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Impact of BRCA Gene Testing on Ovarian Cancer Management

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ABSTRACT

Ovarian cancer is a diverse disease with several cellular subtypes, the most common of which are high-grade serous ovarian cancer (HGSOC). Ovarian cancer is still primarily treated with chemotherapy and surgery. Recent advances in the hereditary understanding of this disease have revealed that the BRCA gene plays an important role. While only a small percentage of HGSOC patients will have a germline BRCA mutation, many more will have tumor genetic aberrations within BRCA or other homologous recombination proteins. Improved preventative measures and therapeutic development have resulted from genetic screening for these BRCA mutations. This review focuses on BRCA mutations and their relationship to the development of ovarian cancer, as well as future therapeutic targets.

Keywords: BRCA mutation, ovarian cancer, PARP inhibitor.

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I. Introduction

Ovarian cancer has the highest mortality rate of any gynecologic cancer in the United States. Ovarian cancer was predicted to take the lives of about 14,240 people in 2016. Despite medical advancements, the 5-year survival rate for newly diagnosed patients has only increased to 46% in the last 20 years. Both the high prevalence of advanced disease at diagnosis and the dearth of novel therapeutic options are major contributors to the stagnation. Most cases of ovarian cancer are diagnosed as epithelial ovarian cancer (EOC), which can be further classified by cell type, grade, and anatomic site. In roughly 70% of cases of EOC, the cancer is of the high-grade serous variety [1]. Traditionally, ovarian cancer has been treated with a combination of cytoreductive surgery and subsequent chemotherapy. Patients who undergo an optimal or complete surgical cytoreduction have been shown to fare better in studies examining this hypothesis, and this benefit has been consistently observed when surgery is performed immediately after diagnosis. Platinum and taxane-based therapy form the backbone of ovarian cancer chemotherapy. Improvements in administration methods, such as intraperitoneal chemotherapy, have slowed the disease's progression and extended patients' lives [2]. While advances have been made in recent years thanks to new targeted therapies (such as bevacizumab), future progress will require a deeper understanding of the genetic basis of the disease to identify new targets.

Particularly aggressive forms of ovarian carcinoma, such as high-grade serous ovarian cancer (HGSOC), are extremely mutagenic. In 2011, The Cancer Genome Atlas (TCGA) conducted a comprehensive analysis of ovarian carcinoma and discovered numerous genes to be significantly mutated; most notably p53, which was mutated in nearly 96% of HGSOC. The BRCA1/2 genes were also found to play a role in many HGSOC, independent of germline status, through this investigation. In addition, pathway analysis revealed that mutations in a single gene involved in homologous recombination function were present in nearly half of all tumors analyzed. These results suggest that tumors with homologous recombination deficiencies play an important role and have therapeutic potential [3].

Pierre Paul Broca discovered a familial link between breast and ovarian cancer in 1866 through his wife's family. There was a long delay before the molecular confirmation of this familial cancer syndrome was made public. The BRCA1 gene locus was originally located at chromosome 17q21 of linkage analysis of families with a history of early-onset breast cancer. In 1994, the gene was cloned, allowing for repeated experiments to be conducted. The BRCA2 gene on chromosome 13 was discovered and cloned shortly afterward [4]. The prognosis and treatment options for BRCA-linked ovarian cancers have come a long way over the past two decades thanks to increased research into these diseases. Improvements in the ability to characterize changes in these

genes could pave the way for the creation of new targeted therapies or the expansion of the clinical utility of existing treatments.

II. The Implication of BRCA in Ovarian Cancer

Genome repair is an essential process for preventing cell death caused by DNA damage from environmental or intracellular sources of derangement. A double-strand break (DSB) is one of the most drastic changes that can be made to DNA and, if unrepaired, will kill the cell. Double-strand breaks (DSBs) are breaks in the DNA that affect both reading frames and are typically the result of damage from something outside the cell, like ionizing radiation. DNA repair is more error-prone at these sites because there is no normal reading frame to which to align the repaired nucleotides. Non-homologous end joining (NHEJ) and homologous recombination are the two main mechanisms by which a cell can repair a DSB (HR). Open DNA ends are stabilized and reconnected without regard to the reading frame by NHEJ, which is triggered by the attachment of binding proteins [5]. DNA mistakes are made as a result. Remediating a non-corrupted reading framework is possible with HR. The two ends can be opened up to make a 3" gap in a single strand. This initiates the recruitment of several proteins (among them RAD51/BRCA2), who then start looking for a suitable sequence to invade and create a D-loop. When done correctly, this method ensures that the reading frame is accurately reconstructed on both ends. When it comes to HR repair, both BRCA1 and BRCA2 have several distinct but complementary roles to play. Some researchers believe that BRCA1 is a component of a larger complex molecule that helps monitor DNA for DSB damage. BRCA2's function is less well understood, but it appears to aid the RAD51 complex in attaching to the repair site, thereby playing a more direct role in the repair process. Both genes play crucial roles in a system of repair molecules. Patients carrying germline mutations in BRCA1/2 are at increased risk for certain cancers compared to the general population. To think logically, this would increase the potential for tumor development in a wide variety of tissues. However, breast and ovarian cancers account for the vast majority of BRCA-linked malignancies. There is evidence to suggest that oxidative stress brought on by the menstrual cycle may contribute to the development of ovarian tumors. Tissue-specificity may also be due to the regulation of hormones, particularly estrogen, which appears to increase DSB [6].

Researchers have studied the prevalence of germline mutations in BRCA1/2 to assign a risk to carriers for the development of breast and ovarian carcinoma. The average cumulative risk of developing ovarian cancer with a BRCA1/2 mutation was 39% and 11% in a landmark paper analyzing over 8000 unselected cases of breast or ovarian cancer [7]. The authors also found strong evidence for an age difference in disease onset between BRCA1/2, with the risk increasing for BRCA1 patients after age 40 and for BRCA2 patients after age 50. This becomes relevant when discussing risk reduction strategies with patients. Patients with serous ovarian carcinoma are significantly more likely to have a germline BRCA mutation (gBRCAmut) than the general population. Of special note is the fact that, above 40% of cases, these patients are the only affected members of their immediate family. Certain ethnic groups may be disproportionately impacted by the BRCA mutation. Compared to the general population, which has a rate of 1/400.23, Ashkenazi Jewish descendants have a 1-2% chance of carrying a BRCA1/2 mutation [8].

III. Clinical Utility of BRCA Mutation Screening in the Detection of Ovarian Cancer

Germline mutations in the BRCA genes can be passed down from mother to daughter and father to son. This is a fundamental concept for any accurate genetic ancestry analysis. In BRCA 1/2, the risks for breast cancer (up to 80% lifetime) and ovarian cancer are typically the focus of attention. However, the increased risk of pancreatic cancer, melanoma, and breast and prostate cancers in men must be emphasized when counseling patients. All women diagnosed with epithelial ovarian, fallopian tube, or peritoneal cancers should be offered cancer genetic counseling and testing for germline BRCA1/2 mutations, according to the Society of Gynecologic Oncology (SGO) and the National Comprehensive Cancer Network (NCCN). A thorough risk assessment based on the patient's personal and family histories is an integral part of genetic counseling, as is the collection of a three-generation pedigree [9].

In a seminal case for molecular genetics, the Supreme Court of the United States ruled in 2013 to invalidate patents on genes. Next-generation sequencing technology for the screening of BRCA mutations was made commercially available thanks to the case. Healthcare providers have begun using multi-gene panel tests as a cost-effective replacement for traditional single-gene/syndrome diagnostics. Particularly when moderate-risk susceptibility genes that have received less research are included, the clinical use of multi-gene panels has been met with skepticism. The National Comprehensive Cancer Network (NCCN) recommends considering multi-gene panel testing in patients with personal and/or family histories that are suggestive of more than one potential hereditary cancer syndrome, but it does not guide for determining which of the many available testing options should be offered in specific clinical situations. Several studies have fortunately detailed the range of gene mutations found in EOC patients. Multigene panel testing results from 1915 unselected patients with EOC were recently reported by Norquist and colleagues; they discovered that 3.3% of patients had mutations in genes other than BRCA1, BRCA2, and the Lynch syndrome-associated mismatch repair genes. Twenty percent of the mutations found in this study were alterations in genes like BRIP1, PALB2, RAD51C, RAD51D, and BARD1, each of which is associated with a 5-15 percent increased risk of ovarian cancer over a lifetime [10]. It's worth noting that the term "moderate-risk genes" is rarely used to describe these inherited traits. Multi-gene panel testing for women with ovarian cancer may be less controversial now that interventions for individuals with mutations in these genes (except for BARD1) are included in the most recent version of the NCCN Guidelines for Genetic/Familial High-Risk Assessment. It is also important to note that providers with expertise in cancer genetics are the best people to order multi-gene panel testing from because of

the extra complexity that comes with it. Informed consent for a genetic test for cancer requires knowledge and skill to provide the essential information. The potential limitations of result interpretation, the application to clinical management, and the possibility of receiving an uncertain test result should all be highlighted during the consent process [11].

Clinical genetic testing should always begin with the patient. This ensures that the results, whether positive or negative for the mutation, are interpreted correctly. The cascade approach to testing begins with a patient's affected family member and moves on to those without the condition. Testing in a healthy individual should only be done first in cases where a patient meets high-risk criteria but has no known living affected relatives. It's possible that a more comprehensive screening strategy would be needed if tests were conducted under these conditions due to the potential for muddled results (i.e. multi-gene panel testing).

IV. Testing for BRCA Mutations and Their Relevance to Ovarian Cancer

Screening family members sooner and, in some cases, taking preventative measures to greatly reduce the risk of cancer, is an opportunity made possible by the discovery of hereditary cancer syndromes like the one associated with the BRCA mutation. Providers can consult this NCCN-compiled list of guidelines for use in genetic risk evaluation counseling. The American College of Obstetricians and Gynecologists (ACOG) and the Society for Genetics and the Family (SGO) have both signed on to a consensus statement on genetic counseling [12]. Notably, genetic counseling and testing for BRCA mutations are strongly suggested for all patients with EOC. Patients with triple-negative breast cancer who are under the age of 60, in addition to those diagnosed with early-onset breast cancer (age 45).

A. The Significance of a BRCA-Positive Result in Ovarian Cancer Screening

Mammography screening for breast cancer continues to be one of the most useful interventions for lowering mortality rates from the disease. Breast cancer screening guidelines for high-risk populations have been the subject of extensive research and media coverage. When it comes to early detection or prevention, the track record of ovarian cancer screening is unfortunately poor. Pelvic ultrasonography and CA-125 testing have been used for trial ovarian cancer screenings. Ovarian cancer is notoriously difficult to monitor because of the short time it takes for the disease to progress from its initial stages to more advanced stages. Screening for ovarian cancer was one of many cancers evaluated in the massive Prostate, Lung, Colorectal, and Ovarian (PLCO) cancer trial conducted in the United States, but it did not result in a decrease in ovarian cancer mortality among a non-selected population [13]. The results of the UK Collaborative Trial of Ovarian Cancer Screening, a randomized clinical trial, confirmed these findings (UKCTOCS). Unfortunately, no screening modality has been shown to effectively reduce mortality or detect early disease, even in high-risk populations. According to NCCN guidelines, screening is an option for patients under the age of 35 who are unwilling to undergo risk-reducing salpingo-oophorectomy (RRSO) because of conflicting data on its efficacy [14].

B. Prevention of Ovarian Cancer Through Prophylactic Surgery in BRCA-Positive Patients

Patients with the gBRCAmut mutation have been found to benefit from preventative ovarian cancer surgery. Two studies examining RRSO were published that year. Patients at high risk for a breast or a BRCA-related gynecologic malignancy who opted for RRSO had a 75% reduced risk of developing ovarian cancer, according to research by Kauff and colleagues. Patients who underwent RRSO had a risk of developing primary cancer of the ovary or fallopian tube of less than 1 percent. The research concluded RRSO reduced the risk of gynecologic cancer caused by the BRCA gene by 96% [15]. Patients with BRCA who have an RRSO have a significantly lower risk of developing ovarian cancer (HR = 0.21), as confirmed by a large meta-analysis. After RRSO, the authors noted a slight but ongoing risk of developing primary peritoneal cancer. Patients who had RRSO had a significantly reduced risk of developing breast cancer (HR = 0.47) [16]. Similarly, the studies used to inform the ages at which RRSO should be considered are presented here. The National Comprehensive Cancer Network and the Society of Gynecologic Oncology currently advise thinking about RRSO after women have finished having children and are at least 35 years old. This is because, after the age of 40, a BRCA1 carrier is at an increased relative risk of developing a gynecologic malignancy. The age-adjusted risk for ovarian cancer in patients with a BRCA2 mutation does not begin to increase until age 50, so it is reasonable to consider delaying RRSO until then [17].

However, these preliminary studies only include patients under the age of 40 who do not want to have their ovaries removed. In a nonselected population, a salpingectomy alone reduces the risk of ovarian cancer by 35%-50% [18]. This theory is grounded in the idea that the fallopian tube is the true site of origin for the vast majority of epithelial ovarian carcinomas, particularly those of the serous variety. Pathologists discovered occult lesions on the fallopian tubes of women with BRCA1/2 mutations after they had undergone preventative surgery, and this observation gave rise to the serous tubal intraepithelial carcinoma (STIC) theory in the late 1990s. STICs are commonly found in patients with HGSOC, and the idea is that they are similar to the cells that make up the fimbria of the fallopian tube [19]. These findings warrant further investigation, but it is too soon to recommend screening for all women at high risk for gynecologic malignancies due to the BRCA1 and BRCA2 genes.

C. Oral Contraceptives and BRCA Mutation Carriers

Patients who discover a BRCA mutation at a younger age often wonder if there is anything they can do to lessen their risk of developing ovarian cancer before undergoing surgery. Ovarian cancer "chemoprophylaxis" studies have looked into the use of oral contraceptive pills (OCPs). Patients who had taken OCPs for any length of time, according to the research by Narod and coworkers, had a roughly 50% reduced risk of developing ovarian cancer [20]. In addition, OCP use for longer than 6 years reduced risk by as much as 60%. This was also supported by a meta-analysis, which found that patients with a BRCA mutation may benefit from OCP use to the same or greater extent as the general population [21]. However, the

potential risk of breast cancer and the effects of hormonal manipulation must be considered when deciding whether or not to use OCPs. Conflicting evidence suggests that OCP use may increase the risk of breast cancer in people who already carry the BRCA mutation. Given the current information gap, BRCA carriers seeking alternative methods to reduce their risk of ovarian cancer should be advised to proceed with caution when considering the use of OCPs.

D. Non-BRCA Gene Mutations and Risk-Reducing Surgery

Hereditary breast and ovarian cancer screening using multi-gene panels have led to a rise in the detection of germline mutations in genes known to increase susceptibility to these cancers. Approximately 6% of ovarian cancer patients were found to have a mutation that was a non-BRCA loss of function, according to research by Walsh and colleagues [22]. BRCA mutations are highly penetrant, while other genes have variable penetrance. Ovarian cancer risk is increased by a factor of 5.88 and 6.30 in women who carry the RAD51C and RAD51D mutations, respectively. The proportion of ovarian cancer patients with RAD51C and RAD51D mutations is also significantly higher in patients than in controls, according to a recent case-control study of more than 3,000 patients with the disease. Scientists found that women with RAD51C had a 5.2% and those with RAD51D had a 12.4% increased risk of developing ovarian cancer by age 70. Patients carrying alterations in the RAD51 genes in the context of family history can be considered for RRSO, though other mutations have yet to yield compelling evidence for preemptive surgical management without careful counseling regarding the early nature of the research [23].

V. Treatment Considerations in Germline BRCA Mutation Carriers for Ovarian Cancer

A. Germline BRCA Mutations and Ovarian Cancer Prognosis

Patients with HGSOC who also carry a germline BRCA mutation (gBRCAmut) have an increased chance of survival compared to those who do not. The first study to examine the outcomes of patients with a BRCA mutation found that they lived longer than those without the mutation 1996 (77 versus 29 months) [24]. Additional research has confirmed that these patients respond favorably to platinum therapy, as compared to patients without BRCA mutations. Carriers of the gBRCAmut also seem to be more responsive to the advantages of intraperitoneal chemotherapy. The overall survival of patients with BRCA1/2 germline mutations was found to be significantly higher than that of patients without a mutation in a large pooled analysis of 26 observational studies. Those who carried the BRCA2 mutation had a 52% chance of surviving 5 years, while only 36% of those who did not do so. The risk of dying from cancer is increased by BRCA2 mutations. This may be because the BRCA2 protein regulates crosslink damage repair more strictly, making these patients more vulnerable to chemotherapy that damages DNA. Unfortunately, the protective effect of a BRCA mutation appears to diminish when looking at survival out to 10 years [25].

B. PARP Inhibitors in the Treatment of Ovarian Cancer

In 1963, the enzyme poly (ADP-ribose) polymerase (PARP) was isolated from a bacterium. PARP belongs to a group of proteins that aid double-strand break (DSB) repair by the HR pathway. Inhibitors of PARP were first discovered in 1980, with the potential application in sensitizing patients to chemotherapy [26]. It was previously believed that the mechanism of action of these molecules would only slow down cancer cell growth rather than induce lethality, ruling them out as a single-agent therapy choice for patients with cancer. A PARP inhibitor combined with BRCA1-deficient cells increased cellular death significantly compared to BRCA1-positive cells. When two molecules in a DNA repair pathway are depleted, either endogenously or exogenously, the cell dies. This phenomenon has been dubbed "synthetic lethality" by researchers working independently. Parathyroid hormone-related protein (PARP) inhibitors gained prominence for their potentially exploitative role in cancers caused by germline BRCA mutations, including breast and ovarian cancers.

Patients with solid tumors and a gBRCAmut were the first to benefit from PARP inhibitor trials. Ovarian tumor patients were overrepresented in the study population because of the inclusion of those with known BRCA mutations. Breast cancer, colon cancer, melanomas, prostate cancer, and sarcomas were also included. A clinical benefit of 63% was seen with olaparib as a single agent in patients with known BRCA1/2 mutations (including disease stabilization) [27]. Based on these findings, researchers decided to conduct a follow-up study (phase IB) focusing exclusively on patients with recurrent ovarian, fallopian tube, or primary peritoneal cancer. Germline BRCA mutation carriers were the only people allowed in the expansion, and they underwent intensive pretreatment. The results showed an overall response rate of 40 percent, with a subanalysis showing a 62 percent response rate in patients who had been platinum-sensitive with their last platinum treatment [28]. A larger phase II randomized study of olaparib was initiated and found it to be as effective as a gold standard treatment (pegylated liposomal doxorubicin). For the first time, patients with recurrent disease who may or may not have a gBRCAmut were enrolled in this trial. The purpose of this study was to determine if patients with a BRCA-like phenotype respond in the same way as those with a true BRCA mutation. Participation in the study was discretionary based on the knowledge of BRCA 1/2 mutation status. Patients needed to have shown an objective response to the most up-to-date platinum chemotherapy to be considered. Both olaparib and a placebo were given in a maintenance setting. Overall, olaparib resulted in a PFS of 8.4 months, compared to 4.8 months with a placebo [29].

The authors also presented a planned subanalysis based on BRCA status in a second paper that updated overall survival. More than half of the patients had either a germline or tumor somatic mutation of BRCA, making the two sides of the coin quite even (the majority were gBRCAm). When comparing olaparib and placebo in this population, progression-free survival was 11.2 months versus 4.3 months (HR 0.18; p 0.0001) [30]. European Medicines Agency approved olaparib for use in the maintenance setting for patients with recurrent HGSOC who are platinum sensitive based on the findings of

this study. Although ovarian tumors made up the bulk of the study population, other solid tumors like those of the pancreas and prostate were also included. All patients in this trial had to have ovarian cancer that had developed resistance to platinum therapy. Each patient was given 800 mg of olaparib twice a day. The tumor response rate (TRR) was the primary endpoint. TRR was 26% overall, but it was 31% for those with ovarian cancer. In addition, a steady disease rate of 40% was observed in patients with ovarian cancer. Among those diagnosed with ovarian cancer, median progression-free survival (PFS) was 7 months, and median overall survival (OS) was 16.6 months, with over 64% of patients still alive after 12 months [31]. Patients with a gBRCAm who have previously been treated with at least three lines of chemotherapy in the United States can now use olaparib as monotherapy thanks to the results of this trial.

More phase III trials for PARP inhibitors have begun as a result of the aforementioned research. Trials in the primary treatment setting and trials in maintenance therapy following initial adjuvant treatment fall under this category. Among patients with recurrent HGSOC, the PARP-1/2 inhibitor rucaparib has demonstrated efficacy. In a recently completed trial, rucaparib was evaluated in patients with recurrent HGSOC. Two phases of the trial were held. Part 1 of the ARIEL2 study focused on patients who had previously undergone at least one platinum-based therapy and were experiencing a recurrence of their disease despite that treatment. Patients with known gBRCA mutations were allowed to enroll, but all tissues underwent BRCA mutation testing and germline status was confirmed by blood testing. In addition, a tumor-derived molecular signal is being investigated to ascertain the prevalence of HRD (homologous recombination deficiency). Loss of heterozygosity (LOH) analysis was used to quantify the degree to which the cancer genome had been scarred during testing. Genomic instability is reflected in high levels of LOH [32]. Patients with germline BRCA mutations or BRCA wildtypes with high levels of LOH (loss of heterozygosity) on tumor testing have a better response than BRCA wildtype patients with low levels of LOH. As an example, when comparing those with a BRCA mutation to those with a BRCA wildtype low-LOH score, the PFS was 12.8 months versus 5.2 months [33]. Using PARP inhibitors to take advantage of the high prevalence of somatic BRCA mutations was a major takeaway from this study. Rucaparib was recently approved for use in patients with germline or somatic BRCA mutations who have had 2 lines of therapy based on the results of ARIEL2 and a smaller phase I/II. In the United States, this was the first approval of a PARP inhibitor for the treatment of ovarian cancer caused by somatic BRCA mutations [34].

Niraparib inhibits PARP-1, PARP-2, and PARP-3, making it the third type of PARP inhibitor. Recurrent HGSOC patients who received niraparib versus placebo in a phase III trial were recently reported. Patients were selected because of their platinum sensitivity, and the study aimed to do two things: (1) determine whether the drug was more effective than a placebo, and (2) locate a biologic marker for HRD (through MyChoice MyriadTM testing). Patients with a gBRCAm were shown to have a PFS of 21 months, significantly longer than those without the mutation (5.5 months). Patients without a gBRCAm and a high HRD score fared significantly better in terms of PFS, the authors found. Not only did patients without a germline or somatic BRCA mutation and a low HRD score have a significant PFS advantage, but this was perhaps the biggest surprise of all [35]. Based on these findings, the FDA has given niraparib its first-ever maintenance indication for platinum-sensitive HGSOC, regardless of BRCA status. Other targeted therapies in addition to PARP inhibitors are being researched. Phase II research comparing olaparib plus cediranib (VEGF inhibitor) to olaparib alone found a statistically significant improvement in PFS [36]. This clinical trial included both people with and without the gBRCAmut gene mutation in the study population. In light of these encouraging findings, the use of PARP inhibitors in ovarian cancer is expected to increase. Future research into PARP inhibitors must address the importance of identifying the best possible target populations and the best possible time to administer these therapies.

VI. Conclusion

Research into how BRCA mutations affect ovarian cancer's progression, response to treatment, and the prognosis is an exciting and expanding field. Understanding the function of BRCA in tumorigenesis and, more recently, as a therapeutic potential, has been the result of research since its discovery in 1990. In addition to helping the patient themselves, the discovery of a BRCA mutation could lead to the prevention of ovarian cancer in other family members through genetic testing. In addition, women with germline or somatic BRCA mutations and tumors with high levels of HRD may benefit greatly from PARP inhibition. There is great potential to not only prevent many cases through improved access to genetic screening but also revolutionize the long-term treatment of patients with this insidious disease, as our knowledge of BRCA and its role in the development and outcomes of ovarian cancer continues to advance.

Conflict of Interest

Authors declare that they do not have any conflict of interest.

References

[1] Siegel RL, Miller KD, Fuchs HE, Jemal A. Cancer Statistics. *CA Cancer J Clin*. 2021; 71(1): 7-33.

[2] Wright AA, Cronin A, Milne DE, Bookman MA, Burger RA, Cohn DE, et al. Use and Effectiveness of Intraperitoneal Chemotherapy for Treatment of Ovarian Cancer. *J Clin Oncol*. 2015; 33(26): 2841-2847.

[3] Adambekov S, Lopa S, Edwards RP, Lemon L, Wang S, Taylor SE, et al. Survival and recurrence after intraperitoneal chemotherapy use: Retrospective review of ovarian cancer hospital registry data. *Cancer Med*. 2020; 9(20): 7388-7397.

[4] Huertas P. DNA resection in eukaryotes: deciding how to fix the break. *Nat Struct Mol Biol*. 2010; 17(1): 11-16.

[5] Hartlerode AJ, Scully R. Mechanisms of double-strand break repair in somatic mammalian cells. *Biochem J*. 2009; 423(2): 157-168.

[6] Murmann-Konda T, Soni A, Stuschke M, Iliakis G. Analysis of chromatid-break-repair detects a homologous recombination to non-homologous end-joining switch with increasing load of DNA double-strand breaks. *Mutat Res Genet Toxicol Environ Mutagen*. 2021; 867: 503372.

[7] Castro E, Goh C, Olmos D, Saunders E, Leongamornlert D, Tymrakiewicz M, et al. Germline BRCA mutations are associated with

higher risk of nodal involvement, distant metastasis, and poor survival outcomes in prostate cancer. *J Clin Oncol*. 2013; 31(14): 1748-1757.

[8] Alsop K, Fereday S, Meldrum C, DeFazio A, Emmanuel C, George J, et al. BRCA mutation frequency and patterns of treatment response in BRCA mutation-positive women with ovarian cancer: a report from the Australian Ovarian Cancer Study Group. *J Clin Oncol*. 2012; 30(21): 2654-2663.

[9] Lancaster JM, Powell CB, Chen LM, Richardson DL. SGO Clinical Practice Committee. Society of Gynecologic Oncology statement on risk assessment for inherited gynecologic cancer predispositions. *Gynecol Oncol*. 2015; 136(1): 3-7.

[10] Jacobs IJ, Menon U, Ryan A, Gentry-Maharaj A, Burnell M, Kalsi JK, et al. Ovarian cancer screening and mortality in the UK Collaborative Trial of Ovarian Cancer Screening (UKCTOCS): a randomised controlled trial. *Lancet*. 2016; 387(10022): 945-956.

[11] Desmond A, Kurian AW, Gabree M, Mills MA, Anderson MJ, Kobayashi Y. Clinical Actionability of Multigene Panel Testing for Hereditary Breast and Ovarian Cancer Risk Assessment. *JAMA Oncol*. 2015; 1(7): 943-951.

[12] Robson ME, Bradbury AR, Arun B, Domchek SM, Ford JM, Hampel HL, et al. American Society of Clinical Oncology Policy Statement Update: Genetic and Genomic Testing for Cancer Susceptibility. *J Clin Oncol*. 2015; 33(31): 3660-3667.

[13] Buys SS, Partridge E, Black A, Johnson CC, Lamerato L, Isaacs C, et al. Effect of screening on ovarian cancer mortality: the Prostate, Lung, Colorectal and Ovarian (PLCO) Cancer Screening Randomized Controlled Trial. *JAMA*. 2011; 305(22): 2295-2303.

[14] Eleje GU, Eke AC, Ezebialu IU, Ikechebelu JI, Ugwu EO, Okonkwo OO. Risk-reducing bilateral salpingo-oophorectomy in women with BRCA1 or BRCA2 mutations. *Cochrane Database Syst Rev*. 2018; 8(8): CD012464.

[15] Rebbeck TR. Prophylactic oophorectomy in carriers of BRCA1 or BRCA2 mutations. *N Engl J Med*. 2002; 346(21): 1616-1622.

[16] Rebbeck TR, Kauff ND, Domchek SM. Meta-analysis of risk reduction estimates associated with risk-reducing salpingo-oophorectomy in BRCA1 or BRCA2 mutation carriers. *J Natl Cancer Inst*. 2009;101(2):80-87. doi:10.1093/jnci/djn442

[17] Kauff ND, Satagopan JM, Robson ME, Scheuer L, Hensley M, Hudis CA, et al. Risk-reducing salpingo-oophorectomy in women with a BRCA1 or BRCA2 mutation. *N Engl J Med*. 2002; 346(21): 1609-1615.

[18] Falconer H, Yin L, Grönberg H, Altman D. Ovarian cancer risk after salpingectomy: a nationwide population-based study. *J Natl Cancer Inst*. 2015; 107(2): dju410.

[19] Kim SH, Frey MK, Blank SV. Occult tubal carcinoma found at risk reducing salpingectomy in a BRCA1 carrier. *Gynecol Oncol Case Rep*. 2014; 9: 1-2.

[20] Narod SA, Risch H, Moslehi R, Dorum A, Neuhausen S, Olsson H. Oral contraceptives and the risk of hereditary ovarian cancer. Hereditary Ovarian Cancer Clinical Study Group. *N Engl J Med*. 1998; 339(7): 424-428.

[21] Moorman PG, Havrilesky LJ, Gierisch JM, Coeytaux RR, Lowery WJ, Peragallo Urrutia R, et al. Oral contraceptives and risk of ovarian cancer and breast cancer among high-risk women: a systematic review and meta-analysis. *J Clin Oncol*. 2013; 31(33): 4188-4198.

[22] Walsh T, Casadei S, Lee MK. Mutations in 12 genes for inherited ovarian, fallopian tube, and peritoneal carcinoma identified by massively parallel sequencing. *Proc Natl Acad Sci U S A*. 2011; 108(44): 18032-18037.

[23] Tung N, Domchek SM, Stadler Z, Nathanson KL, Couch F, Garber JE, et al. Counselling framework for moderate-penetrance cancer-susceptibility mutations. *Nat Rev Clin Oncol*. 2016; 13(9): 581-588.

[24] Rubin SC, Benjamin I, Behbakht K, Takahashi H, Morgan MA, LiVolsi VA, et al. Clinical and pathological features of ovarian cancer in women with germ-line mutations of BRCA1. *N Engl J Med*. 1996; 335(19): 1413-1416.

[25] Kotsopoulos J, Rosen B, Fan I, Moody J, McLaughlin JR, Risch H, et al. Ten-year survival after epithelial ovarian cancer is not associated with BRCA mutation status. *Gynecol Oncol*. 2016; 140(1): 42-47.

[26] Purnell MR, Whish WJ. Novel inhibitors of poly(ADP-ribose) synthetase. *Biochem J*. 1980; 185(3): 775-777.

[27] Fong PC, Boss DS, Yap TA, Tutt A, Wu P, Mergui-Roelvink M, et al. Inhibition of poly(ADP-ribose) polymerase in tumors from BRCA mutation carriers. *N Engl J Med*. 2009; 361(2): 123-134.

[28] Fong PC, Yap TA, Boss DS, Carden CP, Mergui-Roelvink M, Gourley C, et al. Poly(ADP)-ribose polymerase inhibition: frequent durable responses in BRCA carrier ovarian cancer correlating with platinum-free interval. *J Clin Oncol*. 2010; 28(15): 2512-2519.

[29] Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in platinum-sensitive relapsed ovarian cancer. *N Engl J Med*. 2012; 366(15): 1382-1392.

[30] Ledermann J, Harter P, Gourley C, Friedlander M, Vergote I, Rustin G, et al. Olaparib maintenance therapy in patients with platinum-sensitive relapsed serous ovarian cancer: a preplanned retrospective analysis of outcomes by BRCA status in a randomised phase 2 trial. *Lancet Oncol*. 2014; 15(8): 852-861.

[31] Kaufman B, Shapira-Frommer R, Schmutzler RK, Audeh MW, Friedlander M, Balmaña J, et al. Olaparib monotherapy in patients with advanced cancer and a germline BRCA1/2 mutation. *J Clin Oncol*. 2015; 33(3): 244-250.

[32] Korpanty G, Timms K, Abkevich V, Carey M, Gutin A, Li Y, et al. Loss of heterozygosity (LOH) as a measure of whole-genome instability in ovarian cancer correlates with clinical outcomes. *J Clin Oncol.* 2011; 19(15): 5027.

[33] Swisher EM, Lin KK, Oza AM, Scott CL, Giordano H, Sun JE et al. Rucaparib in relapsed, platinum-sensitive high-grade ovarian carcinoma (ARIEL2 Part 1): an international, multicentre, open-label, phase 2 trial. *Lancet Oncol*. 2017; 18(1): 75-87.

[34] Kristeleit R, Shapiro GI, Burris HA, Oza AM, LoRusso P, Patel MR, et al. A Phase I-II Study of the Oral PARP Inhibitor Rucaparib in Patients with Germline *BRCA1/2*-Mutated Ovarian Carcinoma or Other Solid Tumors. *Clin Cancer Res*. 2017; 23(15): 4095-4106.

[35] Mirza MR, Monk BJ, Herrstedt J, Oza AM, Mahner S, Redondo A, et al. Niraparib Maintenance Therapy in Platinum-Sensitive, Recurrent Ovarian Cancer. *N Engl J Med*. 2016; 375(22): 2154-2164.

[36] Liu JF, Barry WT, Birrer M, Lee JM, Buckanovich RJ, Fleming GF, et al. Combination cediranib and olaparib versus olaparib alone for women with recurrent platinum-sensitive ovarian cancer: a randomised phase 2 study. *Lancet Oncol*. 2014; 15(11): 1207-1214.