Hereditary breast and ovarian cancer

Key facts

- Breast cancer is the most commonly diagnosed cancer in the UK, affecting around 1 in 8 women during their lifetime.
- The majority of breast cancer is not due to an inherited condition, but it is important to recognise the less than 5% of breast cancer that occurs due to an inherited predisposition (inherited breast cancer).
- Two major genes associated with familial breast cancer are the *BRCA1* and *BRCA2* genes.
- Women with an alteration in the *BRCA1* or *BRCA2* genes have a significantly increased probability of developing breast and ovarian cancer during their lifetime, and may be offered additional screening. Men with an alteration in the *BRCA1* or *BRCA2* genes have an increased probability of developing prostate cancer and breast cancer.

Clinical features

Clues that may suggest an inherited predisposition to breast cancer include:

- several women who have had breast cancer and/or ovarian cancer on one side of the family;
- breast cancer being diagnosed at a younger age than is usual;
- a breast cancer diagnosed with grade 3 triple negative histology (ie it tests negative for oestrogen, progesterone and HER2 receptors), especially at a young age;
- an individual who has had primary breast cancer more than once or had early breast cancer and ovarian cancer; and
- a male with breast cancer in a family where female relatives have also had breast cancer.

Diagnosis

- Individuals may seek information, either because they have been affected with breast cancer themselves or because they have a family history of breast cancer.
- A family history will first be taken by their breast cancer team or by their GP. If the family history is considered to be significant, then a referral should be made to the local genetics department or family history clinic. Most regional genetic centres publish guidelines on their website for referrals based on information from a family history.
- A detailed risk assessment will then be carried out. This will estimate an individual's lifetime probability of developing breast cancer and also the chance of developing breast cancer over the next 10 years. An assessment can also be done to calculate the chance that there is a *BRCA1* or *BRCA2* gene alteration in the family.
- At this stage, recommendations about additional screening or genetic testing may be offered.
- In some areas, genetic testing for *BRCA1* and *BRCA2* is beginning to be offered in oncology and surgical clinics at the point of diagnosis, particularly for primary serous ovarian cancer.

Genetic basis

- The two main genes associated with familial breast cancer are known as *BRCA1* and *BRCA2*. (There are other genes known to be associated with predisposition to breast cancer, but *BRCA1* and *BRCA2* are those most commonly involved.)

- A woman who inherits an altered *BRCA1* or *BRCA2* gene will not always develop cancer, but her probability of developing breast (and ovarian) cancer will be significantly increased. For women with a *BRCA1* or *BRCA2* alteration, the chance of developing breast cancer before the age of 80 is around 80%. The lifetime probability of developing ovarian cancer is between 10% and 60%.
- *BRCA1* and *BRCA2* mutations are inherited in an autosomal dominant manner. This means that an individual with an inherited predisposition to breast cancer has one usual copy of the gene and one altered copy. An individual with a gene alteration has a 1-in-2 (50%) chance of passing on the usual gene and a 1-in-2 (50%) chance of passing on the altered gene to each of their children, male or female. As mentioned above, if a child inherits a copy of the altered gene, it is likely but not certain that breast cancer will develop in adulthood.
- The products of the *BRCA1* and *BRCA2* genes are important in the repair of DNA double-strand breaks. Alterations (mutations) in these genes cause a reduced ability to repair DNA damage. Consequently, mutations accumulate across the genome, leading to the development of cancer

Clinical management

There are several options available to women at an increased probability of developing breast cancer:

- **Breast screening:** The National Breast Screening Programme offers all women mammograms every three years between the ages of 50 and 70. Depending on the level of risk, breast screening may be offered from an earlier age and on a more frequent basis. Sometimes other types of examinations (such as an MRI scan) may also be offered to women at high risk. NICE guidelines for women with an alteration in the *BRCA1* or *BRCA2* gene suggest annual screening by MRI scan from the age of 30-50 and then by annual mammogram from 50-69, although this may not be available in every area.
- **Risk-reducing surgery:** Some women who have a high probability of developing breast cancer may be offered surgery to reduce their risk. Double mastectomy with reconstruction can reduce their probability of developing breast cancer by up to 90%. However, this is major surgery with potential complications and possible psychological implications.
- **Breast awareness:** Most breast cancers will present as a painless breast lump. It is important that all women are aware of how to check their breasts and know which symptoms to be aware of.

Genetic testing

- NICE guidelines state that genetic testing for *BRCA1* and *BRCA2* gene alterations should be available to women where there is a 10% or greater chance of carrying a gene mutation.
- Genetic testing is most useful if carried out in an affected member of the family first to establish the specific alteration for that family. If a gene alteration is identified in an affected family member, then other relatives can also be tested to see whether they carry the same gene alteration. This is known as predictive genetic testing.
- If there are no affected relatives available to test (eg if everyone who has had breast cancer is deceased) genetic testing may still be possible for unaffected women in the family if there is a strong family history of breast and/or ovarian cancer.

This information is intended for educational use and was current in March 2015. For clinical management, it is recommended that local guidelines and protocols are used.