

# Effects of BRCA1 and BRCA2 gene mutations on female fertility among Chinese women: A systematic review and meta-analysis

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**Abstract. Purpose:** It is still inconsistent whether the mutations of BRCA1 and BRCA2 could reduce the female fertility by increasing the prevalence of breast and ovarian cancer. So we focus on the effects of BRCA1 and BRCA2 mutations on the female fertility among Chinese women in this meta-analysis.

**Material and Method:** The PubMed, Medline, Scopus, Embase, Science Direct, Web of Knowledge and China National Knowledge Infrastructure (CNKI) databases were methodically searched to eclectic relevant studies published from 2000 to 2022 using the key words "BRCA1" and "mutation" and "female fertility or ovarian cancer or cervical cancer or breast cancer" and "China or Chinese or Asia or Asian". The random effects models in RevMan 5.3 software were used to include and evaluate both longitudinal research and randomized controlled trials.

**Results:** This meta-analysis included 13 studies with a total of 10689 Chinese participants. Contact the control group, positive correlations between the mutations of BRCA1 and BRCA2 and female cancers were shown among the Chinese women from 35 to 60 years (OR=5.26) (P<0.00001).

**Conclusions:** The mutations of BRCA1 and BRCA2 may increase the incidence of cancer among Chinese women, especially the older than 40 years, and reduce female fertility, in which more prospective studies on the fertility outcomes are still needed in the future

## 1. Introduction

Recently, it is serious that China has become an aging country. By the end of 2021, there were 190 million people who were 65 years of age or older, making up 13.5% of the overall population(1). In this condition, there are still many factors that affect the cause for aging emergence, such as longer life, lower mortality, lower fertility, improvement of health care and economic development, in which the declining fertility is the most important cause. As shown in the reference (2-3), the fertility rate the China has remained roughly at 1.5 to 1.6 in the last decade, but it has dropped to 1.3 for the first time through the year of 2020, which was below the internationally recognized alert line of 1.5, So improving the female fertility among the Chinese women is important for ameliorating the aging problem.

Recently, many studies have confirmed that many factors could affect the female fertility, such as genetic factors, age, gynecological history, poor sexual behavior, male diseases and environmental factors, in which the genetic mutations are also as one of the key factors, as the BRCA1 and BRCA2, especially the BRCA1 and BRCA2,

play an importantly biological functions by increasing the telomere length maintenance and DNA repair to impact female reproductive longevity (4-5). Besides, the mutations of BRCA1 and BRCA2 can cause the accumulation of meiotic errors to leading the apoptosis and early depletion of ovarian reserve (5-7). So far, it is known that the mutations in BRCA1 and BRCA2 can raise the danger of ovarian, breast and cervical cancer to impact on ovarian reserve and reduce the female fertility. However, it is still controversial(4). Meanwhile, in our country, there is a lack of corresponding evidence-based medical evidence in this regard.

Due to the known limitations of systematic reviews and meta-analyses, such as the lower number of included references, possible confounding factors were not adequately considered, so we conducted a thorough meta-analysis of Chinese BRCA1/2 mutations and female fertility in our study, which is important to provide the values in the management and follow-up of this high-risk population.

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## 2. Material and methods

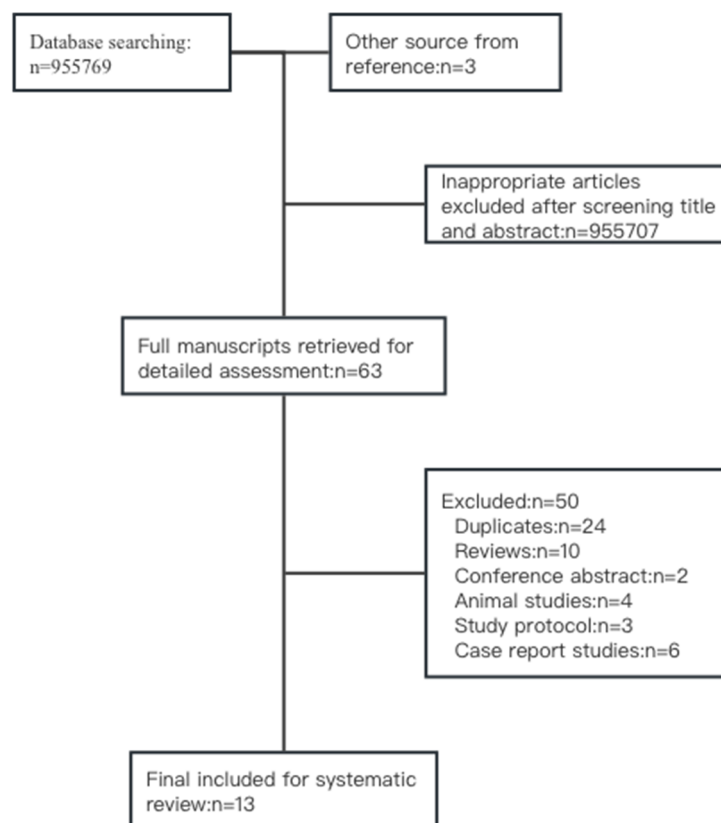
### 2.1 Data identification and selection

The recommended reporting items and meta-analyses (PRISMA) statement served as the foundation for this systematic review and meta-analysis. A comprehensive literature search was conducted from January 2000 to December 2022, in which all eligible studies were included in this research, regardless of the language, authors and research types. Through the use of computerized databases, the data were identified, including the PubMed, Medline, Scopus, Embase, Science Direct, Web of Knowledge database and China National Knowledge Infrastructure (CNKI) using the search terms "BRCA or BRCA1 or BRCA2" and "mutation" and "ovarian reserve or fertility or ovarian cancer or cervical

cancer or breast cancer" and "China or Chinese or Asia or Asian". The women considered for analysis were analyzed their fertile age and assessed using the subgroups. Additionally, the references of the pertinent studies mentioned above were reviewed in order to include the new papers. All published original articles in full length were finally selected.

### 2.2 Inclusion and exclusion criteria

All references included required to be randomized controlled trials from cohort studies and long-term studies on the impact of BRCA1 and BRCA2 gene mutations on female fertility in order to ensure the quality of this research. References to literature reviews, animal studies, and cell lines were disregarded (Figure 1).



**Figure 1.** Flowchart of included studies

Two reviewers were asked to independently assess all of the references and citations during the retrieval process to find research that might be offered by the searching index phrases. Another reviewer arbitrated any conflicts. Additionally, the same person evaluated all potential

publishing biases using funnel plots of the outcome comparisons.

### 2.3 Data extraction and outcomes

Author(year)	Study design	Samples *	Cancer
Ava Kwong, et al.,2009[8]	Cross-sectional study	22 (97)	Breast Ovarian
Yong Alison Wang, et al.,2018 [9]	Cross-sectional study	4 (476)	Breast and ovarian cancer
HY Wei, et al.2018[10]	Retrospective study	76 (361)	Breast
Ang Li, et al., 2018 [11]	Cross-sectional	297 (1034)	Ovarian

Guang Tian Lang, et al., 2017 [12]	Cross-sectional study	2560 (1043)	Ovarian , Fallopian tube, peritoneal
Ava Kwong, et al.,2020 [13]	Cross-sectional study	61 (1277)	Breast and ovarian cancer
Bo Chen, et al.,2020 [14]	Cross-sectional study	58 (466)	Breast cancer
QiuMing Wang, et al.2021[15]	Retrospective study	13 (327)	Breast and ovarian cancer
Shi T. et al., 2017[16]	Cross-sectional study	153 (763)	Breast cancer
Cao WM. et al.,2016[17]	Cross-sectional study	31 (102)	Breast and ovarian cancer
Lin PH. et al., 2016[18]	Cross-sectional study	30 (103)	Breast and ovarian cancer
Wang C. et al., 2015[19]	Cross-sectional study	68 (888)	Breast and ovarian cancer
Kwong A. et al., 2012[20]	Cross-sectional study	13 (366)	Ovarian cancer
Note: <sup>1</sup> Data in the calcium intervention groups and the control groups are shown outside and inside the brackets, respectively.			

Table 2. Characteristics of the studies	
Author(year)	Main outcome
Ava Kwong, et al.,2009[8]	BRCA1/2 mutation group, P=31.8% (7/22), Control group, P=6.7% (6/97).
Yong Alison Wang, et al.,2018 [9]	BRCA1/2 mutation group, P=50.0% (2/4), Control group, P=13.0% (63/476).
HY Wei, et al.2018[10]	BRCA1/2 mutation group, P=24.3% (18/76), Control group, P=9.2% (33/361).
Ang Li, et al., 2018 [11]	BRCA1/2 mutation group, P=22.4% (66/297), Control group, P=0.4% (4/1034).
Guang Tian Lang, et al., 2017 [12]	BRCA1/2 mutation group, P=9.10% (232/2560), Control group, P=0.38% (4/1043).
Ava Kwong, et al.,2020 [13]	BRCA1/2 mutation group, P=6.60% (4/61), Control group, P=2.80% (36/1277).
Bo Chen, et al.,2020 [14]	BRCA1/2 mutation group, P=48.28% (28/58), Control group, P=13.95% (65/466).
QiuMing Wang, et al.2021[15]	BRCA1/2 mutation group, P=53.8% (7/13), Control group, P=1.5% (5/327); BRCA1/2 mutation group, OR=103.58; Control group, OR=75.13.
Shi T. et al., 2017[16]	BRCA1/2 mutation group, P=7.84% (12/153), Control group, P=1.84% (14/763).
Cao WM. et al.,2016[17]	BRCA1/2 mutation group, P=45.16% (14/31), Control group, P=16.67% (17/102).
Lin PH. et al., 2016[18]	BRCA1/2 mutation group, P=16.67% (5/30), Control group, P=12.62% (13/103).
Wang C. et al., 2015[19]	BRCA1/2 mutation group, P=32.40% (22/68), Control group, P=9.80% (87/888).
Kwong A. et al., 2012[20]	BRCA1/2 mutation group, P=23.08% (3/13), Control group, P=1.92% (7/366).
Note: <sup>1</sup> Data in the calcium intervention groups and the control groups are shown outside and inside the brackets, respectively.	

After reviewing the whole references for each study in this meta-analysis, the pertinent data were collected to preserve the study characteristics, and the following information was noted, year of publication, diseases (breast cancer patients undergoing reproductive reserve/cancer-free women undergoing surveillance programs), number/total number of BRCA, study types, patient age (range), matching criteria/adjusted variables and main outcomes (Table 1).

## 2.4 Statistical analysis

To confirm the existence of statistical heterogeneity across all studies, the  $\chi^2$  test for the heterogeneity of data among the proportions was run. The fixed-or random-effects model in Review Manager Software (RevMan version 5.3) was used to generate the pooled odds ratio (OR), according to the sample frame and not on the basis of heterogeneity. Continuous outcomes were presented as the means  $\pm$  SD with a 95% confidence interval (CI). The age intervention carried out the subgroup analysis. The heterogeneity between all the studies included in this research was assessed using the I2 statistic. When the I2

was greater than 50%, a random effects model was applied, when it was lower than 50%, a fixed effects model was applied. A funnel plot was utilized to look for any potential bias. The cutoff point for statistical significance for two-sided P values was  $\alpha < 0.05$ .

### 3. Results

#### 3.1 Basic characteristics in this study

As shown in Figure 1, 955769 articles in all were originally identified through the PubMed, EMBASE, Web of Knowledge and CNKI databases. After reviewing the titles and abstracts, the remaining articles for which the full manuscript could be retrieved for detail assessment were 63 articles. Of these, 50 articles were excluded because 24 of them were removed as duplicates, 10 were reviews, 2 were conference abstracts, 4 were animal studies, 3 were study protocols, and 6 were case report studies. After reviewing the entire text, 13 suitable

manuscripts were finally added to this meta-analysis. (8-20)

In the Table 1, the publication dates in the included studies were varied from 2000 to 2022. From these included studies, eleven were cross-sectional studies, two were retrospective cohort study, and one contained both retrospective cohort study and cross-sectional studies. Meanwhile, the sample sizes were ranged from 4 to 1277, in which three studies included the women were breast cancer and two study included ovarian cancer and two study included women with various cancers.

#### 3.2 Effects of BRCA1/2 mutation carriers on the female cancer

As shown in Figure 2 and 3, a total of 13 studies with a total of 10,689 participants were integrated to investigate the association between BRCA mutations and female malignancies. Using a random effects model, the results of the forest plot (Figure 2) showed a significant positive association (OR=5.26) between BRCA mutations and female malignancies ( $P < 0.00001$ ).

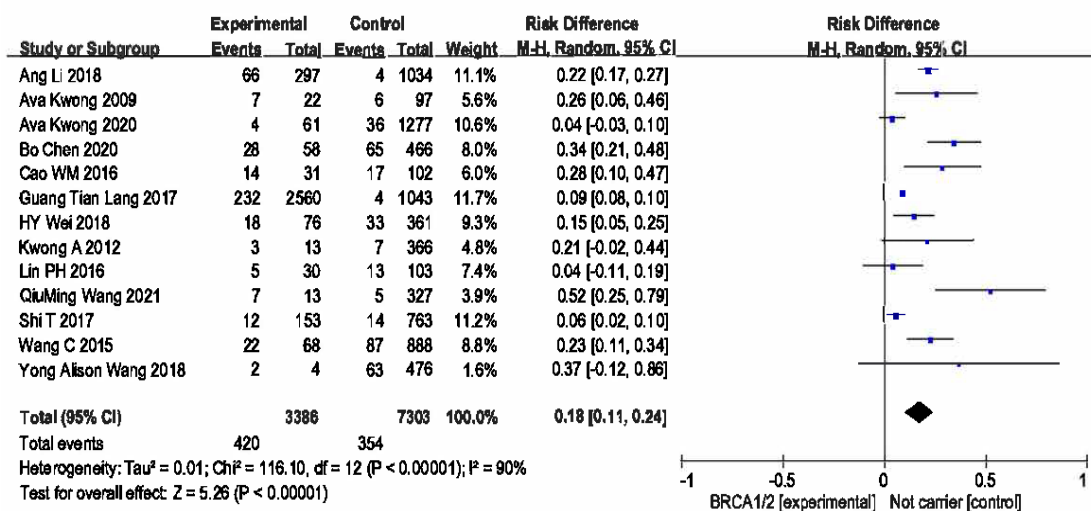


Figure 2. Effects of BRCA1/2 mutation carriers on the female cancer.

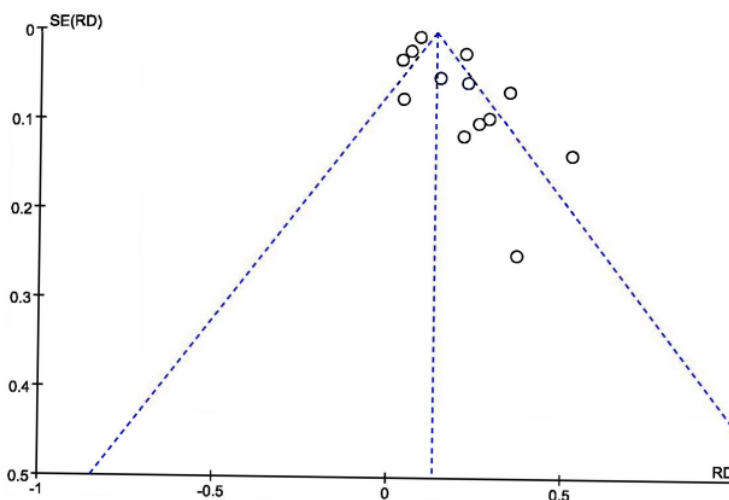


Figure 3. Funnel chart of the included studies

## 4. Discussion

The above outcomes of this meta-analysis with 13 randomized controlled trials determined that the mutations in the BRCA1/2 were could increase the prevalences of cancers to reduce the female fertility using the random effects model among the Chinese women. This is in agreement with the conclusions drawn from their meta-analysis by Matanes, Marchetti et al. (21-23) that there were positive correlations between the female cancer and the mutations of BRCA1 and BRCA2. However, another meta-analysis from Jiang et al. showed there were no evident correlations between the mutations of BRCA1 and BRCA2 and female fertility (24).

Similar to previous studies, BRCA1 and 2 play an important role in regulating DNA damage and repair, cell proliferation and apoptosis, which have a direct impact on DNA repair and maintenance of telomere length. BRCA mutations are among the best known, well-characterized and important genetic alterations that predispose carriers to an increased frequency of cancer in women (25-27). In addition, BRCA mutations could cause the accelerated loss of primordial follicles and increased DNA damages in the oocytes, leading to the reduction in the ovarian reserve (28), and mutations in the results of BRCA on the inability to maintain telomere integrity (29), which is associated with the germ cell lifespan (30). It has also been hypothesized that the mutations in the BRCA may lead to a shortened germ cell lifespan and thus the hypogonadism (31). Taking these data together and the theory of our analysis above suggested that the women with BRCA have poorer ovarian reserve and fertility potential than the wild-type women, and that mutations in the BRCA do affect the female fertility.

Our meta-analysis confirmed that the mutations in the BRCA1/2 were could increase the prevalences of cancers to reduce the female fertility using the random effects model among the Chinese women. However Hu et al. showed there were no direct evidence on the fetal birth rate, serum anti-Müllerian hormone levels, sinus follicle count and ovarian response (32). However, this study did not analyze BRCA1 and 2 separately, and the spiritual fertility suggested in the study did not accurately reflect the female fertility potential. While the results indicated that BRCA carriers and non-carriers had similar fertility experiences, with no differences in age at birth, age at last birth, or mean gestational age between the two groups (33-34). However, this study with a questionnaire, the conclusions obtained were limited by the data collected and no age-stratified analysis was performed. The results of Moslehi et al. (35) indicated that no significant differences in fertility were found between the mutation of BRCA carriers and non-carriers. The results of Gasparri et al. (36) suggested that young BRCA1 mutation carriers had lower AMH levels compared to wild-type women and therefore might have reduced ovarian reserve. However, there was no direct evidence that low AMH levels lead to reduced ovarian reserve and pregnancy rates. However, because significant heterogeneity must be taken into account, the meta-findings analysis's were not entirely trustworthy. and

the sample size discussed in this paper was still insufficient, so more samples are still needed in the future.

## 5. Conclusions

In summary, the references published to date have not clearly demonstrated that the mutations of BRCA could reduce the female fertility by increasing the prevalence of ovarian cancer and cervical cancer. However, after considering age, the effects of calcium absorption on weight loss were evident.

### Contributors

Rui-Chen Ma chartered and conducted the analysis, extracted figures, created graphs, wrote the document, and assessed the quality of the included studies. Yu-hua Ma read the article and cited the data. Jing Zhao reviewed the research and evaluated the caliber of the papers that were incorporated. All authors commented critically on the manuscript and agreed with the final document.

### Declaration of competing interest

All authors affirm that they had no certain or hidden competing financial or personal financing.

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