Prevalence of breast cancer predisposition gene mutations in Chinese women and guidelines for genetic testing

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Abstract

Background: Breast cancer is the most common cancer among Caucasian females. On average, 1 in 12 women will have breast cancer during their lifetime. There is a marked difference in breast cancer incidence in Chinese. In Hong Kong women, the lifetime risk is 1 in 29. BRCA1 and BRCA2 are high-penetrant cancer predisposition genes, but the prevalence and nature of mutations in these genes appear to be ethnic-specific. It is not clear if the differences in cancer incidence between Caucasians and Chinese are due to genetic or environmental factors. Methods: In our investigation of BRCA1 mutations among Chinese female patients in Hong Kong, BRCA1 mutations were found in 3.8% CI: 1.3–8.8% of 130 breast cancer patients. The prevalence was higher in a separate group of 56 early onset patients, aged < 45 years, (8%, CI: 2.2–19.2). Most of the mutations were different from those reported in Caucasians. A deletion 589delCT was found in three unrelated patients, which may represent a common mutation. Similar prevalence of mutations was reported in Taiwan and Singapore Chinese. Other low-penetrant cancer predisposition genes may be important in the pathogenesis of the majority of breast cancers. Conclusions: Although the epidemiology of breast cancer is different between Caucasians and Chinese, the prevalence of mutations in the high-penetrant cancer-predisposition gene of BRCA1 is comparable. It may indicate that the role of genetic contribution to breast cancer may be similar in the two ethnic groups and the difference in epidemiology may be contributed more heavily by environmental factors. © 2001 Elsevier Science B.V. All rights reserved.

1. Introduction

Breast cancer is one of the top three common malignancies among women in Hong Kong and other Chinese communities. In addition, there is an increasing trend for the incidence of breast cancer in most Asian countries [1,2]. However, the epidemiology of breast cancer is markedly different between Chinese and Caucasian populations. The overall incidence of breast cancer in Chinese is only about half of that in Caucasians. The cumulative lifetime risk is about 1 in 10 in Caucasians, while it is 1 in 24 in Hong Kong Chinese [3]. Furthermore, a higher proportion of Chinese patients have early onset cancers, i.e. before the age of 45 years. However, the majority of patients present at older age in Western countries, where the incidence of breast cancer in the age range is lower.
group of 55–64 years was almost three times higher than that of the 35–44-year-age group [1,3].

The inheritance of a defective cancer susceptibility gene is responsible for most familial breast cancer and a significant proportion of early onset breast cancers. The difference in disease epidemiology indicates a difference in the interaction between genetic and environmental carcinogenic factors across populations. Data of the mutation rate and criteria of case selection for genetic testing developed in Western countries might not be applicable to Chinese without prior studies in this population.

Over the past few years, more data of BRCA1/BRCA2 mutations have been reported from Chinese patients. It allows a systemic review of the prevalence and nature of mutations. From these data, a guideline for application of genetic testing in Chinese breast cancer patients is proposed.

2. Risk factors of breast cancer

Risk factors of breast cancer can be broadly divided into environmental and genetic categories. Environmental risk factors have been intensively studied by epidemiologists. Age, race, reproductive history, diet and use of oral contraceptive have been identified to influence the risk of breast cancer [4,5]. In addition, family history of breast cancer was also recognized as a significant risk factor [6]. This finding provided an early clue as to the role of genetic influence in breast cancer.

Genetic predisposition to cancer is conferred by two categories of genes. A minority of patients inherit mutations in high-penetrance genes, which carry a very high (up to 80%) lifetime risk of cancer [7]. The BRCA1 and BRCA2 genes belong to this category. Carriers of these mutations have a more than 10-fold higher risk of breast cancer. Most familial breast cancer patients inherit mutations in BRCA1/BRCA2. For example, germline mutations in BRCA1 account for the inheritance in about 50% of site-specific breast cancer families and more than 80% of breast and ovarian cancer families [8]. BRCA1 and BRCA2-linked cancers tend to be early onset. However, the proportions of breast cancers that are due to BRCA1 and BRCA2 mutations are very different among different populations [9,10].

The other category of genes have a lower penetrance and carriers of mutations in these genes have a modest increase in cancer risk [11]. The magnitude of increased risk of cancer is usually around 2–3-fold. These genes commonly encode for proteins, which are responsible for degradation or activation of carcinogens. Although the relative risks conferred by these mutations are modest, the high-risk alleles are present in a high frequency in the population. Therefore, they are likely to be involved in the pathogenesis of breast cancer in a much larger proportion of patients than the high-penetrance genes [11]. For example, specific alleles of glutathione S-transferase and P450 enzyme families, including CYP1A and CYP17, were found to associate with a 2–3-fold risk of breast cancer risk [12,13].

3. High-penetrance genes and familial breast cancer

Familial breast cancer is inherited in an autosomal dominant mode. Studies of these families led to the identification of two high-penetrance predisposition genes (BRCA1 and BRCA2). A few other high-penetrance cancer syndrome predisposition genes also increase the risk of breast cancer in addition to the risk of other cancers. They include p53 in Li–Fraumeni syndrome, PTEN in Cowden syndrome, and ATM in ataxia–telangiectasia syndrome.

3.1. BRCA1 and BRCA2 genes

The first breast cancer predisposition gene, BRCA1, was found to confer a high risk for both breast cancer and ovarian cancer [14]. BRCA1 is composed of 22 coding and two non-coding exons with a cDNA encoding 1863 amino acids. Subsequently, another breast cancer susceptibility gene located on chromosome 13q12–13, BRCA2, was cloned [15]. It consists of more than 5000 nucleotides spanning over 70 kb. BRCA2 is also linked to hereditary breast cancer, but in contrast to BRCA1, it also confers an increased risk for breast cancer in male members of these families. BRCA1 and BRCA2 mutations account for over 90% of all hereditary
breast cancer, with BRCA2 contributing to equal proportion as for BRCA1 in these families [9,16].

To date, more than 300 heritable mutations in the BRCA1 gene have been found throughout the whole coding sequence and were archived in the Breast Cancer Information Core together with mutations of BRCA2 [17]. Virtually all known BRCA1 mutations are germline and more than 85% are nonsense or frameshift mutations leading to premature termination of protein translation. Similarly, BRCA2 has its mutation distributed over its entire coding region.

Ancient and founder BRCA1 mutations have been identified in specific ethnic groups [10]. The 185delAG mutation in exon 2 is found in more than 1% of all Ashkenazi Jewish and more than 20% Jewish women with early onset breast cancer [18,19]. The 5382insC mutation in exon 20 is another ancient mutation which occurs in Caucasians including Jewish, Russian and Hungarian populations [9,17]. Most of these ancient mutations occur only in specific populations. Founder mutations of BRCA2 have been found in Ashkenazi Jews (6174delT) and Icelanders (999del5) [18,20]. These ethnic-specific mutations suggest that there is a strong regional difference across ethnic groups in the nature and prevalence of BRCA1 and BRCA2 mutations [10].

3.2. Function of BRCA1 and BRCA2 genes

There was little information on the function of BRCA1 when it was first cloned in 1994, though it appeared to be a tumour suppressor protein. Homology studies did not reveal any similarity with known genes or proteins. The lack of a functional assay on the BRCA proteins makes interpretation of mutations found in patients’ samples difficult, particularly for missense mutations. Most truncating mutations could be classified as deleterious and lead to loss of protein function. On the other hand, it is more difficult to determine if a missense mutation represents a benign polymorphism or a deleterious mutation leading to cancer development.

Recent structural and functional studies on the two proteins provided new information and suggested that they were involved in the maintenance of genomic integrity, DNA repair and transcription regulation [21,22]. BRCA1 protein is composed of a RING finger domain, a nuclear localizing signal, a transcription activation domain and a RAD51 binding domain. RAD51 protein is involved in the maintenance of genome integrity during the cell cycle. BRCA1 binds with ZBRK1 to form a nuclear protein complex, which modulates transcription of DNA damage-inducible genes [23]. It also acts as a repressor for Myc-mediated transcription activation through interaction with Myc protein. BRCA2 also contains RAD51 binding sites and transactivation domain, and it interacts with BRCA1 in expression studies. A detailed discussion of the functions of BRCA protein is outside the scope of this review and readers could refer to recent review articles [22,24,25].

3.3. Clinical application of genetic testing for BRCA1/2 in Chinese

There are some practical issues in the clinical application of genetic testing for breast cancer:

1. Which are the BRCA1 and BRCA2 mutations found in the Chinese population? And what is the prevalence of mutation carriers?
2. Is there any mutation that occurs in a high frequency in Chinese population? Is there any founder mutation, such as the 185delAG in Ashkenazi Jews?
3. Is there any particular clinical and pathological feature among patients who carry mutations in BRCA1 or BRCA2? Could any feature be used as an indicator for the selection of patients for genetic testing?

4. Prevalence of BRCA1 and BRCA2 and founder mutations

As BRCA1 and BRCA2 have been studied more extensively in Caucasian populations, the prevalence of these two genes are better established. In Western populations, BRCA1 mutations account for up to 50% of familial cases [16,26]. A slightly lower prevalence of mutation carriers had been found for BRCA2 [9,27]. It is estimated that about 7% of
breast cancer patients carried mutations in either gene and had an inherited breast cancer [10,28].

The prevalence of mutation carriers is higher among patients with early onset breast cancer. As inherited cancers tend to develop earlier than sporadic ones, BRCA1 mutations were found in up to 15% of patients with early onset cancer [29,30].

5. Studies in Chinese and other Oriental populations

However, a lower prevalence of BRCA1 mutations had been reported among Japanese breast cancer families. An early study using linkage analysis showed that none of 11 Japanese breast cancer families were linked to the BRCA1 locus [31]. Subsequent studies by the same group found that a BRCA1 mutation was present in only 2 out of 20 selected high-risk families [32]. This was in contrast to studies in Caucasians in which more than 90% of familial breast cancers were accounted to inherited mutations in BRCA1 and BRCA2 [9]. These early studies led to a suggestion that in Oriental populations, BRCA1 may not be as important as in Caucasians.

We investigated the prevalence of BRCA1 mutations among a sample of 130 breast cancer samples and in an additional 56 patients with early onset cancer (<45 years) [33]. BRCA1 mutations were found in 3.8% (confidence interval, CI: 1.3–8.8%) of all breast cancer patients. The prevalence was higher in the subgroup of early onset patients (<45 years), which was 8% (CI: 2.2–19.2%). Most of the mutations were different from those reported in Caucasians. These prevalence figures are similar to those reported in Caucasians. Subsequent reports from other Asian populations from Japan and Singapore also arrived at similar figures [34–36].

A two-base deletion, 589delCT was found in three unrelated patients, which may represent a common mutation in Hong Kong Chinese. However, a subsequent screening for the 589delCT in another 60 early onset breast cancer patients did not reveal any further carriers of this mutation. Other recurrent mutations found in the Oriental populations are listed in Table 1. They included a 10-base deletion in intron 7 and V191I, in addition to 589delCT. However, no founder mutations in the Chinese population have been established.

6. Clinical and pathological indicators for identifying mutation carriers

Overall, mutations of BRCA1/2 are uncommon in the general population and account for a small proportion (5–7%) in all cases of breast cancer. Unselected screening for mutations is not justified. Therefore, it is important to identify patients who have a high pre-test probability of carrying a mutation to justify genetic testing. The pre-test probability of carrying a mutation has been related to ethnicity, number of affected family members, presence of other cancers related to BRCA1/2, and presence of bilateral tumours and medullary breast cancer [37,38]. However, with a different epidemiology and age-specific incidence, models for estimation of the pre-test probability derived from Caucasian populations

Table 1

<table>
<thead>
<tr>
<th>Exon</th>
<th>Mutation</th>
<th>Cancer type</th>
<th>References</th>
</tr>
</thead>
<tbody>
<tr>
<td>7</td>
<td>IVS7-24delACTGTCTTT*</td>
<td>breast</td>
<td>[41]</td>
</tr>
<tr>
<td>8</td>
<td>589delCT*</td>
<td>breast</td>
<td>[33]</td>
</tr>
<tr>
<td>8</td>
<td>Q172X</td>
<td>ovary</td>
<td>[45]</td>
</tr>
<tr>
<td>9</td>
<td>V191I(?)*</td>
<td>breast</td>
<td>[43]</td>
</tr>
<tr>
<td>10</td>
<td>1080delT</td>
<td>ovary</td>
<td>[45]</td>
</tr>
<tr>
<td>11</td>
<td>1129delA</td>
<td>ovary</td>
<td>[45]</td>
</tr>
<tr>
<td>11</td>
<td>1510delC</td>
<td>breast</td>
<td>[43]</td>
</tr>
<tr>
<td>11</td>
<td>1523delG</td>
<td>breast</td>
<td>[43]</td>
</tr>
<tr>
<td>11</td>
<td>2371delTG</td>
<td>ovary</td>
<td>[45]</td>
</tr>
<tr>
<td>11</td>
<td>2430insC</td>
<td>breast</td>
<td>[43]</td>
</tr>
<tr>
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<td>2732insT</td>
<td>breast</td>
<td>[43]</td>
</tr>
<tr>
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<td>3378/81delG</td>
<td>breast</td>
<td>[43]</td>
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<tr>
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<td>3976delGTGA</td>
<td>ovary</td>
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<td>ovary</td>
<td>[46]</td>
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<td>E879X</td>
<td>breast</td>
<td>[47]</td>
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<tr>
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<td>P1150S(?)</td>
<td>breast</td>
<td>[33]</td>
</tr>
<tr>
<td>11</td>
<td>K1183R(?)</td>
<td>breast</td>
<td>[43]</td>
</tr>
<tr>
<td>13</td>
<td>R1443X</td>
<td>breast</td>
<td>[43]</td>
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<td>14</td>
<td>Q1458X</td>
<td>breast</td>
<td>[33]</td>
</tr>
<tr>
<td>22</td>
<td>IVS22+7A/G (?)</td>
<td>ovary</td>
<td>[45]</td>
</tr>
</tbody>
</table>

(*) The biological significance of these missense mutations is uncertain.

* Mutations were found to be recurrent in Chinese patients, i.e. identified in more than one unrelated families.
Table 2
Guideline for selecting candidate for \textit{BRCA1}/\textit{BRCA2} genetic testing

- Familial breast cancer ± ovarian cancer, inherited in an autosomal dominant mode
- Early onset breast cancer (\(< 45\) years) plus an affected (either breast or ovarian cancer) first-degree relative
- Patients with ovarian cancer
- Patients with medullary breast carcinoma

would not apply to the Chinese, and ethnic group-specific guidelines are required.

Such guidelines can be developed by comparing the clinical and pathological features between inherited breast cancers and sporadic cases. Such differences could be used to form the selection criteria used to identify patients with high probabilities of being mutation carriers for genetic testing. Previous studies in Western countries have identified that strong family history of breast/ovarian cancer, and an early onset of cancer were the most important parameters in determining the probability of carrying a mutation [37,39]. It will provide an important piece of information in genetic counseling and will allow patients to make an informed decision on genetic testing. In addition, genetic testing is expensive; therefore, a better selection of a candidate for genetic testing also enhances its cost-effectiveness. Taking into account the various issues involved in genetic testing, the American Society of Clinical Oncology (ASCO) [40] came to a consensus on the minimal pre-test probability of carrying a mutation required to indicate for a genetic testing. The panel recommended that cancer predisposition tests should be offered to individuals who had greater than 10\% chance of carrying mutations. Therefore, the prevalence data of mutation carriers is important to determine which subset of Chinese patients would benefit most by genetic testing. A guideline for breast cancer predisposition gene testing for Chinese has been developed from presently available data (Table 2).

7. Age and family history

Patients from families with autosomal dominantly inherited breast cancer are indicated for genetic tests. In a study of 18 such families in Taiwan, mutations in either \textit{BRCA1} or \textit{BRCA2} were found in about 30\% [41]. A similar figure was also reported in the Japanese families [36,42].

In our study, 8\% of early onset (\(< 45\) years) cancer patients carried a \textit{BRCA1} mutation. This pre-test probability approaches the probability required by the ASCO for indication of mutation study. In Caucasians, if one or more relatives of these early onset patients had breast cancer, the probability of carrying a \textit{BRCA1} mutation was doubled. The absence of data in Chinese precludes an accurate determination of the risk of carrying \textit{BRCA1}/\textit{BRCA2} mutation. If we assumed that a significant family history doubles the risk of carrying a mutation, as observed in Caucasians, early onset breast cancer patients who also have a first-degree relative affected by breast or ovarian cancer would be a suitable candidate for genetic testing. This assumption was supported by a recent study in Singapore Chinese [43]. They showed that about 8\% of early onset breast cancer had a \textit{BRCA1} mutation and 2 out of 10 early onset patients with a significant family history carried a mutation.

7.1. Pathological features of breast cancer

Medullary breast cancers were found to be more common among mutation carriers [38,44]. In our study in Chinese patients, one out of five cancers with \textit{BRCA1} mutations was medullary type [33]. Similarly, Eisinger et al. [38] found that 19\% of their series of breast cancers with \textit{BRCA1} mutations were medullary breast carcinomas. Medullary breast carcinoma is a rare histological type of breast cancer. In a review of 200 consecutive cases without \textit{BRCA1} mutation, no medullary breast cancers were found [38]. Therefore, diagnosis of medullary breast carcinoma could be a useful indicator for genetic test.

7.2. Ovarian cancer

The lifetime risk of ovarian cancer among \textit{BRCA1} mutation carriers is about 60\%. In the Chinese population, ovarian cancer is rare, on average only 1 in 120 women will develop this cancer in her lifetime. Therefore, patients with ovarian cancer would be potential candidates for \textit{BRCA1} testing. In contrast,
BRCA2 does not lead to an excessive risk of ovarian cancer. Khoo et al. [45] reported that 10% of apparently sporadic ovarian cancer patients had a germline mutation in BRCA1, while one additional patient (2%) had a BRCA2 mutation.

8. Conclusion

Cancer predisposition genetic testing is a complex issue. Ethnic specific data is very important in the practice of genetic counseling and application of genetic testing in a population [10]. There are many other societal and ethical implications, which are also important but could not be included in this review. Other key issues include correct interpretation of results, good communication between genetic counselor and patients, and acceptance and attitude towards pre-symptomatic testing in the cultural context. We reviewed the present information of BRCA1 and BRCA2 mutations in Chinese patients and developed evidence-based guidelines for testing Chinese patients.

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