Short Report

Risk of having BRCA1 mutation in high-risk women with triple-negative breast cancer: a meta-analysis


Testing for BRCA1 mutation has important clinical implications such as identifying risk of second primary cancers and risk of cancer in the family. This study seeks to quantify the risk of having BRCA1 mutation in female breast cancer patients with triple-negative phenotype compared with those with other phenotypes. We undertook a search of MEDLINE and EMBASE databases for relevant studies through 10 May 2013. Outcomes were calculated and reported as risk ratio and risk difference. 12 studies comprising 2533 breast cancer patients were included in the analysis. It was found that almost all eligible studies were performed on high-risk population with breast cancer. By analyzing the incidence rates of BRCA1 mutation in patients with triple-negative breast cancer (TNBC) and non-TNBC, our meta-analysis provides a relative risk of 5.65 [95% confidence interval (CI), 4.15–7.69] and risk difference of 0.22 (95% CI, 0.15–0.29). This implies that, in selected population with high-risk features, women with TNBC are approximately five and a half times more likely to have BRCA1 mutation compared with non-TNBC phenotype, and approximately two in nine women with TNBC harbor BRCA1 mutation. Triple-negative phenotype significantly increases the risk of having BRCA1 mutation in high-risk breast cancer patients compared with non-TNBC.

Conflict of interest

Authors declare that there are no potential conflicts of interest.

BRCA1 and BRCA2 mutations have been estimated to account for about 40% of familial breast cancer (1). Women with BRCA1 mutation have a lifetime risk of breast cancer ranging from 65% to 87% (2, 3), which is about five to seven times greater than that of the general population (risk estimated at 12.4%) (4).

BRCA1-associated breast cancers frequently manifest a ‘triple-negative’ immunohistochemistry profile (estrogen and progesterone receptors negative and HER2 non-overexpressing). The triple-negative phenotype may be a useful adjunct to develop BRCA mutation prediction models (5). Although previous studies have shown an increased incidence of BRCA1 mutation in women with triple-negative breast cancer (TNBC), the risk of having BRCA1 mutation in women with TNBC has not been fully elucidated. Drawing on available data in the literature, this meta-analysis aims to provide the essential link between BRCA1 mutation and TNBC by identifying the relative risk of BRCA1 mutation in TNBC compared with non-TNBC, as well as the risk difference.

Methods

Literature search

Two authors independently performed a literature search by using MEDLINE and EMBASE databases
Tun et al.

through 10 May 2013. The keywords used were ‘brca AND triple-negative’. The abstracts of the resulting citations were reviewed, and full-text manuscripts were retrieved for potential studies. In addition, the references of the selected articles were scrutinized for any additional relevant studies.

Eligibility criteria

Studies were included in the meta-analysis if related data for the number of patients with BRCA1 mutation, TNBC and non-TNBC could be extracted from potential studies. Studies with incomplete data on BRCA1 mutation, estrogen and progesterone receptors and HER2 status were excluded. Studies written in both English and non-English languages were screened. Studies on male breast cancer were excluded. Any discrepancies were addressed by a joint re-evaluation of the original manuscript with a third reviewer.

Data extraction

The following data were extracted from each study: first author’s last name, year of publication, country of origin, method of BRCA1 mutation testing, type of patients such as high-risk or unselected, age range, and the number of patients with BRCA1 mutation, TNBC and non-TNBC. Data extraction was conducted independently by two authors with any discrepancies resolved by consensus and discussion with a third author.

Quality assessment

The quality of each study was evaluated independently by two authors using the Newcastle-Ottawa Scale (NOS) (6). The NOS consists of three parameters of quality assessment: selection, comparability, and exposure (case–control studies) or outcome (cohort studies). The NOS assigns a maximum of four points for selection, two points for comparability, and three points for exposure/outcome. Therefore, nine points on the NOS reflects the highest study quality. Any disagreements were addressed by a joint re-evaluation of the original manuscript with a third author.

Data synthesis and analysis

The number of patients with BRCA1 mutation, TNBC and non-TNBC were ascertained to be from the same sample tested for both BRCA1 mutation and triple-negative phenotype by carefully examining the data and building a $2 \times 2$ table for each potential study. With basic data input, Mantel-Haenszel method was applied to calculate the pooled event-based risk ratio and risk difference with 95% confidence interval (95% CI) using the random-effects model (7). All statistical analyses and graphs except trim-and-fill procedure were obtained by using REVIEW MANAGER (REVMAN) version 5.2 (The Cochrane Collaboration, The Nordic Cochrane Centre, Copenhagen). The level of significance was set at $p < 0.05$. Data from this meta-analysis are presented in accordance with the checklist proposed by the PRISMA Statement (9).

Results

Search results

A total of 12 studies (10–21) comprising 2533 breast cancer patients were eligible for inclusion in our meta-analysis. The detailed steps of the literature search are depicted in Fig. 1.

Characteristics of the studies

Details of the included studies are provided in Table 1. The studies were published between 2006 and 2013. The majority of the studies focused on incidence of BRCA1 mutation, with a few looking at clinical outcomes of patients with BRCA1 mutation and/or triple-negative phenotype. All but one study (19) involved high-risk patient populations (Table 2). The method of BRCA1 testing varied with study location.

Meta-analysis results

Meta-analysis revealed a pooled risk ratio of 5.65 (95% CI, 4.15–7.69) and risk difference of 0.22 (95% CI, 0.15–0.29). The number needed to test was approximately 4.5 patients with TNBC to detect one BRCA1 mutation. Figures 2 and 3 summarize the individual study estimates and overall estimate of risk ratio and risk difference, respectively.

Quality assessment results

The details of the quality assessment for each study are shown in Table 2. The average NOS score was 8.5. The most common bias was representativeness of the exposed cohort.

Heterogeneity and publication bias

Moderate between-study heterogeneity was present for risk difference analysis ($I^2$, 73%). Funnel plots for risk ratio and risk difference showed mild asymmetry, indicating some publication bias. Sensitivity analyses revealed that there was little difference (<5%) between the effect estimates of fixed and random-effects models, and the trim-and-fill method did not identify any studies which would have altered our results significantly.
Risk of BRCA1 mutation in TNBC

Fig. 1. Search Results. BC, patients with breast cancer; TNBC, patients with triple-negative breast cancer.

Table 1. Characteristics of included studies in the meta-analysis

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Country</th>
<th>Method of BRCA1 testing</th>
<th>Study population</th>
<th>Age range (years)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Atchley et al.</td>
<td>2008</td>
<td>USA</td>
<td>Not mentioned</td>
<td>High-risk</td>
<td>25–71</td>
</tr>
<tr>
<td>Bayraktar et al.</td>
<td>2013</td>
<td>USA</td>
<td>Myriad, germline DNA</td>
<td>High-risk</td>
<td>Not specified</td>
</tr>
<tr>
<td>Chen et al.</td>
<td>2009</td>
<td>China</td>
<td>DHLPC, germline DNA</td>
<td>High-risk, Northern Chinese</td>
<td>Not specified</td>
</tr>
<tr>
<td>Comen et al.</td>
<td>2011</td>
<td>USA</td>
<td>Pyrosequencing, germline DNA</td>
<td>High-risk</td>
<td>Not specified</td>
</tr>
<tr>
<td>Haffty et al.</td>
<td>2006</td>
<td>USA</td>
<td>Not mentioned</td>
<td>High-risk</td>
<td>Not specified</td>
</tr>
<tr>
<td>Kwong et al.</td>
<td>2010</td>
<td>Hong Kong</td>
<td>MLPA, germline or tumor DNA</td>
<td>High-risk</td>
<td>Not specified</td>
</tr>
<tr>
<td>Li et al.</td>
<td>2008</td>
<td>China</td>
<td>SSCP and DHPLC, germline DNA</td>
<td>High-risk, Han Chinese</td>
<td>Not specified</td>
</tr>
<tr>
<td>Musolino et al.</td>
<td>2007</td>
<td>Italy</td>
<td>DHLPC, germline DNA</td>
<td>High-risk</td>
<td>&lt;45</td>
</tr>
<tr>
<td>Ou et al.</td>
<td>2013</td>
<td>China</td>
<td>DHLPC, germline DNA</td>
<td>High-risk</td>
<td>&lt;45</td>
</tr>
<tr>
<td>Xu et al.</td>
<td>2012</td>
<td>China</td>
<td>HRM, tumor DNA</td>
<td>Unselected</td>
<td>29–76</td>
</tr>
<tr>
<td>Yip et al.</td>
<td>2009</td>
<td>Malaysia</td>
<td>MLPA, germline DNA</td>
<td>High-risk</td>
<td>Not specified</td>
</tr>
<tr>
<td>Zhang et al.</td>
<td>2012</td>
<td>China</td>
<td>BigDye, germline DNA</td>
<td>Familial, Northern Chinese</td>
<td>Not specified</td>
</tr>
</tbody>
</table>

BigDye, BigDye Terminator Cycle Sequencing Kit; DHLPC, denaturing high-performance liquid chromatography; HRM, high resolution melting analysis; MLPA, multiplex ligation-dependent probe amplification; Myriad, Myriad Genetics Laboratories, Inc. (USA); SSCP, single-strand conformation polymorphism.

Discussion

The incidence of BRCA1 mutation in TNBC varied with the study population and selection criteria of the individual studies. By performing this meta-analysis, we attempted to estimate the relative risk of having BRCA1 mutation in women with TNBC compared with women with non-TNBC. However, analysis of the potential studies revealed that almost all eligible studies were performed on high-risk population with breast cancer (Table 2). The reason for it may be that genetic testing is commonly performed on high-risk population, and is seldom performed on average-risk women with...
non-TNBC. The exclusion of one study (19), which involved selected breast cancer patients, but not high-risk, did not change the results significantly. Hence, the results of this meta-analysis essentially reflect high-risk women with breast cancer.

There is some variation in the recommendations for BRCA mutation testing among governing organizations. The National Comprehensive Cancer Network (NCCN) guidelines include TNBC as one of the testing criteria for BRCA mutations (22). The European Society of Medical Oncology (ESMO) guidelines do not specify triple-negative phenotype as a criterion for BRCA mutation testing; however, it suggests that consideration of triple-negative phenotype in women younger than 50 years may be a cost-effectiveness strategy for mutation detection (23). The recently updated National Institute for Health and Care Excellence (NICE) guidelines recommend genetic testing if the combined BRCA1 and BRCA2 mutation carrier probability is 10% or more in women with breast cancer (24).

NCCN and ESMO guidelines on BRCA mutation testing in women with TNBC are likely based on incidence data of BRCA mutations in TNBC whereas NICE guideline is based on carrier probability calculation models. By analyzing the incidence rates of BRCA1 mutation in both TNBC and non-TNBC, our meta-analysis provides a relative risk of 5.65 (95% CI, 4.15–7.69) and risk difference of 0.22 (95% CI, 0.15–0.29), implying that, in high-risk population, women with TNBC are approximately 5.6 times more likely to have BRCA1 mutation compared with non-TNBC phenotype, and that approximately two in nine...
women with TNBC harbor BRCA1 mutation. These findings may be helpful in implementing effective strategies on BRCA1 mutation testing.

Our meta-analysis has several advantages. First, we synthesized the outcome by using data at the patient level from individual studies rather than using summary results. Second, the overall sample size is substantial, resulting in increased statistical power for the analysis. Third, the conclusions are more generalizable because included studies were from many different geographic locations.

Our study also has some limitations that should be acknowledged. First, as mentioned above, the results mainly reflect high-risk breast cancer patients rather than breast cancer patients in general. Second, there is some variation in specifics of high-risk population among studies although the populations studied were more or less similar (Table 2). On the other hand, this diversity may be a strength as Walker et al. (25) pointed out, ‘the presence of dissimilarities among studies can have advantages by increasing the generalizability of the conclusions’. Third, there is lack of uniformity in how BRCA1 mutation tests were performed (Table 1) that might affect the outcome. Fourth, small studies often show larger treatment effect and thus have more chance of being published, resulting in publication bias (small study effect) (26) that may account for mild asymmetry of the funnel plots. However, sensitivity analysis did not identify any studies that would have altered our results significantly by more than 5%.

In conclusion, the results from this meta-analysis suggest that, among the selected breast cancer patient population with high-risk features, women with TNBC are approximately 5.6 times more likely to have BRCA1 mutation compared with non-TNBC phenotype, and approximately two in nine women with TNBC harbor BRCA1 mutation. These findings may help in developing BRCA1 mutation prediction models and in implementing effective strategies for BRCA1 mutation testing in high-risk breast cancer patients. Further investigations into the incidence rates of BRCA1 mutation in average-risk women with TNBC and non-TNBC are warranted.

References
5. Evans DG, Lalloo F, Cramer A et al. Addition of pathology and biomarker information significantly improves the performance of the


