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POLY (ADP-RIBOSE) POLYMERASE INHIBITOR RESPONSES IN HIGH-GRADE SEROUS OVARIAN CANCER: INSIGHTS FROM *BRCA* GERMLINE-NEGATIVE AND SOMATIC MUTATION-POSITIVE CASES

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Abstract: High-grade serous ovarian cancer (HGSOC) is an aggressive form of epithelial carcinoma associated with poor prognosis. Although relatively uncommon, mutations in the *BRCA1/2* genes are linked to HGSOC. Poly(ADP-ribose) polymerase inhibitors (PARPi) have been approved for treating patients with *BRCA1/2* mutations, significantly improving outcomes for this subgroup. To assess the prevalence of *BRCA1/2* mutations in high-grade serous ovarian cancer (HGSOC) patients who tested negative for germline *BRCA1/2* mutations and to evaluate the potential implications of tumor-based genetic testing for expanding PARPi therapy eligibility. 75 patients who underwent Somatic *BRCA1/BRCA2* Next Generation Sequencing (NGS) and were positive for somatic but negative for germline *BRCA1/2* mutations were selected and included in the study. Tumor tissue samples, either formalin-fixed paraffin-embedded or fresh, were analyzed using NGS to detect somatic mutations in *BRCA1/2* genes. The study also examined variants of uncertain significance (VUS) within these genes. Pathogenic somatic mutations in the *BRCA1/2* genes were identified in 8 patients (11%), while a VUS was detected in 1 patient (1%). Variant mutations c.135-8A>G, c.1084G>T (p.Glu362Ter), c.5095C>T (p.Arg1699Trp), and c.3756_3759del (p.Ser1253fs) were found in the *BRCA1* gene, while c.5073dup (p.Trp1692fs), c.426-1G>A, c.3751_3752insA (p.Thr1251AsnfsTer14), and c.771_775del (p.Asn257fs) were found in the *BRCA2* gene. Our study highlights the importance of expanding the availability of PARPi therapy to patients with somatic *BRCA1/2* mutations and providing targeted therapy to guide patients with high-grade ovarian serous cancer. As treatments evolve, integrating comprehensive genetic testing into clinical practice is vital to improving care.

Keywords: *BRCA1/2*, High-grade serous ovarian cancer, PARPi, Next-generation sequencing, Somatic mutation

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1. Introduction

Ovarian cancer is the most lethal of gynecologic epithelial cancers and is usually diagnosed at an advanced stage, which reduces the chance of cure. Treatment is usually individualized but often includes cytoreductive surgery followed by platinum-based chemotherapy. In advanced-stage patients, this treatment method rarely provides long-term survival, and most patients experience a relapse within 1 to 1.5 years. In the event of relapses, treatment focuses on increasing survival with platinum/taxane-based chemotherapy. However, palliative treatment may be required due to the development of drug resistance. The 5-year survival rate for ovarian cancer is low (Ledermann, 2017).

Women with *BRCA1* and *BRCA2* pathogenic variants have a cumulative lifetime risk of ovarian cancer of 39%– 44% and 11%–17%, respectively (Kuchenbaecker et al., 2017; Antoniou et al., 2003). According to earlier estimates, germ-line mutations in *BRCA1* or *BRCA2* are present in 13–15% of ovarian cancer patients (Pal et al., 2005). In women with *BRCA1* or *BRCA2* mutations, risk-reducing salpingo-oophorectomy considerably lowers overall mortality and ovarian cancer risk (Rebbeck et al., 2009; Domchek et al., 2006). Therefore, determining hereditary

risk for ovarian cancer is crucial for effective and focused prevention. Finding hereditary risk is now much more important due to the new emergence of poly-ADP ribose polymerase (PARP) inhibitors in cancer treatments (Bryant et al., 2005; Farmer et al., 2005). Ovarian carcinomas linked to mutations in *BRCA1* or *BRCA2* can be effectively treated with PARP inhibitors, which are preferentially fatal to cells lacking these genes (Fong et al., 2009). Ovarian cancer risk is elevated by *BRCA1* and *BRCA2* mutations that result in loss of function of the encoded proteins (Kuchenbaecker et al., 2017; Antoniou et al., 2003). Finding a pathogenic *BRCA1* or *BRCA2* variation is crucial clinical information that directs a patient's medical care, including preventative measures, early detection, and, more recently, individualized PARP inhibitor treatment (Pilié et al., 2019). Additionally, one efficient method of lowering the cancer burden in those who are at high risk of getting cancer is to screen close relatives of the carrier of the pathogenic variation (Tuffaha et al., 2018).

After the sensitivity of BRCA-deficient cells to PARPi was first described, the idea that deficiencies in double-stranded DNA repair might predict sensitivity to PARPi was examined (Farmer et al., 2005). DNA double-strand breaks can be repaired using a high-fidelity genetic recombination technique called homologous recombination repair (Heyer et al., 2010). Repair of error-free double-stranded breaks and maintenance of genomic integrity may be enabled by the presence of a sister chromatid or homologous chromosome during the cell cycle (Heyer et al., 2010). A higher risk of ovarian cancer is associated with germline loss-of-function (LOF) monoallelic mutations in genes involved in homologous recombination repair, such as BRCA1 and BRCA2 (Walsh et al., 2015; Lilyquist et al., 2017). The family of cellular enzymes known as PARP involves many biological processes. PARP-1 and PARP-2, the most prevalent and well-characterized members, are involved in the detection and repair of DNA damage (Gibson et al., 2012) in a process known as POLyation or PARylation. Nicotinamide adenine dinucleotide is utilized as a substrate within its catalytic site to create polymers of ADP-ribose (Rouleau et al., 2010). At single-strand breaks, PARP attaches itself to DNA and creates PAR on both it and other DNA- DNA-associated accessory proteins. To repair single-strand breaks, these polymers can subsequently attract proteins that are a part of the base excision repair pathway (Malanga et al., 2005). Preclinical studies have unequivocally demonstrated that cells deficient in BRCA1/2 were vulnerable to PARP inhibition. If a deficiency occurs in a particular combination of two or more genes or gene products, a cell may die, but it can survive with a defect in one gene or gene product. Synthetic lethality is believed to cause this effect (Ashworth et al., 2008). It is assumed that a *BRCA1/2* deficit impairs a cell's potential to repair double-strand breaks by homologous recombination repair. A lethal second deficit is caused by targeted pharmacological inhibition of PARP-1/2 (Helleday et al., 2011). The second class of therapeutic medications is known as PARPi (Ledermann, 2016). These inhibitors, which take advantage of cancer cells' susceptibility to defects in DNA damage repair, have shown impressive results in clinical studies for single-agent therapies and maintenance treatments. In this section, we will look at high-grade serous ovarian cancer (HGSOC) instances that have pathogenic variations in paraffin-embedded or fresh cancer tissue that react to PARPi but do not exhibit germline mutations in the *BRCA 1/2* gene. The purpose of this study was to determine the frequency of *BRCA1/*2 mutations in HGSOC patients who did not test positive for germline *BRCA1/2* mutations and to analyze the possible consequences of tumor-based genetic testing for increasing the eligibility for PARPi treatment.

2. Materials and Methods

2.1. Case Selection and Sample Preparation

This was a retrospective study. Between October 2022 and August 2024, 75 patients underwent Somatic *BRCA1/BRCA2.* Next Generation Sequencing at Umraniye Training and Research Hospital Genetic Center, University of Health Sciences, Istanbul, Türkiye. We used the registered database to select patients. Invasive breast carcinoma, pancreatic adenocarcinoma, prostate adenocarcinoma, uterine cervical carcinoma, and uterine leiomyosarcoma, both somatic and germline mutation-positive cases, were excluded. 75 patients who were diagnosed with high-grade serous ovarian carcinoma and somatic mutation positive, germline mutation negative, were selected. Samples for next-generation sequencing were obtained from formalin-fixed paraffin-embedded (FFPE) blocks of female patients diagnosed with ovarian high-grade serous ovarian cancer. A pathologist involved in the study reviewed the cases, and the histological diagnoses were confirmed.

2.2. Next-Generation Sequencing (NGS)

For each patient, the pathology doctor took 20 (5-micron) sections from paraffin blocks and a few 3-micron pieces from fresh tissue and sent them to the genetics center. DNA isolation was first performed from the primary sample to amplify disease-related genes/gene regions. The quality control of the isolated DNA sample was performed. Target regions were amplified using the DNA-based “Devyser BRCA (Somatic)” kit and sequenced using the next-generation sequencing (NGS) method on the Illumina NextSeq/Novaseq platform. Secondary analyses (data cleaning, alignment, and variant/fusion detection) of the obtained raw data (Fastq) were performed using Dragen software. The hg19 (GRCh37) human reference genome was used in the alignment.

2.3. Data Analysis

The raw data transferred to DRAGEN Amplicon | Version: 4.2 on the BaseSpace Sequence Hub platform was first evaluated regarding Data Quality. After examining these metrics, the appropriate samples were included in the analysis flow and assessed for

the specified disease. Filtering in the analysis flow was performed to scan changes associated with the specified tumor type, primarily considering the patient's clinical information. After filtering, the changes in the obtained lists were classified according to their presence in guidelines and databases, and information such as diagnosis, prognosis, and treatment. The classification was made based on the evidence found about the changes and considering the AMP/ASCO/AMP guideline (PMID: 27993330).

The study prioritized variants with an allele fraction (AF) above 5% and considered significant according to the specified clinical data. Variants specified in the guidelines but with an AF rate lower than 5% were added to the study as long as they matched the patient's clinical characteristics. Some restrictions were used for Tier III (VUS) variants. First, the detected gene is expected to be associated with the specified cancer, and the amino acid change is likely to be in an active region of the gene. Then, these variants were evaluated in terms of their frequency in population databases. New (not previously reported in the literature) variants were included in the Tier III class if they met the specified criteria. The study did not include tier IV (Likely Benign/Benign) variants.

2.4. Classification and Evidence Levels

Tier I: A) Variants in a particular tumor type that are both sensitive to and resistant to FDA-approved and guideline-approved therapies. B) Variants included in extensive, well-researched investigations by professional organizations. Tier II: C) Variants in a different tumor type that are both sensitive to and resistant to FDA-approved and guideline-approved therapies. D) Variants are featured in preclinical research or case reports. Tier III: Variants with unclear clinical implications. Tier IV: Variants with extremely high allele frequencies have not been linked to a particular malignancy.

2.5. Statistical Analysis

The frequency of each clinical finding in person was assessed. Statistical analysis was carried out using a descriptive examination. The statistical program SPSS 21.01 was used for all analyses.

3. Results

3.1. Histopathologic Findings

Gross findings of HGSOC included large, irregularly shaped masses involving the ovaries. The tumors typically exhibited a mixed solid and cystic appearance. The solid areas were firm and associated with areas of necrosis and hemorrhage. The cystic spaces contained serous or hemorrhagic fluid. Extensive peritoneal dissemination, multiple small nodules or plaques on the peritoneal surfaces, and omental thickening were observed. HGSOC was aggressive, involved lymph nodes, and rapidly spread into the peritoneal cavity. In the tumor sample we have attached below, a large ovarian cancer with a solid and cystic yellow-white appearance, accompanied by necrosis and hemorrhage, was observed (Figure 1A).

HGSOC microscopically exhibited mixtures of papillary, glandular, nested, and diffuse/solid growth patterns. The papilla was large and intricate. The papillae's lining epithelium was stratified and shaped like an uneven slit. A micropapillary growth pattern was seen in a few instances. They usually have an admixed solid development pattern and have high-grade nuclei (Figure 1B). The circular, simple, or complicated glands with irregular slit-like gaps were seen in high-grade serous cancer. Diffused sheets of neoplastic epithelium were present in some tumors with such extensive solid architecture. An obvious destructive stromal invasion was present in some cases. Necrosis was common in these high-grade serous carcinomas. Psammoma bodies had been seen but were typically less frequent.

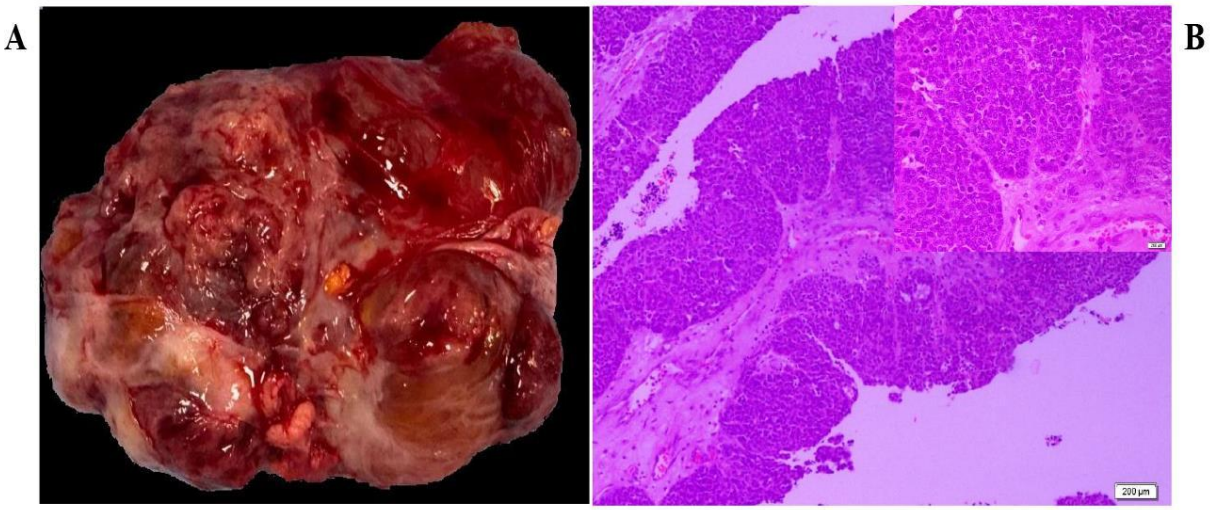

Figure 1. A: High-grade ovarian serous carcinoma with solid and cystic macroscopic appearance including necrosis and hemorrhagic areas. B: The histopathological image of HGSOC showed structural abnormalities such as papillary architecture with high-grade cytological atypia, pleomorphic nuclei, and increased mitotic figures.

Table 1. *BRCA1/2* gene variant mutational information of the patients

Case No	Gene	Transcript	Variant	Protein	COSMIC	Classification according to AMP/ASCO/CAP guideline	FDA approved drug	Response
25	*BRCA1*	NM_007294.3	c.135-8A>G	-	-	Tier-III	-	-
31	*BRCA1*	NM_007294.3	c.1084G>T	p.Glu362Ter	-	Tier-IA	PARPi	+
32	*BRCA1*	NM_007294.3	c.5095C>T	p.Arg1699Trp	10265875	TierIA	PARPi	+
65	*BRCA1*	NM_007294.4	c.3756_3759del	p.Ser1253fs	-	Tier-IA	PARPi	+
19	*BRCA2*	NM_000059.3	c.5073dup	p.Trp1692fs	5078974	TierIA	PARPi	+
30	*BRCA2*	NM_000059.4	c.426-1G>A	-	-	TierIA	PARPi	+
66	*BRCA2*	NM_000059.4	c.426-1G>A			Tier-IA	PARPi	+
70	*BRCA2*	NM_000059.4	c.3751_3752insA	p.Thr1251AsnfsTer14	-	Tier-IA	PARPi	+
71	*BRCA2*	NM_000059.4	c.771_775del	p.Asn257fs	-	Tier-IA	PARPi	+

AMP= association for molecular pathology, ASCO= American society of clinical oncology, CAP= college of American pathologists, FDA= food and drug administration.

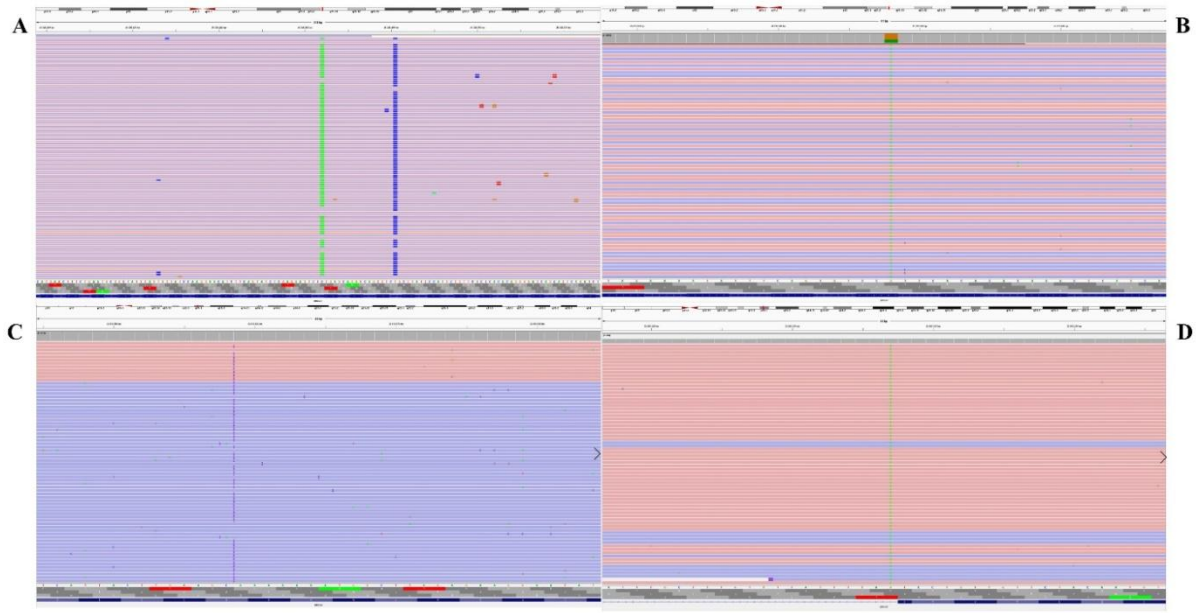

Figure 2. Integrative Genomics Viewer image of *BRCA1* and *BRCA2* gene variant mutations. A: *BRCA1*, NM_007294.3 c.1084G>T (p.Glu362Ter). B: *BRCA1*, NM_007294.3 c.5095C>T (p.Arg1699Trp). C: *BRCA2*, NM_000059.3 c.5073dup (p.Trp1692fs). D: *BRCA2*, NM_000059.4 c.426-1G>A.

3.2. Identification of Somatic Mutations in the Study Cohort

All patients were female, and the mean ± SD of the age of the patients was 59.41 ± 12.57 years. Our patients showed negative results for germline mutations for the *BRCA 1/2* genes, but positive results for somatic mutations. Pathogenic *BRCA1/2* mutations were identified in 11% of women (8 of 75), and VUS was identified in nearly 1% (1/75) with high-grade serous ovarian cancer (Table 1). Among them, *BRCA1* mutations occupy 5% (4/75) and *BRCA2* mutations 7% (5/75), respectively. Variant mutations c.135-8A>G, c.1084G>T (p.Glu362Ter), c.5095C>T (p.Arg1699Trp), and c.3756_3759del (p.Ser1253fs) were found in the *BRCA1* gene, while c.5073dup (p.Trp1692fs), c.426-1G>A, c.3751_3752insA (p.Thr1251AsnfsTer14), and c.771_775del (p.Asn257fs) were found in the *BRCA2* gene (Figure 2).

4. Discussion

Our study identified somatic *BRCA1* and *BRCA2* gene variant mutations in tumor tissue samples from 9 out of 75 patients diagnosed with high-grade serous ovarian cancer. These pathogenic or likely pathogenic variants underscore the importance of somatic *BRCA1/2* mutation testing in tumor tissue to expand eligibility for PARPi therapy. The therapeutic potential of PARPi was first demonstrated in patients with recurrent ovarian carcinoma resistant to platinum-based chemotherapy (Fong et al., 2009). Since then, studies have consistently highlighted their efficacy. Olaparib, a prominent PARPi, has shown remarkable benefits as maintenance therapy, significantly improving progression-free survival in both recurrent platinum-sensitive ovarian carcinoma and newly diagnosed advanced *BRCA1/2*-associated ovarian carcinoma. Olaparib decreased the risk of disease progression or mortality in the SOLO-1 study by 70%

when compared to a placebo (Ledermann et al., 2014; Moore et al., 2018). Olaparib was approved by the FDA in 2014 for the treatment of ovarian cancer, in 2017 for the maintenance of recurrent disease, and in 2019 for the maintenance of post-adjuvant therapy.

In parallel, data from the Cancer Genome Atlas Research Network (2011) revealed that HGSOC is characterized by a near-universal prevalence of *TP53* mutations (96%) and lower frequencies of somatic mutations in other genes, including *BRCA1/2*. Recent evidence further supports the utility of PARPi across the treatment continuum. Three PARPis—olaparib, niraparib, and rucaparib—are now FDA-approved for maintenance therapy in ovarian cancer (AstraZeneca, 2022; GlaxoSmithKline, 2022; Clovis Oncology, 2022). The introduction of PARPi earlier in treatment, especially for newly diagnosed patients, has proven to provide the most substantial clinical benefit, particularly for those with *BRCA1/2* mutations or homologous recombination deficiency (O'Malley et al., 2023). Numerous studies have been conducted on the survival outcomes of women with *BRCA1/2* pathogenic mutations. Even after controlling for variables like stage, grade, histology, and age at diagnosis, a pooled study of 26 observational studies showed higher survival rates for these patients (Bolton et al., 2012). According to other research, people with *BRCA1/2 mutations* have better overall survival, longer progression-free survival, and greater response rates to platinum-based treatments than people without such mutations (Alsop et al., 2012; Dann et al., 2012). Nevertheless, there are no appreciable long-term survival benefits, and this advantage seems to erode over time (McLaughlin et al., 2013). The main strength of our study is the focus on somatic *BRCA1/2* mutations in a germline-negative high-grade serous ovarian cancer cohort, highlighting an important subgroup of patients potentially benefiting from PARPi therapy. However, limitations include the relatively small sample size and the retrospective design, which may restrict the generalizability of the findings. Larger, prospective studies are necessary to validate these results.

Our findings reinforce the clinical value of incorporating tumor-based *BRCA1/2* mutation testing into routine diagnostic workflows to identify additional candidates for PARPi therapy beyond those with germline mutations. Future research should focus on larger, prospective cohorts to confirm the prevalence of somatic mutations and investigate the long-term clinical outcomes of PARPi treatment in this population. Additionally, policy updates may be warranted to recommend comprehensive genetic testing strategies to optimize personalized ovarian cancer management.

5. Conclusion

Our study underscores the critical need to extend PARPi therapy access to patients harboring somatic *BRCA1/2* mutations, enabling more precise targeted treatment for ovarian serous cancer. As therapeutic options continue to advance, the integration of comprehensive genetic testing—including both germline and somatic mutation analysis—into routine clinical practice is essential to improve patient outcomes. Ensuring equitable access to validated genetic testing methods, in alignment with clinical guidelines and policies, is vital for ovarian cancer patients to fully benefit from PARPi therapies.

Author Contributions

The percentages of the authors' contributions are presented below. All authors reviewed and approved the final version of the manuscript.

	M.E.	G.H.	M.H.Y.	F.G.A.	E.K.P.	M.A.	M.O.
C	20	20	10	10	10	10	20
D	20	20	10	10	10	10	20
S	40	30					30
DCP	20		20		20	20	20
DAI	25	25	10	10	10	10	10
L	15	15	15	10	15	15	15
W	35	40	5	5	5	5	5
CR	15	15	15	10	15	15	15
SR	20	30	10	10	10	10	10
PM	30	20	10	10	10	10	10

C=Concept, D= design, S= supervision, DCP= data collection and/or processing, DAI= data analysis and/or interpretation, L= literature search, W= writing, CR= critical review, SR= submission and revision, PM= project management, FA= funding acquisition.

Conflict of Interest

The authors declared that there is no conflict of interest.

Ethical Consideration

This study was approved by the Ethical Committee of Umraniye Training and Research Hospital (approval date: October 03, 2024, protocol code: B.10.1.TKH.4.34.H.GP.0.01/320), School of Medicine, University of Health Sciences, Istanbul, Türkiye. Informed consent was obtained from all participants involved in the study

Data Sharing Statement

Data is shared upon request from the corresponding author under the Personal Data Protection Law.

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