Genetic Testing for Hereditary Breast and Ovarian Cancer

- BRCA1/2 ANALYSIS -

January 2005
Breast cancer is considered to be one of the most prevalent cancer in women. The overall frequency of breast cancer has increased in Europe, with a particularly tremendous increase over the past 20 years among younger women. However, the mortality rate for this cancer has decreased over the last 6 years. In Germany there are about 45,000 new cases of breast cancer being reported each year, approximately 18,000 women die due to this form of cancer every year.

**There are both genetic and non-genetic factors contributing to the overall risk of breast cancer.**

Around the age of 40 a considerable increase for the risk of breast cancer can be observed. (see Figure 1). Women without a genetic risk have a chance of 10 % to develop a tumour.

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**Fig 1**: Probability in percent for the development of a carcinoma, in presence of a mutation (BRCA1), a positive family history, or in absence of a specific mutation. Every child of a mutation carrier has a chance of 50 % to inherit the mutation.

An accumulated occurrence of breast carcinomas in single families (men can also be affected in rare cases) is indicative for a genetic component. Besides a more frequent occurrence of bilateral breast carcinomas in several consecutive generations within a family, the age at first diagnosis is the most important criteria for a genetic predisposition.
For example, when the age of the patient at diagnosis is significantly below 40, the probability for a genetic background is considerably increased. A familial preponderance of breast carcinomas can be observed in up to 25% of all cases. For 5 – 10% of these cases the relevant genes are known. These are the 1994 and 1996 isolated genes \textbf{BRCA1} and \textbf{BRCA2} which were discovered mainly by scientists from the American company Myriad. Since in more than 80% of hereditary breast carcinomas these genes are involved, a molecular genetic analysis of these genes should especially be offered to individuals with significantly increased risk. In addition, carriers of a BRCA mutation do have a 10-fold increased risk of developing ovarian cancer as compared to the normal population.

\textbf{RISK OF BRCA MUTATION CARRIERS FOR DEVELOPING BREAST AND OVARIAN CANCER}

- Up to 85% lifetime risk of breast cancer (see Table 1)
- Up to 60% lifetime risk of ovarian cancer (see Table 1)

\begin{table}[h]
\centering
\begin{tabular}{|c|c|c|}
\hline
\textbf{Cancer} & \textbf{BRCA1} & \textbf{BRCA2} \\
\hline
Breast cancer (women) & 80-85 & 80-85 \\
Breast cancer (men) & - & 6 \\
Ovarian cancer & 45-60 & 25-30 \\
Prostate cancer & 15 & 20 \\
Other cancer & increased & 25 \\
\hline
\end{tabular}
\caption{Cancer risk of BRCA1/2 mutation carriers for various carcinomas (according to Kiechle et al., 2001)}
\end{table}

\textbf{INCREASED RISK OF SECOND CARCINOMA OF MUTATION CARRIERS ALREADY DIAGNOSED WITH CANCER}

- up to 20% risk of second breast cancer within 5 years of initial diagnosis
- up to 64% risk of second breast cancer by age 70 of BRCA1 mutation carriers
- up to 52% risk of second breast cancer of BRCA2 mutation carriers
- 10-fold increased risk for the development of ovarian cancer compared to women without mutation
- up to 16% lifetime risk of breast cancer patients to develop ovarian cancer later in life
INDICATIONS FOR A GENE ANALYSIS OF BRCA1/2

RECOMMENDATIONS ACCORDING TO A SPECIAL PROGRAM OF THE GERMAN KREBSHILFE „FAMILIAL BREAST AND OVARIAN CANCER“

- Families with $\geq 2$ affected individuals with breast or ovarian cancer, $1 < 50$ years. The age limit will not be valid in families with 3 or more affected individuals
- Families with 1 affected individual with unilateral breast cancer, age $\leq 30$ (35*) years
- Families with 1 affected individual with bilateral breast cancer, age $\leq 40$ years
- Families with 1 affected individual with ovarian cancer, age $\leq 40$ (50*) years
- Families with 1 affected individual with breast and ovarian cancer
- Families with 1 male affected with breast cancer

* some of the larger cooperating centers have set the inclusion limits at higher ages as indicated in parentheses

RECOMMENDATIONS OF THE AMERICAN SOCIETY OF CLINICAL ONCOLOGY (ASCO)

- Individuals with an estimated risk of $>10\%$ should be tested

In Table 2 (page 5) the prevalence of BRCA1 and BRCA2 mutations with the corresponding risk estimates for the various groups is indicated.
# Cancer Risk and Prevalence of BRCA1 and BRCA2 Mutations

<table>
<thead>
<tr>
<th>Patient's History</th>
<th>Family History*</th>
<th>No Breast cancer &lt; 50 y, or ovarian cancer in any relative**</th>
<th>Breast cancer &lt; 50 y in one relative; no cancer ovarian cancer in any relative</th>
<th>Breast cancer &lt; 50 y in more than one relative; no ovarian cancer in any relative</th>
<th>Ovarian cancer at any age in one relative; no breast cancer &lt; 50 y in any relative</th>
<th>Ovarian cancer in more than one relative; no breast cancer &lt; 50 y in any relative</th>
<th>Breast cancer &lt;50 y and ovarian cancer at any age***</th>
</tr>
</thead>
<tbody>
<tr>
<td>No breast cancer or ovarian cancer at any age</td>
<td>3.4%</td>
<td>4.5%</td>
<td>9.1%</td>
<td>5.3%</td>
<td>8.9%</td>
<td>14.0%</td>
<td>14.0%</td>
</tr>
<tr>
<td></td>
<td>40/1171</td>
<td>80/1774</td>
<td>164/1793</td>
<td>41/777</td>
<td>46/519</td>
<td>248/1775</td>
<td></td>
</tr>
<tr>
<td>Breast cancer ≥ 50 y</td>
<td>2.9%</td>
<td>7.5%</td>
<td>11.1%</td>
<td>5.6%</td>
<td>13.3%</td>
<td>18.2%</td>
<td>18.2%</td>
</tr>
<tr>
<td></td>
<td>26/898</td>
<td>69/916</td>
<td>60/540</td>
<td>23/414</td>
<td>13/98</td>
<td>89/490</td>
<td></td>
</tr>
<tr>
<td>Breast cancer &lt; 50 y</td>
<td>7.3%</td>
<td>14.4%</td>
<td>32.5%</td>
<td>18.5%</td>
<td>28.2%</td>
<td>42.1%</td>
<td>42.1%</td>
</tr>
<tr>
<td></td>
<td>260/3566</td>
<td>436/2510</td>
<td>487/1498</td>
<td>170/920</td>
<td>59/209</td>
<td>525/1247</td>
<td></td>
</tr>
<tr>
<td>Ovarian cancer at any age, no breast cancer</td>
<td>9.8%</td>
<td>24.3%</td>
<td>42.2%</td>
<td>21.7%</td>
<td>37.4%</td>
<td>50.0%</td>
<td>50.0%</td>
</tr>
<tr>
<td></td>
<td>41/420</td>
<td>54/222</td>
<td>46/109</td>
<td>63/290</td>
<td>43/115</td>
<td>141/282</td>
<td></td>
</tr>
<tr>
<td>Male breast cancer</td>
<td>12.5%</td>
<td>25.6%</td>
<td>45.8%</td>
<td>27.3%*</td>
<td>None tested</td>
<td>75.0%*</td>
<td>75.0%*</td>
</tr>
<tr>
<td></td>
<td>16/128</td>
<td>11/43</td>
<td>11/24</td>
<td>3/11</td>
<td></td>
<td>9/12</td>
<td></td>
</tr>
<tr>
<td>Breast cancer ≥ 50 y and ovarian cancer at any age</td>
<td>14.8%</td>
<td>29.2%</td>
<td>42.9%</td>
<td>27.0%</td>
<td>53.8%*</td>
<td>63.3%</td>
<td>63.3%</td>
</tr>
<tr>
<td></td>
<td>16/108</td>
<td>14/48</td>
<td>12/28</td>
<td>10/37</td>
<td>7/13</td>
<td>19/30</td>
<td></td>
</tr>
<tr>
<td>Breast cancer &lt; 50 y and ovarian cancer at any age</td>
<td>37.6%</td>
<td>53.4%</td>
<td>60.0%</td>
<td>66.7%</td>
<td>71.4%*</td>
<td>78.8%</td>
<td>78.8%</td>
</tr>
<tr>
<td></td>
<td>38/101</td>
<td>31/58</td>
<td>18/30</td>
<td>18/27</td>
<td>10/14</td>
<td>41/52</td>
<td></td>
</tr>
</tbody>
</table>

* Includes at least one 1st or 2nd degree relative

** May include families with breast cancer ≥ 50 y (in women or men)

*** Includes family members with either or both diagnoses

According to recommendations of the ASCO (American Society of Clinical Oncology) persons with a risk of > 10% should be tested

Table 2: Prevalence of mutations in the genes BRCA1 and BRCA2 depending on the family history (according to Myriad®, Salt Lake City). The numbers below the percentages indicate the number of mutations detected and the number of persons who have been tested. The family history provided includes at least one relative of first and second degree.
PREVENTIVE MEASURES

If a breast cancer associated mutation has been identified, there are a number of different measures which can be offered to mutation carriers. Such prophylactic measures may have a protective effect of up to 97% (see Figure 2).

INCREASED SURVEILLANCE

- Monthly breast self-exams starting at age 18 to 21 and annual or semiannual clinical breast exams, beginning at age 25
- Yearly mammography beginning at age 30
- Annual or semiannual clinical exams and transvaginal ultrasound
- Testing for the tumour marker CA-125 beginning between ages 25 to 35 to detect ovarian cancer
- In certain cases magnetic resonance tomography (MRT) may be indicated

CHEMOPREVENTION

- Drugs such as tamoxifen greatly reduce the risk of breast cancer in women with BRCA mutations. In Germany this therapy is only allowed for patients already diagnosed with breast cancer.
- In addition, there are currently several, still ongoing prevention studies to test other drugs/drug classes like SERMs (Selective Estrogen Receptor Modulators, e.g. raloxifen), aromatase inhibitors (anastrozole) and GnRH analoga with regard to their efficacy in the chemoprevention of breast cancer in patients who are at increased risk for the development of such cancer (family history, BRCA mutation carrier). The evaluation of the results of these studies will show if these substances can be recommended for chemotherapeutic treatment. However, individuals positively tested to be carrier of a BRCA mutation, should be offered to participate in such studies.
- Oral contraceptives have been associated with a 50% to 60% reduction of the risk of ovarian cancer in women with BRCA mutations.
PROPHYLACTIC SURGERY

- Preventive mastectomy reduces the risk of breast cancer by at least 90% in women with BRCA mutations. (see Figure 2)

- Preventive removal of the ovaries reduces the risk of ovarian cancer by at least 90%, and also breast cancer, in women with BRCA mutations.

![Risk Reduction of BRCA Mutation Carriers](image)

**Fig. 2:** Comparison of the risk reduction of BRCA mutation carriers with or without prophylactic mastectomy/oophorectomy, as well as the treatment with tamoxifen or oral contraceptives.

MOLECULAR BRCA1/2 ANALYSIS

The molecular genetic analysis of BRCA1 and BRCA2 is the only available test up to now to clearly identify patients as mutation carriers. Therefore it is reasonable for a patient to evaluate the possibilities of a genetic test in determining his personal risk and to decide if he is willing to undergo genetic testing or not.

The genetic testing procedure implemented by Bioscientia/Myriad (comprehensive sequence analysis of BRCA1 and BRCA2 genes) guarantees an unsurpassed quality standard and maximal power for result interpretation. Due to technical reasons larger rearrangements which do occur rather seldom, so far could not be detected.
Introducing the detection of large genomic rearrangements in the BRCA1 gene

Bioscientia is pleased having introduced end of 2002 a new technological advancement of the BRCA1/2 analysis genetic susceptibility test. This new technology allows us to test for the presence of a panel of five large gene abnormalities that are undetectable by standard PCR – sequencing based technologies, thereby increasing the sensitivity of BRCA analysis. These recurring large genomic deletions and duplication have been linked to hereditary breast and ovarian cancer. In fall 2005 we expect to be able to offer our customers an additional extension of this testing procedure allowing then the detection of all possible BRCA1 and BRCA2 large genomic rearrangements (BART). This technological improvement should once more increase the sensitivity and accuracy of the current BRCA analysis considerably.

All comprehensive BRCA1/2 analysis samples initiated into testing will now include the large rearrangement panel analysis.

In detail, the panel identifies the following large rearrangements in the BRCA1 gene:

4 large deletions (exons 8 and 9; exon 13; exon 22; exons 14 – 20):
- a 7.1 kb deletion involving exons 8 and 9, reported in susceptible breast/ovarian cancer patients of northern European descent (Genes Chr. & Cancer 28: 300-307, 2000)
- a 3.8 kb deletion involving exon 13, represents a major founder mutation in Dutch breast cancer patients (Nature Genetics 17: 341-345, 1997)
- a 510 bp deletion involving exon 22, represents a major founder mutation in Dutch breast cancer patients (Nature Genetics 17: 341-345, 1997)
- a 26 kb deletion involving exons 14-20 (Myriad, submitted for publication)

1 duplication (exon 13):
- a 6 kb duplikation involving exon 13, reported in susceptible breast/ovarian cancer patients of northern European descent (Am. J. Hum. Genet. 67: 207-212, 2000)

How will the large rearrangement panel affect the overall sensitivity of BRCA genetic testing?

It is estimated that a small but significant number of mutations in BRCA1 are attributable to these deletions and duplication. The large rearrangement panel enhances the existing test due to the ability to detect a greater number of deleterious mutations, resulting in an even higher percentage of informative results.

With this test enhancement Bioscientia can guarantee its customers the highest possible quality standard and accuracy of BRCA genetic testing together with short analysis times (4 - 6 weeks).
GENERAL INFORMATION

Important: An informed consent of the patient, a questionnaire of the family history, as well as a signed confirmation that the costs of BRCA analysis will be covered, have to be included with each sample (necessary documents may be downloaded from our website or are being sent by mail on request).

- **Forms**
  Molecular genetic diagnostics

- **Sample material**
  2 samples with each 10 ml EDTA blood samples (a closed system like Vacutainer® or Monovettes® should be used)
  
  Transport of the sample at room temperature (within maximally 3 days after blood sampling)

- **Shipping**
  Courier or mail

- **Analysis time**
  4 - 6 weeks

- **Results**
  The final report contains a detailed interpretation of the test result.
  
  Following each report, there will be a regular update of all reports by comparison with data entries in national and international data bases (strictly observing data protection). In such a way all reports will be updated according to later scientific results. If needed, a new interpretation of the original test result will be reported. We strongly recommend, that the transfer of test results and reports should be accompanied by qualified genetic counselling of the patient.

ANONYMITY OF THE TEST RESULT

Anonymity of the test result is guaranteed through our institution. Results will only be reported to the patient’s physician. The update of any test result by comparison with available data bases will only be performed strictly observing existing data protection rules. (Anonymisation of personal data).
REFERENCES (selected)


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