Largest ever screening study for BRCA1/2 Mutations in Breast Cancer patients in China


*Corresponding author  Institution: Southwest Hospital of Third Military Medical University  Email: jcbd@medmail.com.cn

Funded by China Health Promotion Foundation

Background

- Lack of basic BRCA mutations information hinders construction of risk prediction model of breast cancer (BC) in China with fast growing BC incidence.

- To determine the prevalence and spectrum of BRCA mutations in Chinese BC patients.

Methods

- Chinese Clinical Trial Registry: ChiCTR-EOC-15007126. Sep 2015
- Every study center was approved by their local medical ethics committee. Every subject signed an informed consent.
- A cross-section cohort of 1106 in 1328 selected patients from 15 provinces of China (16) was built during 10/2015 to 10/2016. Criteria: age <35y or ≥1 BC/ovarian cancer (OC) relatives or two primary BC(TBC) or BC&OC (+OC) or male BC (MBC).
- 5 ml/subject fresh blood was sent for free full BRCA sequenced testing by NGS with Illumina provided by Anitori Gene Technology (Beijing) Co. Ltd (Fig.2).
- Every subject obtained a sealed file of test result and free genetic consultation.

Results

- Total of 13.3% BRCA mutation rate (202/1106).

| Groups      | BRCA Mutation (%) | N (n=932) | Area | Criteria
|-------------|-------------------|-----------|------|-----------
| ≤35y        | 190(16.9)         | 529(56.9)| North| Only ≤35y
| ≥35y        | 104(10.2)         | 390(41.7)| South| 1 BC/OC relative
| Mixed       | 150(16.7)         | 296(31.8)| West | ≥2 BC/OC relatives
| Mixed       | 134(14.6)         | 23(2.5)  | Criteria| ≥1 criterion

- Median age was 35 (Range 8-77).
- 12.9% of mutation rate for BC subjects ≤35y
- The rate of only ≤35y group was much lower than those with other criteria (≤35y mixed)

| Groups      | BRCA Mutation (%) | N (n=932) | P
|-------------|-------------------|-----------|------
| ≤35y        | 190(16.9)         | 529(56.9)| 0.4 |
| Only ≤35y   | 190(16.9)         | 529(56.9)| <0.0001 |
| ≤35y mixed  | 150(16.7)         | 296(31.8)| <0.0001 |

- 56-60y was the peak age of mutation rate for both general and triple-negative breast cancer (TNBC) patients.

- The most common other tumors of family relatives of probands were endometrial cancer for BRCA1, lung cancer for BRCA2 alone.

- BC and BC&OC family histories increase the risk of BRCA1 mutation alone

Molecular Types ([n=1070, HER2 Types were excluded due to low mutation rate (2/110)]

<table>
<thead>
<tr>
<th>Gene</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (n=932)</td>
<td>LuminalA (n=768)</td>
<td>LuminalA (n=762)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>94(4.7)</td>
<td>81(13.5)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>98(4.0)</td>
<td>10(10.2)</td>
</tr>
</tbody>
</table>

- Compared with BRCA-, BRCA1 mutation increased the probability of luminal A BC happening. BRCA2 increased the probability of luminal B BC happening.

- Compared with BRCA-, BRCA1 mutation increased the risk of higher Ki67(≥14%)

<table>
<thead>
<tr>
<th>Gene</th>
<th>BRCA1</th>
<th>BRCA2</th>
</tr>
</thead>
<tbody>
<tr>
<td>N (n=932)</td>
<td>Ki67 (%)</td>
<td>N (n=932)</td>
</tr>
<tr>
<td>BRCA1</td>
<td>149(4.4)</td>
<td>14% (n=762)</td>
</tr>
<tr>
<td>BRCA2</td>
<td>4.9(1.8, 13.5)</td>
<td>3.002 &lt;0.0001</td>
</tr>
</tbody>
</table>

- Sites uninvestigated duplicated more than twice:
  - BRCA1:c.15470 T -> C, 7 times
  - BRCA2:c.11270 T -> G, 3 times
  - BRCA1: 1121 G -> T, 4 times
  - BRCA1: 2880, 2808A -> AAAC, 3 times

Mutation sites

- Total of 150 different mutation sites (BRCA1 66, BRCA2 84) were found from 202 carriers, included 68 (45.3%) novel (Red) and 17 (11.3%) variants of unknown significance (VUS) (Blue).

- BRCA1 c.16_17del was novel involved male rectal cancer.


- The most common other tumors of family relatives of probands were endometrial cancer for BRCA1, lung cancer for BRCA2 alone.

- A similar prevalence in BC patient ≤35y in that in the West with no geographical differences.
- The age of BC diagnosis, including TNBC, should be increased to 60y in China for BRCA testing.
- Prognosis with BRCA2 mutation is worse, due to higher Ki67 and high risk of TNBC.
- BRCA2 mutation is more common in China.
- BRCA related hereditary tumors in China were different with common known cancers (pancreas, prostate).

Conclusions

<table>
<thead>
<tr>
<th>Family</th>
<th>N (n=1195)</th>
<th>Mutation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Null</td>
<td>551</td>
<td>488</td>
</tr>
<tr>
<td>BC</td>
<td>390</td>
<td>296</td>
</tr>
<tr>
<td>OC</td>
<td>30</td>
<td>23</td>
</tr>
<tr>
<td>BC&amp;OC</td>
<td>22</td>
<td>10</td>
</tr>
<tr>
<td>Others</td>
<td>113</td>
<td>87</td>
</tr>
</tbody>
</table>

- Screening 40 panel breast cancer related genes from the same cohort
- Investigation of family pedigrees of the probands
- Follow-up of healthy carriers