The Genetics of Ovarian Cancer

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ABSTRACT

Ovarian cancer is the fifth most common malignancy among North American women and the fourth leading cause of cancer death [1]. Ovarian cancer is mostly a disease of perimenopausal and postmenopausal women [2].

Approximately 140,000 new cases of ovarian cancer occur worldwide yearly. This number represents 4% of all female cancers, and the disease is more prevalent in developed countries [3].

The factor most strongly associated with ovarian cancer risk (after controlling for age) is a family history of ovarian cancer [1,4,5]. It is now estimated that between 5% and 13% of all ovarian cancers result from the autosomal dominantly inheritance of a germ-line mutations in a cancer predisposing genes [6-8].

About 23% of ovarian tumors have hereditary susceptibility and, in about 65-85% of these cases, the genetic abnormality is a germline mutation in BRCA genes [9,10].

Several other suppressor genes and oncogenes have been associated with hereditary ovarian cancers, including the mismatch repair (MMR) genes in Lynch syndrome, the tumor suppressor gene, TP53, in the Li-Fraumeni syndrome, and several other genes involved in the double-strand breaks repair system, such as CHEK2, RAD51, BRIP1, and PALB2 [11-13].
To date, at least 16 genes are known to be involved in the mechanism of hereditary ovarian tumorigenesis and several other mutations remain unknown and cannot be detected by specific tests [11,14].

The next-generation sequencing technologies (NGS) and the identification of mutations in ovarian cancer susceptibility may provide potential targets for biologic agents and guide treatment decision-making [11,15,16].

**Keywords:** Ovarian cancer; Family history; Hereditary risks; Predisposing genes; Mutations; Susceptibility

**Abbreviations:** BRCA: Breast Cancer; MMR: Mismatch Repair Genes; TP 53: Tumor Protein 53; CHEK2: Checkpoint Kinase 2; RAD51: Human Rad51 Protein; BRIP1: BRCA1-Interacting Protein 1; PALB2: Partner and Localizer of BRCA2; NGS: Next-Generation Sequencing Technologies; BRCA1: Breast Cancer Gene 1; BRCA2: Breast Cancer Gene 2; DNA: Deoxyribonucleic Acid; ARID1A: AT-rich Interacting Domain-Containing Protein 1A Gene; HRT: Hormone Replacement Therapy; MLH1: MutL Homolog 1; MSH2: MutS Homologue 2; HNPPC: Hereditary Nonpolyposis Colorectal Cancer; TP 53: Tumor Protein 53; CA-125: Cancer Antigen 125 (or) Carbohydrate Antigen 125; SELDI: Surface Enhanced Laser Desorption/Ionization

**INTRODUCTION**

Ovarian Cancer is a disease which cause malignant abnormal cells in the ovary to proliferate in an uncontrolled manner and spread to the rest of the ovary or outside the ovary [17].

In general population, about 1.3% of woman will develop ovarian cancer [18].

**BIOLOGICAL BASIS OF OVARIAN CANCER**

BRCA1 and BRCA2 are human genes that produce tumor suppressor proteins. The function of the BRCA genes is to repair cell damage and keep breast and ovarian cells growing normally [19].

Tumor suppressor proteins help repair damaged DNA and play an important role in ensuring the stability of the human genetic material. When these genes is mutated, DNA damage may not be repaired properly, and cells are more likely to develop additional genetic alterations [20].

Specific inherited mutations in BRCA1 and BRCA2 increase the risk of female breast and ovarian cancers. When these genes contain mutations that are passed from generation to generation, the genes don’t function normally and breast and ovarian cancer risk increase.

39% of women who inherit a harmful BRCA1 mutation and 11-17% of women who inherit a harmful BRCA2 mutation will develop ovarian cancer by age 70 years [21,22].

Together, BRCA1 and BRCA2 mutations account for about 20-25 % of hereditary breast cancers and about 5 -10 % of all breast cancers [22,23].
In addition, mutations in BRCA1 and BRCA2 account for 15% of ovarian cancers overall. Breast and ovarian cancers associated with BRCA1 and BRCA2 mutations tend to develop at younger ages than their nonhereditary counterparts [24].

Women with an abnormal BRCA1 or BRCA2 gene have a much higher-than-average lifetime risk of ovarian cancer; estimates range from 15% to 60% [21].

It is important to specify that other special features of a particular woman can make her cancer risk higher or lower. These particular features include her family history of ovarian cancer, and, other cancers; the specific mutations she has inherited; and other risk factors.

At this time, based on current data, none of these other factors seems to be as strong as the effect of carrying a harmful BRCA1 or BRCA2 mutation.

Because harmful BRCA1 and BRCA2 gene mutation are relatively rare in the general population, most experts agree that mutation testing of individuals who do not have cancer, should be performed only when the person's individual or family history suggests the possible presence of a harmful mutation in BRCA1 or BRCA2 [25].

**CAUSES OF OVARIAN CANCER**

The most common type of ovarian cancer is the epithelial carcinoma of the ovary. The cause of ovarian cancer is not known.

**Risk Factors of Ovarian Cancer**

Risk factors that may increase the developing of ovarian cancer are:

1. Family history of ovarian cancer - is the strongest risk factor.

   Women with a single first-degree relative with ovarian cancer have 3-4 times the risk of developing the disease, compared with general population.

   However, only 10% of cases arise in women with a positive family history.

   Families in which three or more first-degree relatives have ovarian cancer or ovarian plus breast cancer are likely to have a cancer-susceptibility genetic mutation that is transmitted in an autosomal-dominant inheritance pattern.

2. Presence of BRCA1 and BRCA2 genes.

   Women with a prior history of ovarian cancer or breast cancer have an increased risk of ovarian cancer. BRCA1 gene confers familial susceptibility for the breast-ovarian cancer syndrome.

3. History of other forms of cancer (breast or colon).

Studies suggest a link between ovarian endometriosis and clear-cell ovarian cancer, possibly linked to mutation of the ARID1A gene.

5. Age over 50 years.

Hereditary ovarian cancer is most commonly diagnosed after age 50 years [26,27].


Diets high in saturated animal fats seem to confer an increased risk for ovarian cancer, by unknown mechanisms ... For example, Japanese women who move in United States have an increased ovarian cancer risk.

7. Talcum powder use and Asbestos exposure.

Asbestos chrysotile is ubiquitous in the environment and that there is background exposure in everyone. Theoretically, talc powders (or asbestos) placed on the perineum can reach the ovaries via retrograde flow through the cervix and fallopian tubes. The possible link between perineal talc use in genital hygiene and ovarian cancer was initially reported by Cramer and coauthors in 1982 [28,29]. The authors reported a relative risk of 1.9 [p < 0.03] for ovarian cancer among talc users. The relative risk was 3.28 for women who used talcum powder on perineal napkins and dusting powder on the perineum.


Whittemore reporting on 12 U.S. case control studies reported that ovulatory women who had sexual intercourse unprotected by any type of contraception had a nearly double risk for developing ovarian cancer [30].

10. Use of fertility drugs (Clomifene) or Hormone Replacement Therapy (HRT).

In 1992, Whittemore reported the combined analysis of 12 U.S. case control studies on the possible association of fertility drugs in women with physician diagnosed infertility [31]. The odds ratio was 2.8 (95% CI 1.3-6) for women who took fertility drugs as compared to infertile women who did not.

In 1994, Rossing and co-authors reported an increased ovarian cancer risk RR 2.3; (95% CI 0.5-11.4) for women attending an infertility clinic in Seattle, WA, treated with Clomid [32]. For those women who took ≥12 monthly courses of Clomid, the RR was 11.1 (95% CI 1.5 - 82.3) but there was no increase risk for those women who took only 1-11 courses.

11. Early menarche.

12. Late menopause.

13. Ethnicity
Ovarian cancer is higher in white woman, and is higher in north America, and northern Europe than Japan.

**Protective Factors of Ovarian Cancer**

Protective factors include any factor which prevents or inhibits ovulation:

1. **Childbearing**, 
2. **Multiparity: First pregnancy before age 30**.

Results from the analysis of 12 U.S. case control studies observed a 15% reduction in risk for ovarian cancer for each subsequent pregnancy after the first [31].

3. **Breastfeeding**, 
4. **Lactation would theoretically reduce the risk for ovarian cancer by inhibiting pituitary luteinizing hormone and thus suppressing ovulation.**

5. **Early menopause**, 
6. **Histerectomy (Salpingectomy/Fimbriectomy)**
7. **Bilateral oopherectomy - reduce the risk of ovarian cancer by 80% to 95%**
   
   Is recommended for BRCA1 and BRCA2 carriers after childbearing, and may be recommended for those with strong family history of breast and ovarian cancer without a known mutation.

   Bilateral prophylactic oopherectomy can be done laparoscopically with minimal recovery time.

   The risks of prophylactic oopherectomy are: surgical risks (bleeding, infection, injury to bowel or urinary tract), menopausal symptoms and possible increased risks of osteoporosis and cardiac disease.

8. **Oral Contraceptives: decreases approx. 11% per year use.**

   Max. of 46% after 5 years of use.

9. **Laboratory and epidemiologic evidence suggest a potential role for vitamin D, retinoids, NSAIDs as preventive agents for ovarian cancer.**

**Hereditary Cancer Risks of Ovarian Cancer**

Most hereditary ovarian carcinomas are the result of mutations in two genes, BRCA1 and BRCA2 [33].

The genes BRCA1, BRCA2, MLH1and MSH2, encode proteins that repair mutations in other genes.
The BRCA1 and BRCA2 proteins are responsible for repairing double-stranded breaks in DNA [34]. The protein products of these genes prevent the accumulation of mutations and thus suppress the development of cancer. Such genes are generally considered to be tumor suppressor genes.

When an inherited mutation in a critical tumor suppressor gene is inherited from a parent, each cell is approximately one million times more likely than a normal cell to undergo malignant transformation [35,36].

Mutations in BRCA1 are associated with a risk of ovarian carcinoma between 28% [37] and 44% [38,39] by age 70.

Family history suggestive of BRCA mutations includes:
1. Breast cancer diagnosis at age < 50 years,
2. Bilateral breast cancer,
3. Individual with two primary tumors: breast and ovarian / fallopian / peritoneal cancer,
4. Male breast cancer,
5. Multiple cases of breast cancer in the family,
6. Ashkenazi Jewish ethnicity.

The risks of ovarian carcinoma conferred by mutations in BRCA2 appear to be somewhat lower than for BRCA1, about 27% by age 70 [33].

Mutations in these genes confer higher ovarian cancer risk in some families than in others [40,41]. For example, genes on chromosome 11 and the X chromosome have been specifically implicated as modifiers of ovarian cancer risk in women who carry mutations in BRCA1 [42,43].

Mutations in BRCA1, BRCA2, MLH1, and MSH2 confer cancer risk in an autosomal-dominant fashion, with offspring having an equal chance each of either being at greatly increased risk of cancer or of being at the general population risk.

Features of Hereditary Ovarian Cancer

Hereditary ovarian cancers, whether due to BRCA1, BRCA2, MLH1, or MSH2, are epithelial.

Most hereditary ovarian carcinomas are invasive, although tumors of low malignant potential have also been reported in affected families. The majority of the carcinomas reported in women with inherited mutations in BRCA1 and BRCA2 are papillary serous [44,45].

Inherited mutations in BRCA1 and BRCA2 are associated with improved survival compared to sporadic ovarian cancer [46].
The features of HNPCC-associated ovarian cancer are not as well-defined as those due to mutations in BRCA1 and BRCA2, but the histologic spectrum appears to be similar to that of sporadic ovarian carcinoma [38].

Mutations in BRCA1 and BRCA2 have been identified in 5 - 10% of presumed sporadic ovarian carcinomas [47,48] in which the mutation is present in the cancer, but not in the woman's germline.

The prevalence of somatic MLH1 and MSH2 mutations in sporadic ovarian cancer has not yet been characterized.

**Identification of Hereditary Risk of Ovarian Cancer**

Most hereditary ovarian cancer occurs in association with a family history of other cancers.

An inherited mutation in BRCA1 or BRCA2, for example, is suggested by one or more relatives with breast cancer diagnosed before age 50, often in the absence of a known family history of ovarian cancer. Even a single first-degree or second-degree relative with breast cancer under 50 indicates an approximately 40% chance that a woman's ovarian cancer is due to a mutation in BRCA1 or BRCA2 [49].

When hereditary ovarian cancer is due to HNPCC the family history usually includes at least one first-degree or second-degree relative with colorectal and/or endometrial cancer diagnosed before age 50. In assessing a family history it is important to keep in mind that mutations in BRCA1, BRCA2, MLH2, or MSH2 can be inherited from either a woman's father or mother. Fully half of women with hereditary risk of ovarian cancer inherited the causative mutation from their father's side of the family. Women who inherit such mutations from their fathers have the same increased risk of ovarian cancer as if they inherited it from their mother.

Assessment of family history can identify the possibility of hereditary risk of ovarian cancer but cannot confirm whether an individual woman is herself at risk. This is because increased cancer susceptibility due to BRCA1, BRCA2, MLH1, and MSH2 is inherited as an autosomal dominant trait, so that each off-spring of a mutation carrier has an equal chance of being at greatly increased risk of cancer, or not, depending upon whether she inherited the abnormal copy of the gene.

Direct analysis of these genes can provide a “tissue diagnosis” of hereditary cancer risk, which is useful because risk assessment based on family history alone will likely underestimate a woman's risk of cancer if she actually carries the mutation in her family and overestimate that risk if in fact she does not.

Specific interventions are available for women found to carry mutations that increase the risk of ovarian cancer [50,51,52] while those found not to carry the mutation in their family can avoid unnecessary interventions that might otherwise have been recommended on the basis of their family history.
Genetic testing for hereditary risk of ovarian cancer is not a general population screen but is appropriate only for women with a greatly increased chance of carrying a mutation compared to the general population.

Unfortunately, there are no good screening methods for ovarian cancer at present. Such tests can be obtained only by a healthcare professional.

Indication for testing in hereditary ovarian cancer are:

1. A family with 2 or more ovarian cancer, at least 2 between first-degree relatives,
2. Two first-degree relatives affected by breast cancer and ovarian cancer respectively breast cancer and ovarian cancer in the same patient

**Serum CA-125**, one of the earliest identified biomarkers for cancer [53], is the most extensively evaluated tumor marker in ovarian cancer screening.

CA-125 also known as mucin 16 or MUC16 is encoded by the MUC16 gene.

CA-125 is a biomarker or tumor marker that may be elevated in the blood of some patients with specific types of cancers or other benign condition.

Also, CA-125 may be elevated in: other gynecologic malignancies (endometrial cancer, fallopian tube cancer, germ cell tumors, adenocarcinoma of the cervix, Sertoly-Leyding cell tumors of the ovary), benign gynecologic conditions (endometriosis, adenomyosis, several diseases of the ovary, functional ovarian cysts, pelvic inflammatory disease, uterine fibroids, leiomyomata, Meigs’ syndrome, menstruation and pregnancy, ovarian hyperstimulation), nongynecologic conditions (Liver disease and cirrhosis, colitis, congestive heart failure, diabetes, lupus, diverticulitis, mesothelioma, pericarditis, polyarteritis nodosa, postoperative period, renal disease, tuberculosis, sarcoidosis, pleural effusion, ascites, appendicitis, previous irradiation) and nongynecologic cancers (breast cancer gastrointestinal cancer, lung cancer, pancreas cancer) [54].

Measurement of serum CA-125 levels, particularly at a reference value of 35 U/mL, is not sufficiently sensitive to be used alone as a screening test for the detection of ovarian cancer [55].

Population based studies from Norway and Maryland have documented CA-125 elevations up to 5 years before the diagnosis of ovarian cancer [55,56].

Elevation in apparently healthy postmenopausal women is a powerful predictor of increased risk of ovarian cancer [57].

Postmenopausal women with serum levels of CA-125 higher than 35U/mL or premenopausal women with CA-125 levels higher than 200U/mL should be referred to a gynecologic oncologist.

Ovarian cancer screening is not recommended for woman with no risk factors.
For woman with increase risk, after evaluating risks and benefits, ovarian cancer screening with CA-125 and/or transvaginal ultrasonography can be done.

In woman at inherited risk, usually with mutations in ovarian cancer susceptibility genes, should receive screening by a combination of transvaginal ultrasonography and CA-125 [58].

For patients with mutations in BRCA-1 or the mismatch repair genes, MLH1, MSH2 and MSH6, screening should being around 30 - 35 years old.

For patients with mutations in BRCA-2, ovarian cancer screening should be performed around 35 - 40 years old.

In the next decade, the challenge will be to identify new markers that will complement CA-125 in monitoring ovarian cancer and facilitate screening for occult early-stage disease.

The expression of growth factors and their receptors and application of monoclonal antibodies to immunohistochemistry and radionuclide imaging may also provide new areas of diagnostic application for monoclonal antibodies in gynecologic oncology [59].

Also, new technologies including expression array and SELDI are likely to identify a wealth of new candidate markers. Development of an effective strategy to select and prioritize them is essential.

For ovarian cancer, Liotta and Petricoin et al, demonstrated that a SELDI multi marker profile has sensitivity (100%) and specificity (95%), compared to the poor performance of the CA-125 test [60].

**GENETIC COUNSELING**

Genetic counseling is strongly recommended before and after any genetic test, and documentation of informed consent is required, for an inherited cancer syndrome. This counseling should be performed by a specialist in cancer genetics. Genetic counseling usually covers many aspects, including discussion about the appropriateness of genetic testing, medical implications of a test result, the psychological risks and benefits of genetic test results, the risk of passing a mutation to children, etc.

The most sensitive test for hereditary ovarian cancer risk is gene sequence analysis in which the genes are “proofread” in their entirety.

It is important to note that professional societies do not recommend that children, even those with a family history suggestive of a harmful BRCA1 or BRCA2 mutation, undergo genetic testing for BRCA1 or BRCA2, because no risk-reduction strategies exist for children. After children with a family history suggestive of a harmful BRCA1 or BRCA2 mutation become adults, they may want to obtain genetic counseling about whether or not to undergoing genetic testing [56].
References


