Contribution of xeroderma pigmentosum complementation group D gene polymorphisms in breast and ovarian cancer susceptibility
A protocol for systematic review and meta analysis
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Abstract
Background: The role of xeroderma pigmentosum complementation group D (XPD) gene polymorphisms in breast and ovarian cancer development has long been controversial and existing data were inconsistent. Here, we conducted a comprehensive systemic review and meta-analysis to better clarify the association.

Methods: Relevant case-control studies published in electronic data base from October 1999 to September 2019 were assessed. The statistical analyses of the pooled odds ratios (ORs) and the corresponding 95% confidence intervals (95%CIs) were calculated by using Revman 5.2 software (Cochrane Collaboration, Copenhagen).

Results: 31 articles including 38 case-control studies and 2 XPD polymorphisms (rs1799793 and rs238406) were analyzed. The results showed statistical significance in heterozygous mutants among Asian population for rs1799793 (GA vs GG + AA: OR = 1.38, 95%CI = 1.21–1.56), and Caucasian population for rs238406 (CA vs AA +CC: OR = 0.63, 95%CI = 0.49–0.80), while the rest comparisons including overall groups and subgroups stratified by cancer types and ethnicity failed to indicate any association with breast and ovarian cancer risk.

Conclusions: The current meta-analysis suggested no concrete correlation of XPD rs1799793(G/A) and rs238406(C/A) polymorphisms with breast cancer or ovarian cancer susceptibility. However, it indicated that heterozygous genotypes might share different pathophysiologic mechanism from not only homozygous wildtypes but also homozygous mutants. More case-control studies with well-adjusted data and diverse populations are essential for validation of our conclusion.

Abbreviations: 95%CIs = 95% confidence intervals, NOS = Newcastle-Ottawa scale, OR = odds ratio, XPD = xeroderma pigmentosum complementation group.

Keywords: breast cancer, ovarian cancer, polymorphism, risk, susceptibility, xeroderma pigmentosum complementation group D, xeroderma pigmentosum complementation group

1. Introduction
Breast and ovarian cancers are 2 leading causes of mortality in women globally. It is reported that 1 in 8 women in the United States will develop breast cancer in her lifetime and 5-year survival rate of ovarian cancer remains in an extremely poor rate of 30% to 40%.[1,2] Although multiple etiologic factors and corresponding therapies have been explored for breast and ovarian cancer risk, the most recent breakthrough in breast and ovarian cancer treatment is the endorsement of PARP inhibitor, which was approved in pts that harbor mutations in either BRCA1 or BRCA2, the 2 most important genes that are involved in homologous recombination triggered by DNA double strand break.[3–5] This implies the importance of detecting inherited DNA repair related genes to prevent carcinogenesis and of
developing new therapies that target those genes in breast and ovarian cancer.

Despite homologous recombination repair pathway, there are multiple other pathways to repair different types of DNA damage and maintain genomic integrity. Among these pathways is nucleotide excision repair (NER) pathway that repairs damages including cross-links, oxidative damage and bulky adducts. Xeroderma pigmentosum complementation group D (XPD), also known as ERCC2, plays important roles in the nucleotide NER pathway. The XPD gene is located on chromosome 19q13.3, comprises 23 exons, and spans approximately 54,000 base pairs.\textsuperscript{6-8} It encodes an evolutionarily conserved helicase that participates in DNA unwinding and the recognition of bulky adducts and thymidine dimers.

The relation between XPD and multiple cancer types has been recently explored, but with inconsistent results. For instance, Costa et al analyzed DNA samples from 141 ovarian cancer patients and 202 control subjects for XPD polymorphisms using polymerase chain reaction - restriction fragment length polymorphism and observed that XPD rs1799793 genotype carriers have increased susceptibility of ovarian cancer, especially for early stage diseases.\textsuperscript{9} However, Bernard-Gallon compared 51 ovarian cancer cases with 1000 controls and conclude that neither homologous mutants nor heterozygous genotypes in rs1799793 had any association with increased risk of ovarian cancer compared with wild genotypes.\textsuperscript{10} Gomes-Diaz et al conducted a case-control study to explore the association between the ERCC1 and ERCC2 gene variants and 3 different types of cancer in Mexican patients, but only concluded that rs1799793 was associated with breast cancer.\textsuperscript{11} Notably, several meta-analyses were published to clarify the relationship between XPD and various cancer types. For example, one study incorporated 86 articles with 38,848 cases and 48,925 controls including head and neck cancer, gastric cancer, lung cancer, bladder cancer, colorectal cancer as well as hematological malignancies. It concludes that XPD Asp312Asn polymorphism was associated with increased cancer risk, particularly in Asian populations.\textsuperscript{12} However, the problem is that not all cancer types share same extent of risks to certain DNA damage genes considering the heterogeneity of different cancer types, thus the conclusion may be confounded by XPD susceptible cancers and is hard to transfer to every cancer type. In consideration of the interactive management of breast and ovarian cancer patients, we conducted a comprehensive systemic review and meta-analysis of relevant case-control studies published in electronic databases, with objective to better clarify the association of XPD polymorphisms in the risk of breast cancer and ovarian cancer.

2. Materials and methods

2.1. Search for eligible literature

A comprehensive electronic search was performed using PubMed, Medline (Ovid), Embase, Weipu, Wanfang and CNKI databases for studies published from October 1999 to September 2019 with the following terms and keywords “xeroderma pigmentosum complementation group D”, “XPD”, “ovarian cancer”, “breast cancer”, “polymorphism”, “variant” and “mutation”. The search was updated every week until September 25, 2019. No ethical approval and patient consent are required because all analyses were based on previously published studies. The analysis is not a registered study.

2.2. Inclusion and exclusion criteria

Articles fulfilling the following criteria were included:

(1) studied possible XPD polymorphisms in breast and ovarian cancer patients,
(2) provided sufficient data in both case and control groups to calculate the odds ratios (ORs) and the corresponding 95% confidence intervals (95% CIs)
(3) pooled polymorphism should be studied in at least 2 independent studies in order to conduct meta-analysis.
(4) case-control studies.

When duplicate data were present in different articles, only the latest 1 would be taken into consideration. In addition, Newcastle-Ottawa Scale (NOS) was used to assess the quality of the observational studies included. Three aspects of selection, comparability, and exposure (9 scores in total) were carefully assessed. Studies of moderate or high quality were included (score higher than 5).\textsuperscript{13} Articles that didn’t fulfill the criteria mentioned above were excluded.

2.3. Data extraction

All potential studies were investigated by 2 independent reviewers from the author list. The following items were extracted: first author, year of publication, ethnicity, cancer type, single nucleotide polymorphisms with breast and ovarian cancer risk. Single nucleotide polymorphisms of XPD were considered as binary with dominant allele and mutated allele. Different contrast models were judged:

(1) homozygous mutants contrast (mut/mut vs dom/mut+dom/ dom),
(2) homozygous and heterozygous mutants contrast (mut/mut + dom/mut vs dom/dom),
(3) heterozygous mutants contrast (dom/mut vs dom/dom + mut/mut),
(4) homozygous mutants contrast in homoyzygotes (mut/mut vs dom/dom),
(5) mutant allelic contrast (mutated allele vs dominant allele).

(6) Besides the overall comparisons, we also performed subgroup analyses stratified by cancer type and ethnicity. Heterogeneity assumptions were tested using Higgins $I^2$ test. When the $I^2$ value was less than 50%, a fixed-effects model was used otherwise a random-effects model was applied.\textsuperscript{14} The Z test was performed to determine the significance of the pooled ORs where $P$ less than .05 would be considered statistically significant.\textsuperscript{15} The presence of publication bias was evaluated by visually inspecting the asymmetry in funnel plots. When the funnel plots showed visible asymmetry, Egger test was performed to further measure the bias, which was considered as existing when $P$ was less than .05.\textsuperscript{16} The pooled ORs and corresponding 95% CIs were calculated using the Revman 5.2 software (Cochrane Collaboration, Copenhagen) while the Egger test was performed using STATA 14.0 (StataCorp LP, College Station, TX).
3. Results

3.1. Search results

235 results returned after the primary search. Based on titles and abstracts, 10 articles were duplicates, 92 articles were not related to XPD polymorphisms and cancer risk while 42 articles reported XPD polymorphisms in other cancer types such as lung cancer and bladder cancer thus were excluded. 36 studies were excluded for non-case-control studies such as meta-analysis and lab research. Furthermore, 24 articles were excluded for analyzing different types of mutated alleles that could not be pooled with other independent articles (Fig. 1). For the remaining 31 articles, 23 were of moderate quality (NOS score of 6 or 7) and 8 were of high quality (NOS score of 8 or 9) therefore were all included in this meta-analysis (Table 1).[9-11,17-44]

3.2. Characteristics of included studies

The 31 enrolled articles consisted 38 case-control studies with 2 XPD polymorphisms (rs1799793 in 32 studies and rs238406 in 6 studies), 30 studies focused on breast cancer while 8 studies explored ovarian cancer. Different genotyping methods were utilized including polymerase chain reaction, TaqMan, restriction fragment length polymorphism, and matrix-assisted laser desorption -ionization time of flight mass spectrometry. Ethnicities included Asian, Caucasian, Mexican, Moroccan, Puerto Rican, and mixed. The control sources were either population based or hospital based (Table 1). All studies reported the numbers of corresponding genotypes for both case and control groups as to recessive mutants, heterogeneous mutants, and dominant wild types (Tables 2 and 3).

3.3. XPD rs1799793(G/A) polymorphisms

Pooled ORs and corresponding 95% CIs were shown in Table 4. By analyzing 32,663 participants of 32 case-control studies, the meta-analysis displayed no association of XPD rs1799793(G/A) polymorphisms with breast and ovarian cancer risk in the overall group (AA vs GA+GG; OR = 1.04, 95% CI = 0.90–1.19; AA+GA vs GG; OR = 1.08, 95% CI = 0.98–1.20; GA vs GG+AA: OR = 1.06, 95% CI = 0.97–1.17; AA vs GG; OR = 1.08, 95% CI = 0.92–1.27; A vs G: OR = 1.06, 95% CI = 0.97–1.15) (Fig. 2). The insignificant results were consistent with the outcomes of subgroup analysis for breast cancer and ovarian cancer. However, if stratified by ethnicity, 1 comparison model among Asian population for rs1799793 (GA vs. GG+AA: OR = 1.38, 95% CI = 1.21–1.56) was considered as statistically significant in fixed effect models. Though 5,846 participants were included, the results brought little confidence to conclude that GA was a detrimental factor for breast and ovarian cancer for Asian population. In general, it indicates that G to A variation in the XPD rs1799793 polymorphisms might not correlate with breast and ovarian cancer susceptibility.
## Table 1

### The characteristics of included articles.

| First author       | Year | Cancer type | Polymorphism       | Ethnicity | Source of control | Genotyping methods | NOS score |
|--------------------|------|-------------|--------------------|-----------|-------------------|--------------------|-----------|
| Bernard-Gallon     | 2008 | Breast, Ovarian | rs1799793 | Caucasian | HB                | Taqman             | 7         |
| Crew               | 2007 | Breast, Ovarian | rs1799793 | Unknown   | PB                | Taqman             | 8         |
| Debrak             | 2006 | Breast, Ovarian | rs1799793 | Caucasian | PB                | RFLP               | 7         |
| Gomez-Diaz         | 2015 | Breast, Ovarian | rs1799793 | Mexican   | Unknown           | TaqMan             | 6         |
| Hardi              | 2018 | Breast, Ovarian | rs1799793 | Moroccan  | PB                | TaqMan             | 8         |
| He                 | 2016 | Breast, Ovarian | rs1799793, rs238406 | Asian     | HB                | MALDI-TOF          | 8         |
| Hussien            | 2012 | Breast, Ovarian | rs1799793 | Caucasian | HB                | PCR                | 7         |
| Jakubowska         | 2010 | Breast, Ovarian | rs1799793 | Caucasian | PB                | RFLP               | 7         |
| Jelenek            | 2007 | Breast, Ovarian | rs1799793 | Unknown   | PB                | TaqMan             | 7         |
| Justenhoven        | 2004 | Breast, Ovarian | rs1799793 | Caucasian | Unknown           | MALDI-TOF          | 6         |
| Kuchel             | 2005 | Breast, Ovarian | rs1799793 | Mixed     | PB                | TaqMan             | 7         |
| Lee                | 2005 | Breast, Ovarian | rs1799793 | Asian     | HB                | PCR                | 7         |
| Mechanic           | 2006 | Breast, Ovarian | rs1799793 | Caucasian, African-American | PB | PCR-RFLP | 8 |
| Perez-Mayoral      | 2013 | Breast, Ovarian | rs1799793 | Puerto Rican | HB | TaqMan | 7 |
| Oguz               | 2017 | Breast, Ovarian | rs1799793 | Caucasian | Unknown           | PCR-RFLP          | 7         |
| Shadrina           | 2014 | Breast, Ovarian | rs1799793 | Caucasian | HB                | Real-time PCR      | 8         |
| Shen               | 2006 | Breast, Ovarian | rs1799793 | Mixed     | PB                | TaqMan             | 7         |
| Shi                | 2004 | Breast, Ovarian | rs1799793 | Caucasian | PB                | RFLP               | 7         |
| Smith              | 2006 | Breast, Ovarian | rs1799793 | Caucasian, African-American | HB | PCR | 7 |
| Tang               | 2002 | Breast, Ovarian | rs1799793 | Mixed     | PB                | RFLP               | 7         |
| Wang               | 2010 | Breast, Ovarian | rs1799793 | Asian     | HB                | PCR-RFLP          | 7         |
| Wang               | 2014 | Breast, Ovarian | rs1799793 | Asian     | HB                | TaqMan             | 6         |
| Zhang              | 2005 | Breast, Ovarian | rs1799793 | Asian     | PB                | PCR-RFLP          | 7         |
| Zhu                | 2010 | Breast, Ovarian | rs1799793, rs238406 | Asian | Unknown | MALDI-TOF | 6 |
| Costa              | 2007 | Breast, Ovarian | rs1799793, rs238406 | Caucasian | PB | PCR-RFLP | 7 |
| Khokhrin           | 2012 | Breast, Ovarian | rs1799793 | Caucasian | PB                | PCR-RFLP          | 8         |
| Montero            | 2014 | Breast, Ovarian | rs1799793 | Caucasian | PB                | PCR-RFLP          | 8         |
| Yin                | 2009 | Breast, Ovarian | rs238406 | Asian     | PB                | RFLP               | 6         |
| Romanowicz         | 2017 | Breast, Ovarian | rs238406 | Caucasian | Unknown           | RFLP               | 6         |
| Zhao               | 2018 | Breast, Ovarian | rs238406 | Asian     | HB                | Real-time PCR      | 8         |

HB = hospital based, MALDI-TOF = matrix-assisted laser desorption - ionization time of flight mass spectrometry, NOS = Newcastle-Ottawa scale, PB = population-based, PCR = polymerase chain reaction, RFLP = restriction fragment length polymorphism.

## Table 2

### Genotype distributions in cases and controls for XPD rs1799793(G/A) polymorphisms.

| Author          | Year | Cancer type | Ethnicity | Source of control | Genotyping methods | NOS | Genotype | Case  | Control |
|-----------------|------|-------------|-----------|-------------------|--------------------|-----|----------|-------|---------|
| Bernard-Gallon  | 2008 | Breast      | Caucasian | HB                | Taqman             | 7   | GG       | 458   | 418     |
| Crew            | 2007 | Breast      | Unknown   | PB                | Taqman             | 8   | GA       | 450   | 454     |
| Dubnik          | 2006 | Breast      | Caucasian | PB                | RFLP               | 7   | AA       | 118   | 118     |
| Gomez-Diaz      | 2015 | Breast      | Mexican   | Unknown           | TaqMan             | 6   | GG       | 8     | 236     |
| Hardi           | 2018 | Breast      | Moroccan  | PB                | TaqMan             | 8   | GA       | 1     | 1       |
| He              | 2016 | Breast      | Asian     | PB                | TaqMan             | 7   | AA       | 8     | 10      |
| Hussien         | 2012 | Breast      | Asian     | HB                | PCR                | 7   | GG       | 25    | 50      |
| Jakubowska      | 2010 | Breast      | Caucasian | PB                | RFLP               | 7   | GA       | 106   | 135     |
| Jelenek         | 2010 | Breast      | Caucasian | HB                | TaqMan             | 7   | AA       | 104   | 163     |
| Jorgensen       | 2007 | Breast      | Asian     | HB                | TaqMan             | 6   | GA       | 102   | 142     |
| Justenhoven     | 2004 | Breast      | Mixed     | PB                | TaqMan             | 7   | AA       | 1401  | 1437    |
| Kuchel          | 2005 | Breast      | Asian     | HB                | PCR                | 7   | GG       | 458   | 418     |
| Lee             | 2005 | Breast      | Asian     | HB                | PCR                | 6   | GA       | 450   | 454     |
| Mechanic        | 2006 | Breast      | African-American | PB | PCR-RFLP | 8 |
| Oguz            | 2017 | Breast      | Caucasian | PB                | RFLP               | 7   | GA       | 54    | 1       |
| Perez-Mayoral   | 2013 | Breast      | Puerto Rico | HB | TaqMan | 7 |
| Shadrina        | 2014 | Breast      | Caucasian | HB                | RFLP               | 7   | AA       | 81    | 65      |
| Shen            | 2006 | Breast      | Mixed     | PB                | TaqMan             | 7   | GG       | 25    | 50      |
| Shi             | 2004 | Breast      | Caucasian | PB                | RFLP               | 7   | GA       | 106   | 135     |
| Smith           | 2008 | Breast      | African-American | PB | PCR-RFLP | 8 |
| Smith           | 2008 | Breast      | Caucasian | PB                | RFLP               | 7   | AA       | 104   | 163     |
| Tang            | 2002 | Breast      | Mixed     | PB                | TaqMan             | 7   | GG       | 102   | 142     |
| Wang            | 2010 | Breast      | Asian     | HB                | PCR-RFLP          | 7   | GA       | 1401  | 1437    |
| Wang            | 2014 | Breast      | Asian     | PB                | RFLP               | 7   | AA       | 458   | 418     |
| Zhang           | 2005 | Breast      | Asian     | PB                | RFLP               | 7   | GG       | 25    | 50      |
| Zhu             | 2010 | Breast      | Asian     | HB                | RFLP               | 7   | GA       | 106   | 135     |
| Bernard-Gallon  | 2008 | Breast      | Caucasian | HB                | TaqMan             | 7   | GG       | 458   | 418     |
| Costa           | 2007 | Breast      | Caucasian | PB                | RFLP               | 7   | GA       | 54    | 1       |
| Jakubowska      | 2010 | Breast      | Caucasian | PB                | PCR-RFLP          | 7   | AA       | 25    | 50      |
| Khokhrin        | 2012 | Breast      | Caucasian | HB                | Real-time PCR      | 6   | GG       | 458   | 418     |
| Montero         | 2014 | Breast      | Caucasian | PB                | PCR-RFLP          | 8   | GA       | 102   | 142     |

XPD = xeroderma pigmentosum complementation group.
3.4. XPD rs238406(C/A) polymorphisms

The results of the association of XPD rs238406(C/A) polymorphisms with breast and ovarian cancer risk were shown in Table 5. With 6 studies and 3,360 participants pooled, the results showed a protective trend (OR < 1) of heterozygous mutants for breast and ovarian cancer but statistical significance was only found in Caucasian population (CA vs AA+CC: OR = 0.63, 95% CI = 0.49–0.80). The rest comparisons failed to demonstrate statistically significant ORs, either in overall group analysis (AA vs CA+CC: OR = 1.11, 95%CI = 0.78–1.58, CA vs. AA+CC: OR = 0.85, 95%CI = 0.69–1.05, AA vs CC: OR = 1.30, 95%CI = 0.75–2.24; A vs C: OR = 1.16, 95%CI = 0.85–1.59) or subgroup analysis (either stratified by cancer type and ethnicity) (Fig. 3). The above data suggested that XPD rs238406(C/A) polymorphisms did not pose an increased risk for breast and ovarian cancer, while heterozygous mutants showed a protective trend specifically in Caucasian population, but no solid conclusion should be drawn based on the current statistical derivation.

3.5. Publication bias

The publication bias was visually examined on the funnel plots generated by Revman 5.2 software. No obvious asymmetry could be observed (Fig. 4). We further conducted Egger tests in the 3 analyses that indicated significant ORs (2 for rs1799793 polymorphisms and 1 for rs238406 polymorphisms). The results demonstrated no significant publication bias (P > .05, data not shown).

4. Discussion

Since the widely use of poly ADP ribose polymerase (PARP) inhibitors as targeted therapy for BRCA mutated patients and

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### Table 3

| Author | Year | Cancer | Country | CC | CA | AA | CC | CA | AA |
|--------|------|--------|---------|----|----|----|----|----|----|
| He     | 2016 | Breast | Asian   | 128| 227| 95 | 128| 216| 86 |
| Yin    | 2009 | Breast | Asian   | 41 | 56 | 32 | 55 | 102| 48 |
| Zhu    | 2010 | Breast | Asian   | 87 | 151| 60 | 86 | 151| 61 |
| Costa  | 2007 | Ovarian| Caucasian| 36 | 61 | 21 | 38 | 109| 40 |
| Romanowicz | 2017 | Ovarian| Caucasian| 76 | 135| 189| 122| 186| 92 |
| Zhao   | 2018 | Ovarian| Asian   | 13 | 44 | 32 | 95 | 168| 93 |

XPD = xeroderma pigmentosum complementation group.

### Table 4

| Genotypes       | Group | Participants | OR (95%CI) | Z value | P value | I² (%) | Effect model |
|-----------------|-------|--------------|------------|---------|---------|--------|--------------|
| AA vs GA+GG     | Overall | 32,663        | 1.04 [0.90, 1.19] | 0.55 | .58 | 61 | Random       |
|                 | Breast  | 30,330        | 1.04 [0.89, 1.20] | 0.48 | .63 | 62 | Random       |
|                 | Ovarian | 2,333         | 1.03 [0.86, 1.29] | 0.12 | .91 | 60 | Random       |
|                 | Asian   | 5,846         | 0.85 [0.41, 1.77] | 0.43 | .67 | 70 | Random       |
|                 | Caucasian| 14,348        | 1.06 [0.89, 1.26] | 0.61 | .54 | 55 | Random       |
| AA+GA vs GG     | Overall | 32,663        | 1.08 [0.98, 1.20] | 1.54 | .12 | 72 | Random       |
|                 | Breast  | 30,330        | 1.08 [0.97, 1.21] | 1.36 | .17 | 76 | Random       |
|                 | Ovarian | 2,333         | 1.03 [0.83, 1.29] | 0.12 | .91 | 60 | Random       |
|                 | Asian   | 5,846         | 1.18 [0.87, 1.60] | 1.04 | .30 | 76 | Random       |
|                 | Caucasian| 14,348        | 1.05 [0.90, 1.23] | 0.59 | .55 | 73 | Random       |
| GA vs GG+AA     | Overall | 32,663        | 1.06 [0.97, 1.17] | 1.37 | .17 | 62 | Random       |
|                 | Breast  | 30,330        | 1.06 [0.96, 1.17] | 1.18 | .24 | 65 | Random       |
|                 | Ovarian | 2,333         | 1.08 [0.87, 1.34] | 0.66 | .51 | 38 | Fixed        |
|                 | Asian   | 5,846         | 1.38 [1.21, 1.56] | 4.87 | .001| 47 | Fixed        |
|                 | Caucasian| 14,348        | 0.99 [0.88, 1.11] | 0.14 | .89 | 52 | Random       |
| AA vs GG        | Overall | 19,917        | 1.08 [0.92, 1.27] | 0.94 | .35 | 67 | Random       |
|                 | Breast  | 18,587        | 1.07 [0.90, 1.28] | 0.75 | .45 | 70 | Random       |
|                 | Ovarian | 1,330         | 1.15 [0.93, 1.41] | 0.83 | .41 | 45 | Fixed        |
|                 | Asian   | 4,551         | 0.92 [0.40, 2.11] | 0.21 | .84 | 75 | Random       |
|                 | Caucasian| 7,938         | 1.90 [0.87, 1.36] | 0.77 | .44 | 67 | Random       |
| A vs G          | Overall | 65,326        | 1.06 [0.97, 1.15] | 1.29 | .20 | 76 | Random       |
|                 | Breast  | 60,660        | 1.06 [0.97, 1.16] | 1.20 | .23 | 79 | Random       |
|                 | Ovarian | 4,666         | 1.06 [0.91, 1.25] | 0.75 | .46 | 40 | Fixed        |
|                 | Asian   | 11,692        | 1.10 [0.82, 1.48] | 0.64 | .52 | 82 | Random       |
|                 | Caucasian| 28,696        | 1.04 [0.92, 1.17] | 0.60 | .55 | 77 | Random       |

XPD = xeroderma pigmentosum complementation group.
accumulating number of PARPi resistant patients identified, increasing attention has been paid to other gene aberrations involved in DNA repair pathways. XPD genes participate in DNA repair and therefore, when mutated, may contribute to genome instability. Pre-clinical studies have found that XPD aberrance plays a role in activating apoptosis through interaction between p53 and TFIH to remove damaged cells.[45,46] To date, many publications have shown an association between the XPD polymorphism and risk of cancer. However, the results remain controversial. One meta-analysis in 2014 studied rs1799793 polymorphisms and breast cancer susceptibility. A total of 22 studies with 18,136 cases and 18,351 controls were included. The conclusion was that XPD rs1799793 polymorphisms were not associated with breast cancer.[47] Since then, several new case-control studies were published and no meta-analysis was conducted to see the association between rs1799793 polymorphisms and ovarian cancer, while the correlation between XPD rs238406 polymorphisms with breast and ovarian cancer have not been systematically studied yet. Thus, in order to draw a more concrete conclusion, we searched all related publications and performed a meta-analysis for the 2 XPD polymorphisms by enrolling 38 studies from 31 articles.

The current meta-analysis presented that there was no association of XPD rs1799793(G/A) polymorphisms with breast and ovarian cancer risk in the overall groups and subgroups for breast cancer and ovarian cancer. One comparison model for heterozygous mutants among Asian population was considered as statistically significant. However, the result was hard to transfer to the conclusion that the heterozygous mutant of GA was a detrimental factor for breast and ovarian cancer for Asian population. This also reflects the complicated role between genes variants and protein functions. The XPD exon 10 rs1799793 polymorphisms were characterized by a G/A nucleotide substitution, causing an Asp/Asn amino acid change at codon 312 of XPD gene.[48] Though the biological function of this amino acid substitution has not yet been elucidated, the fact is that this residue has been highly conserved through evolution.[49] Whether the conservation indicates a protective role in DNA variance against function effect or suggests a strong effect in the enzymatic activity remains to be further studied. The results of XPD rs238406(C/A) polymorphisms showed a protective trend (OR < 1) of heterozygous mutants for breast and ovarian cancer but statistical significance was only found in Caucasian population. The rest comparisons failed to demonstrate statisti-
cally significant ORs. This is similar to the result of rs1799793 polymorphisms, suggesting that heterozygous mutants might share different pathophysiologic mechanism from not only homozygous wildtypes but also homozygous mutants, in potentially certain ethnicities. By looking at the separate studies, one case-control study was found to display a strong relationship between XPD rs238406(C/A) polymorphisms and ovarian cancer risk. The variant A allele increased almost 2-fold of the risk of ovarian cancer, which was confirmed in certain histological grades and FIGO staging. The study focused only in Polish population and the authors emphasized that they included only a small group of patients and the obtained results should
then be approached as preliminary. Whether ethnicity difference plays a role in the cancer risk brought by the gene variance remains to be solved.

Despite our efforts to include all available publications, several limitations to our meta-analysis should not be ignored. First, most of the original data pooled were unadjusted, not mentioning the reported imbalance of patient characteristics in certain included studies. Those underlying imbalanced risk factors might lead to an inaccurate explanation of pooled data. Whereas, we found no evidence of publication bias thus it convinced us of the reliability of the current meta-analysis. Second, the populations of included studies were limited. It is epidemiologically acknowledged that other ethnicities such as Hispanics and Blacks are also cancer susceptible,[50,51] thus, the lack of data for these populations might affect the overall results, especially when one study suggested a strong relationship between XPD rs238406 (C/A) polymorphisms and ovarian cancer risk in Polish population. Third, although the number of pooled participants was so far the largest, the number of several subgroup analyses was still very limited, especially for ovarian cancer patients.

In conclusion, the current meta-analysis suggested no concrete correlation of XPD rs1799793(G/A) and rs238406(C/A) polymorphisms with ovarian cancer risk. However, further comprehensive studies are needed to address these limitations and provide more reliable evidence.

### Table 5

Summary of different comparative results for XPD rs238406(C/A) polymorphisms.

| Genotypes     | Group     | Participants | OR (95%CI) | Z value | P value | I² (%) | Effect model |
|---------------|-----------|--------------|------------|---------|---------|--------|--------------|
| AA vs CA + CC | Overall   | 3360         | 1.30 [0.83, 2.03] | 1.15     | .25     | 85     | Random       |
|               | Breast    | 1810         | 1.04 [0.83, 1.31] | 0.35     | .72     | 0      | Fixed        |
|               | Ovarian   | 1550         | 1.61 [0.75, 3.45] | 1.22     | .22     | 88     | Random       |
|               | Asian     | 2255         | 1.12 [0.91, 1.37] | 1.06     | .29     | 0      | Fixed        |
|               | Caucasian | 1105         | 1.58 [0.43, 5.81] | 0.69     | .49     | 94     | Random       |
| AA + CA vs CC | Overall   | 3360         | 1.11 [0.78, 1.58] | 0.60     | .55     | 77     | Random       |
|               | Breast    | 1810         | 0.98 [0.80, 1.21] | 0.16     | .88     | 0      | Fixed        |
|               | Ovarian   | 1550         | 1.33 [0.61, 2.88] | 0.71     | .48     | 87     | Random       |
|               | Asian     | 2255         | 1.08 [0.80, 1.46] | 0.53     | .60     | 52     | Random       |
|               | Caucasian | 1105         | 1.06 [0.54, 2.04] | 0.10     | .92     | 93     | Random       |
| CA vs AA + CC | Overall   | 3360         | 0.85 [0.69, 1.05] | 1.52     | .13     | 53     | Random       |
|               | Breast    | 1810         | 0.96 [0.80, 1.16] | 0.43     | .67     | 0      | Fixed        |
|               | Ovarian   | 1550         | 0.76 [0.53, 1.10] | 1.44     | .15     | 61     | Random       |
|               | Asian     | 2255         | 0.98 [0.82, 1.16] | 0.26     | .80     | 0      | Fixed        |
|               | Caucasian | 1105         | 0.63 [0.49, 0.80] | 3.72     | .01     | 0      | Fixed        |
| AA vs CC      | Overall   | 1754         | 1.30 [0.75, 2.24] | 0.94     | .35     | 86     | Random       |
|               | Breast    | 907          | 1.02 [0.78, 1.33] | 0.13     | .90     | 0      | Fixed        |
|               | Ovarian   | 847          | 1.70 [0.59, 4.89] | 0.99     | .32     | 90     | Random       |
|               | Asian     | 1140         | 1.15 [0.90, 1.47] | 1.10     | .27     | 49     | Fixed        |
|               | Caucasian | 614          | 1.30 [0.49, 7.96] | 0.37     | .71     | 95     | Random       |
| A vs C        | Overall   | 6720         | 1.16 [0.85, 1.59] | 0.94     | .35     | 89     | Random       |
|               | Breast    | 3620         | 1.01 [0.88, 1.15] | 0.10     | .92     | 0      | Fixed        |
|               | Ovarian   | 3100         | 1.36 [0.75, 2.47] | 1.01     | .31     | 92     | Random       |
|               | Asian     | 4510         | 1.08 [0.90, 1.30] | 0.86     | .39     | 51     | Random       |
|               | Caucasian | 2210         | 1.27 [0.47, 3.40] | 0.47     | .64     | 96     | Random       |

**OR** = odds ratio, XPD = xeroderma pigmentosum complementation group.

### Figure 3

Representative forest plots for XPD rs238406(C/A) polymorphisms. (A) AA vs CA + CC in overall group analysis. (B) AA + CA vs CC in overall group analysis. (C) A vs C in overall group analysis. (D) CA vs AA + CC in Caucasian group analysis. XPD = xeroderma pigmentosum complementation group.
morphisms with breast cancer or ovarian cancer susceptibility. However, it indicated that heterozygous genotypes might share different pathophysiologic mechanism from not only homozygous wildtypes but also homozygous mutants. More case–control studies with well-adjusted data and diverse populations are essential for validation of our conclusion.

Author contributions
YT and CB contributed to study concept and design; YT, XL, and FY contributed to literature search and data extractions; YT and JZ contributed to data analysis and the study quality evaluation; YT and KY contributed to the methodology. XL and CB contributed to the supervision of all the study processes. All the authors contributed to writing the manuscript. All authors approved the final version of the manuscript.

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