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CHAPTER 3

BRCA Mutations and Ovarian Cancer

Deepika Verma

INTRODUCTION

Amongst all gynecological malignancies ovarian cancer leads to highest mortality and at initial diagnosis, more than two-thirds of patients have advanced disease. The majority (90%) of ovarian cancers are epithelial ovarian cancers (EOCs). Germline mutations in *BRCA1* or *BRCA2* carries high risk of developing ovarian cancer. *BRCA1* and *BRCA2* are tumor suppressor genes located on chromosomes 17 and 13, respectively.

These genes regulate genomic stability. In BRCA-mutated patients, there is a defect in repair mechanism of damaged DNA which results into uncontrolled cell proliferation with development of cancer.

Epithelial ovarian cancer (EOC) is further subdivided into various cell types, grades, and anatomic locations. The most common variety is high-grade serous ovarian cancer [HGSOC—70%]. It is the most prevalent and lethal form among EOCs. Approximately 20% of patients with this histology have germline BRCA1/2 mutations. Therefore identification of patients with germline mutation in BRCA1/2 and their clinical assessment is very crucial.

Less common types are endometrioid (10%), clear cell (5%), mucinous (5%), transitional, and undifferentiated carcinomas, with the last two types representing less than 1% of epithelial lesions. This classification is based on histologic pattern that resembles the epithelium in the lower genital tract.

Known risk factors for ovarian cancers include familial history of cancer, early menarche, late menopause, nulliparity, obesity, diabetes, and smoking.

GENETIC RISK FOR EPITHELIAL OVARIAN CANCER

Most epithelial ovarian cancers are sporadic. Most of the hereditary ovarian cancers result from pathogenic mutations in either the *BRCA1 or BRCA2* genes. Many studies have found that at least 15% of women with high-grade non-mucinous ovarian cancers have germline mutations in BRCA1/BRCA2 out of which 40% do not have a family history of breast/ovarian cancer. Some other low-to-moderate—penetrance genes responsible for ovarian cancer are DNA mismatch repair genes, double-stranded DNA break repair genes such as *CHEK2* and *ATM*, and the BRCA1-associated complex or the BRCA2/Fanconi anemia pathway genes (including *BRIP1, BARD1, PALB2, RAD50,*

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RAD51C, RAD51D among others). About 80% of mutations were in BRCA1 or BRCA2.

A study done in UK, Holland, and France concluded that the incidence of ovarian cancer was 3.6 times higher among BRCA1 than BRCA2 carriers. A woman with a first or second-degree relative with premenopausal ovarian cancer carries a higher probability of being a BRCA carrier. Women with BRCA germline mutations tend to be diagnosed at a younger age than women with sporadic ovarian cancers.

FOUNDER EFFECT

In women of Ashkenazi Jewish descent, Icelandic women, and some other ethnic groups, there is a higher carrier rate of BRCA1 and BRCA2 mutations. Three specific founder mutations carried by the Ashkenazi population are:

1. 185delAG and 5382insC on BRCA1
2. 6174delT on BRCA2.

Amongst Ashkenazi Jewish descent there are 2.5% chance of having a mutation in BRCA1 or BRCA2, in contrast to 1 in 500 risk in the Caucasian population. This increased risk is due to founder effect, in which a higher rate of specific mutations occurs in an ethnic group from a defined geographic area.

PREVENTION

A full pedigree analysis is essential because the mutations are carried in an autosomal dominant pattern.

All women with high-grade invasive ovarian cancers should undergo genetic testing, even if they do not have a family history of breast/ovarian cancer. Protective factors are parity, oral contraceptive pills and prophylactic salpingo-oophorectomy (most effective way).

The oral contraceptive pill is the only documented method of chemoprevention for ovarian cancer.

MANAGEMENT OF WOMEN AT HIGH RISK FOR OVARIAN CANCER

The management in case of unaffected woman with a germline BRCA (gBRCA) mutation or in cases of strong family history of epithelial ovarian cancer with absent mutation must be individualized and should depend on age, reproductive desires and the overall prognosis. BRCA1 and BRCA2 mutation must be checked. All women who have epithelial ovarian cancer other than mucinous cancers, must undergo testing whether she has a family history of breast/ovarian cancer or not. The American Society of Clinical Oncology offered guidelines that emphasize careful evaluation by geneticists, careful maintenance of medical records, and a genetic screening to effectively

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counsel and manage these patients. The lifetime risk of ovarian cancer is 54% with BRCA1 mutation and 23% with a BRCA2 mutation, and in both groups, there is an 82% lifetime risk of breast cancer.

It is advisable to consider the prophylactic hysterectomy along with salpingo-oophorectomy in women with BRCA mutations who are potentially at increased risk of an endometrial cancer, but this decision should depend upon patient's profile and overall risk assessment.

BRCA-mutated patients have increased sensitivity to platinum drugs and to the newer agents, poly (ADP-ribose) polymerase (PARP) inhibitors. PARP inhibitors in BRCA mutation carriers may improve overall survival.

As per ACOG practice bulletin no. 182, Most BRCA2-related ovarian cancers tend to occur after the age of 50, whereas BRCA1-related cancers occur at an earlier age. In BRCA1 carriers, risk-reducing salpingo-oophorectomy is recommended at age 35–40 years with the highest lifetime risk of ovarian cancer, whereas in women with BRCA2 mutation, it may be delayed until age of 40–45 years because of later onset of ovarian cancer. Women should be counseled that this operation does not offer absolute protection, because peritoneal carcinomas can occur even after performing bilateral salpingo-oophorectomy. Risk-reducing bilateral mastectomy also should be offered to such carriers. For women aged 30 years and older with known BRCA mutations or other breast cancer mutations, breast cancer surveillance is recommended and it includes annual mammography and annual breast MRI with contrast, alternating every 6 months. Women with a personal or family history of breast or ovarian cancer but who do not have a documented mutation in BRCA1 or BRCA2 or other hereditary breast or ovarian cancer associated genes should be managed based on their family history.

TREATMENT OPTIONS

The treatment of ovarian cancer has been surgical cytoreduction followed by adjuvant chemotherapy.

The main stay of chemotherapy for ovarian cancer is platinum and taxane-based treatment. Advances in the route of administration, including intraperitoneal chemotherapy, have delayed the disease progression and increased survival. Bevacizumab is the new promising molecule.

Olaparib is FDA approved for the treatment of patients with gBRCA-mutated germline BRCA mutation (gBRCAmut) recurrent ovarian cancer who have received three or more prior lines of chemotherapy.

Rucaparib is approved for treatment of BRCA-mutation–associated advanced ovarian cancer after completion of treatment with two or more chemotherapy regimens regardless of whether patients are platinum-sensitive or resistant.

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Patients who have germline mutations in either BRCA1/2 are at a higher risk for certain cancers compared to others who do not have such mutations, although majority are of either breast or ovarian origin.

The presence of a germline BRCA mutation (gBRCAmut) in a patient with HGSOC offers a survival benefit in comparison to patients without the mutation, because these patients have a better response to platinum therapy compared to patients without BRCA mutations. gBRCAmut carriers also respond better to intraperitoneal chemotherapy.

BRCA2 mutations carry a higher survival rate because of its mechanism of action since BRCA2 protein more closely regulates the process of crosslink damage repair thereby making these patients more sensitive to DNA damaging chemotherapy.

Computed tomography (CT) and magnetic resonance imaging (MRI) play a decisive role in the diagnosis and staging. Contrast-enhanced CT has accuracy of about 94% for ovarian cancer staging and is the current imaging modality of choice for preoperative assessment of cancers.

High-grade serous (HGS) ovarian cancer represents a major surgical challenge as the aim is to resect all visible disease. Optimal therapy includes maximal surgical cytoreduction to almost nil gross disease, or at least optimal debulking (<1 cm of residual disease), followed by platinum-based combination chemotherapy. These cancers carry highest fatality rate of all the gynecologic malignancies.

Despite so many advances, two crucial factors that increase overall mortality are presentation at advanced stage and lack of new therapeutic options.

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