# Familial and genetic cancers in gynaecology

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## Abstract

The diagnosis of inherited cancer-susceptibility syndromes can enable identification of individuals at increased risk for early-onset cancer. The treatment and prognosis of patients diagnosed with malignancy due to a germ-line mutation may differ from the standard therapy.

Hereditary breast and ovarian cancer (HBOC) syndrome and hereditary non-polyposis colon cancer (HNPCC) syndrome are the two most important syndromes responsible for inherited cancers in gynaecology. Genetic testing is available for both these syndromes. BRCA testing is affordable and easy in South Africa for patients with Afrikaner or Ashkenazi ancestry, as the mutation patterns are known.

Women's health care clinicians must be well informed about these cancer syndromes. Families with a potential genetic mutation should be identified and referred for investigation or counselled for genetic testing. Counselling pre-requisites include complete information about the disease, genetic tests, estimated cancer risk and cancer risk management.

Individualised cancer risk can be estimated based on genetic and/or clinical information. Breast, endometrial and ovarian cancers are potentially either preventable or qualify for early detection through advanced screening techniques. Surgical and hormonal prevention is effective, but has important economic, psychosocial and clinical implications. Early detection techniques offer less protection and a smaller improvement in morbidity and mortality. Screening is also a costly option but may be more acceptable to some patients.

In colon cancer syndromes, the risk for endometrial and ovarian cancer is much elevated. These risks should be recognised and addressed, as these diseases are easy to prevent.

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## Introduction

The diagnosis of an inherited cancer-susceptibility syndrome in a family can enable the clinician to identify individuals at an increased risk of developing life-threatening malignant disease. In addition, the optimal management and prognosis of diagnosed malignant disease may be different in an individual known to harbour a mutation in one of the genes that causes these syndromes. However, the recognition, diagnosis and management of families and individuals with these syndromes are complicated. Detailed knowledge and understanding of the fields of clinical genetics, oncology, gynaecology and psychology are essential. Involved clinicians should have knowledge and experience in counselling, cancer risk evaluation, cancer prevention and techniques for early detection of disease. For this reason, management by a multidisciplinary team skilled in all these aspects is highly recommended.[1]

The recognition and accurate diagnosis of inherited susceptibility also depend on the availability of reliable and affordable genetic tests. Identification and cloning of the culprit gene is usually followed by a description of common mutations, which may be specific for a population group or not. Knowledge of the mutation patterns for the group makes the test much more affordable, especially when a large gene or more than one gene is concerned. Communication with the scientific geneticist and laboratory can help clinicians to interpret test results, especially when limited genetic testing renders a negative result.

Two important syndromes are responsible for the majority of inherited cancers in the gynaecologic organs. These are:

- Hereditary breast and ovarian cancer (HBOC) syndrome, including site-specific ovarian cancer syndrome (SSOC); and

- Hereditary non-polyposis colon cancer (HNPCC) syndrome.

For both these syndromes, the genes involved and the recognition and testing of patients and family members will be reviewed in this article. In addition, an update of the currently suggested optimal management of these individuals will be presented. Recently published South African data will be mentioned and interpreted in terms of implications for clinical practice. [2,3]

The fields of both clinical genetics and cancer prevention are rapidly evolving. The outcome of these women is significantly determined by the way in which they are counselled and managed. Physician belief and knowledge influence advice and patient care and thus all involved have the responsibility to constantly keep updated.

## Hereditary breast and ovarian cancer syndrome (HBOC)

Germ-line mutations in the BRCA1 (chromosome 17p) and BRCA2 (chromosome 13q) genes are found in the large majority of families with a pattern of inherited cancer of the breast and/or ovaries.

Both these genes encode for tumour suppressor proteins and more than 1200 different mutations have been described in each of these large genes.

**Table I**: Markers of families with HBOC syndrome

| One or more of the following in the family history |
|---|
| • Multiple cases of breast and/or ovarian cancer |
| • Early or premenopausal diagnosis of breast cancer |
| • Bilateral breast cancer |
| • Any single individual with both these diseases |
| • Male breast cancer |

### *Recognition and risk assessment*

While gynaecologists are not part of the primary breast cancer treatment team (in South Africa), the diagnosis and prevention of both breast and ovarian cancer fall within the domain of every gynaecologist. Estimation of a woman's risk for breast and gynaecological cancer forms a part of preventative care as much as cytological screening and cardiovascular and osteoporosis risk management. Cancer risk estimates should be based on genetic as well as epidemiologic risk factors.

Basic questions about the family history of related cancer will detect the majority of families who harbour a mutation in either the BRCA1 or BRCA2 genes. Indeed, family history also remains the strongest independent breast cancer risk factor available and is the backbone of risk calculation to estimate the appropriateness and cost effectiveness of gene testing. The diagnosis of ovarian cancer is a stronger predictor of mutation in the family than breast cancer. Some authorities now recommend that BRCA mutation analysis should be offered to each woman diagnosed with ovarian cancer, as this may be an effective way to diagnose inheritance and, therefore, to detect healthy carriers.[4]

Genetic risk can also be calculated with family history alone, using the Claus model.[5] The Gail model takes the epidemiological risk factors into account as well.[6] The Claus model allows for an estimated lifetime breast cancer risk as high as 45%, based on the assumption that the family has a mutation. Inheritance of the assumed mutation in the family can be determined only by specific gene mutational analysis in the individual.

Family history can be used as a tool to calculate or estimate the chance that gene testing will be positive. Tables are available in the literature and on the internet that can be used to evaluate the cost effectiveness of genetic testing in an individual.

Generally, these models do not have a high discriminatory accuracy and genetic testing far outperforms any other risk estimate.[7]

### *Genetic diagnosis*

It is recommended that all individuals with an estimated 20% or higher chance of a mutation should undergo gene testing, while genetic analysis may be helpful for any women with a chance above 5% to have a mutation.

**Table II**: Aims of genetic counselling

| |
|---|
| **Risk assessment** |
| • Empiric risk factors |
| • Genetic risk |
| **Behavioural and clinical management options** |
| • Decrease cancer risk |
| • Ensure early cancer detection |
| **Psychological assessement** |
| • Evaluation |
| • Support |

It is most useful and cost effective to begin testing in a family with an individual who has a diagnosis of cancer. Once the mutation in the family is identified, further testing is easy and inexpensive, as it is limited to the single mutation. "Predictive testing" is offered to family members without a personal cancer history.

Genetic mutation analysis can be based on one of two models:

- In certain population groups, so-called "founder mutations" are present. These groups are typically characterised by a small ancestral group and BRCA mutations occur much more frequently. In such groups, analysis may be limited to the **frequently occurring mutations**, which is much more cost effective.

- In individuals or populations where "founder mutations" are not known to occur, the only useful testing is to do **full gene screening** of both BRCA1 and BRCA2 genes.

In South Africa, founder mutations are known for Ashkenazi Jews (incidence of about 1 in 40 to 1 in 100) and Afrikaners (frequency unknown). In all other population groups, or in individuals of mixed ancestry, full gene screening should be done. The founder mutations for both these groups are published and known to the genetic fraternity. Confirming an inherited BRCA mutation in any female individual is estimated to translate into a lifetime breast cancer risk of 70 – 80% and an ovarian cancer risk of about 20 – 50%. In families reporting a high frequency of both diseases, it is thought that the risk is higher, and risk will be considerable even at an earlier age. South African data[2] suggest a similar cancer risk profile of non-South African mutation carriers, with an increase in stomach cancer in BRCA2 mutation carriers vs. the general population.

Genetic diagnosis is only ethical and useful if combined with counselling and implementation of risk-management strategies. The patient should be fully informed about the condition, the test and the management of the inherited risk. Prerequisites for genetic testing, as developed by clinical genetics specialists, were reworked and are listed in Table 3.

**Table III**: Counselling prerequisites before genetic testing

| |
|---|
| **The condition**<br>• Penetrance and clinical presentation of the condition<br>• Patterns of inheritance and implications for family members and children<br>• Alternative to genetic testing for risk estimation<br>• Risk for mutation based on family history and available information |
| **The test**<br>• Information on the specific test and laboratory<br>• Implications of possible positive and negative results<br>• Possibility of a non-informative result<br>• Technical accuracy of the test<br>• Costs involved in testing and counselling |
| **The management of inherited risk**<br>• Possibilities and limitations of surveillance and preventative options<br>• Risk of psychological distress and insurance discrimination<br>• Confidentiality issues |

### *Risk reduction strategies*

Cancer risk management must be highly individualised and based on a consensus between a well-informed physician (or a physician-led team) and a motivated and equally well-informed patient. Without a personalised, clear plan, the detection and quantification of a significantly elevated cancer risk leads to anxiety without clinical benefit.

### *Breast cancer risk reduction*

Risk reduction includes methods to:
- Improve survival rate
- Reduce the risk of developing cancer

*Early diagnosis*
Current surveillance guidelines for women known to have a disease-causing BRCA mutation include the following, from 25 years or earlier:
- Clinical breast examination every 6 months; plus
- Annual mammography; plus
- Annual MRI screening

The role of breast ultrasound is probably for diagnostic purposes rather than for screening and the value and sensitivity of breast self-examination is seriously doubted. A major problem with breast MRI is the high incidence of a false positive test result.[8]

It is emphasised again that these diagnostic strategies will not impact on the incidence of the disease or the chance of getting breast cancer, but aims to improve survival by down-staging. The impact of any or all of these measures on survival is difficult to estimate or model.

*Prevention of second primary disease*
While lobectomy and breast conservation with irradiation of the conserved breast tissue is effective local treatment for early breast cancer, it is debatable whether this is an optimal strategy for treatment of a BRCA mutation carrier.

In spite of the rigorous surveillance that women undergo after breast cancer diagnosis, the second primary breast cancer (in the same breast or in the contralateral one) is not always diagnosed in an early and thus curable stage. Many authors even report a poorer survival of the second breast malignancy. The reported incidence of a contralateral second primary tumour in mutation carriers is between 20% and 30% within the first 10 years of diagnosis,[9] often in spite of tamoxifen therapy. In addition, at the time of prophylactic mastectomy about 20% of histology sam ples will already reveal a pre-invasive or invasive malignancy.[10]

In the light of these risks, the young woman who develops breast cancer and who is known to have a strong family history or any potential BRCA mutation carrier should be offered time and information to decide on optimal surgery. Reflex breast sparing lobectomy and irradiation without discussion of the different options and implications is not an acceptable approach in these women, as it denies the woman an informed decision about risk management. In addition breast irradiation seriously compromises future reconstructive efforts. It is a myth that immediate treatment initiation is of huge importance in this disease with such a protracted preclinical phase.

Various studies have demonstrated a projected survival benefit from prophylactic contralateral mastectomy. Removal

of the remaining breast tissue of the affected breast (ipsilateral prophylactic mastectomy) should also be considered strongly. This aggressive approach is of increased importance in the BRCA1 subgroup, as it seems that hormonal prevention as discussed below (both oophorectomy and oestrogen blockade) is less effective in these patients.[11]

*Chemoprevention*
Tamoxifen use may reduce the risk to get breast cancer by 30-60% in women with BRCA2 mutations. Unfortunately it seems less effective in reducing oestrogen independent cancer, so is also less effective in BRCA1 mutation carriers. Premenopausal use and the optimal duration of use remain problematic.

While raloxifene had equal cancer-risk reduction ability in the general population, this drug has not been tested sufficiently in BRCA families.

*Surgical prevention*
Surgical removal of the breasts remains the most effective method to prevent breast cancer and can provide risk reduction of 90-95%. Admittedly, it is also the most invasive. This method is most suited for women with a very high estimated breast cancer risk, mainly BRCA mutation positive patients.[12]

Prophylactic bilateral mastectomy (in women without previous breast cancer diagnosis) may be skin-sparing but should include the nipple-areola complex. The incidence of premalignant (around 35%) and malignant lesions (6%) in specimens from women with known mutations is high despite normal radiology.[13] Recommendation includes bilateral breast reconstruction.

The decision about prophylactic mastectomy is difficult and extensive preoperative counselling and support is essential. Young mothers are most likely to choose this option, together with women intimately involved with affected family members like siblings and mothers. Patients differ in preference about counselling style (directive or non-directive).[14] In a large international study, it was found that less than half of BRCA mutation carriers will undergo preventative mastectomy. This probably demonstrates that patients believe in the effectiveness of breast cancer screening methods.[15]

*Hormonal prevention or oophorectomy*
Risk reducing early surgical menopause is estimated to reduce breast cancer risk by about 30-60%. The magnitude of the risk reduction depends on the age at the time of surgery and is possibly better in BRCA2 mutation carriers. So far, the positive effect seems to persist in spite of sex hormone replacement of relatively low dose and short duration.

*Other strategies*
Various authors have indicated that physical activity may reduce the risk of developing breast cancer. This opinion was recently confirmed in BRCA mutation carriers.[16] Dietary factors may play some role, but the ideal diet is difficult to find and to adhere to. The effect of these factors on breast cancer risk is not quantified.

### *Ovarian cancer risk reduction*

The real risk of ovarian cancer in mutation-positive women is expected to increase if the survival of breast cancer is improved. To accurately counsel patients, it is important to know that the ovarian cancer risk for BRCA2 mutated women is much smaller than for BRCA1 families. In the recent South African study an incidence of 9.6% was reported for BRCA1 families and only 1.9% for the BRCA2 group.[2] The two groups are both expected to have some underreporting.

*Ovulation suppression*
Oral contraceptives (OCs) reduce ovarian cancer risk moderately in the general population and probably also in BRCA positive women. Although some authors suggest an increase in breast cancer risk through OC use, most expert counselling teams would still consider OC use in family members or mutation carriers to be reasonable advice.

*Surgical prevention*
Removal of the complete fallopian tube (suspected by many to be an important site for the development of serous papillary carcinoma) and ovary with a segment of the ovarian vessels will reduce ovarian cancer risk by at least 90%.[17] It is recommended that this surgery be done between ages 35 and 40. The complete surgical specimens should be thoroughly sectioned and examined for early or even in-situ cancer. Occult or clinical primary cancer in both the ovaries and tubes as well as breast cancer metastases are not uncommon in this patient population.[18] Peritoneal washings should be obtained and examined by cytology. It seems that previous reports overestimated the incidence of primary peritoneal carcinoma following preventative oophorectomy, possibly due to missed diagnosis of early or occult cancer at the time of surgery.[19]

This surgery can be done with or without a hysterectomy and can be followed by hormone replacement without apparent detrimental effect.[20]

*Ovarian cancer screening*
Screening for ovarian cancer cannot prevent the disease at all and it is seriously doubted whether it will really improve survival significantly in women at very high risk for the disease.

Ovarian cancer screening should never be supported in BRCA-mutation carriers over the age of 40, but can be considered in younger women or possibly in women who decline the offer of oophorectomy for a personal reason.

### *Other cancers*
South African data demonstrated an increased stomach cancer risk in families with a BRCA2 mutation when compared to the general population and the BRCA1 families.[2] These data

suggest that stomach cancer screening may be indicated in known mutation carriers.

### Hereditary non-polyposis colon cancer (HNPCC) syndrome

This syndrome is characterised by a strong family history of colon (and other gastric and bowel) cancers in both male and female members of the family. Many families will also report a history of endometrial and/or ovarian cancer.

The so-called "strict Amsterdam criteria" will exclude most families without mutations in the described HNPCC genes, but may be too strict to diagnose all families with a mutation in these mismatch repair genes.

Similar to the breast and ovarian cancer syndrome genes, this syndrome is caused by mutation in one of the genes coding proteins important in DNA repair. The genes involved include the MSH2, MLH1, PMS1 and PMS2 genes, any of which can harbour any mutation. In women from these families, the most common cancer is endometrial cancer (usually reported as "uterine"), followed by colon cancer. Mutations in these genes also explain about 10% of families with a pattern of inherited ovarian cancer. The endometrial and ovarian cancer risk is so high that prophylactic hysterectomy with bilateral salpingo-oophorectomy is suggested as the standard preventative strategy, rather than any form of surveillance.[21]

Combined hormone replacement or progesterone treatment may be considered as a way of preventing colon cancer. Frequent screening colonoscopy is indicated, as is mammography. In the absence of a hysterectomy, endometrial screening by histology is essential.

### Conclusion

Genetic evaluation, counselling and testing is an essential part of modern medicine. This can be used together with models to estimate risk using clinical parameters.[21] Once cancer risk is identified and also "quantified", it has to be addressed. Active cancer prevention is the most effective way to prevent morbidity and premature cancer-related death in women known to have mutations in the genes causing HBOC and HNPPC syndromes.

Specialists who have an intimate knowledge and understanding of the field can best support patients to make the correct decisions to protect themselves. It is best to use a multidisciplinary team approach. Care givers should be very careful not to contradict each other or to be judgmental about patient choices.

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