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Annals of Oncology Case Reports

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BRCA1 Promoter Methylation Leading to "BRCAness" and Response to Olaparib in BRCA1/2 Mutation-Negative High-Grade Serous Ovarian Carcinoma: A Case Report

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Received: Mar 26, 2026

Accepted: Apr 13, 2026

Published Online: Apr 20, 2026

Journal: Annals of Oncology Case Reports

Publisher: MedDocs Publishers LLC

Online edition: http://meddocsonline.org/

Keywords: Basal cell carcinoma vulva; BCC; Dextrocardia; Left-right asymmetry; Mirror-image transposition; Right hemi-vulvectomy; Rodent ulcer; Situs inversus totalis; Vulval carcinoma.

Abstract

Background: BRCA1 and BRCA2 mutations are strongly associated with homologous recombination deficiency in ovarian cancer and predict response to poly (ADP-ribose) Polymerase (PARP) inhibitors [1,2]. However, tumors lacking detectable BRCA mutations may still demonstrate a "BRCAness" phenotype through alternative molecular mechanisms such as BRCA1 promoter methylation [3,4].

Case presentation: We report the case of a 48-year-old woman diagnosed with advanced high-grade serous ovarian carcinoma. Germline and somatic testing using a hereditary cancer panel did not identify clinically significant BRCA1 or BRCA2 mutations. The patient demonstrated poor response to neoadjuvant chemotherapy with paclitaxel and carboplatin and subsequently underwent cytoreductive surgery. Comprehensive genomic profiling of surgical tissue revealed BRCA1 promoter methylation, suggesting homologous recombination deficiency [5]. Based on this finding, the patient was treated with the PARP inhibitor olaparib, resulting in significant clinical improvement. The patient remains disease-free on follow-up.

Conclusion: This case highlights the importance of evaluating BRCA1 promoter methylation in BRCA mutation–negative ovarian cancers, as epigenetic silencing of BRCA1 may confer sensitivity to PARP inhibitor therapy [5,6].

Introduction

High-Grade Serous Ovarian Carcinoma (HGSOC) is the most common histological subtype of epithelial ovarian cancer and accounts for the majority of ovarian cancer–related deaths [7,8]. The disease is characterized by extensive genomic instability and frequent defects in the Homologous Recombination (HR) DNA repair pathway [4].

Mutations in BRCA1 and BRCA2 represent the most well-established genetic drivers of homologous recombination deficiency and occur in approximately 15–25% of ovarian cancer cases [9]. Tumors harboring BRCA mutations are particularly sensitive to PARP inhibitors, which exploit the concept of synthetic lethality [2,10].

Cite this article: Bhargava A, Kulkarni S, Kapoor M. BRCA1 Promoter Methylation Leading to "brcaness" and Response to Olaparib in BRCA1/2 Mutation-Negative High-Grade Serous Ovarian Carcinoma: A Case Report. Ann Oncol Case Rep. 2026; 6(1): 1030.

However, not all tumors that respond to PARP inhibitors harbor BRCA mutations. A subset of ovarian cancers exhibits a molecular phenotype referred to as "BRCAness," characterized by homologous recombination deficiency despite the absence of BRCA mutations [3]. This phenotype may arise through mechanisms including genomic instability, alterations in other HR genes, and epigenetic silencing of BRCA1 via promoter methylation [4,5].

Identification of such alterations has important therapeutic implications because these tumors may still benefit from PARP inhibitor therapy. In this report, we present a patient with BRCA1/2 mutation-negative high-grade serous ovarian carcinoma with BRCA1 promoter methylation who demonstrated a favorable response to olaparib.

Case presentation

A 48-year-old woman presented with abdominal distension for 7–10 days. Her past medical history included hypertension, with no history of diabetes, cardiovascular disease, or neurological disorders.

Serum CA-125 levels were elevated. A contrast-enhanced PET-CT scan revealed bilateral adnexal masses, peritoneal carcinomatosis, ascites, and liver metastases, consistent with advanced ovarian carcinoma.

A diagnostic core biopsy confirmed papillary serous carcinoma with omental involvement.

The patient received six cycles of neoadjuvant chemotherapy with paclitaxel and carboplatin, which represents standard first-line treatment for advanced ovarian cancer [11,12].

Genetic testing using next-generation sequencing revealed no clinically significant BRCA1 or BRCA2 mutations.

Due to persistent disease, the patient underwent cytoreductive surgery, including hysterectomy, bilateral salpingo-oophorectomy, omentectomy, peritonectomy, and appendectomy. Intraoperative findings indicated poor response to chemotherapy.

Subsequent genomic profiling identified BRCA1 promoter methylation, indicating homologous recombination deficiency [5].

The patient was started on olaparib (300 mg twice daily). She demonstrated significant clinical improvement and remains disease-free on follow-up.

Discussion

High-Grade Serous Ovarian Carcinoma (HGSOC) is defined by profound genomic instability, most commonly driven by defects in Homologous Recombination (HR) DNA repair pathways [4]. While germline or somatic mutations in BRCA1 and BRCA2 account for a substantial proportion of HR-deficient tumors, a clinically significant subset of patients lacks detectable BRCA mutations yet exhibits similar biological behavior and therapeutic vulnerabilities.

This observation has led to the concept of "BRCAness," which describes tumors that phenocopy BRCA-mutated cancers at the molecular and functional level [3]. These tumors display HR deficiency, genomic instability, and sensitivity to DNA-damaging therapies, including platinum agents and PARP inhibitors. Importantly, the mechanisms underlying BRCAness extend beyond canonical BRCA mutations and include alterations in other HR pathway genes, as well as epigenetic modifications.

Among these, BRCA1 promoter methylation represents a key and potentially under-recognized mechanism of functional BRCA1 inactivation. Promoter hypermethylation suppresses gene transcription, leading to reduced BRCA1 expression and impaired HR repair capacity [5,13,14]. As a result, tumors harboring this alteration may acquire a phenotype analogous to BRCA-mutant cancers, with consequent therapeutic sensitivity to PARP inhibition.

The clinical relevance of this mechanism is highlighted in the present case. Despite being BRCA1/2 mutation-negative, the patient demonstrated poor response to standard platinum-based chemotherapy, raising suspicion of an alternative molecular driver of HR deficiency. Subsequent genomic profiling identified BRCA1 promoter methylation, which provided a biologically plausible explanation for the observed disease behavior and enabled a shift toward targeted therapy.

The patient's favorable response to olaparib reinforces the emerging evidence that epigenetic silencing of BRCA1 can predict sensitivity to PARP inhibitors [6]. This finding is particularly important because current clinical workflows often restrict molecular stratification to BRCA mutation testing alone, potentially overlooking patients with actionable HR deficiencies mediated by epigenetic mechanisms.

Mechanistically, PARP inhibitors such as olaparib exploit synthetic lethality by blocking repair of single-strand DNA breaks, leading to accumulation of double-strand breaks during DNA replication. In HR-deficient tumors, including those with BRCA1 promoter methylation, these lesions cannot be effectively repaired, resulting in genomic catastrophe and tumor cell death [2,15]. This therapeutic principle provides a strong biological rationale for extending PARP inhibitor use beyond BRCA-mutant populations.

From a clinical perspective, this case underscores the limitations of conventional genetic testing paradigms. Reliance solely on BRCA mutation status may fail to identify a subset of patients who could benefit from targeted therapies. Incorporating broader assessments of homologous recombination deficiency—including epigenetic alterations—may therefore improve patient selection and therapeutic outcomes. However, several challenges remain. The clinical utility of BRCA1 promoter methylation as a predictive biomarker is not yet fully standardized, and variability in detection methods may influence reported prevalence and clinical interpretation [11]. In addition, emerging evidence suggests that epigenetic modifications may be dynamic and potentially reversible, raising questions about their stability as long-term predictors of treatment response.

Despite these limitations, this case contributes to the growing body of evidence supporting the expansion of molecular diagnostics in ovarian cancer beyond canonical BRCA testing. Identifying epigenetic drivers of homologous recombination deficiency has the potential to refine therapeutic decision-making and broaden access to effective targeted treatments such as PARP inhibitors.

BRCA1 promoter methylation can produce a BRCAness phenotype in BRCA mutation–negative ovarian cancer, enabling effective treatment with PARP inhibitors [5,6].

Comprehensive genomic profiling should be considered in patients with advanced ovarian cancer who fail to respond to conventional chemotherapy, as it may identify actionable therapeutic targets [4,11].

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