The Genetics of Ovarian Cancer

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1. Introduction

Health Care providers managing patients with Epithelial Ovarian Cancer (EOC) must be familiar not only with the diagnosis, staging, treatment and follow-up of this disease, but also with the current knowledge on carcinogenesis, genetics and prevention/early diagnosis. This knowledge is needed in order to provide the best possible care to the patients and at the same time to provide the best possible advice to their relatives.

For the general population of women, the lifetime risk of developing ovarian cancer is 1.4%, which means that a woman's average risk of developing ovarian cancer during her lifetime is about one in 70. The lifetime risk of dying from ovarian cancer is 1.04%. Ovarian Cancer can be called a rare disease but at the same time it is the ninth most common cancer in the USA, with an estimated 22,280 new cases in 2012, and the fifth most deadly, with an estimated 15,500 deaths in 2012.The median age at diagnosis is 63 years. The poor ratio of survival to incidence in EOC results from the high percentage of cases diagnosed at an advanced stage. It is hard to find ovarian cancer early, as it may not cause any symptoms. When symptoms do appear, disease is often advanced and it is well known that the prognosis largely depends on its extent at diagnosis. Less than one-fourth of women present with localized disease. Despite advances in surgery and chemotherapy, survival of patients with EOC stands at about 31-45% at 5 years. Despite the efficacy of platinum-based chemotherapy, over 75% of women with stage III/IV EOC ultimately relapse and die from their disease. Median survival for women whose disease does not respond or in whom duration of response is short is less than 12 months. Although new drugs hold the potential of improved responses in advanced and recurrent EOC, a greater impact could be made by recognition of high-risk patients and by offering the proper advice and risk-reducing surgery when indicated. It is important that health care professionals can recognize women with possible hereditary Ovarian Cancer and have the basic knowledge to inform them of their management

options. Details about the Genetics of Breast and Ovarian Cancer are available at the National Cancer Institute site and other relevant sites and publications [1-6].

2. The pathogenesis of ovarian cancer – The role of genes

The pathogenesis of ovarian carcinoma remains unclear and represents a fascinating research area. It is possible that several pathways lead to ovarian cancer. Certain theories have been proposed to explain its epidemiology including the theory of incessant ovulation, gonadotropin stimulation, excess androgenic stimulation, and inflammation. Associated risk factors for ovarian cancer support some or all of these hypotheses. Multiparity, oral contraceptive use, and breastfeeding are associated with a decreased risk of ovarian cancer. Oophorectomy reduces but does not completely eliminate the risk of ovarian cancer. A history of tubal ligation or hysterectomy with ovarian conservation is also associated with a decreased risk of ovarian cancer. Risk is increased in women with a family history of ovarian cancer, with the postmenopausal use of hormone therapy, and among women who have used fertility drugs. Obesity, tall height, and high body mass index have also been associated with increased risk of ovarian cancer. Perineal exposure to talcum powder has been investigated as possible risk factor for ovarian cancer. It is very important to note that some women are at an increased risk due to an inherited susceptibility to ovarian cancer with the magnitude of that risk depending on the affected gene and specific mutation [1-5,7,8].

There is significant heterogeneity within the EOC group. Histologically defined subtypes such as serous, endometrioid, mucinous, and low- and high-grade malignancies all have variable clinical manifestations and underlying molecular signatures. Substantial advances have been made in understanding the genetic alterations and biologic processes in ovarian cancer; however, the etiology remains poorly understood. According to a recent publication by S Vaughan et al the term ovarian cancer is misleading. Ovarian Cancer is not a single disease, and a considerable proportion of tumors do not arise from ovarian tissue. "The unifying clinical feature of all ovarian cancers is frequent loco-regional dissemination to the ovary and related pelvic organs. We considered whether the term ovarian cancer should be replaced with the terms pelvic or peritoneal cancer but we recognized the confusion that might ensue for patients and physicians, as well as in the scientific literature, especially during a transition period. Before the term ovarian cancer is abandoned, the disparate origins of this disease need to be more widely understood by patients, physicians and scientists."[1-5, 7, 8]

While approximately 90% of ovarian cancers occur sporadically, 10% of women with ovarian cancer have inherited genetic changes that predisposed them to ovarian cancer. It is very important to identify these persons and properly manage them. The following information is very useful for the candidates of genetic testing: Genes carry information in the form of DNA within each cell of the human body. There are 30,000 different genes in each cell's chromosomes and there are 23 pairs of chromosomes in each cell. One chromosome of each pair is inherited from the person's father and one from the person's mother. Genes control

how a cell functions, including how quickly it grows, how often it divides, and how long it lives. To control these functions, genes produce proteins that perform specific tasks and act as messengers for the cell. Therefore, it is essential that each gene have the correct instructions or "code" for making its protein so that the protein can perform the proper function for the cell [1-5].

Many cancers begin when one or more genes in a cell are mutated creating an abnormal protein or no protein at all. The information provided by an abnormal protein is different from that of a normal protein, which can cause cells to multiply uncontrollably and become cancerous. A person may either be born with the genetic mutation in all of their cells (germline mutation) or acquire a genetic mutation in a single cell during his or her lifetime. An acquired mutation is passed on to all cells that develop from that single cell (somatic mutation). A germline mutation or a hereditary mutation, according to the NCI definition, is a gene change in a body's reproductive cell that becomes incorporated into the DNA of every cell in the body of the offspring. Germline mutations are passed on from parents to offspring. Somatic mutations, according to the NCI, are alterations in DNA that occur after conception. Somatic mutations can occur in any of the cells of the body except the germ cells and therefore are not passed on to children. These alterations can (but do not always) cause cancer or other diseases. If the mutant cell continues to divide, the individual will come to contain a patch of tissue of genotype different from the cells of the rest of the body. So this is a change in the genetic structure that is neither inherited nor passed to offspring. These changes can be caused by environmental factors such as ultraviolet radiation from the sun and cigarette smoke or can occur if a mistake is made as DNA copies itself during cell division. Mutations may also occur in a single cell within an early embryo. As all the cells divide during growth and development, the individual will have some cells with the mutation and some cells without the genetic change. This situation is called mosaicism. Some genetic changes are very rare; others are common in the population. Genetic changes that occur in more than 1 percent of the population are called polymorphisms. They are common enough to be considered a normal variation in the DNA. Polymorphisms are responsible for many of the normal differences between people such as eye color, hair color, and blood type. Although many polymorphisms have no negative effects on a person's health, some of these variations may influence the risk of developing certain disorders [1-5, 9-17].

Most ovarian cancers (about 85% to 90%) are considered sporadic, meaning that the damage to the genes occurs by chance after a person is born and there is no risk of passing on the gene to a person's children. Inherited ovarian cancers are less common (about 10% to 15%) and occur when gene mutations are passed within a family, from one generation to the next. Every cell usually has two copies of each gene: one inherited from a person's mother and one inherited from a person's father. Most types of hereditary ovarian cancer follow an autosomal dominant inheritance pattern, in which a mutation needs to happen in only one copy of the gene for the person to have an increased risk of getting the disease. This means that a parent with a gene mutation may pass on a copy of the normal gene or a copy of the gene with a mutation. Therefore, a child who has a parent with a mutation has a 50% chance of inheriting that mutation. A brother, sister, or parent of a person who has a gene mutation

also has a 50% chance of having the same mutation. Autosomal dominant inheritance of breast/ovarian cancer is characterized by transmission of cancer predisposition from genera-tion to generation, through either the mother's or the father's side of the family, with an in-heritance risk of 50%. Although the risk of inheriting the predisposition is 50%, not everyone with the predisposition will develop cancer because of incomplete penetrance and/or gen-der-restricted or gender-related expression. Both males and females can inherit and transmit an autosomal dominant cancer predisposition. A male who inherits a cancer predisposition can still pass the altered gene on to his sons and daughters [1-5, 9-17].

3. The BRCA1 and BRCA2 genes

Breast and ovarian cancer are components of several autosomal syndromes but most strong-ly associated with both cancers are the BRCA1 or BRCA2 mutation syndromes, which ac-count for about 90% of hereditary cases. The BRCA1 gene is located on chromosome 17q21, while BRCA2 is located on chromosome 13q12. BRCA1 and BRCA2 play major roles in the repair of DNA doublestrand breaks by homologous recombination. Homologus recombina-tion repairs doublestrand breaks that occur in late S and G2 phase of the cell cycle and also has a key role in repairing doublestrand breaks that result from unrepaired single-strand break. BRCA1 signals the presence of doublestrand breaks, while BRCA2 is directly in-volved in the mechanism of homologous recombination. So the BRCA1 and BRCA2 proteins are considered caretakers of the genome, and play key roles in the signaling of DNA dam-age, the activation of DNA repair, the induction of apoptosis, and the monitoring of cell cy-cle checkpoints. Cells that lack functional BRCA have increased aneuploidy, centrosome amplification, and chromosomal aberrations, which make them susceptible to further muta-tions. BRCA appears to function as a cofactor for a variety of transcription factors, and the associated ovarian cancers are more likely to be high grade and of serous histopathology. In the absence of BRCA1 or BRCA2, alternative DNA repair pathways are used, which result in chromosomal instability and cell death. Normal cell of carriers are usually heterozygote with loss of the second allele occurring during tumorigenesis in the tumor cells of these women. [1-5, 7,8].

There are several genetic conditions linked to an increased risk of ovarian cancer involving mutations in several other genes, including TP53, PTEN, STK11/LKB1, CDH1, CHEK2, ATM, MLH1, and MSH2.Some of the most common hereditary cancer syndromes associated with ovarian cancer risk are the following:

1.   **Hereditary breast and ovarian cancer syndrome.** This syndrome is associated with mu-tations in the BRCA1 or BRCA2 genes (BRCA stands for BReast CAncer) and it is relat-ed with an increased risk of breast cancer and ovarian cancer. There have also been reports of a small number of families with an excess of ovarian cancer, but no breast cancer, called site-specific ovarian cancer families. These families have been linked to mutations in BRCA1 and are thought to represent a unique phenotype of the hereditary breast-ovarian syndrome. The majority of hereditary breast cancers can be accounted

for by inherited mutations in BRCA1 and BRCA2. Overall, it has been estimated that inherited BRCA1 and BRCA2 mutations account for 5 to 10 percent of breast cancers and 10 to 15 percent of ovarian cancers among white women in the United States. When examining consecutive series of patients with ovarian cancer who have been unselected for family history, approximately 10% to 15% of patients have a deleterious mutation in either of these genes. When studying patients with ovarian cancer who have a family history of ovarian cancer or early onset breast cancer, the likelihood of finding a BRCA1 or BRCA2 mutation rises considerably. In fact, it is generally stated that the majority of hereditary ovarian cancer is explained by BRCA1 or BRCA2 abnormalities. The Gynecologic Oncology Group conducted a prospective study of women with ovarian cancer and a positive family history. Specifically, they enrolled patients with ovarian cancer who had any of the following features: a first degree relative with ovarian cancer, a second-degree relative with ovarian cancer plus a first-degree relative with early-onset breast cancer (defined as younger than 50 years), or a first- and second-degree relative with early onset breast cancer. Of 26 eligible patients screened for mutations, 12 had deleterious alterations, eight in BRCA1 and four in BRCA2 [1-5, 7, 8]. Although reproductive, demographic, and lifestyle factors affect risk of ovarian cancer, the single most important ovarian cancer risk factor is a family history of the disease. A large meta-analysis of 15 published studies estimated an odds ratio of 3.1 for the risk of ovarian cancer associated with at least one first degree relative with ovarian cancer. The family characteristics that suggest hereditary breast and ovarian cancer predisposition include the following: 1) Multiple cancers within a family. 2) Cancers that are usually diagnosed at an earlier age than in sporadic. 3) History of two or more primary cancers in a single particular individual. The Claus and the Gail models are widely used in research studies and clinical counseling. Both have limitations, and the risk estimates derived from the two models may differ for an individual patient. Several other models, which include more detailed family history information, are also in use. The use of these models requires specific knowledge and expertise. 4) Cases of male breast cancer are definitely indications for genetic testing [1-5, 9-17].

2. **Lynch syndrome or hereditary nonpolyposis colon cancer (HNPCC).** Lynch syndrome increases a woman's risk of ovarian cancer. It is caused by mutations in several different genes and it also increases the risk of colorectal cancer, as well as cancers of the stomach, small intestine, liver, bile duct, urinary tract, endometrium, the brain and central nervous system, and possibly breast cancer. Defects in mismatch repair in patients with Lynch syndrome account for approximately 10% of hereditary ovarian cancers and for 1% to 2% of overall cases. Patients with this syndrome, however, individually carry an approximately 12% risk of developing ovarian cancer. The mechanism of increased risk is through defects in the mismatch-repair machinery and its resulting genetic instability that places cells at risk of multiple mutations; however, carcinogenesis in ovarian cancer has not been well studied beyond a description of mismatch repair defects.

Genetic conditions that are also associated with a small increased risk of ovarian cancer are the following:

1. **Peutz - Jeghers syndrome.** This syndrome is caused by a specific genetic mutation in the STK11 gene and is associated with multiple polyps in the digestive tract that become noncancerous tumors, increased pigmentation on the face and hands and with an increased risk of ovarian, breast, uterine, and lung cancers.

2. **Nevoid basal cell carcinoma syndrome or Gorlin syndrome** is associated with a mutation in PTCH and a 20% life time risk of developing stromal tumors and fibromas of the ovaries. There is a small risk that these fibromas could develop into fibrosarcoma. People with Gorlin syndrome often have multiple basal cell carcinomas and jaw cysts and may develop medulloblastoma in childhood.

3. **Li-Fraumeni syndrome.** The Li-Fraumeni syndrome is a rare condition associated with a specific genetic mutation. People with Li-Fraumeni syndrome have a higher risk of developing osteosarcoma, soft tissue sarcoma, leukemia, breast cancer, brain cancer, and adrenal cortical tumors.

4. **Ataxia telangiectasia.** Ataxia telangiectasia is a rare disorder associated with a specific genetic mutation. It causes progressive neurological problems and an increased risk of leukemia, lymphoma, and possibly sarcoma, breast, ovarian and stomach cancer. Germline mutations in the genes responsible for those syndromes produce different clinical phenotypes of characteristic malignancies and, in some instances, associated nonmalignant abnormalities.

A study of genetic disorders can provide great insight into the etiology and early events in carcinogenesis. Evaluation of BRCA1 and BRCA2 mutant and sporadic tumors with gene expression profiling has demonstrated that the greatest contrast in expression patterns was between that of BRCA1 and BRCA2 mutant tumors and that sporadic tumors shared characteristics of both. This intriguing finding suggests that BRCA1 and BRCA2 tumors may have variable pathways in carcinogenesis and that even sporadic tumors may develop as a result of alterations in either pathway. Ovarian carcinogenesis, as in most cancers, involves multiple genetic alterations. A great deal has been learned about proteins and pathways important in the early stages of malignant transformation and metastasis, as derived from studies of individual tumors, microarray data, animal models, and inherited disorders that confer susceptibility. However, a full understanding of the earliest recognizable events in epithelial ovarian carcinogenesis is limited by the lack of a well-defined premalignant state common to all ovarian subtypes and by the paucity of data from early-stage cancers. Evidence suggests that ovarian cancers can progress both through a stepwise mutation process (low-grade pathway) and through greater genetic instability that leads to rapid metastasis without an identifiable precursor lesion (high-grade pathway). In an interesting review, CN Landen et al. discuss many of the genetic and molecular disorders in each key process that is altered in cancer cells, and present a model of ovarian pathogenesis that incorporates the role of tumor cell mutations and factors in the host microenvironment important to tumor initiation and progression [1-5, 9-17]. Borderline tumors have a much less frequent incidence of BRCA mutations, which also suggests a different molecular origin. Other than in hereditary syndromes, BRCA genes are rarely mutated in sporadic ovarian cancers, although epi-

genetic changes alternate splicing, and other genetic factors may affect BRCA function in as many as 82% of sporadic occurrences.

An analysis of genomic changes in ovarian cancer has provided the most comprehensive and integrated view of cancer genes for any cancer type to date. Ovarian serous adenocarcinoma tumors from 500 patients were examined by The Cancer Genome Atlas (TCGA) Research Network and analyses were reported in 2011.These findings confirm that mutations in a single gene, TP53, are present in more than 96 percent of all such cancers. TP53 encodes a tumor suppressor protein that normally prevents cancer formation. Mutations in the gene disrupt this protein's function, which contributes to uncontrolled growth of ovarian cells. Several less-frequent mutations in other genes have also been identified and was also established how sets of genes are expressed in a fashion that can predict patient survival, identifying patterns for 108 genes associated with poor survival and 85 genes associated with better survival. Patients whose tumors had a gene-expression signature associated with poor survival lived for a period that was 23 percent shorter than patients whose tumors did not have such a signature. To identify opportunities for targeted treatment, the investigators searched for existing drugs that might inhibit amplified or over-expressed genes that were suggested to play a role in ovarian cancer. Sixty-eight genes have been identified that could be targeted by existing or experimental therapeutic compounds. One type of drug, a PARP (Poly ADP ribose polymerase) inhibitor, might be able to counteract the DNA repair gene observed in half of the ovarian tumors studied. These drugs could be effective against the disease, this study revealed that 50 percent of tumors might be responsive to drugs that exploit the genetic instability of the tumors and induce the cancer cells to die. The results of this study support the existence of four distinct subtypes of the disease, based on the patterns seen in the transcription of RNA from DNA. They also support the existence of four related subtypes based on the patterns of DNA methylation—a chemical reaction in which a small molecule called a methyl group is added to DNA, changing the activity of individual genes. These patterns likely reflect the functional changes associated with ovarian serous adenocarcinoma, but are not strongly associated with survival duration. In this study, approximately 21 percent of the tumors showed mutations in BRCA1 and BRCA2 genes. Analysis of these tumors confirmed observations that patients with mutated BRCA1 and BRCA2 genes have better survival odds than patients without mutations in these genes. If either of the BRCA1 and BRCA2 genes is mutated, there is improved survival duration. However, if BRCA1 activity is instead reduced by methylation, there is no improved survival duration [1-5, 9-17].

4. Genetic testing

Only genetic testing can determine whether a person has a genetic mutation. Most experts strongly recommend that people considering genetic testing first consult a genetic counselor if possible. Genetic counselors are trained to explain the risks and benefits of genetic testing. If a Genetic counselor is not available the clinician treating a patient with Ovarian Cancer

has the duty to take its role. He/she must consider if each patient with ovarian cancer is a candidate for genetic testing. Hereditary cancer syndromes have a major ethical, legal and psychological impact on the individual as well as family members and the caring physician. As a result, a careful counseling before, during and after the testing is necessary. There are many issues that one has to know before proceeding with the genetic testing.

Criteria for recommending genetic testing: Currently, there are no standard criteria for recommending or referring someone for BRCA1 orBRCA2 mutation testing American Society of Clinical Oncology (ASCO) has published some guidelines for Genetic Testing of cancer patients and their families. ASCO also encourages Oncologists to assume the responsibility of genetics counseling with patients and their families. ASCO General recommendation as to indications for genetic testing in generally are the following: 1) When a person has a strong family history of cancer or very early age of onset of disease. 2) Test can be adequately interpreted. 3) Result will influence medical management of the patient/family member. In a family with a history of breast and/or ovarian cancer, it may be most informative to first test a family member who has breast or ovarian cancer. If that person is found to have a harmful BRCA1 or BRCA2 mutation, then other family members can be tested to see if they also have the mutation. Women who have a relative with a harmful BRCA1 or BRCA2 mutation and women who appear to be at increased risk of breast and/or ovarian cancer because of their family history should consider genetic counseling to learn more about their potential risks and about BRCA1 and BRCA2 genetic tests.

ASCO Recommendation as to indications for genetic testing for Breast and Ovarian cancers are the following: 1) Family with more than two breast cancer cases and one or more cases of ovarian cancer diagnosed at any age. 2) Family with more than three breast cancer cases diagnosed before age 50. 3) Sister pairs with two of the following cancers diagnosed before age 50: two breast cancers; two ovarian cancers; or a breast and ovarian cancer.4) Relatives of individuals with breast cancer diagnosed before the age of 30.Despite the above recommendations, there are individuals who do not fit any of the above categories and yet like to be tested. Such individuals need to be counseled to determine the appropriateness of genetic testing [1-5, 9-17].

Genetic counseling: Genetic counseling is generally recommended before and after a genetic test. This counseling should be performed by a health care professional experienced in cancer genetics. Genetic counseling usually involves a risk assessment based on the individual's personal and family medical history and discussions about the appropriateness of genetic testing, the specific test(s) that might be used and the technical accuracy of the test(s), the medical implications of a positive or a negative test result, the possibility that a test result might not be informative (an ambiguous result), the psychological risks and benefits of genetic test results, and the risk of passing a mutation to children. In case genetic testing turns positive health care professional must explain to her that a positive test result indicates that a person has inherited a known harmful mutation in BRCA1 or BRCA2 and, therefore, has an increased risk of developing cancer. Women considering genetic testing must know in advance certain facts about the risk to develop Ovarian Cancer if the tests are positive as well as the available prevention options. The lifetime risk for women who are BRCA1

carriers is about 40-50% and for BRCA2 carriers about 10-20%. The following information must be provided to genetic testing candidates according to the NCI. Women must know that in addition to family history, other environmental and lifestyle factors may increase their risk of ovarian cancer. Discussing their family history and personal risk factors with a doctor helps them to better understand their risk. People with a higher than average risk may benefit from genetic counseling, and the implementation of early detection and prevention strategies.

There can be benefits to genetic testing, whether a person receives a positive or a negative result. The potential benefits of a negative result include a sense of relief and the possibility that special preventive checkups, tests, or surgeries may not be needed. A positive test result can bring relief from uncertainty and allow people to make informed decisions about their future, including taking steps to reduce their cancer risk. In addition, many people who have a positive test result may be able to participate in medical research that could, in the long run, help reduce deaths from breast cancer. The direct medical risks, or harms, of genetic testing are very small, but test results may have an effect on a person's emotions, social relationships, finances, and medical choices. People who receive a positive test result may feel anxious, depressed, or angry. They may choose to undergo preventive measures, such as prophylactic surgery, that have serious long-term implications and whose effectiveness is uncertain. People who receive a negative test result may experience "survivor guilt," caused by the knowledge that they likely do not have an increased risk of developing a disease that affects one or more loved ones. Because genetic testing can reveal information about more than one family member, the emotions caused by test results can create tension within families. Test results can also affect personal choices, such as marriage and childbearing. Issues surrounding the privacy and confidentiality of genetic test results are additional potential risks.

Ovarian cancer may run in the family if first-degree relatives (mother, sisters, daughters) or many other family members (grandmothers, aunts, nieces, granddaughters) have had ovarian cancer. If a woman's first-degree relatives developed ovarian cancer, her risk of ovarian cancer is about three times higher than the average woman's risk of ovarian cancer. The risk increases if other close relatives have had ovarian cancer. When using family history to assess risk, the accuracy and completeness of family history data must be taken into account. A reported family history may be erroneous, or a person may be unaware of relatives affected with cancer. In addition, small family sizes, premature deaths, immigration and poor medical records may limit the information obtained from a family history. Breast or ovarian cancer on the paternal side of the family usually involves more distant relatives than on the maternal side and thus may be more difficult to obtain. When comparing self-reported information with independently verified cases, the sensitivity of a history of breast cancer is relatively high, at 83% to 97%, but lower for ovarian cancer, at 60%. [1-5, 10,11]

However, **a positive test** result provides information only about a person's risk of developing cancer. It cannot tell whether an individual will actually develop cancer or when. It must be stressed that not all women who inherit a harmful BRCA1 or BRCA2 mutation will develop breast or ovarian cancer. A positive genetic test result may have important health and

social implications for family members, including future generations. Unlike most other medical tests, genetic tests can reveal information not only about the person being tested but also about that person's relatives. Both men and women who inherit harmful BRCA1 or BRCA2 mutations, whether they develop cancer themselves or not, may pass the mutations on to their sons and daughters. However, not all children of people who have a harmful mutation will inherit the mutation. How a **negative test** result will be interpreted depends on whether or not someone in the tested person's family is known to carry a harmful BRCA1 or BRCA2 mutation. If someone in the family has a known mutation, testing other family members for the same mutation can provide information about their cancer risk. If a person tests negative for a known mutation in his or her family, it is unlikely that they have an inherited susceptibility to cancer associated with BRCA1 orBRCA2. Such a test result is called **a "true negative."** On the other hand having a true negative test result does not mean that a person will not develop cancer; it means that the person's risk of cancer is probably the same as that of people in the general population. In cases in which a family has a history of breast and/or ovarian cancer and no known mutation in BRCA1 or BRCA2 has been previously identified, a negative test result is not informative. It is not possible to tell whether an individual has a harmful BRCA1 or BRCA2 mutation that was not detected by testing and this is called a **"false negative test"** or whether the result is a true negative. In addition, it is possible for people to have a mutation in a gene other than BRCA1 or BRCA2 that increases their cancer risk but is not detectable by the test(s) used. If genetic testing shows a change in BRCA1 or BRCA2 that has not been previously associated with cancer in other people, the person's test result may be interpreted as **"ambiguous"** and the result is considered as uncertain. It is estimated that 10 percent of women who underwent BRCA1 and BRCA2 mutation testing had this type of ambiguous result. Because everyone has genetic differences that are not associated with an increased risk of disease, it is sometimes not known whether a specific DNA change affects a person's risk of developing cancer. As more research is conducted and more people are tested for BRCA1 or BRCA2 changes, we expect to learn more about these changes and cancer risk [1-5, 9-17].

Genetic tests: Several methods are available to test for BRCA1 and BRCA2 mutations. Most of these methods look for changes in BRCA1 and BRCA2 DNA. At least one method looks for changes in the proteins produced by these genes. Frequently, a combination of methods is used. A blood sample is needed for these tests. The blood is drawn in a laboratory, doctor's office, hospital, or clinic and then sent to a laboratory that specializes in the tests. It usually takes several weeks or longer to get the test results. Genetic tests are expensive and this represents a major problem in every day practice.

5. Management of women with mutated genes

The options available today for women who have tested positive can be divided into secondary and primary prevention. Methods of secondary prevention, such as surveillance, attempt to diagnose cancers at an early stage, while primary prevention prevents cancer development. Chemoprevention and prophylactic oophorectomy are examples of

primary prevention. Not all methods are appropriate for all patients, and potential adverse effects, complications, cost, and efficacy of these interventions must be considered and reviewed with patients before implementation. It must be stressed that having a particular genetic mutation linked to ovarian cancer cannot predict that a person will develop cancer. [1-5, 18-29].

Cancer prevention is action taken to lower the chance of getting cancer. By preventing cancer, the number of new cases of cancer in a group or population is lowered. Hopefully, this will lower the number of deaths caused by cancer. To prevent new cancers from starting, we must consider risk and protective factors. Anything that increases one person's chance of developing cancer is called a cancer risk factor; anything that decreases the chance of developing cancer is called a cancer protective factor. Some risk factors for cancer can be avoided, but many cannot. For example, both smoking and inheriting certain genes are risk factors for some types of cancer, but only smoking can be avoided. Regular exercise and a healthy diet may be protective factors for some types of cancer. Avoiding risk factors and increasing protective factors may lower the risk but it does not mean that cancer will be avoided. Different ways to prevent cancer are being studied, including: Changing lifestyle or eating habits, avoiding things known to cause cancer or taking medicines to treat a precancerous condition or to keep cancer from starting[1-5,18-29]. According to the NCI's PDQ cancer information about **Ovarian cancer prevention** the following risk factors may **increase** the risk of ovarian cancer: Family history of ovarian cancer, inherited risk, hormone replacement therapy, fertility drugs, talc and obesity. Factors associated with a **decreased** risk of ovarian cancer include: (a) using oral contraceptives, (b) having and breastfeeding children, (c) having a bilateral tubal ligation or hysterectomy, and (d) having a prophylactic oophorectomy. Multiple studies have consistently demonstrated a decrease in ovarian cancer risk in women who take oral contraceptives. The protective association increases with the duration of oral contraceptive use and persists up to 25 years after discontinuing oral contraceptives. A review of the literature demonstrated a 10% to 12% decrease in risk associated with use for 1 year and an approximate 50% decrease after 5 years of use. This reduced risk was present among both nulliparous and parous women. A protective association between oral contraceptives and risk of ovarian cancer has been observed in most studies among women who carry a mutation in BRCA1 and BRCA2 genes but a population-based study did not observe an association between oral contraceptives and ovarian cancer, while parity was protective. There may be a slight increase in a woman's risk of breast cancer during the time she is taking oral contraceptives. This risk decreases over time. Pregnancy and breastfeeding are linked to a decreased risk of ovarian cancer. Ovulation stops or occurs less often in women who are pregnant or breastfeeding and women who ovulate less often have a decreased risk of ovarian cancer. Factors that increase risk for ovarian cancer include increasing age and nulliparity, while those that decrease risk include surgical history and use of Oral contraceptives. Relatively few studies have addressed the effect of these risk factors in women who are genetically susceptible to ovarian cancer. Ovarian cancer incidence rises in a linear fashion from age 30 years to age 50 years and continues to increase, though at a slower rate, thereafter. Before age 30 years, the risk of developing epithelial ovarian cancer is remote, even in hereditary cancer families. Nulliparity is consistently associated with an increased

risk of ovarian cancer, including among BRCA1/BRCA2mutation carriers. Risk may also be increased among women who have used fertility drugs, especially those who remain nulligravid. Evidence is growing that the use of menopausal HRT is associated with an increased risk of ovarian cancer, particularly in long-time users and users of sequential estrogen-progesterone schedules [1-5].

Surveillance means cancer **screening**, or a way of detecting the disease early. Screening does not, however, change the risk of developing cancer. The goal is to find cancer early, when it may be most treatable. **Screening,** looking for cancer before a person has any symptoms, can help find cancer at an early stage and increase the chances for cure or prolong survival. By the time symptoms appear, the disease may have begun to spread and treatment results are usually disappointing. Before recommending screening it is important to estimate women who have increased risk to develop ovarian cancer in order to suggest the proper screening tests, when to start screening and how often to repeat it. If screening tests are abnormal then the physician has to proceed to diagnostic tests. There are unfortunately no satisfactory standard screening tests for ovarian cancer. Family members of ovarian cancer patients must be informed that tests that may detect ovarian cancer are the following: Pelvic examination, transvaginal ultrasound and CA-125 assay. Although screening for ovarian cancer has not been proven to decrease the death rate from the disease, this approach is the only available screening today for the possible early diagnosis for Ovarian Cancer and this is what we must follow. Several biomarkers with potential application to ovarian cancer screening are under development but have not yet been validated or evaluated for efficacy in early detection and mortality reduction. The Pap test, which is considered by many women as the "screening for Gynecological Cancer", may occasionally detect malignant ovarian cells, but it is not sensitive, the reported sensitivity is about 10%–30%, and has not been evaluated for the early detection of ovarian cancer. Other methods of detection, including cytologic examination of peritoneal lavage obtained by culdocentesis and proteomics used to identify patterns or specific serum markers that may be used in place of, or in conjunction with, CA 125 measurements remain under study. Given the low incidence of ovarian cancer in the general population, the use of these modalities has not been adopted for screening purposes in the general population. To be cost effective and avoid unnecessary surgical interventions, the use of transvaginal ultrasound and CA-125 would need to be nearly 100% specific and sensitive. Premenopausal women in particular have a high incidence of benign ovarian cysts. Although CA-125 can be a reliable marker for recurrence in women with a previous diagnosis of ovarian cancer, only 50% of early-stage ovarian cancers are associated with an abnormal CA-125. It must be noted that CA-125 can also show spurious elevations in association with any process, which irritates the peritoneal or pleural cavity, such as endometriosis, pneumonia, pulmonary embolism, or even normal menses. Prospective screening trials, using ultrasound and CA-125, in women in the general population have resulted in approximately 30 surgeries for every cancer diagnosed and have failed to detect disease at an early stage. Given the higher prevalence of ovarian cancer in patients with BRCA mutations, there has been speculation that pelvic ultrasound and CA-125 may be useful screening strategies for these patients. In fact, annual or semiannual screening with pelvic examination, transvaginal ultrasonography, and serum CA-125 was recom-

mended as appropriate interventions for women at high risk of ovarian cancer in a National Institutes of Health consensus conference although they did concede that there was no evidence of efficacy. Indeed, multiple investigations have been performed that cast doubt on the efficacy of these interventions. For example, a recent study prospectively screened 1,110 women with increased risk of ovarian cancer with pelvic ultrasound and CA-125 measurements. About half of patients were at moderate risk of developing ovarian cancer, with a 4% to 10% lifetime risk and half were at high risk with more than 10% lifetime risk. Invasive ovarian cancer was diagnosed in 12 patients. Two patients had stage I disease, one had stage II, four had stage III, and one had stage IV. These screening techniques missed an additional two patients with stage III disease and one patient with stage IV ovarian cancer. Based on abnormal ultrasound findings, 29 additional women underwent surgery for what turned out to be benign processes. The positive predictive value was 17%, and the sensitivity was less than 50%. These screening techniques are especially problematic for premenopausal women (the cohort with BRCA mutations is of highest interest) in which the false-positive rate was 79%. The conclusion is that the use of pelvic ultrasound and CA-125 does not meet World Health Organization screening standards for women with an increased risk for ovarian cancer. The advantages of surveillance include avoidance of premature menopause and the fact that there is no intervention for those without disease. It allows management with other techniques, which may be available in the future. However, surveillance does not prevent disease, and an objective assessment of the data on screening for ovarian cancer does not support the use of these modalities, even in patients at elevated risk. For women who have not finished childbearing or are deferring prophylactic oophorectomy for other reasons, current practice guidelines from the National Comprehensive Cancer Network recommends concurrent transvaginal ultrasound and CA-125 every 6 months starting at age 35 or 5 to 10 years earlier than the earliest ovarian cancer diagnosis in the family (and preferably days 1 to 10 of cycle for premenopausal women). If initiated, it is important for these women to understand the shortcomings of surveillance. They should be aware of the high likelihood of an abnormal scan in ovulating women, and also understand that a normal scan does not guarantee absence of disease, even in the advanced stages [1-5, 18-29].

Chemoprevention involves the use of natural or synthetic substances to reduce the risk of developing cancer or to reduce the chance that cancer will come back. It has been postulated that incessant ovulation may be one mechanism by which ovarian cancer develops. Consistent with this theory is the observation that parity is associated with a reduction in risk. **The use of oral contraceptives** has also been shown to reduce ovarian cancer risk by as much as 50% in the general population. However, there have been relatively few investigations studying the effect of oral contraceptive use on ovarian cancer risk in women with BRCA mutations. Unfortunately, the available data are conflicting. In one retrospective investigation of 451 patients with BRCA mutations, women who used oral contraceptives for 6 or more years had an odds ratio of ovarian cancer of 0.62 (95% confidence interval [CI], 0.35–1.09). Although not a statistically significant reduction in risk, this study suggests that oral contraceptives may be an effective form of chemoprevention in carriers. In contrast, Modan et al performed a case-control study of 1,591 Jewish women, 257 of whom underwent genetic testing and were found to have a BRCA mutation. They did not find clear evidence of a

protective effect with oral contraceptive use in BRCA carriers. Given the low incidence of adverse effects, before more definitive investigations are available, the use of oral contraceptives as a chemopreventive strategy would appear to be a reasonable approach for the patient who declines prophylactic salpingo-oophorectomy and for whom prevention of pregnancy is acceptable. However, the conflicting data should be reviewed with the patient before initiation [1-5, 18-29].

Prophylactic salpingo-oophorectomy. The use of oral contraceptives, having and breastfeeding children do not certainly offer enough protection for BRCA1/BRCA2 carriers. The removal of the "at-risk" tissue is the most important step to prevent Ovarian Cancer. Women who have a high risk of ovarian cancer must be informed about the possibility of a prophylactic oophorectomy. This includes women who have inherited certain changes in the BRCA1 and BRCA2 genes or in the genes linked to hereditary nonpolyposis colon cancer (HNPCC). It is very important to have a cancer risk assessment and counseling before making this decision. These and other factors should be discussed: Early menopause: 90% reduction in risk of ovarian cancer observed among women with a BRCA1 or BRCA2 mutation. BRCA1 or BRCA2 mutations occur in 0.1–0.8% of the general population and are inherited in an autosomal dominant manner. They are well recognized to have a higher incidence in certain ethnic groups, such as women of Ashkenazi Jewish descent. S Vaughan Given the newly appreciated importance of the fallopian tube in the genesis of high-grade serous ovarian cancer, it is recommended that the complete removal of the fallopian tube should become standard of care in any woman undergoing hysterectomy and/or removal of the ovaries (oophorectomy). Oophorectomy in premenopausal women induces early menopause. As a consequence, and with the changed view of the role of the fallopian tube in ovarian cancer, some clinicians have recommended that only the fallopian tubes should be removed (salpingectomy) in women with germline BRCA1 or BRCA2 mutations, or in women with a strong family history of breast and/or ovarian cancer34. However, until comprehensive comparative data are available, it is premature to recommend that only the fallopian tubes are removed in high-risk women [1-5, 30-43].

Women who have completed childbearing are candidates for surgery. For the majority of women, this surgery can be performed laparoscopically as an outpatient procedure. In contrast to surveillance and chemoprevention, this intervention is very effective in reducing the risk of ovarian cancer. Bilateral tubal ligation and hysterectomy are associated with reduced ovarian cancer risk, including in BRCA1/BRCA2 mutation carriers. Ovarian cancer risk is reduced more than 90% in women with documented BRCA1 or BRCA2 mutations who chose risk-reducing salpingo-oophorectomy. In this same population, prophylactic removal of the ovaries also resulted in a nearly 50% reduction in the risk of subsequent breast cancer. In a retrospective analysis of 551 patients, Rebbeck et al showed that women who had undergone prophylactic salpingo-oophorectomy had an odds ratio of 0.04 for ovarian cancer, compared with carriers without prophylactic salpingo-oophorectomy. Over a median follow-up of 8.8 years, two primary peritoneal cancers were diagnosed in the 259 women who underwent prophylactic salpingo-oophorectomy compared with 58 ovarian/peritoneal cancers in the 292 women who did not have prophylactic salpingo-oophorectomy. An added benefit

was a 47% reduction in the risk of breast cancer in premenopausal women who had prophy-
lactic salpingo-oophorectomy. The effectiveness of prophylactic salpingo-oophorectomy in
reduction of ovarian cancer risk has also been demonstrated in prospective studies. Prophy-
lactic salpingo-oophorectomy failures may be divided into groups of those patients who are
found to harbor an occult malignancy at the time of surgery and those who go on to develop
carcinoma at a later time. The existence of occult ovarian cancer in BRCA carriers with appa-
rently healthy ovaries has been documented in small samples for a number of years. In a
recent investigation that included 555 women who underwent prophylactic salpingo-oopho-
rectomy, the rate of occult fallopian tube or ovarian cancer was 2.2%, consistent with prior
reports. Although a low incidence, this risk should routinely be discussed with patients be-
fore surgery and highlights the need for an extensive pathologic assessment of the entire ad-
nexa, including the fallopian tubes [30-43]. Development of primary peritoneal carcinoma
(PPC) represents the vast majority of failures after prophylactic salpingo-oophorectomy. In a
multicenter investigation of 1,828 carriers, the cumulative risk of PPC was 4.3% at 20 years
after prophylactic salpingo-oophorectomy.24 It is hypothesized that PPC arises from the
peritoneal coelomic epithelium, derived from the same embryonic tissue that gives rise to
the epithelial covering of the ovaries. Ovarian and peritoneal epithelium share common em-
bryonal origin, originating both from the coelomic epithelium (mesodermal origin). Coelo-
mic epithelium is thought to be of mesonephric origin. With the overall point being that
normal ovarian and peritoneal tissue is derived from the mesonephros. On the contrary, fal-
lopian tube epithelium, endometrium and endocervix are related to paramesonephros (Mül-
lerian duct). Surprisingly, epithelial ovarian cancer and primary peritoneal cancer are
histologically similar to the Mullerian epithelium; not their embryonal origin, the meso-
nephros. Either a metaplasia has occurred or Mullerian remnants have been left behind in
coelemic epithelium, which have turned oncogenic. Although the precise causes are not
known, a link with certain variants of BRCA1/2 has been described. Furthermore, women
with BRCA1/2 mutation have a 5% risk of developing primary peritoneal cancer even after
prophylactic oophorectomy. Primary peritoneal carcinoma shows similar rates of tumor
suppressor gene dysfunction (p53, BRCA, WT1) as ovarian cancer and can also show an in-
creased expression of HER-2/neu. An association with vascular endothelial growth factor
has been observed. Although the absolute risk of fallopian tube cancer is unknown in pa-
tients with BRCA mutations, it is agreed that it is substantially elevated, with a relative risk
of 120 in one study. It remains unknown if the 4.3% failure rate found by Finch et al consists
entirely of PPC or if a proportion is in fact peritoneal recurrences of a fallopian tube carcino-
ma missed at the time of prophylactic salpingo-oophorectomy. Regardless, it is widely ac-
cepted that removal of the fallopian tubes is essential at the time of prophylactic surgery.
There is an abundance of evidence supporting the efficacy of prophylactic salpingo-oopho-
rectomy, but less information exists to counsel the clinician as to the optimal timing of pro-
phylactic surgery. Reasonable guidelines can be inferred from existing data regarding the
onset of ovarian cancer in BRCA carriers. The cumulative incidence of breast cancer is 11.6%
by age 40 for women with BRCA1 mutations. In contrast, the rate is only 2.3% for ovarian
cancer by age 40. By age 45, 6.5% of BRCA1 carriers will be diagnosed with ovarian cancer;
13.2% by age 50. As a result, for BRCA1 carriers, most physicians recommend prophylactic

salpingo-oophorectomy between ages 35 to 40 years. However, performing prophylactic sal-pingo-oophorectomy before age 45 must be considered in the context of the potential mor-bidity of estrogen deprivation at an early age. Oophorectomy before age 45 has been associated with a hazard ratio of 1.96 for death from all causes (p 0.002). However, adminis-tration of estrogen replacement eliminated this risk. Many physicians consider estrogen therapy for women without a personal history of breast cancer who undergo prophylactic salpingo-oophorectomy before the age of 45.29 It should be noted that early prophylactic salpingo-oophorectomy is less important for BRCA2 carriers who are known to develop ovarian cancer at approximately the same age as patients with sporadic cancer. Only 1.2% of BRCA2 carriers will have ovarian cancer by the age of 50, so prophylactic salpingo-oopho-rectomy may safely be delayed until these patients are closer to menopause. The disadvan-tages of prophylactic salpingo-oophorectomy include the fact that it is an invasive surgical intervention, there is loss of ovarian tissue with accompanying hormone deprivation, and it is an irreversible decision. However, in contrast to surveillance and chemoprevention, pro-phylactic salpingo-oophorectomy has proven efficacy over an extended time period. Cost analyses comparing surveillance, oral contraceptives, and prophylactic salpingo-oophorec-tomy have shown that although any primary prevention strategy was cost effective, prophy-lactic salpingo-oophorectomy dominated all other strategies in women with BRCA mutations. Consequently, prophylactic salpingo-oophorectomy is recommended for all BRCA carriers, with timing dependent on the type of BRCA1 or BRCA2 mutation, childbear-ing status, and the age of onset of ovarian cancer within the family. The resultant physical and emotional outcomes of repeated gynecological screening or prophylactic oophorectomy must be discussed before and after genetic testing. A study of 315 women with documented HNPCC–associated germline mutations found no ovarian cancer among 47 women who had bilateral salpingo-oophorectomy and 12 cases (5%) among women with mutations who had not had surgery for a prevented fraction of 100% (95% CI, 62%–100%).

The degree of risk of ovarian cancer, potential morbidity and mortality of surgery, and the risks associated with early menopause, should be taken into account when consider-ing prophylactic oophorectomy for high-risk women. Adverse effects of bilateral oopho-rectomy and premature menopause include infertility, vasomotor symptoms, decline in sexual interest and activity, cardiovascular disease, and osteoporosis. Among women who have not taken hormone therapy, women undergoing bilateral oophorecotmy were twice as likely to have moderate or severe hot flashes than women who underwent nat-ural menopause (odds ratio [OR] = 2.44; 95% CI, 1.03–5.77). Women at increased heredi-tary risk of ovarian cancer who underwent oophorectomy without hormone therapy reported statistically significantly more vasomotor symptoms than women choosing screening or those using hormone replacement therapy (HRT). These women also report-ed lower sexual function scores but the difference was not statistically significant. A meta-analysis of early menopause as a risk factor for cardiovascular disease observed a pooled risk of 4.55 (95% CI, 2.56–8.01) among women with bilateral oophorectomy and early menopause (defined as younger than 50 years). Early menopause is also associated with an increased risk of fracture (OR = 1.5; 95% CI, 1.2–1.8).

6. Treatment

Over the past ten years, the focus of management for BRCA1/2mutation carriers has been on cancer prevention and early cancer detection. However, despite prophylactic measures to reduce risk of EOC, many BRCA1/2 carriers have cancer at the time their mutation is diagnosed and more will develop in the future. The treatment of patients with BRCA associated EOC is so far identical to those with sporadic disease. Data suggested that cancers associated with BRCA mutations responded differently to chemotherapy. Tan et al. compared 22 BRCA-positive patients with EOC to 44 nonhereditary EOC controls in a matched case-control study. They found that BRCA-positive patients have higher response rates to first line platinum-based treatment (81.8%versus 43.2%, P =.004) as well as to subsequent lines of platinum-based treatments (second line, 91.7% versus 40.9%, P =.004), third line, 100% v 14,3% (P<. 002) and time of first relapse (5v 1.6 years; P<. 001). They conclude that BRCA-positive EOC patients have better outcomes than nonhereditary EOC cases. There exists a clinical syndrome of BRCAness that includes serous histology, high response rates to first and subsequent lines of platinum-based treatment, longer tumor free interval between relapses and improved overall survival [44].

Over recent years the investigation of DNA repair in cancer cells has been a very active area of translational research. All cells have a number of overlapping pathways to protect the genome from DNA damage, which occurs as a result of normal cell cycling, environmental insults, or cytotoxic chemotherapy. It is well recognized that when mutations occur within these DNA repair pathways there is an increased risk of malignant transformation and chemotherapy resistance. Much research has focused on protecting cells from DNA damage and/or restoring DNA repair function. However, emerging data suggest that the concept of "synthetic lethality," that is, exploiting the vulnerability of cancer cells, which have lost one mechanism of DNA repair by targeting a second pathway, may be a particularly attractive therapeutic approach.. Targeting the nuclear enzyme PARP-1 represents a new and novel approach to the treatment of EOC and appears to be particularly promising for those carrying mutations in the BRCA1 and 2 genes. Poly(ADPribose) polymerase (PARP) is an enzyme, which plays an important role in the recognition and repair of single-strand DNA breaks via the base excision repair pathway. Over the last few years it has become apparent that in cells, which have lost BRCA1 or BRCA2, components of a second DNA repair pathway, homologous recombination, are particularly sensitive to PARP inhibition. These data suggest that PARP inhibitors may be particularly useful for the treatment of women with hereditary BRCA1/2-associated EOC. Targeted therapy using PARP inhibitors has become an important novel strategy for treating those with hereditary ovarian cancer. Furthermore the identification of other subpopulations of women with EOC who may benefit from this approach is an active area of research. There are currently 17 members of the PARP superfamily identified. PARP-1 is the most studied enzyme. In the preclinical setting, PARP-1 inhibitors enhance the cytotoxic effects of ionizing radiation and cytotoxic chemotherapy. Additionally, in the preclinical setting, the use of PARP-1 inhibitors as single agents did not cause any measurable toxicity, but the combination of PARP-1 inhibitor with temozolomide in the tumor bearing mice caused significant toxicity. There did not seem to be a correlation,

however, between the antitumor activity and the toxicity of the PARP inhibitor-temozolo-mide combinations, suggesting that toxicity and chemosensitization were by different mech-anisms. In 2005, two preclinical papers demonstrated the sensitivity of BRCA1- and BRCA2-deficient cell lines to PARP inhibition. The first paper by Bryant et al. demonstrated reduced survival of BRCA2-deficient cell lines with four PARP inhibitors. They concluded that BRCA2- deficient cells were sensitive to PARP inhibition, and that monotherapy with one of these agents could selectively kill cancer cells. In the same year, Farmer et al. demonstrated how both BRCA1- and BRCA2-deficient cells lines were sensitive to inhibition of PARP-1, and that BRCA2 deficient cells were more than 1000 times more sensitive to nanomolar con-centrations of PARP inhibitor. Both of these papers demonstrated how homozygotes (tumor cells) are sensitive to the mechanism of PARP inhibition, whereas heterozygotes (the rest of the patient's cells) are insensitive to this mechanism and should not exhibit toxicity. These findings from two independent groups using different chemical classes of PARP inhibitors on different BRCA deficient cell lines were the first to suggest the potent effect of PARP in-hibition. A number of PARP inhibitors have entered the clinic in both intravenous and oral formulations. The four, which are furthest along in terms of development, are AGO14699 (Pfizer), AZD2281 (AstraZeneca), ABT-888 (Abbott), and BSI-201 (BI Par), and all four of these compounds demonstrate profound inhibition of PARP-1.Olaparib (AZD2281, KU-0059436, AstraZeneca) is an oral small-molecule PARP inhibitor. Yap et al. presented the first clinical evidence demonstrating the sensitivity of BRCA-mutated cancers to PARP in-hibitor monotherapy in a study in 2007. This phase I trial included 44 patients, of which 11 patients had a BRCA mutation associated cancer. Dose escalation was guided by toxicity, pharmacokinetic and pharmacodynamic data. Based on the encouraging antitumor activity, many in whom had BRCA1/2 mutations, the trial was subsequently expanded to concentrate on cancers in patients with BRCA mutations. The drug was well tolerated in both BRCA mutated and normal populations. Most toxicities were grade 1-2 (≥95%), consisting of fati-gue (28%), nausea (28%), vomiting (18%), loss of taste (13%), and anorexia (12%). Grade 3-4 toxicities were rare, consisting of myelosuppression (≤5%), nausea and vomiting (2-3%), and dizziness or mood changes (2- 3%) [27]. Of the 60 patients that were enrolled and treated, 19 of 23 BRCA-positive carriers were evaluable. 12 of the 19 (63%) had a clinical benefit from olaparib, with radiologic or tumor marker responses, or stable disease for 4 months or more. Patient response was seen in those receiving a minimum of 100 mg twice daily up to 400 mg twice daily. Response was the greatest in patients with platinum-sensitive disease, although duration of response was the same regardless of the platinum-free interval. Recently data was presented from a phase II study of olaparib in women with advanced EOC with known mutations in BRCA1/2. Two patient cohorts received continuous oral olaparib in 28-day cy-cles; 33 patients received 400 mg orally twice daily, while 24 patients received 100 mg twice daily. The choice of dosing and schedule was based on the phase I trial above. The objective response rate measured by RECIST criteria was 33% at the 400 mg dose, and 12.5% at the 100 mg dose, suggesting that there may be a dose response effect. The toxicity profile was mainly mild, consisting of grade 1 or 2 nausea (44%) and fatigue (35%), with few grade 3 or 4 toxicities. Interestingly, although numbers were low, in this study there appeared to be a higher response rate in platinum resistant patients (38% versus 14%), which was opposite to

that observed in the earlier phase I study, where response was the greatest in platinum-sensitive patients. Laboratory studies have previously suggested that platinum resistant patients may reacquire BRCA function thus potentially making them resistant to the effects of PARP inhibition. Taken together, the clinical data suggest that we still have a lot to learn with regard to target populations and the role of PARP inhibition. Furthermore, data from the phase II study appears to give an early indication that response (both RECIST and CA125) may be greater in those patients with BRCA2 mutations. This would be in line with the known mechanism of action of the two BRCA proteins as BRCA2 plays a key role in the repair pathway; whereas BRCA1 functions as a signaling molecule. This phase II study concluded that oral olaparib is well-tolerated and highly active in advanced, chemotherapy refractory BRCA-deficient EOC, with greater activity seen at a higher dose of 400 mg twice daily. The optimal patient group with respect to platinum sensitivity has not been defined. Reassuringly in the clinical studies there does not appear to be an increase in toxicity between BRCA mutation carriers compared to noncarriers, supporting the theory that PARP inhibitors should not result in increased toxicity to heterozygote cells. These recent phase I and phase II trials are particularly promising for patients with BRCA-associated EOC. Further phase II trials are currently underway which will help further elucidate the role and potential for this new targeted therapy. Loss of BRCA1/2 function is not exclusive to inheriting a mutation in the BRCA1/2 genes. The results seen in known BRCA1 and 2 mutation carriers may also be relevant to the sporadic EOC patient population. Epigenetic gene inactivation is a well-recognized phenomenon with 31% of EOC exhibiting aberrant methylation of the BRCA1 promoter. Furthermore, genetic or epigenetic events occurring in other components of the HR pathway can be found in sporadic EOC. These tumors seem to be similar to BRCA1- or BRCA2-mutated tumors, even though they do not have mutations to either of these genes, a concept called "BRCAness." One molecular characterization study suggested that over 50% of patients with high-grade EOC had loss of BRCA function, either by genetic or epigenetic events [34]. Studies have shown that the loss of functional proteins in the HR pathway may lead these cells to be sensitive to PARP inhibition. Identification of "BRCA-like" EOC populations who may benefit from this new therapy through the identification and validation of biomarkers is an active area of ongoing research. Several PARP inhibitors are under investigation either as single agents and/or in combination with other agents or treatment modalities. Phase II studies in women with advanced EOC in both BRCA1/2 mutation carriers and high-grade EOC of unknown BRCA status are ongoing. Currently, olaparib is being evaluated in a randomized phase II trial comparing this agent with pegylated liposomal doxorubicin in patients with BRCA-mutated EOC with a platinum-free interval of 0–12 months. More combination studies in women with both hereditary and sporadic EOC are expected in the future. Further defining the role of PARP inhibitors in the clinic is ongoing. Olaparib is being evaluated in a randomized placebo-controlled trial as a maintenance therapy in patients with sporadic EOC at high risk of early recurrence. Furthermore, some suggest that PARP inhibitors could be used to prevent cancers in patients who are BRCA mutation carriers. This approach, however, requires careful consideration and some caution with the potential for the development of drug resistance in long-term use of PARP inhibitors. Investigation of the PARP inhibitors in the nonhereditary EOC population is very ac-

tive with both the impact of treatment on patients without BRCA defects and the search for populations of women who have lost functional proteins in the HR pathway. Investigation of PARP inhibitor resistance and ways to overcome this resistance are emerging fields. The emerging data regarding the use of PARP inhibitors in patients with BRCA-associated EOC are encouraging. Identification of further patient groups who will benefit from this approach is also indicated. Clinical trials underway will hopefully improve the prognosis of women with Epithelial Ovarian Cancer [45-53].

7. Conclusions

Genetic testing can identify women with a hereditary increased risk to develop Ovarian Cancer. This information is extremely useful if the candidate for genetic testing is willing to accept prophylactic surgery. For patients who already have Ovarian Cancer Genetic testing will offer useful information for the relatives but it can also help plan their own treatment. Published data regarding the use of PARP inhibitors in patients with BRCA-associated EOC are encouraging. Studies in combination with chemotherapy are also producing encouraging results and there are several ongoing studies in patients with hereditary and sporadic cancer as well. These studies will clarify the mechanisms of DNA repair and how this can be exploited to improve treatment results. The development of diagnostic tests in order to select patients likely to be sensitive to PARP inhibitors will also be very useful. The combination of prevention, early diagnosis and more effective disease management will hopefully improve EOC prognosis in the near future.

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