

## Familial Ovarian Cancer

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### 1. Introduction

Ovarian cancer represents the fifth most significant cause of cancer-related death for women and is the most frequent cause of death from gynecological neoplasia in the Western world. The incidence of ovarian cancer in the United Kingdom (U.K.) is over 5000 new cases every year, accounting for 4275 deaths per year (*1*). The lifetime risk of ovarian cancer for women in the U.K. is approximately 1 in 80. Most (80–90%) ovarian tumors are epithelial in origin and arise from the coelomic epithelium. The remainder arise from germ-cell or sex cord/stromal cells. A hereditary component in the latter group is rare, but includes granulosa-cell tumors in patients with Peutz–Jeghers syndrome (*2*) and autosomal dominant inheritance of small-cell carcinoma of the ovary (*3,4*). Because of their limited contribution to familial ovarian cancer, these nonepithelial tumors will not be considered further in this chapter.

Epithelial ovarian cancer has the highest case fatality rate of all gynecological malignancies, and an overall five-year survival rate of only 30%. This poor prognosis is largely because of the fact that 75% of cases present with extra-ovarian disease, which in turn, reflects the absence of symptoms in early-stage disease. Advanced stage ovarian cancer (stage IV) has a five-year survival rate of approximately 10% whereas early stage (stage I) ovarian cancer has a five-year survival rate of at least 85%. These figures suggest that there may be a survival benefit from the detection of ovarian cancer at an early stage. To be able to develop appropriate screening strategies for ovarian cancer, there is a need to understand the processes of carcinogenesis and tumor progression. For ovarian cancer, there are no recognizable precancerous lesions that could be targeted for screening purposes; this contrasts with other types of cancer (e.g., colorectal or cervical cancer) where many of the critical histological alterations in the development of cancer have been identified. In these cancer types, the precancerous lesions have subsequently been linked to specific molecular genetic events (*5*). Because very little is still known about the morphological and molecular genetic steps involved in initiation and progression of epithelial ovarian cancer, detection and treatment of premalignant lesions is not yet feasible.

Three large randomized controlled trials of screening for ovarian cancer in the general population are currently underway. Because of the potential survival benefit from

the detection and treatment of early-stage disease, these studies aim to detect early-stage cancer, rather than premalignant disease. However, none of the current studies have yet reached the stage at which information about the impact on mortality is available. To optimize the efficacy of screening, it may be desirable to target women at the highest risk of developing the disease. Most of the established risk factors for ovarian cancer are associated with the theory of “incessant ovulation” (6,7) and include nulliparity, an increased number of ovulatory cycles, early menarche (age at first menstruation), and late menopause (age of last menstruation). Oral contraceptive use and multiparity as well as breast feeding reduce the risk of ovarian cancer. It has long been recognized, however, that the most important risk factor for ovarian cancer besides age, is a positive family history for the disease. In recent years, two genes associated with a genetic predisposition for breast and ovarian cancer, the *BRCA1* and *BRCA2* genes, have been identified. This has led to a growing awareness among the public as well as the medical profession that cancer may be hereditary and the demand for risk counseling and molecular testing has increased dramatically. This chapter aims to provide an integrated overview of both the clinical and molecular genetic background of familial and hereditary ovarian cancer.

## 2. Familial and Hereditary Contribution to the Ovarian Cancer Burden

As ovarian cancer affects approximately 1% of women some families will have a history of ovarian cancer in two or more family members or in combination with a common cancer diagnosed at a young age, just by chance. About 15% of all ovarian cancer patients report a positive family history for the disease and can be included in a working definition of “familial ovarian cancer.” Such examples of familial ovarian cancer could be explained by chance, common lifestyle, or exposure to carcinogenic factors or a shared genetic susceptibility. However, an estimated 5–10% of all ovarian cancer cases are thought to be the result of an autosomal-dominant susceptibility factor with high penetrance. These cases can be defined as “hereditary ovarian cancer.”

## 3. Clinical Diagnosis

The initial evidence for a hereditary component in ovarian cancer was derived from three observations. First, a family history of ovarian cancer was found to confer the greatest risk of all known factors for developing the disease (8,9). This effect is especially strong in families with more than one relative affected. Analysis of population-based series of ovarian cancer cases has shown that the risk of ovarian cancer in a woman who has a first-degree relative (mother or sister) with the disease is 1 in 30 by the age of 70. This risk is around one in four when two first-degree relatives are affected (10,11). Second, population-based epidemiological studies have shown that there is a significant excess of specific types of cancer in the relatives of ovarian cancer patients. These include additional ovarian cancer cases, breast cancer, colorectal, and stomach cancer (12). Finally, many case reports have identified families with multiple cases of ovarian cancer. The first of these describes ovarian cancer in twins (13). Others have described families with multiple cases of ovarian cancer, often in combination with other types of cancer (14). The occurrence of ovarian cancer in these families is best explained by an autosomal-dominant inheritance factor.

### 3.1. Clinical Syndromes

In families where there is insufficient evidence to diagnose autosomal-dominant disease, ovarian cancer can occur alone or in combination with other types of cancer. These familial cancers are to be distinguished from families where autosomal-dominant inheritance of ovarian cancer is likely. In the latter families, epidemiological studies have provided evidence for three distinct clinical, autosomal-dominant cancer syndromes.

1. Hereditary breast-ovarian cancer (HBOC). Families with a pattern of autosomal-dominant inheritance of ovarian and (usually early-onset) breast cancer.
2. Hereditary ovarian cancer (HOC). Families with clear autosomal-dominant inheritance of ovarian cancer, but without apparent excess of breast cancer.
3. Hereditary nonpolyposis colorectal cancer (HNPCC). Families with an autosomal-dominant pattern of early-onset colorectal cancer often in combination with endometrial cancer and sometimes ovarian cancer.

## 4. Molecular Genetic Diagnosis

The final proof that a genetic predisposition is responsible for familial clustering of a disease was initiated by extensive genetic linkage analysis of several large families. Hall et al. (15) identified a susceptibility locus on chromosome 17q21 in several families with autosomal-dominant breast cancer. Narod et al. (16) confirmed linkage to the same marker in breast-ovarian cancer families. The putative gene was named *BRCA1* (BReast CAncer1). Subsequent analyses showed this gene to be responsible for over 80% of families with cases of breast and ovarian cancer or ovarian cancer alone (17). The discovery of a candidate gene by Miki et al. (18) was confirmed by several studies describing the segregation of inactivating germline mutations in this gene with the breast and ovarian cancer cases in these families. In accordance with the notion that the *BRCA1* gene acts as a tumor suppressor gene, allelic deletions affecting the 17q21 locus have invariably been shown to involve the wild-type allele (19).

### 4.1. BRCA1

The *BRCA1* gene consists of 22 coding exons distributed over 100 kb of genomic DNA. It has 5592 bp of coding sequence and encodes a protein of 1863 amino acids. To date, more than 300 distinct mutations have been described and scattered throughout the gene. Although there are some well-defined founder mutations (20,21), there are no specific hot-spots in the gene and only a minority of mutations are recurrent. Approximately 80% of all mutations are nonsense or frameshift mutations causing a truncation of the protein. Some have suggested a relation between the position of the mutation and penetrance as well as tissue specificity. Gayther et al. (22) found a significant correlation between the localization of the mutation in the gene and the ratio of breast and ovarian cancer cases within a family. They found that mutations on the three prime third of the gene conveyed a lower risk of ovarian cancer. Apart from this study, genotype-phenotype correlations within *BRCA1* have not been confirmed. Another possibility is that environmental circumstances and/or modifier genes may influence the penetrance of a specific type of cancer in germline mutation carriers. Phelan et al. (23) suggested that the risk of ovarian cancer may be increased in women with a *BRCA1*

mutation who carried one of two rare variants of the *HRAS* variable number of tandem repeats (VNTRs) compared to women with the common allele.

It has become clear that mutations in the *BRCA1* gene are responsible for the majority of HBOC and HOC families and, therefore, the clinical distinction between these two syndromes may have become obsolete. Initially it was anticipated that somatic mutations in *BRCA1* would be as important in sporadic ovarian cancer as germline mutations are in hereditary cases. This seemed likely as loss of heterozygosity analysis of unselected ovarian cancers has constantly revealed a very high frequency of LOH on chromosome 17q (24,25). However, thus far only a few somatic mutations have been detected in sporadic ovarian cancer cases (26). The explanation for the high frequency of LOH of the 17q locus in these cases remains unclear and may be because of another tumor suppressor gene in the vicinity of *BRCA1* as suggested by the LOH-results of Jacobs et al. (27).

## 4.2. BRCA2

Localization and cloning of the *BRCA2* gene followed soon after the identification of *BRCA1*. In 1994, Wooster et al. (28) localized the gene at chromosome 13q12–13. Only months later, the same group identified the gene by showing segregation of inactivating mutations of mostly breast cancer in families linked with the 13q locus (29). The *BRCA2* gene consists of 26 coding exons distributed over approximately 70 kb of genomic DNA. It has 10,254 bp of coding sequence and encodes a 3418 amino acid protein which has little homology to previously identified proteins (30). To date, some 100 distinct mutations have been described and as is the case for *BRCA1* these are scattered throughout the coding sequence and apart from several distinct founder mutations (31,32) there are no specific hot-spots. The most frequent type of *BRCA2* mutations are frameshifts, most commonly deletions. It appears that missense mutations are rarer than in *BRCA1*. The contribution of *BRCA2* to hereditary breast cancer (HBC) appears to be similar to the contribution of *BRCA1* whereas only a minority of cases of HBOC and HOC are caused by *BRCA2* germline mutations. Although the overall penetrance for ovarian cancer in *BRCA2* germline mutation carriers is estimated at approximately 25% (17), Gayther et al. (33) found evidence for an “ovarian cancer cluster-region” in exon 11. Mutations in this OCCR were suggested to confer a higher risk of ovarian cancer. To a lesser extent than is the case for *BRCA1*, LOH at the *BRCA2* locus is frequent in sporadic ovarian cancer (34) and somatic mutations of *BRCA2* are rare in ovarian cancer.

## 4.3. Function of BRCA1 and BRCA2

The 7.8 kb mRNA *BRCA1*-transcript is expressed most abundantly in the testis and thymus and at lower levels in the breast and ovary. The mRNA *BRCA2*-transcript shows a similar tissue-specific expression (30,35). Although *BRCA1* and *BRCA2* are unrelated at the sequence level, there are some intriguing similarities. Both have a large exon 11, which contains more than half of the coding sequence. In both genes, translation site starts at codon 2 and both are relatively A-T rich. Defining the biochemical and biological functions that are responsible for tumorigenesis in large genes such as *BRCA1* and *BRCA2* has proven to be difficult. Both genes probably have several functional domains. The presence of a “zinc-finger” motif suggests a role as a transcription factor for the *BRCA1* protein. *BRCA2* has homology with known transcription factors

(36). Similar motifs have been found in genes directly controlling cellular proliferation and in that respect it is important that *BRCA1* has been found to inhibit cell growth (37). The similarity between *BRCA1* and *BRCA2* also includes their ability to bind and complex with Rad51, a protein involved in the repair of double-strand DNA breaks (38,39). For both *BRCA1* and *BRCA2*, a similar “granin” motif has been described, suggesting that the proteins are secreted in secretory vesicles (40). The localization of the *BRCA1* protein, however, is unclear, conflicting reports have localized the protein in the nucleus as well as the cytoplasm (41,42). Explaining the function of both *BRCA1* and *BRCA2* in tumorigenesis remains a major challenge and will be the subject of research activity for some time.

#### 4.4. *BRCA1 and BRCA2 Mutation Testing*

The risk of a mutation and the penetrance of this mutation determine an individual's risk of (hereditary) cancer. The level of cancer-risk at which to offer a woman testing for germline mutations in *BRCA1* or *BRCA2* is arbitrary and the decision of whether or not a test should be considered is also dependent on the purpose it serves for patients or healthy family members.

The chance that cancer in a given family is because of a *BRCA*-germline mutation can be estimated from data collected by the Breast Cancer Linkage Consortium (17). In summary, the risk of detecting a mutation increases with the following: a) an increasing number of affected relatives; b) a young age at diagnosis; and c) occurrence of related cancers in successive generations.

Furthermore, the chance of detecting a *BRCA1* mutation in a given family increases when ovarian cancer is frequent, when patients with both breast and ovarian cancer are present, and when bilateral breast cancer cases occur. The risk of a *BRCA2* mutation increases when male breast cancer occurs in a family. In specific populations, mutations may also be detected in far less remarkable families especially in populations with a high population frequency of founder mutations, such as the Ashkenazi Jewish population. In this population, up to 39% of ovarian cancer patients with a minimal or negative family history have been found to be caused by *BRCA1* or *BRCA2* germline mutations (31).

DNA testing for cancer predisposition may serve several purposes. Especially for breast cancer patients, the treatment modality and follow-up strategies may be modified if the disease is resulting from a genetic predisposition. For ovarian cancer, there is currently no evidence that treatment should differ if the disease is hereditary in nature. Healthy carriers of predisposing mutations may benefit from screening or preventative surgery. The clearest advantage of testing is obtained in at-risk family members who test negative after a mutation has been identified in the family. For this group preventative measures are no longer indicated. Finally, patients and at-risk relatives may wish to be tested on behalf of their children.

Nondirective counseling and education based on prior risk assessment is aimed at reaching a decision whether or not an individual would like to pursue genetic testing. For the initial mutation testing, the cooperation and consent of live affected relatives will usually be required. It is important to test all available affected family members because coincidental cases of either breast or ovarian cancer (phenocopies) may occur. When a mutation is identified in a family, carrier status for individual unaffected fam-

ily members can be determined. When a mutation cannot be found, the false–negative rate of the test should be considered. A large variety of methods is currently available for the detection of mutations. There is no one technique that is ideally suited to a complete analysis of *BRCA1* and/or *BRCA2*. Some techniques are simple to perform, but not very sensitive whereas others may be very sensitive but laborious and, therefore, usually expensive. The most commonly used techniques include:

- Direct (semiautomated) sequencing (DS)  
Generally considered the gold standard for mutation detection because of its high sensitivity. Disadvantages are the time-consuming and laborious procedures involved, although the availability of semiautomated, fluorescent sequencing systems has increased the feasibility of this method for large-scale (clinical) use.
- Allele-Specific Oligonucleotide Analysis (ASO)
- Single-Strand Conformation Polymorphism Analysis (SSCP/SSCA) and Heteroduplex Analysis (HA)  
Both techniques are easy to perform and relatively quick. Compared to DS, the sensitivity is much lower at a reputed 60–80%.
- Conformational Sensitive Gel Electrophoresis (CSGE)  
This method has an increased sensitivity compared to HA and SSCP, but is more labor intensive.
- (Constant) Denaturing Gradient Gel Electrophoresis (DGGE/CDGE)  
This techniques, which is based on the melting behavior of the DNA double helix is more sensitive than SSCP, however, the technique only detects differences between both alleles, therefore additional techniques are required to identify the precise nature of the mutation. Another disadvantage of all techniques mentioned thus far is that it may be difficult to distinguish between benign polymorphisms and pathogenic mutations. This problem is overcome by the
- Protein Truncation Test (PTT)  
This method detects nonsense and frameshift mutations that result in a stop codon by visualizing a truncated protein in an in vitro transcription–translation assay.
- Southern Analysis (for genomic deletions)  
Recently, specific founder mutations have been identified that consist of the loss of large fragments of coding sequence. Such genomic alterations can be detected by southern analysis in specific populations, which have a high-expected frequency of such alterations.

Detailed, frequently updated protocols for each of the aforementioned techniques are available from the Breast Cancer Information Core database @[http://www.nhgri.nih.gov/Intramural\\_research/Lab\\_transfer/Bic/](http://www.nhgri.nih.gov/Intramural_research/Lab_transfer/Bic/)

#### **4.5. HNPCC-Related Ovarian Cancer**

Hereditary nonpolyposis colorectal cancer (HNPCC) is characterized by the autosomal dominant inheritance of early onset colorectal cancer, without the multiple (usually >100) adenomas that constitute familial adenomatous polyposis (FAP). Endometrial cancer is often seen in HNPCC families and should be considered part of the clinical syndrome. Other cancers, including ovarian cancer are encountered in HNPCC families, but are infrequent. Germline mutations in one of five mismatch repair genes are responsible for the syndrome. *hMSH2* (chromosome 2p), *hMLH1* (chromosome 3p), *hPMS1* (chromosome 2q), *hPMS2* (chromosome 7p), and *hMSH6* (chromosome 2p) are all part of a family of genes involved in the repair of DNA-



replication errors. Tumors arising in patients with germline mutations in one of these genes are in the vast majority of cases genetically unstable and have an RER (replication error) phenotype, which can most easily be detected by studying somatic length alterations in simple nucleotide repeat sequences. Although mutations in all five genes have been detected in HNPCC-related colorectal cancers, 90% of mutations occur in either the *hMSH2* or *hMLH1* gene. Mutation detection of these genes is particularly arduous because they, too, are large—2.2 to 2.8 kb of coding sequence—and as for *BRCA1* and *BRCA2* mutations, are not confined to specific hot spots. The contribution of germline mutations in one of these five mismatch-repair (*MMR*) genes to the total burden of hereditary ovarian cancer is limited, as the penetrance for ovarian cancer is low at approximately 5%.

## 5. Are There Clinicopathological Differences Between Hereditary and Sporadic Ovarian Cancer?

Because family history of ovarian cancer is not a definitive indicator of an underlying germline mutation, other characteristics of ovarian cancer patients have been suggested to be indicative of hereditary disease. In contrast with HNPCC-related cancers of which the vast majority exhibits the *RER*-phenotype, there are no definitive criteria that allow distinction between hereditary and sporadic ovarian cancer. Differences in histopathological characteristics and clinical presentation, as well as prognosis have, however, been reported. The mean age of hereditary ovarian cancer appears to be on average some eight years younger than in sporadic disease (43–45). Hereditary ovarian cancers are more often of the serous type and are more frequently advanced stage with, according to some authors, higher grade than sporadic ovarian cancer. It has been suggested that despite these unfavorable prognostic factors, hereditary ovarian cancer patients have a better prognosis compared to age and stage-matched controls (44). Survival analyses of patients with hereditary cancer are prone to selection bias and other studies could not confirm this favorable prognosis for hereditary ovarian cancer patients (46,47).

Apart from clinical differences, there are intriguing differences between hereditary and sporadic ovarian cancer at the molecular level. Somatic mutations in *BRCA1* and *BRCA2* are infrequent in sporadic ovarian cancer. Knowledge of the somatic molecular events involved in the pathway of carcinogenesis in both hereditary and sporadic ovarian cancer is emerging. The *p53* tumor suppressor gene has been studied in relation to *BRCA*-associated ovarian cancer and was found to play an important, but probably not essential role (48,49). Limited analysis of *HER-2/neu*, *K-ras*, *C-MYC*, and *AKT2* suggests that these genes may be less important in hereditary than in sporadic ovarian cancer (49). Although a number of somatic genetic events have been identified, their role in tumor development and progression in hereditary ovarian cancer remains largely unknown.

## 6. Integration of Clinical and Molecular Information

Mutation detection in *BRCA1* and *BRCA2* has until recently been performed in a research setting and been restricted to families that either showed linkage to the *BRCA1* or *BRCA2* locus or had a clear pattern of autosomal dominant inheritance. From these families, the lifetime risks (LTR) of breast and ovarian cancer have been estimated

(17,50,51). For *BRCA1*, the LTR of either breast or ovarian cancer was calculated at 95% at age 70. The LTR of breast cancer at 85% and of ovarian cancer 40–60%. For *BRCA2*, the risk of breast cancer is similar to the risk in *BRCA1* mutation carriers whereas the risk of ovarian cancer is lower (approximately 25%). It is likely that these estimates are artificially high because of ascertainment bias in which families with high-penetrant mutations have been preferentially included and, especially for *BRCA2*, are based on the analysis of a relatively small number of families. Now that germline mutation detection for *BRCA1* and *BRCA2* is available for individual patients several studies have been performed to identify mutations in unselected ovarian cancer cases (not based on family history). Mutations in *BRCA1* and/or *BRCA2* are consistently detected in approximately 5% of such cases (52,53). There is evidence of varying penetrance between families. Germline mutations have been detected in families with a weak or moderate history of breast or ovarian cancer and even in apparently sporadic cases. This particularly seems to be the case for *BRCA2* germline mutations. Translation of molecular test results to clinical management and individual risk estimation is therefore difficult outside families with clinically recognisable autosomal dominant disease.

## **7. Multidisciplinary Approach to Ovarian Cancer Families**

The recent progress of research into the molecular basis of cancer in general and hereditary cancer in particular, has provided more insight into the aetiology of hereditary cancer. At the same time, publicity about research progress has raised the awareness in the medical profession and lay public that cancer may be hereditary in nature. In the case of ovarian cancer, a disease with a dismal prognosis, many women with a positive family history have come forward to request risk assessment and advice regarding screening and prevention. To provide such families with adequate advice requires expertise in the fields of genetics, screening, oncology, and surgery and, consequently, requires the input of several clinical specialities. Furthermore, genetic testing may have far-reaching emotional and social implications and require psychological support (54). A multidisciplinary approach using protocols established by clinical geneticists for other inherited disorders (55) may be beneficial for the management of such families.

### **7.1. Pedigree Analysis**

Risk assessment is still primarily based on the family history. An extensive pedigree analysis is required to establish whether an autosomal dominant pattern of inherited susceptibility is likely to be present in a family. Confirmation of reported diagnoses by medical reports, death certificates, or histopathological reevaluation is essential because, especially for gynaecological malignancies, the family history data alone may be unreliable because of recall bias (56).

### **7.2. Genetic Testing**

To initiate genetic testing, the cooperation of a live affected relative is usually required. Only when a pathogenic mutation has been detected in an affected family member is testing of healthy at-risk individuals informative. The implications of *BRCA1* and *BRCA2* mutation testing and the available techniques are discussed in Subheading 4.4.



### 7.3. Risk Assessment

Analysis of pedigree data in combination with the results of genetic testing should lead to the most accurate individual risk assessment. Often, a level of uncertainty will remain and families will need education on how to interpret their risk to be able to take decisions regarding screening and prevention in their own hands. Psychological support throughout this whole process is essential.

### 7.4. Screening and Prevention

The major aim of individual risk assessment for ovarian cancer is to identify women at the highest risk of developing the disease in the hope that mortality can be reduced for these women by screening and/or prevention. There is currently no evidence about the impact of screening for ovarian cancer on mortality. Many of the problems that occur in screening for the general population (57) may be overcome by directing efforts at a high-risk population, but prospective studies are still required to determine the value of specific screening strategies. The most commonly used screening strategy, which is currently the subject of a large U.K.-based prospective study, involves annual transvaginal ultrasonography and serum CA 125 from age 35 (or 5 yr before the youngest cases of ovarian cancer was diagnosed in the family, whichever comes first). Owing to the lack of evidence that screening for ovarian cancer and the subsequent early intervention reduces mortality and the absence of a detectable premalignant stage, some women at the highest level of risk may opt for a prophylactic oophorectomy to prevent ovarian cancer. Unfortunately, even this procedure may not entirely prevent “ovarian” cancer because several studies have reported the occurrence of intraperitoneal carcinomatosis, resembling primary ovarian cancer (58–60) and women should therefore be counseled that prophylactic oophorectomy does not provide absolute protection.

Use of the oral contraceptive pill has consistently been shown to reduce the risk of ovarian cancer in the general population. This risk reduction may be as high as 50%. A recent case-control study by Narod et al. (61) suggested that this protective effect also applies to women with hereditary ovarian cancer. There is some concern that use of oral contraceptives to prevent ovarian cancer or the use of hormonal replacement therapy after prophylactic oophorectomy may increase the already high risk of breast cancer in these women. Further research is needed to address the issue of whether or not these risks outweigh their obvious benefits.

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