ovarian cancer action

hereditary ovarian cancer

A guide for GPs

Known inherited gene mutations that result in a strong predisposition to ovarian cancer

GP Guide: hereditary ovarian cancer

All cancers are the result of genetic mutations in the tissue in which they arise. Sometimes, certain inherited mutations can increase the chance of a cancer being initiated. Different types of those inherited mutations can have a strong or weak effect.

Heritable gene mutations that increase the chance of ovarian cancer[i]

In about 15-20% of ovarian cancer cases, it is likely that the inheritance of a particular gene mutation plays a strong part.

There are two familial cancer conditions that can increase a woman's risk of developing ovarian cancer. These are:

- **Familial breast and ovarian cancer – due to BRCA1 or BRCA2 gene mutations; and**
- **Lynch Syndrome (also known as Hereditary Non-Polyposis Colorectal Cancer [HNPCC]) – due to 'mismatch repair' gene mutations**

BRCA1/2 genes[ii]

BRCA1 and BRCA2 are genes that we all have two copies of. Their normal function is to prevent cells from growing and dividing too rapidly. Mutations in these genes can cause cells to become abnormal and grow in an uncontrolled way. Having a mutation in one copy of these genes can increase a women's risk of both breast and ovarian cancer. The genes are large and many different mutations have been described, but on average a woman with a BRCA1 or 2 gene mutation will have a 45-90% chance of developing breast cancer in her lifetime and a 10-60% chance of developing ovarian cancer in her lifetime. The chance of developing ovarian cancer for a woman in the general population is 1-2% in her lifetime. There are other cancers associated with mutations in these genes; for example, pancreatic cancer and melanoma, but the lifetime risks of these cancers are lower than for breast or ovarian cancer. For men, a BRCA2 mutation increases the chance of developing prostate cancer by up to 28% as well as male breast cancer by up to 12%
Approximately 1 in 400 people in the general population will have a BRCA1/2 gene mutation. However the prevalence is much higher in certain populations, such as the Ashkenazi Jewish community where about 1 in 40 has a BRCA1/2 mutation. This is because particular 'founder' mutations have been passed on in groups that were at one time geographically or culturally isolated. Similar founder BRCA1/2 mutations are seen in other groups such as people from Icelandic, Norwegian, Dutch, Pakistani and Polish populations although the prevalence is not thought to be as high as in the Ashkenazi population.

Lynch Syndrome[iii]

Lynch Syndrome results from an inherited genetic mutation in any of the following genes: MLH1, MSH2, MSH6, PMS2 and EpCAM. These genes are known as mismatch repair genes and their main function is to correct any alterations that may develop in our DNA during cell copying. If these genes become mutated they are less able to perform this protective role and this increases the chance of developing ovarian, bowel, womb, stomach, pancreatic, biliary and bladder cancers. A female carrier of one of these genetic mutations has an up to 10% chance of developing ovarian cancer within her lifetime.

Identifying patients who may have an inherited increased risk of ovarian cancer[iv]

It is important to identify patients who are at a high risk of developing ovarian cancer so that steps can be taken to reduce their risk.

Despite the advent of faster and cheaper genetic testing, the best way to identify patients at increased risk is still to take a detailed family history as an initial step. This should include the types of cancer, the family members affected, how they are related to each other, and what age the cancer was diagnosed in those family members. This will help indicate the chance of a BRCA gene mutation or mismatch repair gene mutation being present. The stronger the family history and the more related cancers, especially if at young ages, the greater the chance of finding one of these mutations.

The following types of family history may indicate the presence of a high risk gene mutation:

- Two or more cases of ovarian cancer at any age on the same side of the family
- Two or more cases of breast cancer under 60 on the same side of the family
- A combination of 2 cases of either breast cancer under 60 and/or ovarian cancer at any age on the same side of the family
- Two or more cases of bowel or ovarian cancer on the same side of the family
- Any relative with two separate cancers (that aren't spread from one to the other) counts as two affected relatives in the above list
- Being from a high risk population, including: Ashkenazi Jewish, Icelandic, Norwegian, Dutch, Pakistani and Polish.

Steps to take if a patient has a strong family history[v]

If a patient falls into one of these categories it is important that you refer her to your local regional genetics service for further assessment and discussion of whether genetic testing is indicated. This will likely involve a more detailed family history assessment and histological confirmations of the cancers in the patient's family.
The latter can take some time, as consent from relatives will need to be sought and hospital records accessed. However it is important because a large proportion of reported family histories of ovarian cancer turn out to be something different, for example cervical cancer, once records are checked.

Genetic testing will be discussed if the chances of finding an ovarian cancer predisposing mutation are increased. The NICE clinical guideline CG164 1.5.11 states that the affected relative should be offered genetic testing first before any other family members, so testing will usually be first done in a family member who has had cancer.
If the familial mutation can be found in this person, then unaffected relatives can have a highly accurate predictive genetic test to see whether they have inherited it.

The following table shows patient's eligibility for BRCA testing based on their individual circumstance, and the action they might take:

Circumstance	Entitlements	Next Steps
Patient has no personal history of breast or ovarian cancer, but has a living relative who does and is available to be tested.	The **NICE clinical guideline CG164 1.5.11** states that the patient's affected relative should usually be offered genetic testing before the patient, or any other relative. In order to access this **NHS England E01/P/b** says that genetics testing will be offered where their relative's carrier probability is more than 10%. If the patient's relative tests positive **NHS England E01/P/b** says that genetics testing will be offered where their carrier probability is more than 10%.	The patient's relative should speak to their clinical oncology team about being referred for genetic testing. If they test positive the patient will be informed and invited to go to their local genetics centre and discuss BRCA testing with a genetic counsellor. If the relative tests positive and the patient is not invited to see a genetic counsellor they can go and see their GP and ask for a referral by explaining the situation. If the patient's relative tests negative for BRCA1/2 gene mutations they will not require testing. It is always a good idea for patients to find out about the cancer history in the other side of their family, and seek advice from their GP if they are concerned. **BRCA1/2 gene mutations are not just carried on a mother's side, it is possible for a father to carry the mutation and pass it on to his children too.**

Circumstance	Entitlements	Next Steps
Patient has no personal history of breast or ovarian cancer. They have a relative who does but they are unavailable for testing.	The **NICE clinical guideline CG164 1.5.12** states that if the patient's relative is unavailable they may still be able to access testing by speaking to their GP. **NHS England E01/P/b** says genetics testing will be offered where their carrier probability is more than 10%.	If the person is unavailable because they have died then the patient should go to their GP to discuss their family history and request referral for genetic testing. If there is a tumour sample available this would assist with the process, but it is not essential. If the person is unavailable because the patient has no contact with them then they should go to their GP to discuss the family history that they are aware of and explain the situation. The GP may then refer the patient to their local genetics centre for further discussion with a genetics counsellor.
The patient has a family member who has already tested positive for a BRCA1/2 gene mutation.	There are no specific NICE guidelines in this situation. **NHS England E01/P/b** says the patient will be offered genetics testing where their carrier probability is more than 10%.	The patient's family member may have already advised them to contact their local genetics centre, or passed their details on to them to contact the patient directly. If this has not happened the patient can go and see their GP and discuss their family history with them. The GP can refer the patient on to their local genetics centre for further discussions about family history.

Circumstance	Entitlements	Next Steps
The patient has not had breast or ovarian cancer, no known history of either disease and no known BRCA gene mutations in the family.	In this situation it is unlikely that the patient would be eligible for testing under any of the current guidelines.	If the patient has concerns over breast or ovarian cancer then they should familiarise themselves with key information about the disease. If they have concerns about BRCA1/2 gene mutations they should try and find out about any family history of cancer. They could also make an appointment to see their GP and explain their concerns.

You can find the details of your nearest genetic specialist clinic on The British Society for Genetic Medicine's website (www.bsgm.org.uk). Genetics services are nationally commissioned through the NHS so **GPs do not have to pay for referrals.**

Most genetic services have an on-call service or telephone hotline. You can enquire here if you are unsure about whether a woman should be referred to them.

Supporting patients who have an inherited genetic mutation [vi]

General practitioners play an important role in providing support to patients and families affected by inherited genetic mutations. Genetic services will always send a detailed clinical summary with recommendations for reassurance, surveillance, surgery or testing. This will help you co-ordinate and advise patients about their management options. Onward referral to other services, such as those for surveillance, preventative surgery or psychological support may be recommended or arranged via the genetic service. A key consideration for patients with inherited cancer predisposing mutations is whether and how communication of possible risk to family members needs to take place. Your skills are crucial here.

What options are available to patients who have an inherited genetic mutation? [vii] [viii]

For patients with a BRCA1/BRCA2 mutation or a mismatch repair gene mutation (Lynch Syndrome), their risk of developing ovarian cancer starts to increase from around the age of 40. Depending on the age of the patient, risk reducing surgery involving the removal of their ovaries and fallopian tubes (bilateral salpingo-oophorectomy) should be considered. This will dramatically reduce their risk of developing ovarian cancer, although cannot remove it altogether because a 2-3% chance of primary peritoneal cancer will remain. Referral to a specialist may be indicated.

Removing a woman's ovaries will immediately precipitate a surgical menopause so the timing of such an operation requires careful consideration. The patient must be made fully aware of this so she can make an informed decision, particularly around fertility issues.

Different genetic mutations increase risk at different ages, therefore recommended age for preventive surgeries for women varies according to the mutatiion. They are summarised below; please bear these in mind when timing your referrals.

BRCA1	**Bilateral Salpingo-oopherectomy**	Between age 35-40yrs
BRCA2	**Bilateral Salpingo-oopherectomy**	Between age 40-45yrs
Lynch Syndrome	**Total hysterectomy and bilateral salpingo-oophorectomy**	Between age 40-45yrs

Ovarian surveillance would be a desirable alternative to risk reducing surgery but none of the modalities that have been studied so far (CA125 blood test and trans-vaginal ultrasound scan) have been very effective at diagnosing cancers at an early, treatable stage, and are therefore not offered as routine screens. They can however be very useful in women with symptoms. You should have a low threshold for onward referral as ovarian cancer does not cause reliable clinical symptoms.

Patients with ovarian cancer

Patients diagnosed with non-mucinous epithelial ovarian cancer without a family history of related cancer are eligible for genetic testing just on this diagnosis alone (stated by NHS England guideline E01/P/b).

Your patient's oncologist should already have discussed/ arranged genetic testing with them but, if not, you should have this discussion with them and refer them to their regional genetics service. Knowing whether she has inherited a genetic mutation has a direct impact on her treatment path, responsiveness to certain types of drugs and her ability to take part in clinical trials. Furthermore, it is important that the patient knows her BRCA status so she can take the necessary precautions related to the increased, genetic-based risk of breast cancer associated and also discuss the possibility of genetic testing with her family.

More information

For more information you can contact:

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i Pal T et al. BRCA1 & 2 mutations account for a large proportion of ovarian carcinoma cases. American Cancer Association 2005; 104(12): 2807-5

ii NHS England. Clinical Commissioning Policy: Genetic Testing for BRCA1 & BRCA2 Mutations. E01/p/b. 2015

iii University Hospital Southampton NHS Foundation Trusts. Hereditary non-polyposis cancer (HNPCC)/Lynch Syndrome. 2016

iv Antoniou A et al. Average risks of breast and ovarian cancer associated with BRCA1 or BRCA2 mutations detected in case series unselected for family history: combined analysis of 22 studies

v NICE Clinical Guideline 164. Familial Breast Cancer: classification, care and managing breast cancer and related risks in people with a family history of breast cancer

vi The Royal Marsden NHS Foundation Trust, A Beginners Guide to BRCA1 & BRCA2. 2013

vii Royal College of Obstetricians & Gynaecologists: management of women with a genetic predisposition to ovarian cancer. 2015.

viii Lu K.H & Daniels M.
Familial Cancer (2013) 12:273. doi:10. 1007/s10689-013-9664-5