;75(1):1–15. [DOI: 10.1007/s00280-014-2566-x] [PMID: 25143300]
41. Bertholee D, Maring JG, van Kuilenburg AB. Genotypes Affecting the Pharmacokinetics of Anticancer Drugs. Clin Pharmacokinet. 2017;56(4):317–37. [DOI: 10.1007/s40262-016-0450-z] [PMID: 27641154]
42. Simic P, Pljesa I, Nejkovic L, Jerotic D, Coric V, Stulic J, et al. Glutathione Transferase P1: Potential Therapeutic Target in Ovarian Cancer. Medicina (Kaunas). 2022;58(11):1660. [DOI: 10.3390/medicina58111660] [PMID: 36422199]
43. Pljesa-Ercegovac M, Savic-Radojevic A, Matic M, Coric V, Djukic T, Radic T, et al. Glutathione Transferases: Potential Targets to Overcome Chemoresistance in Solid Tumors. Int J Mol Sci. 2018;19(12):3785. [DOI: 10.3390/ijms19123785]

44. Sau A, Pellizzari Tregno F, Valentino F, Federici G, Caccuri AM. Glutathione transferases and development of new principles to overcome drug resistance. Arch Biochem Biophys. 2010;500(2):116–22. [DOI: 10.1016/j.abb.2010.05.012] [PMID: 20494652]
45. Ishikawa T, Wright CD, Ishizuka H. GS-X pump is functionally overexpressed in cis-diamminedichloroplatinum (II)-resistant human leukemia HL-60 cells and down-regulated by cell differentiation. J Biol Chem. 1994;269(46):29085–93. [PMID: 7961875]
46. Horton JK, Roy G, Piper JT, Van Houten B, Awasthi YC, Mitra S, et al. Characterization of a chlorambucil-resistant human ovarian carcinoma cell line overexpressing glutathione S-transferase mu. Biochem Pharmacol. 1999;58(4):693–702. [DOI: 10.1016/s0006-2952(99)00142-2] [PMID: 10413308]
47. Jin Y, Hao Z. Polymorphisms of glutathione S-transferase M1 (GSTM1) and T1 (GSTT1) in ovarian cancer risk. Tumour Biol. 2014;35(6):5267–72. [DOI: 10.1007/s13277-014-1685-7] [PMID: 24532428]
48. Simic P, Coric V, Pazin V, Pljesa I, Pljesa-Ercegovac M. The role of glutathione transferase omega class variant alleles in individual susceptibility to ovarian cancer. Int J Mol Sci. 2024;25(9):4986. [DOI: 10.3390/ijms25094986] [PMID: 38732205]
49. Simić P, Radojičić. The Association of Polymorphism of O1 Glutathione Transferase Gene (Rs4925) To the Risk of Ovarian Cancer. 59. Kongres studenata biomedicinskih nauka Srbije sa internacionalnim učešćem (59; 2018; Kopaonik). Kragujevac: Fakultet medicinskih nauka; 2018. p. 819.
50. Simic P, Pljesa-Ercegovac M, Coric V, Pazin V. The importance of oxidative stress in the pathogenesis of ovarian cancer. Srp Med Časopis Lek Komore. 2024. [DOI: 10.5937/smclk5-50413]
51. Mansoori B, Mohammadi A, Davudian S, Shirjang S, Baradaran B. The Different Mechanisms of Cancer Drug Resistance: A Brief Review. Adv Pharm Bull. 2017;7(3):339–48. [DOI: 10.15171/apb.2017.041] [PMID: 29071215]
52. Zhang J, Xie S, Zhou L, Tang X, Guan X, Deng M, et al. Up-regulation of GSTT1 in serous ovarian cancer associated with resistance to TAXOL / carboplatin. J Ovarian Res. 2021;14(1):122. [DOI: 10.1186/s13048-021-00873-2] [PMID: 34535163]
53. Liblab S, Vusuratana A, Areepium N. ERCC1, XRCC1, and GSTP1 Polymorphisms and Treatment Outcomes of Advanced Epithelial Ovarian Cancer Patients Treated with Platinum-based Chemotherapy. Asian Pac J Cancer Prev. 2020;21(7):1925–9. [DOI: 10.31557/APJCP.2020.21.7.1925] [PMID: 32711417]
54. Kolwijck E, Zusterzeel PL, Roelofs HM, Hendriks JC, Peters WH, Massuger LF. GSTP1-1 in ovarian cyst fluid and disease outcome of patients with ovarian cancer. Cancer Epidemiol Biomarkers Prev. 2009;18(8):2176–81. [DOI: 10.1158/1055-9965.EPI-09-0098] [PMID: 19661073]
55. Nagle CM, Chenevix-Trench G, Spurdle AB, Webb PM. The role of glutathione-S-transferase polymorphisms in ovarian cancer survival. Eur J Cancer. 2007;43(2):283–90. [DOI: 10.1016/j.ejca.2006.09.011] [PMID: 17084623]
56. O'Brien M, Kruh GD, Tew KD. The influence of coordinate overexpression of glutathione phase II detoxification gene products on drug resistance. J Pharmacol Exp Ther. 2000;294(2):480–7. [PMID: 10900222]
57. Khrunin AV, Khokhrin DV, Moisseev AA, Gorbunova VA, Limborska SA. Pharmacogenomic assessment of cisplatin-based chemotherapy outcomes in ovarian cancer. Pharmacogenomics. 2014;15(3):329–37. [DOI: 10.2217/pgs.13.237] [PMID: 24533712]
58. Kim HS, Kim MK, Chung HH, Kim JW, Park NH, Song YS, et al. Genetic polymorphisms affecting clinical outcomes in epithelial ovarian cancer patients treated with taxanes and platinum compounds: a Korean population-based study. Gynecol Oncol. 2009;113(2):264–9. [DOI: 10.1016/j.ygyno.2009.01.002] [PMID: 19203783]
59. Wu JH, Batist G. Glutathione and glutathione analogues; therapeutic potentials. Biochim Biophys Acta. 2013;1830(5):3350–3. [DOI: 10.1016/j.bbagen.2012.11.016] [PMID: 23201199]
60. Roco A, Cayún J, Contreras S, Stojanova J, Quiñones L. Can pharmacogenetics explain efficacy and safety of cisplatin pharmacotherapy? Front Genet. 2014;5:391. [DOI: 10.3389/fgene.2014.00391] [PMID: 25452763]

Повезаност полиморфизама за глутатион-трансферазу са ризиком за оваријални карцином и појаву хемиорезистенције

Петар Симић[1], Марија Плъеша-Ерцеговац[2,3,4]

[1]Гинеколошко-акушерска клиника „Народни фронт", Београд, Србија;
[2]Универзитет у Београду, Медицински факултет, Београд, Србија;
[3]Институт за медицинску и клиничку биохемију, Београд, Србија;
[4]Центар изврсности за редокс медицину, Београд, Србија

САЖЕТАК

Карцином јајника се сматра најсмртоноснијим гинеколошким карциномом са петогодишњим преживљавањем испод 45%. Он представља седми најчешћи рак међу женама. С обзиром на то да је доступност биомаркера карцинома јајника ограничена, као и да не постоје поуздане методе скрининга, у току су многа истраживања фактора који повећавају ризик за настанак овог тумора. Након исцрпљивања хируршких и хемиотерапијских метода лечења карцинома јајника, развој хемиорезистенције постаје критичан фактор у напредовању болести. Глутатион-трансферазе су фамилија ензима који играју кључну улогу у процесу детоксикације. У генима који кодирају глутатион-трансферазе постоје полиморфизми, који могу довести до потпуног или делимичног губитка функције ензима. Цитосолну активност глутатион-трансфераза чини много различитих изоензима који каталишу интеракције између глутатиона и токсичних једињења, укључујући канцерогене, лекове против рака и продукте оксидативног стреса. Циљ овог прегледног чланка је да разјасни повезаност најчешћих полиморфизама гена за глутатион-трансферазе са ризиком за настанак рака јајника и његовом хемиорезистенцијом.

Кључне речи: глутатион-трансфераза; карцином јајника; полиморфизми; ризик; хемиорезистенција