Comparison of Lifelong Risk on The Basis of Studies on The Origin of Breast and Ovarian Carcinoma

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Abstract

Introduction: Breast carcinoma is currently one of the most frequently discussed and also the most frequently occurring cancerous diseases in women. Inheritance plays a significant role in development of breast carcinoma, as in most other cancerous diseases. The genes that play a significant role in diagnosis of breast ca are called the BRCA1/2 genes.

Methods: A number of studies were performed, which prove that the BRCA1/2 genes have a serious effect on the risk of breast ca or ovarian ca. These studies are constantly varied and the environment in which we live also plays a significant role here. 8 studies were chosen from the papers published between 2013-2018 (from Great Britain, Holland, China, Israel, USA, Korea). These studies were compared to studies published in 2000-2010.

Results: The results from studies performed before 2010 do not differ significantly from the results in subsequent years. But there is a visible difference between the lifelong risk of breast carcinoma between eastern and western countries. The risk of breast ca in western countries remains higher than in studies from eastern countries. The Near East, a study carried out on Israeli Jewish women, falls somewhere in the middle of these two margins.

Conclusion: The difference between western and eastern countries undoubtedly results from different living conditions, lifestyle and probably also the level of advancement of the western culture. Whether this concerns education, later pregnancy, use of hormonal contraception and similar.

Keywords
Breast, BRCA1, BRCA2, Carcinoma, gene.

Introduction
Breast carcinoma (breast cancer) is currently one of the most frequently discussed and also the most frequently occurring cancerous diseases in women. Up to 6,500 new breast carcinomas are diagnosed in the Czech Republic every year. This is approximately 130 patients per 100 thousand women. Annual mortality ranges at around 2,000, which is 35 patients per 100 thousand women [1]. Incidence continues to rise over time, while mortality is stagnating or falling marginally [2]. Breast carcinoma is the most frequent cause of death in women aged between 20-59 years and this was one of the reasons why regular nationwide mammographic screening was implemented in 2002 [1]. Compared to the rest of the world the Czech Republic rates 19th in relation to incidence. On a European scale it comes 15th, on the basis of conversion to 100 thousand residents [2].

Risk factors that contribute to origin of breast carcinoma include hormonal and nutritional factors, and external environmental factors. Genetic factors also play an important role. Inheritance plays a significant role in development of breast carcinoma, as in most other cancerous diseases [3]. In the case of inheritance this usually concerns a bilateral tumour (occurring on both sides). Direct relatives of the female proband (mother, sister, daughter) are affected in most cases. Their risk is significantly higher. High-risk persons also appear in families where accumulation of various
tumours occurs (LiFraumeni syndrome, Cowden’s syndrome). In such cases the human DNA has been damaged in crucial gene areas, which work to repair DNA or initiate cellular death. Gene function is very useful. Genes are capable of repairing damaged DNA in another sector so that cancerous growth does not occur subsequently. Genes that play a significant role in diagnosis of breast ca are called the BRCA1 and BRCA2 genes. Damage to either of these genes appears as breast ca, ovarian ca and, to a lesser degree, also as prostate ca [2-4].

According to Czech statistics the lifelong cumulative risk of breast ca in women with a confirmed mutation in the BRCA1 or BRCA2 genes ranges at 55-85%, and 15-45% in relation ovarian ca, but women with a confirmed sequential variant in the BRCA2 gene have a worse prognosis. In the case of women who are carriers, the probability of transferring this mutation to their child (male or female) is up to 50%. This is why the proband’s relatives, who have not yet been diagnosed with this disease, also undergo this genetic testing. However, this fact does not mean that they do not carry the damaged part of either of these genes. Nor does the fact that they do not have this disease themselves mean that they are not carriers to the next generation. The risk for women who are carriers is less than 85% not 100%. Such testing is called predictive. Inherited forms of breast tumour appear in 5-7% [4,5].

The BRCA1 and BRCA2 genes are members of a group of tumour suppression genes, which repair damaged DNA so that it prevents cellular growth. Mutations in one of these genes result in an increased lifelong risk of tumours of the breasts and ovaries [6].

**Main section - Materials and Methods**

Studies have been conducted, which demonstrate that the BRCA1/2 genes have a serious impact on the risk of origin of breast ca and ovarian ca. These studies are constantly being varied and the environment we live in also plays a substantial role. Eight studies from various parts of the world, which were published between 2013 and 2018, summarise this data.

In 2013 Mavaddat et al. published a study that was conducted in Great Britain. This study was carried out on 1,887 women, carriers of pathogenic variants in the BRCA1 or BRCA2 gene (978 BRCA1, 909 BRCA2). This concerned one of the biggest prospective studies. 988 women were healthy at the beginning of the study. 1,509 women were not affected by ovarian ca at all and 651 women were diagnosed with unilateral breast ca. A calculation of the cumulative risk of origin of breast ca was performed for the 988 healthy women. At age 70 this was 60% for mutations in the BRCA1 gene and 55% for the BRCA2 gene. Of the 1,509 women without prior effects of ovarian ca, the results were as follows. The cumulative risk of origin of ovarian ca is 59% for the BRCA1 and 16.5% for the BRCA2 gene. In conclusion it was found that the potential risk of carriers of the BRCA1/2 mutation is very high. 651 women diagnosed with unilateral breast ca were found to be at potential risk of origin of contralateral breast ca, in 83% cases for BRCA1 and in 62% for BRCA2 (Table 1) [7].

A study (Brohet et al.), which included 758 families with a positive family anamnesis in the BRCA1 or BRCA2 gene, was published in the same year. Out of the analysed sample 2,546 individuals were carriers and 2,221 individuals were non-carriers. The cumulative risk of breast ca at age 70 was calculated at 45% for the BRCA1 gene and 27% for the BRCA2 gene. The cumulative risk of ovarian ca was calculated at 31% for BRCA1 and 6% for BRCA2 (Table 1). The average age at which women were diagnosed with breast ca was 45 years for the BRCA1 gene and 48 years for the BRCA2 gene. In 2006 the age of diagnosis fell to 40 years and 44 years for the BRCA1 and BRCA2 genes respectively. The average age of diagnosis of ovarian ca is 52 years for the BRCA1 gene and 54 years for the BRCA2 gene. The age for diagnosis in relation to the BRCA2 gene rose to 55 years in 2006 [8].

A year later, in 2014 a study was conducted on a sample of Israeli Jewish families. It found 211 female carriers of the BRCA1/2 gene mutation. The study was carried out by Gabai-Kapara et al. and indicated that the lifelong cumulative risk of origin of breast ca at age 60 is 41% and at age 80 it is 60% for the BRCA1 gene. For the BRCA2 gene the risk is 26% at age 60 and 40% at age 80. The lifelong cumulative risk of ovarian ca was calculated at 27% at age 60 and 53% at age 80 for the BRCA1 gene. For the BRCA2 gene the risk was calculated at 7% and 62% (age 60 and 80 years) (Table 1) [9].

With regard to the fact that most studies before 2015, which focused on the risk of breast ca and ovarian ca if there was a positive result in the BRCA1/2 genes, were conducted mostly on Caucasian populations, the Chinese study (Yang et al.) focused on the Chinese population. This study was carried out on a sample of 20 families with a BRCA1 or BRCA2 mutation, in which 64 positive cases were found. The cumulative lifelong risk of breast ca at age 70 was calculated at 67.2% in relation to BRCA1 and 76.8% in relation to BRCA2 (Table 1). The value for BRCA1 did not rise at age 80, but did increase to 93.1% for the BRCA2 gene. Because these values are high, the clinical significance of testing for mutations in the BRCA1/BRCA2 gene in the high-risk Chinese population is very important [10].

In 2015 Mersch et al. published a study in which 587 BRCA1 carriers and 406 carriers of a mutation in the BRCA2 gene participated. Of the carriers of a mutation in the BRCA1 gene, 345 women were diagnosed with breast ca and 178 were diagnosed with ovarian ca. Of the carriers of a mutation in the BRCA2 gene, 246 women were diagnosed with breast ca and 87 women were diagnosed with ovarian ca. The cumulative risk of breast ca was calculated at 59% for the BRCA1 gene and 61% for the BRCA2 gene. The cumulative risk of ovarian ca was 30% for BRCA1 and 21% for the BRCA2 gene (Table 1) [6].

The cumulative risk of breast ca in western countries is higher than in East Asian countries. This is caused by differences in environmental and lifestyle factors. This statement is also confirmed by a Korean study, which was published in 2015 (Park et al.). This study found 151 families with a BRCA1 mutation
and 225 families with a BRCA2 mutation. The cumulative risk of breast ca at ages 50 and 70 was calculated at 27% and 49% respectively for the BRCA1 gene. The risk was calculated at 18% at age 50 and at 35% at age 70 for the BRCA2 gene (Table 1). The average age of diagnosis of breast ca with a positive family anamnesis was estimated at 41.9 years for BRCA1 and 44.8 years for BRCA2. For carriers of the mutation in the BRCA1 gene the value was 37.8 years and for BRCA2 it was 42.1 years [11].

The Chinese study (Yao et al.), which was published in 2016, focused on establishing the cumulative risk of breast ca. The reason for this was that the risk linked to mutations in the BRCA1/2 genes in Chinese women was not previously known. The study included 7,365 women (of this 1,816 had breast ca). 70 mutations in the BRCA1 gene and 55 mutations in the BRCA2 gene were confirmed in these women whose BRCA genes were analysed. Approximately 5% of women diagnosed with breast ca had a mutation in one of the aforementioned genes. The cumulative risk of breast cancer at age 50, 60 and 70 years for the BRCA1 gene was calculated at 9.9%, 29.3% and 37.9%. For the BRCA2 gene these values were 10.7%, 27.2%, and 36.5% at age 70 (Table 1) [12].

According to the most recent study from 2018 (Kuchenbaecker et al.) it was found on a sample of 9,856 probands (6036 BRCA1 and 3820 BRCA2 women carriers, of these 5,046 were healthy and 4,810 had breast ca or ovarian ca or both) with proven mutations that the lifelong cumulative risk of breast ca at age 80 was 72% for the BRCA1 gene and 69% for the BRCA2 gene. The risk of ovarian ca at age 80 is 44% for the BRCA1 gene and 17% for the BRCA2 gene. The risk differs depending on the family anamnesis and type of mutation. Estimates of the risk at age 70 range from 40 – 87% for the BRCA1 gene and 27-84% for the BRCA2 gene. For ovarian ca these values are 16-68% for the BRCA1 gene and 11-30% for the BRCA2 gene. For contralateral breast ca the cumulative risk 20 years after diagnosis was 40% for BRCA1 and 26% for BRCA2 (Table 1) [13].

Similar studies had been conducted previously, before the results of the studies from 2010-2018 were known, however, these did not focus on eastern countries. These studies focused on western countries only. These selected studies concerning breast and ovarian ca were published between 2000 and 2008.

A group of British scientists published a study in 2000, which was conducted on a sample of 1,220 patients with breast ca who were genetically tested for the presence of mutations in the BRCA1/BRCA2 genes. 8 carriers of BRCA1 and 16 carriers of BRCA1 were confirmed. The cumulative risk of breast ca was calculated at 48% at age 80 for the BRCA1 gene and 74% for BRCA2. The cumulative risk of ovarian ca at age 80 was estimated at 22% for both genes (Table 2) [14].

In the study published by Satagopana et al. in 2001, the lifelong risk of breast ca in Jewish women at age 80 was calculated at 59% for the BRCA1 gene and 38% for the BRCA2 gene (Table 2) [15].

A study was conducted in 2002 (Brose et al.) on 483 female carriers of mutations in the BRCA1 gene in 147 families. The cumulative risk of breast ca for this gene was estimated at 72.8% and the risk of ovarian ca at 40.7% (Table 2) [16].

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of probands</th>
<th>Number of established mutations in the BRCA1 gene</th>
<th>Number of established mutations in the BRCA2 gene</th>
<th>Age</th>
<th>BRCA1 breast ca</th>
<th>BRCA2 breast ca</th>
<th>BRCA1 ovarian ca</th>
<th>BRCA2 ovarian ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mavaddat et al. 2013, GB</td>
<td>1,887 carriers from GB [7]</td>
<td>978</td>
<td>909</td>
<td>70</td>
<td>60%</td>
<td>55%</td>
<td>59%</td>
<td>16,5%</td>
</tr>
<tr>
<td>Brohet et al. 2013, Holland</td>
<td>758 families with a positive family anamnesis from Holland</td>
<td>582 families</td>
<td>176 families</td>
<td>70</td>
<td>45%</td>
<td>27%</td>
<td>31%</td>
<td>6%</td>
</tr>
<tr>
<td>Gabai-Kapara et al. 2014, Israel[9]</td>
<td>Jewish families from Israel, with 211 carriers</td>
<td></td>
<td></td>
<td>60</td>
<td>41%</td>
<td>26%</td>
<td>27%</td>
<td>7%</td>
</tr>
<tr>
<td>Yang et al. 2015, China[10]</td>
<td>20 families from China, with 64 carriers</td>
<td></td>
<td></td>
<td>70</td>
<td>67.2%</td>
<td>76.8%</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Mersch et al. 2015, USA[16]</td>
<td>993 carriers from the USA</td>
<td>587</td>
<td>406</td>
<td>x</td>
<td>59%</td>
<td>61%</td>
<td>30%</td>
<td>21%</td>
</tr>
<tr>
<td>Park et al. 2015, Korea[11]</td>
<td>376 positive families from Korea</td>
<td>2,472</td>
<td>3,879</td>
<td>50</td>
<td>27%</td>
<td>18%</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Yao et al. 2016</td>
<td>7,365 women from China</td>
<td>70</td>
<td>55</td>
<td>50</td>
<td>9.9%</td>
<td>10.7%</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Kuchenbaecker et al. 2018 GB</td>
<td>9,856 carriers from GB, Holland and France [13]</td>
<td>6,036</td>
<td>3,820</td>
<td>40-87%</td>
<td>27-84%</td>
<td>16-68%</td>
<td>11-30%</td>
<td>17%</td>
</tr>
</tbody>
</table>

Table 1: Classification of individual studies between 2013-2018.
Another study from 2003 (King et al.) also focused on Jewish women with inherited mutations in the BRCA1/2 genes and established the risk of breast and ovarian ca. 1,008 women underwent molecular genetic testing, regardless of their family anamnesis. The lifelong cumulative risk of breast ca in carriers of mutations reached 82%. It was found that the risk is rising over time. The risk of breast ca at age 50 (persons born before 1940) was 24%, after 1940 this risk rose to 67%. The lifelong cumulative risk of ovarian ca was calculated at 54% for sequential variants in the BRCA1 gene and at 23% for the BRCA2 gene 23% (Table 2). It was also found that more activity and the absence of obesity during adulthood contributed to a significant delay of the age at which breast ca appeared [17].

Chen et al. (2006) conducted a study on Jewish families and families living outside the United States of America. The study included 676 Jewish families and 1,272 families from other ethnic groups. Out of this these number 283 mutations in the BRCA1 and 143 mutations in the BRCA2 gene were confirmed. The cumulative risk for breast ca was estimated at 46% at age 70 for the BRCA1 gene and 43% for the BRCA2 gene. The cumulative risk for ovarian ca was estimated at 39% for the BRCA1 gene and 22% for the BRCA2 gene (Table 2) [18].

A subsequent study from 2008 (Milne et al.) was carried out in Europe, specifically in Spain. 155 carriers of mutations in the BRCA1 gene and 164 carriers of mutations in the BRCA2 gene were included in the analysis. The cumulative risk of breast ca up to age 70 was estimated at 52% for the BRCA1 gene and 47% for the BRCA2 gene. The cumulative risk for ovarian cancer is 22% for BRCA1 and 18% for BRCA2 (Table 2) [19].

The last study conducted by Evans et al. (2008) included 385 families with mutations in the BRCA1/2 genes (223 with BRCA1 and 162 with BRCA2). 904 mutation carriers were confirmed and in 1,442 women it was assumed they carried some sequential variant in the aforementioned genes. The cumulative risk of breast ca was estimated at 68% and 79.5% at age 70 and 80 respectively for BRCA1 and at the same ages these values were 75% and 88% for BRCA2 (Table 2) [20].

### Table 2: Classification of individual studies between 2000-2008.

<table>
<thead>
<tr>
<th>Study</th>
<th>Number of probands</th>
<th>Number of established mutations in the BRCA1 gene</th>
<th>Number of established mutations in the BRCA2 gene</th>
<th>Age</th>
<th>BRCA1 breast ca</th>
<th>BRCA2 breast ca</th>
<th>BRCA1 ovarian ca</th>
<th>BRCA2 ovarian ca</th>
</tr>
</thead>
<tbody>
<tr>
<td>English group. 2000, GB</td>
<td>1,220 women with breast ca in GB</td>
<td>8</td>
<td>16</td>
<td>80</td>
<td>48%</td>
<td>74%</td>
<td>22%</td>
<td>22%</td>
</tr>
<tr>
<td>Satagopan et al. 2001, USA</td>
<td>Jewish women</td>
<td>x</td>
<td>x</td>
<td>80</td>
<td>59%</td>
<td>38%</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td>Brose et al. 2002, USA</td>
<td>483 carriers in the USA</td>
<td>483</td>
<td>x</td>
<td>x</td>
<td>72.8%</td>
<td>x</td>
<td>40.7%</td>
<td>x</td>
</tr>
<tr>
<td>King et al. 2003, USA</td>
<td>1,008 Jewish women</td>
<td>x</td>
<td>x</td>
<td>50</td>
<td>67%</td>
<td>67%</td>
<td>54%</td>
<td>23%</td>
</tr>
<tr>
<td>Chen et al. 2006, USA</td>
<td>676 Jewish families, 1,272 families from other ethnic groups</td>
<td>283</td>
<td>143</td>
<td>70</td>
<td>46%</td>
<td>43%</td>
<td>39%</td>
<td>22%</td>
</tr>
<tr>
<td>Milne et al. 2008, Spain</td>
<td>319 carriers from Spain</td>
<td>155</td>
<td>164</td>
<td>70</td>
<td>52%</td>
<td>47%</td>
<td>22%</td>
<td>18%</td>
</tr>
<tr>
<td>Evans et al. 2008, VB</td>
<td>385 families with a positive family anamnesis in GB</td>
<td>223 families</td>
<td>162 families</td>
<td>70</td>
<td>68%</td>
<td>75%</td>
<td>x</td>
<td>x</td>
</tr>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>80</td>
<td>79.5%</td>
<td>88%</td>
<td>x</td>
<td>x</td>
</tr>
</tbody>
</table>

### Discussion

The average lifelong cumulative risk of breast ca and ovarian ca differs in individual countries and continents, both in per cent values and also in the frequency of occurrence of sequential variants in the BRCA1 or BRCA2 gene. Eight studies were chosen as a basis for comparison of the risk of individual carcinomas in various countries worldwide between 2013 and 2018.

Three of the selected studies focused on Europe (1 Great Britain, 2x Holland). These studies provided us with similar results for the estimate of the cumulative lifelong risk of breast ca at age 70. A large number of probands was examined (n=9,856) in the study from Great Britain. It is clear that the risk of breast ca increases with age, but this increase is not as noticeable in relation to ovarian ca. Higher per cent values are evident in the study by Mavaddat et al., however this is probably the result of the lower input value of probands, compared to the other two studies. In the American study (Mersch et al.) the risk of carcinoma was determined similarly to the European studies. However, the sample of probands is an order lower (n=993). The number of sequential variants in the BRCA1 gene is greater than in BRCA2 in both the European and the American studies.

Lower per cent values compared to western countries are evident after examination of studies carried out in East Asian countries (2x in China, 1x in Korea). This is probably the result of risk factors affecting humans, which differ in eastern and western countries. The East Asian study by Yang et al. gives much higher results than other eastern studies. This may be caused by the lower number of examined probands (20 families, with 64 positive carriers of the BRCA1/2 mutation), however, it is clear from the results of this study that the per cent values of breast cancer are higher in carriers of mutations in the BRCA2, gene than in the BRCA1 gene. But this does not apply in the Korean study by Park et al. The results for...
both BRCA1 and BRCA2 are very similar in the study published by Yao et al., whereas they differ by just one per cent.

On the contrary, the study by Yao et al. gives a much lower percentage of risk thanks to the higher number of probands. 7,365 probands were included in the study, 1,816 of these with breast ca and only 125 established mutations. Compared to similar numbers of examined probands with breast ca (e.g. the study by Mavaddata et al. from Great Britain) the risk of breast ca is much lower, by up to 20%. The number of sequential variants in BRCA1/2 is much lower in eastern countries. The number of mutations in the BRCA2 gene (Park et al.) is much higher than in the BRCA1 gene. This is contrary to the European and American studies. In the Chinese study by Yao et al. the number of sequential variants in these two genes is approximately similar.

The Israeli study (Gabai-Kapara et al.) also investigated ovarian ca. It focused on Israeli Jewish women. A high risk of ovarian ca was calculated for the 211 carriers at age 80. Unfortunately, this could not be compared to East Asian studies, because these focused only on breast ca, not on ovarian ca. Compared to western countries the result is a high percentage of risk of ovarian ca.

Within the terms of comparison of the two groups from 2000-2008 and from 2013-2018, when the aforementioned studies were published, it is clear that the risk of breast ca is lower in East Asian countries than in Europe and the USA. Unfortunately, no studies have been carried out in eastern countries (such as China and Korea) in recent years, but it can be stated that the incidence of breast ca is lower in East Asian countries in the studies dating from the 2014 – 2016 period.

During comparison of the groups from the European studies from 2000-2008 and 2013 – 2018, it can be stated that the results are similar. In both earlier studies (the British group 2000 and Roger et al. 2008) it is evident that the number of mutations is greater in the BRCA2 gene than in the BRCA1 gene. Which is contrary to today’s studies (2013 – 2018).

There is a visible difference in the European studies from Great Britain dating from 2000 and 2013. In 2000 the study was conducted on 1,220 women with breast ca and in 2013 this number was 1,887. Although cumulative lifelong risks are estimated for age 80 in the case of the study from 2000 and for age 70 in the case of the study from 2013, there is a clear difference. The cumulative risk for breast ca in relation to the BRCA2 gene was higher in 2000 than in 2013. The risk of ovarian ca in 2000 was much lower than in 2013.

When comparing the USA studies from 2002 and 2015, the estimate of the lifelong cumulative risk of carcinoma reached a much higher percentage in previous years than it does now. This may partially be caused by the number of probands entering the studies. Only the BRCA1 gene can be compared, not BRCA2 because the risk was not calculated in 2002.

Studies, which were conducted on Israeli Jewish women in 2003 and 2014, give the following results. The study from 2003 (King et al.) gives a higher percentage value for the risk of breast ca at age 50 compared to the later study (Gabai and Kapara et al. 2014), which focused on a later age (60 and 80). In studies from 2003 women carrying a mutation of the BRCA1 gene had a much higher risk of ovarian ca (at age 50) than in the subsequent study. The risks balanced out for age 80. On the contrary, the study from 2014 gave a high risk of ovarian ca for women carrying a mutation in the BRCA2 gene. This risk rose rapidly with age. At age 60 it was 7% and at age 80 it was 62%.

Mutations in the BRCA1 gene predominated in individual studies between 2000 and 2008. On the contrary, in European studies (English group and Roger et al.), there were higher numbers of mutations in the BRCA2 gene.

Conclusion - Results

The results from studies carried out until 2010 do not differ significantly from the results from later years. But there is a visible difference between the lifelong risk of breast cancer between eastern and western countries. The risk of breast ca in western countries continues to be higher than in studies conducted in eastern countries. The Near East, the study conducted on Israeli Jewish women, falls somewhere in the middle of these two margins. The difference between western and eastern countries is undoubtedly the result of different living conditions, lifestyle and probably also the level of advancement of western cultures. Whether this concerns education, later pregnancy, use of hormonal contraceptives and similar. East Asian countries have not yet focused on ovarian ca, so these risks cannot be compared between the western and eastern worlds.

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