UNIKLINIK KÖLN
Zentrum für Familiären Brust- und Eierstockkrebs

CIO Centrum für Integrierte Onkologie Köln Bonn

Univ.-Prof. Dr. med. Rita Schmutzler
Direktorin

Kerpener Str. 34, 50931 Köln
Tel.: 0221/478-86509

Information about Genetically Related Breast and Ovarian Cancer

What is the significance of heredity?

About 5-10% of all breast and ovarian cancers are due to hereditary factors. Breast and ovarian cancers that are related to a genetic predisposition display common features that include a history of occurrence with other family members, occurrence at an early age as well as secondary tumours of both the breast as well as the ovaries. To date, two genes are known of which mutated forms may bring about genetically related breast and ovarian cancer. These genes, BRCA1 and BRCA2, are together responsible for 50% of all hereditary cases.

What is 'autosomal dominant inheritance'?

Hereditary breast cancer is an 'autosomal dominant' genetic trait. This type of inheritance can be explained as follows: The human chromosome complement consists of 22 so-called autosomes, which are present in pairs, and the two sex chromosomes X and Y. In a case of autosomal dominant inheritance a risk of a disease being contracted already exists when only one of the two paired genes has changed in an 'unfavourable' way. Since only one of the two genes is passed on to children, the risk for a first-degree related offspring to take on the mutation is 50%. In autosomal dominant inheritance the sex of those involved is irrelevant. This means that both men and women can inherit the mutation and/or pass it on to their offspring.

What findings may result from a genetic test of a blood sample?

It is possible in principle to perform a search for mutations (genetic changes) in a person's genetic material by means of molecular-genetic techniques. If a mutation is discovered in these genes, a clear diagnosis can be made. First of all a blood test from a person suffering from a disorder is required. Then analyses can be performed for each family member to see if the mutation exists. For instance, clarification can be obtained for daughters or sisters of female patients as to whether they themselves have the hereditary disposition to contract cancer. These molecular-genetic studies are complicated and generally take several months.

If an unequivocally disease-triggering (pathogenic) mutation in one member of a family is found, then a **predictive genetic analysis** in healthy relatives is performed in our clinic **only** following extensive gynaecological, human-genetic and as required psychotherapeutic counselling.

If **no** change found in any of the genes known to date (BRCA1 / BRCA2), it is unfortunately not possible to exclude the possibility of an 'unfavourable' genetic predisposition for breast and ovarian cancer with absolute certainty. As already mentioned, the genes BRCA1 / BRCA2 are responsible for only about 50% of hereditary diseases. Beyond these two genes, no further risk genes have been identified so far. In such cases our recommendation for preventative action depends on your individual risk according to a statistical model. We assess this risk using a standardized and computer-based risk calculation program. The risk is considered to be high if your lifetime likelihood of contracting a disease is greater than 30% or your risk of having a predisposition for a mutation is greater than 20%.

When is genetic testing recommended?
Genetic testing of BRCA1 and BRCA2 is indicated for the following situations in which the probability of a mutation is at least 10%.
Families with:

- at least two women who have contracted breast cancer, one of whom was less than 51 years old when the disease was first contracted
- at least one woman who has contracted breast cancer and another woman who has contracted ovarian cancer
- at least one woman who has contracted breast cancer and ovarian cancer
- at least two women who have contracted ovarian cancer, regardless of their ages
- at least one woman under 51 years of age who has contracted bilateral (on both sides) breast cancer
- at least one woman under 36 years of age who has contracted unilateral (on only one side) breast cancer
- at least one man who has contracted breast cancer
- at least three women who have contracted breast cancer, regardless of their ages

When is participation in an intensified breast cancer screening programme recommended?
As part of the counselling session in which the genetic findings are communicated we inform you of your individual risk that you may contract a disease. If a BRCA1 or BRCA2 mutation has been diagnosed, the likelihood of your contracting breast cancer later in life is around 40% to 80% and there is a 20% to 50% risk of your contracting ovarian cancer. When the genetic findings are communicated to you we will provide you with more specific risk assessments. For women for whom no evidence of a pathogenic mutation in one of the high-risk genes BRCA1 or BRCA2 has been found the risk of contracting the disease is significantly lower. The breast cancer screening programme takes account of the different risks in these two groups (i.e. those who are BRCA1 or BRCA2 mutation carriers on the one hand and those with a family related risk for whom no evidence has been found for BRCA1 or BRCA2 mutations on the other hand); further details are provided below.

Please note: The usual follow-up examinations after breast cancer remain unaffected by the intensified screening programme. You should continue to have follow-up examinations done by the physician who has been treating you. If an X-ray mammography is performed in the course of a follow-up examination, you should arrange for this to be done around the same time as the magnetic resonance imaging appointment.

1. Intensified breast cancer screening programme for women with a <u>BRCA1 or BRCA2 mutation</u>

When does the intensified breast cancer screening programme begin?
Women with a mutation in one of the BRCA genes are adopted into the intensified screening / follow-up programme at the age of 25 years or 5 years before the earliest age of onset in the family (if breast cancer has been contracted by somebody in the family under the age of 30 years).

When does the breast cancer screening programme end?
The intensified screening / follow-up programme including magnetic resonance imaging (MRI) is continued at least until the age of 50 and at most until the age of 70 or up the point at which very

good mammographic assessment remains possible (ACR density index 1). Thereafter, patients revert to the standard care programme.

What tests are performed?

1. **Magnetic Resonance Imaging (MRI)** for both breasts every 12 months. This investigation must be performed between the 6th and 16th day of menstruation (the 1st day is the 1st day of the menstrual period when bleeding starts).

2. **Ultrasound** for both breasts every 6 months.

3. **Mammography** for women **before their 39th birthday** only if this is indicated by other findings. For women **after their 39th birthday**, depending on the degree of assessability provided by the other investigation methods, on the gland tissue density and on the mammographic findings, at least every 2 years.

2. Intensified breast cancer screening programme for women with a computational risk but without evidence of a pathogenic mutation in BRCA1 and BRCA2 or for whom a mutation in the genes RAD51C, RAD51D, CHEK2, PALB2 that are moderately penetrant for breast cancer has been found.

When does the intensified breast cancer screening programme begin?
Women at risk who have **not contracted the disease** are adopted into the intensified screening/follow-up programme at the earliest at the age of 30 years or 5 years before the earliest age of onset in the family (if breast cancer has been contracted by somebody in the family under the age of 35 years). Women at risk **who have contracted breast cancer** can be admitted to the program from the age at which the disease is first contracted.

When does the intensified breast cancer screening programme end?
Both those women at risk who **have contracted the disease** and those who **have not** are discharged from the intensified screening/follow-up programme on reaching the age of 50 and referred to the care of their local gynaecologist.

What tests are performed?

1. **Magnetic Resonance Imaging (MRI)** for both breasts every 12 months. This investigation must be performed between the 6th and 16th day of menstruation (the 1st day is the 1st day of the menstrual period when bleeding starts).

2. **Ultrasound** for both breasts every 12 months.

3. **Mammography** for women **before their 39th birthday** only if this is indicated by other findings. For women **after their 39th birthday**, depending on the degree of assessability provided by the other investigation methods, on the gland tissue density and on the mammographic findings, at least every 2 years.

What other preventive measures exist?

Possible preventive measures include the prophylactic removal of breast gland tissue or ovaries. Such a decision is preceded by intensive consultations that enable the person affected to take the decision that is best for her.

You should continue to have the other preventive gynaecological check-ups (Pap etc.) carried out. We ask you to keep us up to date with the results of these check-ups. As part of the tumour after-care of patients who have already contracted a disease, the same tests are carried out in our Centre for detection of a second tumour as are carried out for detection of a first tumour.

What risks apply to men with a BRCA mutation?

Men with a BRCA1 or BRCA2 mutation also have an increased risk of breast cancer. This is particularly the case for carriers of a BRCA2 mutation. The risk remains at around 5-7% throughout the person's lifespan. Furthermore, there appears to be an increased risk of prostate cancer, although this is still being investigated.

We do not carry out breast cancer screening on male carriers of mutated genes as a matter of clinical routine, but we recommend them to keep a check on changes in the area of the breast and have it medically examined if necessary.

Regarding the increased prostate cancer risk, we provide intensified screening as part of a clinical study (***impact study***). You can obtain further information on this from our administration office.