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Review Article

# Genetic Susceptibility to Epithelial Ovarian and Endometrial Cancer

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**Abstract**

Multigene next generation sequencing (NGS) panel technology, massive parallel sequencing, can efficiently and economically analyze genes in 3 to 6 weeks. There are agreed criteria based on which to suspect hereditary ovarian and endometrial cancer and thus to make a referral to clinical genetic unit.

The geneticist interprets the genetic results and the information from pedigree. When a person is diagnosed with pathogenic variant (mutation) with genetic susceptibility to ovarian and endometrial cancer, counseling is provided on the associated cancer risk and appropriate monitoring is organized. Healthy family members with mutation can participate in recommended surveillance. Identifying carriers allows treatment and follow-up to reduce the morbidity and mortality for cancer patients and their healthy relatives.

This is a case report on gene test results in hereditary breast and ovarian cancer syndrome (HBOC) families who have ovarian cancer in southwestern Finland. And a review of genetic susceptibility to ovarian and endometrial cancer.

## INTRODUCTION

The amount of genetic counseling given due to a suspicion of hereditary breast and/or ovarian cancer has increased ably — in 15 years it has increased about fivefold in southwestern Finland (Department of Clinical Genetics in Turku University Hospital, Finland) (unpublished result). In Finland, a woman's risk of developing breast cancer during her life is approximately 13%, for ovarian cancer less than 2% and for uterine cancer the risk is approximately 2.5% (2012-2016) [1].

Currently approximately 20 genes are known, with scientific results to be strongly associated with hereditary epithelial ovarian and endometrial cancer [2,3]. Cancer risk is significantly increased in inherited epithelial ovarian and endometrial cancer when compared to the average population. *BRCA1* and *BRCA2* genes are associated with high risk for epithelial ovarian cancer [4]. Several other DNA repair genes, such as *BRIP1*, *RAD51C* and *RAD51D* have been identified as moderate risk of epithelial ovarian cancer genes [5]. Lynch syndrome genes are mismatch repair genes. Patients with Lynch syndrome are especially at risk of colorectal cancer and gynecological cancers — ovarian cancer is increased and uterus cancer is considerably increased [6,7]. Also, such novel genes as *POLE* and *POLD1* have been observed to be associated with endometrial cancer risk in uterus, but more scientific research are required for defining exact cancer risk [3].

### Identifying Hereditary Ovarian ja Endometrial Cancer

There are agreed criteria based on which to suspect hereditary ovarian and endometrial cancer and thus to make a referral to clinical genetic unit [8,9]. Suspicion of hereditary breast and ovarian cancer syndrome arises, when the patient has the following characteristics: an early age of onset compared to average cancer patient, specific type of histological pattern, breast and ovarian cancer in same patient and triple negative breast cancer (Table 1). By evaluating the family history of diagnosed cancer cases and diagnostic gene test results of the cancer patient, clinical geneticist can identify families of hereditary breast and ovarian cancer with high and moderate risk [10].

Internationally, it has been established that over 15% of ovarian cancer tumors have a mutation in *BRCA1* or BRCA2 genes [11-13]. However, in southwestern Finland the number is lower, only 9% (unpublished result). Also, in southwestern Finland in approximately half of these cases BRCA1 or BRCA2 mutation has been inherited (unpublished result).

Lynch syndrome is difficult to identify based on family records. The prevalence of genetic defects causing Lynch syndrome in the population is much higher than thought [14,15]. Therefore, screening is currently used which directly or indirectly measures microsatellite instability of the tumor [16]. However, if the result of this study is normal, family data still needs to be analyzed if [17], Amsterdam criteria (Table 2) are fulfilled [18].

**Table** 1: Factors suggesting inherited cancer syndrome [8,9].

| |
|---|
| Multiple close relatives with cancers of the syndrome (2 or more ovarian cancers in 1st or 2nd degree relatives) |
| Atypically young age of onset for cancer of the syndrome |
| Relative with two tumors of the syndrome (two examples below)<br>• Ovarian cancer and breast cancer<br>• Colon cancer and endometrial cancer in the uterus |
| Typical histological finding (e.g., rare subtype such as medullary breast cancer) or clinical picture (such as bilaterality or triple-negativity) |

| **Table 2**: Suspicion of intestine and uterine cancer [17]. |
|---|
| Typical tumors: especially colorectal cancer, endometrial cancer in uterine, epithelial ovarian cancer<br>3 cases in two generations<br>• 1 at under 50 years<br>More than 2 cancers on the same person<br>1 case under 40-45 years* |
| *PREMM risk analysis, Lynch syndrome prediction model from Dana-Farber Cancer Institute, can be used to define if there is more than 5 % probability the pathogenic variant in Lynch gene to be found, https://premm.dfci.harvard.edu/ |

It is possible that there exists only a single hereditary cancer syndrome case in the family due to de novo mutations (autosomal dominant) which means that the person's parents do not have the same mutation. There are hot spot regions in genes where mutation can easier develop during meiosis of germ cells. However, in BRCA1 and BRCA2 genes, de novo mutations are extremely rare as only a few reports are published. Autosomal recessive MUTYH-associated colorectal polyposis increases slightly for ovarian cancer [19].

The risk of hereditary breast and ovarian cancer is linked to some congenital multisystem syndromes, such as breast cancer in neurofibromatosis type 1 and breast and ovarian cancer in ataxia telangiectasia [20]. Appropriate follow-up care is provided as with hereditary cancer families. Identifying the families with increased risk for ovarian and endometrial cancer allows clinicians to improve the prognosis of persons with genetic cancer susceptibility.

## Basic Cancer Genetics

Current understanding is that approximately four to seven mutations in key driver genes is sufficient to cause cancer [21]. Normal genome regulation is impaired in hereditary and sporadic cancer [22]. Cancer susceptibility is caused by both inherited germline gene mutations and somatic gene mutations [23]. Cancer risk is also influenced by protective genes. Some individuals who inherited a cancer mutation will develop cancer in their lifetime.

Genetic susceptibility is a continuum. There are low-risk variants, medium-risk variants, and high-risk variants. Traditionally high-risk variants are those that are referred to as hereditary variants and predispose to so-called hereditary cancer. However, today we are also increasingly interested in finding out the variants of moderate risk from a cancer patient. In sporadic cases the inherited gene mutations cause low risk for cancer [24]. According to Vogelstein's research group, chance has a major impact in the development of cancer-causing mutations during DNA replication in normal, noncancerous stem cells [25-31].

## Gene test results in hereditary breast and ovarian cancer syndrome (HBOC) families who have ovarian cancer in southwestern Finland

In 2017, genetic panels were used in 17% of diagnostic studies in HBOC families in southwestern Finland. Other diagnostic test analyzed *BRCA1* and *BRCA2* genes. In 2019, multigene next generation sequencing was used in all screening studies to obtain a family diagnosis. The gene panel consists of 18 high and moderate risk genes (*ATM, BRCA1, BRCA2, BRIP1, CDH1, CHEK2, EPCAM, FANCM, MLH1, MSH2, MSH6, PALB2, PMS2, PTEN, RAD51C, RAD51D, STK11* and *TP53). For selected genes the syndromes related to them are described in Table 3*. In retrospective analysis there were 140 families with ovarian cancer, and 109 of them were HBOC families. The results are seen in Table 4.

The willingness to participate in prophylactic salpingo-oophorectomy was studied. Of the 20 healthy *BRCA1* and *BRCA2* carriers over 43 years of age 18 (90%) participated in prophylactic salpingo-oophorectomy. The results are seen in Table 5.

This study is a hospital quality research, which has been authorized and has valid ID. In the study analyzed data was from patients who had been treated at the hospital. As no new samples were required a separated ethics board permit was not required. The Turku Clinical Research Center provides services in the field

**Table 3**: Ovarian Cancer Risk on Different Types of Cancer Syndromes.

| | ***BRCA1/2*-associated hereditary breast and ovarian cancer** | **Lynch syndrome** | **Peutz- Jeghersin polypoosi** | **Li-Fraumeni syndrome** | ***PALB2*-associated hereditary ovarian cancer** | ***RAD51C/D*-associated hereditary ovarian cancer** |
|---|---|---|---|---|---|---|
| Typical tumors in addition to breast cancer | Breast cancer, ovarian cancer | Colorectal, endometrial in uterus or ovarian cancer | Mucocutaneous pigmentation, cancer in gastrointestinal tract, ovarian cancer, endometrial cancer in uterus, Sertoli cell testicular tumor | Brain tumor, sarcoma, leukemia | Pancreas cancer, ovarian cancer | Diffuse gastric cancer, lobular breast cancer |
| Lifetime risk of ovarian cancer | 10-45% [26] | 10-17% [7] | 20% [27,30] | slightly increased but not established [41,42] | ~3% [43] | 10-30% according to family history [31] |
| Gene | *BRCA1, BRCA2* | *MLH1, MSH2, MSH6, PMS2, EPCAM* | *STK11* | *TP53* | *PALB2* | *RAD51C/D* |

**Table** 4: Ovarian cancer families counseled in HBOC families in southwestern Finland.

| Gene | Ovarian cancer families with mutation positive result | Cancer families with pedigree of high breast ± ovarian cancer risk | In how many families pathogenic variant was identified in ovarian cancer patient |
|---|---|---|---|
| ***BRCA1*** | 33 | 31 | 33 |
| ***BRCA2*** | 27 | 24 | 27 |
| ***RAD51C*** | 1 | 1 | 1 |
| ***BRIP1*** | 1 | 1 | 1 |
| ***PALB2*** | 3 | 3 | 3 |
| ***CHEK2*** | 4 | 2 | 1 |
| ***FANCM*** | 2 | 2 | 2 |
| **No pathogenic variant identified** | 140 | 109 | NA |
| **Not analyzed** | 65 | 36 | NA |
| **Total** | | 209 | |

**Table 5:** Risk-reducing salpingo-oophorectomy (RRSO) in 20 healthy *BRCA1* and *BRCA2* carriers over 43 years in southwestern Finland.

| Procedure | Number of patients / total patients (percentage) |
|---|---|
| RRSO done | 18/20 (90%) |
| RRSO not done | 2/20 (10%) |

of health scientific research for researchers of the University of Turku and the Turku special responsibility area.

## Discussion on our results

Since 2019, next generation sequencing has been used in all cases to obtain a family diagnosis, where the criteria are met. Before that, the most important studies in HBOC families were to explore *BRCA1* and *BRCA2* genes. Table  shows that moderate ovarian cancer, such as *RAD51C* and *BRIP1*, risk families have been found as gene panels have been taken into use. As population frequency of moderate risk alleles is higher than in high-risk alleles and sequencing technology is developing, it is expected that moderate risk families will be identified in growing numbers in the future. In this study moderate breast cancer risk genes were observed in ovarian cancer families. *CHEK2* mutation should not be associated with ovarian cancer but they are associated with breast cancer [8]. *PALB2* mutations may slightly increase ovarian cancer risk. Previously, unknown or insufficient evidence have been found between *PALB2* and ovarian cancer risk [11]. Now, findings point to stronger association between *PALB2* and ovarian cancer risk [5,8]. We also found ovarian cancer in some *PALB2* families.

## Diagnostic gene testing with panels, family mutation testing and surveillance

The heredity assessment carried out by the clinical geneticist is based on the result of genetic research and the examination of pedigree. Diagnostic gene testing on cancer patients is carried out in the clinical genetic unit. For patients with gynecological cancer, diagnostic genetic testing can also be ordered by the treating oncologist or surgeon. There are established criteria for considering genetic testing in the case of a suspected hereditary cancer (Table 6) [32] — American Society of Clinical Oncology (ASCO) recommends genetic testing if there is a genetic test that is appropriate for the situation. Before testing individuals, informed consent should be requested after adequate information and counseling provided [33]. There are ethical practices for reporting a secondary finding: a secondary find is reported to the patient if the patient has given their consent [28].

The clinical geneticist interprets the results of gene test variants and patient's cancer risk due to inherited high risk and moderate risk variants. Currently, only part of the normal variation of the genome is known. This leads to some of the genome variants found to be so-called variant of unknown significance (VUS) is a change whose significance is currently unknown, and which cannot be classified as harmless (benign) or pathogenic, that explains susceptibility to cancer. When additional information becomes available, VUS classification may changes. Genetic variants are currently classified according to a five-level ACMG classification [29]. In counselling when talking about a mutation, a pathogenic variant is meant. A likely pathogenic variant is variant that most likely causes patient's cancer, probability is between 90% and 99%. The genotype-phenotype correlation is gaining more and more understanding through scientific research [4]. Clinical geneticist instructs follow-up (Table 7) [34-38].

The result of genetic testing provides information on the cancer risk for relatives. Healthy relatives at risk should have access to genetic counseling and predictive genetic testing after counseling if they desire (Council of Europe's The Convention on Human Rights and Biomedicine in Article 12, 1997). Almost always, the increased risk of cancer applies only to adults not to children. Clinical genetics units offer this service. The clinical geneticist provides the examining laboratory with reliable information about the family mutation and arranges the DNA sample of the family's index patient and that of the counselled relative, to obtain a reliable test result. Counseling before predictive genetic testing is nondirective and includes insight of

| **Table 6**: ASCO 2010 criteria for genetic testing. |
|---|
| Hereditary cancer is suspected<br>The result of the gene test should be adequately interpreted<br>Gene testing has one of the following benefits:<br>• Improves diagnosis<br>• Guides to the appropriate medical surveillance for the carriers of gene mutation<br>• Provides information about strategies for prevention in the carriers of gene mutation |
| The ASCO has provided guidance on when genetic testing for cancer families should be considered [32,33]. The following three conditions should be met. If the family mutation is found, the access for healthy relatives to genetic counseling should be arranged. |

| **Table 7**: How to improve prognosis in the carriers of hereditary gene mutation. |
|---|
| The aim is to improve the early detection of cancer<br>Occurrence can be prevented by removing the precursors identified in the monitoring<br>• In the carriers of Lynch syndrome mutation, removal of colon adenomas decreases the risk of colon cancer<br>• Occurrence can be prevented by surgical procedures [34]<br>• In the carriers of Lynch syndrome mutation, removal of uterus by menopause decreases the risk of endometrial<br>• carcinoma in uterus [35]<br>• The risk of ovarian and breast cancer can be greatly reduced by salpingo-oophorectomy [36]<br>• Sometimes genetic information can guide the choice of medication or other treatment<br>• Regular aspirin reduces the risk for colorectal cancer in Lynch syndrome families [37,38]<br>• In the carriers of p53 mutation, radiation therapy and X-ray imaging will be avoided |

the patient and the family. In counseling, the patient and family receive not only information but also support.

Participation in predictive genetic testing has been studied in the Finnish Lynch syndrome families, which are at high risk for colorectal cancer and endometrial carcinoma in the uterus. Approximately 80% of the members of the family participate in genetic counseling, and 95% of them performed genetic prediction [34]. The main reasons for participating in predictive genetic testing are the potential for cancer detection surveillance, improved treatment options in many Lynch syndrome cancer types, and improved cancer prognosis.

## CONCLUSION

Genetic susceptibility is a continuum: there are low-risk variants, medium-risk variants and high-risk variants. High-risk variants are those that are referred to as hereditary variants. Nowadays, we are also increasingly interested in identifying moderate risk variants from cancer patient [5]. Gene associated cancer risks have been explored in large prospective studies [6,7]. However, mutation profile in local geographical areas is still required for efficient care.

Currently, scientific studies are examining the possibility to use polygenic risk scores to predict the risk of contralateral breast cancer of a breast cancer patient and also the risk for 1st degree relatives [39]. Poly ADP–ribose polymerase (PARP) inhibitors can induce synthetic lethality in mutated *BRCA1/2* tumor cells and are associated with improved progression-free survival as targeted therapy in *BRCA*-mutated (germline and/or somatic) cancer patients in high-grade epithelial ovarian, fallopian tube and peritoneal cancer [40]. Additionally, reduced survival has been observed among patients who has *FANCM* mutation and has not received radiotherapy but not among those patients with *FANCM* mutation whose breast cancer has been treated with radiotherapy [40]. Increased knowledge of cancer genetics is likely to enable the development of targeted drug and other therapies.

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