**XRCC1** Arg399Gln Polymorphism Confers Risk of Breast Cancer in American Population: A Meta-Analysis of 10846 Cases and 11723 Controls

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**Abstract**

**Background:** In the X-ray repair cross-complementing group 1 (**XRCC1**) gene, a polymorphism, Arg399Gln (rs25487), has been shown to change nonconservative amino acid and thus result in alternation of DNA repair capacity. Numerous studies have investigated the association between Arg399Gln and breast cancer risk in the American population, but yielding inconsistent results. This study aimed to clarify the role of this polymorphism in susceptibility to breast cancer.

**Methods:** Literatures were searched in multiple databases including PubMed, Springer Link, Ovid, EBSCO and ScienceDirect databases up to April 2013. A comprehensive meta-analysis was conducted to estimate the overall odds ratio (OR), by integrating data from 18 case control studies of 10846 cases and 11723 controls in the American population.

**Results:** Overall, significant association was observed between the Arg399Gln polymorphism and breast cancer risk under the random-effects model (OR for dominant model = 1.12, 95% CI: 1.02–1.24, \( P_{\text{heterogeneity}} = 0.003 \); OR for additive model = 1.07, 95% CI: 1.01–1.14, \( P_{\text{heterogeneity}} = 0.017 \)). Further sensitivity analysis supported the robust stability of this current result by showing similar ORs before and after removal of a single study.

**Conclusions:** This meta-analysis suggests that the **XRCC1** Arg399Gln polymorphism may significantly contribute to susceptibility of breast cancer in the American population.

**Introduction**

Breast cancer is the most common cancer and a predominate cause of cancer related-death in female population worldwide [1]. In 2013, an estimated 232,340 new cases in women were expected to occurred and 39,620 women were expected to die from breast cancer in the USA [2]. Breast cancer is a complex trait caused by environmental and genetic factors. Multiple environmental factors for breast cancer have been identified, including age at first birth, menarche and menopause, and family history, but the underlying genetic basis remained largely unknown [3].

Base-excision repair (BER), an important DNA repair pathway, is responsible for the repair of base damage resulting from exposure to X-rays, oxygen radicals, and alkylating agents [4,5,6]. In the BER pathway, the X-ray repair cross-complementing group 1 (**XRCC1**) gene, encoding a scaffolding protein, involved in the repair of single-strand breaks, the most common lesions in cellular DNA [7]. Molecular studies showed if lacking the **XRCC1** active cell would be hypersensitive to DNA damage. In the **XRCC1** gene, a functional polymorphism, Arg399Gln (rs25487) has been extensively investigated in many cancers [8,9,10,11]. Regarding breast cancer, multiple studies have been conducted to explore the association of this polymorphism and the disease risk in the USA [12,13,14,15,16,17,18,19,20,21,22,23,24,25,26]; however, results were inconsistent. For instance, Duell et al. suggested that the variant of Arg399Gln might confer increased risk of breast cancer [12], whereas Dawei Bu et al. reported no association of this polymorphism and breast cancer [18]. Based on previously published studies, four meta-analysis have been conducted on the Arg399Gln and breast cancer risk [27,28,29,30], but not special in the American population. Maybe due to heterogeneity across different countries, no conclusion has been drawn yet. Unfortunately, in the two most recent meta-analysis [27,29], some errors in the data extraction have introduced the incorrect results. Herein, we believed that it is essential to conduct an update...
comprehensive meta-analysis including studies published since 2001 to provide a more precise assessment of the association between the Arg399Gln in XRCC1 and breast cancer risk in the American population.

**Materials and Methods**

**Literature Search**

Relevant articles published before April 1st, 2013 were identified through a electronically search in the PubMed, Springer Link, Ovid, EBSCO and ScienceDirect databases using the combination of key words: ‘XRCC1’, ‘polymorphism’, ‘Arg399Gln’, ‘SNP’, ‘variant’, ‘BC’ and ‘breast cancer’. References of retrieved publications were also screened. Disagreements were resolved through discussions between the two authors (Yang Peng and Yong Sun).

**Inclusion and Exclusion Criteria**

In our meta-analysis, studies were included if they met the all of the following criteria: (a) case-control studies investigated the relationship between XRCC1 Arg399Gln and breast cancer risk; (b) patients should be confirmed with histologically breast cancer; (c) studies should provided data about the frequencies of alleles or genotypes. (d) American population is meant that all the inhabitants of America. Meta-analysis, letters, reviews or editorial articles were excluded. If studies shared the same participants, only the one with the largest population or the most complete information was included. If more than one ethnical population were included in one publication, each population was considered separately. The meta-analysis was conducted according to the guidelines of Preferred Reporting Items for Systemic Reviews and Meta-Analyses statement (PRISMA) [31], as shown in Checklist S1 (http://www.prisma-statement.org).

**Quality Assessment of Included Studies**

Two authors independently assessed the quality of included studies according to the 9-star Newcastle-Ottawa Scale. The study quality was assessed by the 9-star Newcastle-Ottawa Scale. A full score is 9 stars, and a score ≥6 stars is considered to be high quality. The quality of case-control studies was assessed as follows: adequate definition of cases, representativeness of cases, selection of controls, definition of control, control for the most important factor or the second important factor, exposure assessment, same method of ascertainment for all subjects, and non-response rate. The score of each individual publications was shown in Table S1.

**Statistical analysis**

For each study, odds ratios (ORs) and their 95% confidence intervals (CIs) as the metrics of effect size were recalculated for additive, dominant [(Gln/Gln+Arg/Gln) versus Arg/Arg] and recessive [Gln/Gln versus Arg/Gln + Arg/Arg] genetic models. For additive model, common homozygotes, heterozygotes, and rare homozygotes were assigned as scores of 0, 1, and 2, respectively, and then ORs per unit score were calculated by comparing between cases and controls in logistic regression model. The χ² based Cochran’s Q statistic test was employed to test between-study heterogeneity, and heterogeneity was considered significant when P<0.1 for Q statistic. Heterogeneity was quantified by I² statistic examining the percentage of heterogeneity (I² = 0–25%, no heterogeneity; I² = 25–50%, moderate heterogeneity; I² = 50–75%, large heterogeneity; I² = 75–100%, extreme heterogeneity) [32]. For pooling ORs and 95% CIs. A random-effects model using the DerSimonian and Laird’s method was utilized. Furthermore, subgroup analyses were performed by ethnicity, menopausal status, genotyping method and control source, to explore the source of heterogeneity. Sensitivity analysis was also conducted to assess influence of single study on the overall estimate, by sequential removal of individual studies. Publication bias was estimated by funnel plot and Egger’s test [33]. All analyses were carried out by using the Stata 12.0 software.

**Results**

**Characteristics of included studies**

Figure 1 shows the procedure of study selection. A total of 15 publications with 18 case-control studies of 10846 breast cancer cases and 11723 controls were finally included in this meta-analysis. Among them, 10 studies were conducted in mixed ethnicity population, 3 studies were in the African-American, and 5 studies in Caucasians. The characteristics of individual studies are summarized in Table 1.

**Overall meta-analysis**

In the overall meta-analysis, significant between-study heterogeneity were observed for all genetic models (P for heterogeneity = 0.003, 0.003 and 0.017 for dominant, recessive and additive models, respectively), and thus the random-effects model was employed. Significant associations were observed between the XRCC1 Arg399Gln and breast cancer risk in both of the dominant and additive models (OR for dominant model = 1.12, 95% CI: 1.02–1.24; OR for additive model = 1.07, 95% CI: 1.01–1.14; Figure 2–3), but no association was found in recessive model (OR = 0.95, 95% CI: 0.84–1.08; Figure S1).

**Subgroup meta-analysis**

When subgroup analysis was performed by ethnical populations, for the dominant model, only the subgroup with mixed population showed significant association of the Arg399Gln without evidence of heterogeneity (OR = 1.10, 95% CI: 1.01–1.20; Figure 2), whereas heterogeneity still existed and no associations were found for both subgroups of African-Americans and Caucasians, possibly due to their relatively small sample size and the moderate effect of this polymorphism under the dominant model. For the additive model, heterogeneity was effectively removed in African-Americans and Caucasians, but only the African-American population showed significant association (OR = 1.25, 95% CI: 1.05–1.48; Figure 3). For recessive model, heterogeneity was effectively removed in African-Americans and Caucasians, but there was still no association in any subgroups.

3 studies provided data according to premenopausal or postmenopausal status (Table S2) [17,21,26]. Heterogeneity was effectively removed in postmenopausal subgroup (Figure S2, S3, S4), but no significant association was detected. We considered that based on current limited data, it may lack of sufficient power.
Potential relevant papers identified by electronic databases (April 1st, 2013)  
(n=149)

Abstract retrieved for further evaluation  
(n=91)

Full-text retrieved for detail evaluation  
(n=42)

Studies included in this meta-analysis  
(n=15)
15 publications with 18 studies:  
(n=10) Mixed ethnicity population;  
(n=5) Caucasians;  
(n=3) African-American

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

| First author | Year | Ethnicity | Case (AA) | Control (AA) | Population based | HWE | Sample material | Genotyping methods |
|--------------|------|-----------|-----------|--------------|------------------|-----|----------------|--------------------|
| Duell [12]   | 2001 | African   | 164       | 198          | Population       | Y   | Blood           | PCR-RFLP           |
| Duell [12]   | 2001 | Caucasian | 162       | 164          | Population       | Y   | Blood           | PCR-RFLP           |
| Smith [13]   | 2003 | Mixed     | 99        | 115          | Hospital         | Y   | Blood           | PCR-RFLP           |
| Smith [15]   | 2003 | Caucasian | 70        | 119          | Hospital         | Y   | Peripheral lymphocyte | PCR-RFLP |
| Han [14]     | 2003 | Mixed     | 391       | 545          | Population       | Y   | Blood           | Pyrosequencing     |
| Shen [17]    | 2005 | Mixed     | 412       | 444          | Population       | Y   | Blood           | PCR-RFLP           |
| Patel [16]   | 2005 | Mixed     | 196       | 194          | Population       | Y   | Buffy coat      | TaqMan Real Time PCR |
| Bu [18]      | 2006 | Mixed     | 84        | 42           | Hospital         | Y   | Blood           | PCR-RFLP           |
| Zhang [21]   | 2006 | Caucasian | 392       | 360          | Population       | Y   | Mouthwash cytobrush | PCR-RFLP |
| Brewster [20]| 2006 | Mixed     | 108       | 126          | Population       | Y   | Blood           | PCR-RFLP           |
| Thyagarajan [19]| 2006 | Mixed    | 57        | 135          | Population       | Y   | Blood, normal tissue | PCR-RFLP |
| Pachkowski [22]| 2006 | African  | 536       | 493          | Population       | Y   | Blood           | TaqMan Real Time PCR |
| Pachkowski [22]| 2006 | Caucasian| 504       | 480          | Population       | Y   | Blood           | TaqMan Real Time PCR |
| Ali [23]     | 2008 | Mixed     | 11        | 21           | Population       | Y   | Normal tissues  | PCR-RFLP           |
| Smith [24]   | 2008 | Caucasian | 135       | 179          | Population       | Y   | Blood           | MassARRAY Sequenome |
| Smith [24]   | 2008 | African   | 38        | 58           | Population       | Y   | Blood           | MassARRAY Sequenome |
| Zippirich [25]| 2010 | Mixed     | 126       | 139          | Population       | Y   | Blood           | SYBR Green PCR      |
| Roberts [26] | 2011 | Mixed     | 104       | 164          | Hospital         | Y   | Blood, mouthwash | MassARRAY Sequenome |

Figure 1. Flow chart of literature search and selection in the meta-analysis.
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to detect the real effect of this polymorphism according to premenopausal or postmenopausal status.

When stratified by the genotyping method, the significant effect was effectively removed in TaqMan Real Time PCR and MassARRAY Sequenome subgroup, but no association was found. In the PCR-RFLP subgroup, heterogeneity was seen (for dominant model: $P = 0.005$, $I^2 = 62.0\%$; for additive model: $P = 0.001$, $I^2 = 62.2\%$), possibly due to the different sources of controls and ethnicity. Significant association was also seen in this subgroup, with ORs for dominant model and additive model were 1.27 (95% CI = 1.08–1.49) and 1.15 (95% CI = 1.02–1.29), respectively.

Subgroup analysis was also performed by sources of controls (Table 2). The population based subgroup showed significant association, but with evidence of heterogeneity (for dominant model: $P = 0.001$, $I^2 = 63.4\%$; for additive model: $P = 0.006$, $I^2 = 55.5\%$). No heterogeneity and no significant association were seen in the hospital based subgroup.

Sensitivity Analysis and Publication Bias

Given the significant between-study heterogeneity for the Arg399Gln polymorphism, we performed a sensitivity analysis to assess the effects of single study on pooled ORs under a random-effects model (Figure 4–5, Figure S5). The pooled ORs were similar before and after removal of each study, suggesting no single study significantly changes the pooled ORs. As reflected by funnel plots (Figure 6–7 and Figure S6) and Egger’s tests, there was no publication bias in the dominant and recessive models ($P$ for Egger’s test >0.10). For the additive model, a borderline significant publication bias was observed ($P$ for Egger’s test = 0.04).

**Discussion**

This meta-analysis incorporated 18 studies of 10846 breast cancer cases and 11723 controls concerning the Arg399Gln in *XRCC1*. The Arg399Gln variant presented significant association breast cancer risk in the American population. Further sensitivity analysis suggested the stability of the current results, by showing similar ORs before and after sequential removal of single study. This meta-analysis, based on updated published data, has further increased sample size and enlarged the statistical power to reflect the precision effect of the Arg399Gln in breast cancer in the American population.

*XRCC1* plays an important role in the BER pathway, which has been thought of as the predominant DNA-damage repair pathway for the processing of small base lesions derived from oxidation and alkylation damage [34]. The major significance of *XRCC1* in maintaining genomic stability has been raised by high frequency of chromosome deletions or aberrations in the gene mutant cells, and thus the *XRCC1* gene has been posed as a candidate gene for many cancer susceptibility. In the coding region of *XRCC1*, the nonsynonymous polymorphism, Arg399Gln, has caught much attention in breast cancer risk for years. This polymorphism is
Figure 3. Forest plot of the association between the XRCC1 Arg399Gln polymorphism and breast cancer risk for the additive model. doi:10.1371/journal.pone.0086086.g003

Table 2. Results of overall analysis and subgroup analysis in this meta-analysis.

| Group           | Dominant model | Additive model | Recessive model |
|-----------------|----------------|----------------|-----------------|
| **Ethnicity**   |                |                |                 |
| Caucasian       | 1.13 (0.90–1.41) | 1.02 (0.96–1.08) | 1.08 (0.92–1.27) |
| African-American| 1.09 (0.75–1.58) | **1.24 (1.05–1.47)** | 0.56 (0.30–1.03) |
| Mixed           | **1.10 (1.01–1.21)** | 1.07 (0.96–1.18) | 0.95 (0.84–1.09) |
| **Menopausal status** |            |                |                 |
| Premenopausal   | 1.90 (0.73–4.91) | 1.08 (0.98–1.19) | 2.24 (0.48–10.35) |
| Postmenopausal  | 0.98 (0.86–1.12) | 0.93 (0.86–1.01) | 1.02 (0.87–1.21) |
| **Genotyping method** |            |                |                 |
| PCR-RFLP        | **1.27 (1.08–1.49)** | **1.15 (1.02–1.29)** | 0.90 (0.70–1.17) |
| TaqMan Real Time PCR | 1.08 (0.96–1.22) | 1.04 (1.00–1.13) | 0.93 (0.72–1.20) |
| MassARRAY Sequenome | 0.83 (0.68–1.02) | 0.98 (0.88–1.09) | 0.97 (0.83–1.13) |
| **Control source** |            |                |                 |
| Population      | **1.14 (1.02–1.28)** | **1.09 (1.01–1.18)** | 0.95 (0.80–1.13) |
| Hospital        | 1.03 (0.83–1.29) | 1.00 (0.89–1.10) | 0.95 (0.82–1.10) |
| Overall OR      | **1.12 (1.02–1.24)** | **1.07 (1.01–1.14)** | 0.95 (0.84–1.09) |

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located in the critical COOH-terminal side of PARP-binding BRCT-domain [35,36]. The amino acid substitution caused by this variant in the BRCT domain has been shown to completely disrupt the function of XRCC1, and thus may result in reduction of DNA repair capacity [37]. In view of its functional significance, it is biologically possible that the Arg399Gln polymorphism may modulate the risk of breast cancer. As expected, this meta-analysis provides an obvious evidence that the XRCC1 Arg399Gln polymorphism is significant associated with breast cancer in the American population. Intriguingly, the significant association was presented in the dominant and additive models, which is inconsistent with the most recent meta-analysis [27,29]. In these previous meta-analysis, the authors have wrongly extract the control’s AA frequency. In the original article by Patel AV et al., the AA genotype frequency in controls was 194; however, in the meta-analysis by Huang Y et al. and Wu K et al., it changed to 280, which would influence the accuracy of the pooled analysis. Additionally, Caucasian and African-American assessed in the previous meta-analysis were distinct with our meta-analysis, possibly resulting in the inconsistent result with our meta-analysis.

The association of XRCC1 with breast cancer has been investigated in many other countries. In China, Liu L et al. reported XRCC1 -77T>C may be a genetic determinant for developing breast cancer [38]. For lung cancer, Liu L et al. find...
that \( XRCC1 \) T-77C could be genetic determinant for prognosis of advanced non-small-cell lung cancer patients treated with platinum-based chemotherapy [39]. Thus, we believed that \( XRCC1 \) Arg399Gln polymorphism maybe also associate with breast cancer.

Nevertheless, significant between-study heterogeneity was seen in this meta-analysis. To explore the source of heterogeneity, we performed subgroup analysis. After stratified by premenopausal or postmenopausal status, heterogeneity was significant removed, indicating that the premenopausal or postmenopausal status may be one source of heterogeneity. According to ethnicity, we found that for recessive and additive models, heterogeneity was effectively removed in Africans and Caucasians, whereas for dominant model, it retained in Africans and Caucasians, but in the mixed population, no evidence of heterogeneity was shown, suggesting ethnical population may also partly explained the heterogeneity of this meta-analysis. With regard to the control source, heterogeneity was removed in hospital-based subgroup, but was detected in population-based subgroup. Furthermore, the results of PCR-RFLP subgroup analysis were similar to population

\[ \text{Figure 6. Funnel plot of the association between the } XRCC1 \text{ Arg399Gln and breast cancer risk for the dominant model.} \]
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\[ \text{Figure 7. Funnel plot of the association between the } XRCC1 \text{ Arg399Gln and breast cancer risk for the additive model.} \]
\[ \text{doi:10.1371/journal.pone.0086086.g007} \]
based subgroup analysis. Heterogeneity was also partly explained by population based and genotyping method of this meta-analysis. Moreover, all the included studies showed high quality (≥6 stars) by the 9-star Newcastle-Ottawa Scale, and no publications bias was observed in dominant and recessive models.

Several limitations in this meta-analysis should be figured out. First, in the subgroup analysis by ethnicity and premenopausal/postmenopausal status, the sample size was relatively small and the statistical power might be insufficient. Second, potential sources of heterogeneity in this meta-analysis could include other factors, such as family history of breast cancer, staging of breast cancer, history of begin breast disease. However, due to the limited data, we failed to further explore these factors in the current meta-analysis. Finally, multiple epidemiological studies have demonstrated gene-gene or gene- environment interactions may play more important role in cancer development as compared with genetic factors [40,41]. However, gene-gene interactions and gene-environment interactions could not be appraised in this meta-analysis owing to a lack of special data.

In conclusion, this meta-analysis provided evidence that the XRCC1 Arg399Gln polymorphism was significantly associated with risk of breast cancer in the American population. Nevertheless, in the future, well-designed studies with large sample sizes will be warranted in diverse populations.

Supporting Information

Checklist S1 The PRISMA 2009 Checklist.

Table S1 Quality assessment of case–control studies included in this meta-analysis.

Table S2 Data of premenopausal or postmenopausal studies.

Author Contributions

Conceived and designed the experiments: YHG SDC LL TB. Performed the experiments: YS YP LZ. Analyzed the data: TB. Contributed reagents/materials/analysis tools: YS YP LDZ XL. Wrote the paper: TB LL.

References

1. Parkin DM, Bray F, Ferlay J, Pisani P (2001) Estimating the world cancer burden: Globocan 2000. International journal of cancer 94: 153–156.
2. American Cancer Society. Cancer Facts & Figures 2013. Atlanta: American Cancer Society; 2013.
3. Espinosa E, G A Maza-Pozo A, S A Nchez-Navauro A, Pinto A, Casta N Eda CA, et al. (2012) The present and future of gene profiling in breast cancer. Cancer and Metastasis Reviews 31: 41–46.
4. Hoornmakers JH (2001) Genome maintenance mechanisms for preventing cancer. Nature 411: 366–374.
5. Wood RD, Mitchell M, Ngouros J, Lindlatt T (2001) Human DNA repair genes. Science 291: 1289–1289.
6. Goode EL, Ulrich CM, Potter JD (2002) Polymorphisms in DNA repair genes and associations with cancer risk. Cancer Epidemiology Biomarkers & Prevention 11: 1513–1530.
7. Turdek B (2007) Base excision repair modulation as a risk factor for human cancers. Molecular aspects of medicine 28: 250–273.
8. Huang G, Cai S, Wang W, Zhang Q, Liu A (2013) Association between XRCC1 and XRCC3 Polymorphisms with Lung Cancer Risk: A Meta-Analysis from Case-Control Studies. PLOS ONE 8: e68457.
9. Guo S, Li X, Gao M, Li Y, Song B, et al. (2013) The relationship between XRCC1 and XRCC3 gene polymorphisms and lung cancer risk in northeastern Chinese. PLoS one 8: e52613.
10. Li Y, Liu F, Tan S, Wang Y, Li S (2012) X-ray repair cross-complementing group 1 (XRCC1) genetic polymorphisms and cervical cancer risk: a huge systematic review and meta-analysis. PLoS One 7: e44441.
11. Yuan P, Liu L, Wu C, Zheng R, Yu D, et al. (2010) No association between XRCC1 polymorphisms and survival in non-small-cell lung cancer patients treated with platinum-based chemotherapy. Cancer biology & therapy 10: 854–859.
12. Duell EJ, Milikan RG, Pitman GS, Winkel S, Lunn RM, et al. (2001) Polymorphisms in the DNA repair gene XRCC1 and breast cancer. Cancer Epidemiol Biomarkers Prev 10: 217–222.
13. Smith TR, Levine EA, Perrier ND, Miller MS, Freimans RI, et al. (2005) DNA repair genetic polymorphisms and breast cancer risk. Cancer Epidemiol Biomarkers Prev 12: 1200–1204.
14. Han J, Hankinson SE, De Vivo I, Spiegelman D, Tamimi RM, et al. (2005) A prospective study of XRCC1 haplotypes and their interaction with plasma carotenoids on breast cancer risk. Cancer Res 63: 8536–8541.
15. Smith TR, Miller MS, Lohman K, Lange EM, Case LD, et al. (2003) Polymorphisms of XRCC1 and XRCC3 genes and susceptibility to breast cancer. Cancer Let 190: 183–190.
16. Patel AV, Calle EE, Pavluck AL, Feigelson HS, Thun MJ, et al. (2005) A prospective study of XRCC1 (X-ray cross-complementing group 1) polymorphisms and breast cancer risk. Breast Cancer Res 7: R1168–R1173.
17. Shen J, Gannon MD, Terry MB, Wang L, Wang Q, et al. (2005) Polymorphisms in XRCC1 modify the association between polycyclic aromatic hydrocarbon-DNA adducts, cigarette smoking, dietary antioxidants, and breast cancer risk. Cancer Epidemiol Biomarkers & Prevention 14: 336–342.
18. Bu D, Tomlins G, Lewis CM, Zhang C, Kidlebeck E, et al. (2006) An intronic polymorphism associated with increased XRCC1 expression, reduced apoptosis and familial breast cancer. Breast Cancer Res Treat 99: 257–263.
19. Ishigurogan B, Anderson KE, Folsom AR, Jacobs DJ, Lynch CF, et al. (2006) No association between XRCC1 and XRCC3 gene polymorphisms and breast cancer risk: Iowa Women’s Health Study. Cancer Detect Prev 30: 313–321.
20. Brawner AM, Jorgensen TJ, Ruczinski I, Huang HY, Hoffman S, et al. (2006) Polymorphisms of the DNA repair genes XPD (Lys751Gln) and XRCC1 (Arg399Gln and Arg194Trp): relationship to breast cancer risk and familial predisposition to breast cancer. Breast Cancer Res Treat 95: 73–80.
21. Zhang Y, Newcomb PA, Egan KM, Timasheff SN, Chanock S, et al. (2006) Genetic polymorphisms in base-excision repair pathway genes and risk of breast cancer. Cancer Epidemiology Biomarkers & Prevention 15: 336–339.
22. Pachkowski BF, Winkel S, Kubota Y, Swanberg JA, Milikan RG, et al. (2006) XRCC1 genotype and breast cancer: functional studies and epidemiologic data show interactions between XRCC1 codon 280 His and smoking. Cancer Res 66: 2869–2869.
23. Ali MF, Meza JL, Rogan EG, Chakravarti D (2008) Prevalence of BER gene polymorphisms in sporadic breast cancer. Oncol Rep 19: 1033–1038.
24. Smith TR, Levine EA, Freimans RI, Akman SA, Allen GO, et al. (2008) Polymorphic model of DNA repair genetic polymorphisms in human breast risk. Carcinogenesis 29: 2132–2139.
25. Zipprich J, Terry MB, Brandi-Rauf P, Freyer GA, Liao Y, et al. (2010) XRCC1 polymorphisms and breast cancer risk from the New York Site of the Breast Cancer Family Registry: A family-based case-control study. J Carcinog 9: 4.

26. Roberts MR, Shields PG, Ambsosone CB, Nie J, Marian C, et al. (2011) Single-nucleotide polymorphisms in DNA repair genes and association with breast cancer risk in the web study. Carcinogenesis 32: 1223–1230.

27. Huang Y, Li L, Yu L, (2009) XRCC1 Arg399Gln, Arg194Trp and Arg280His polymorphisms in breast cancer risk: a meta-analysis. Mutagenesis 24: 331–339.

28. Li H, Ha TC, Tai BC (2009) XRCC1 gene polymorphisms and breast cancer risk in different populations: a meta-analysis. Breast 18: 183–191.

29. Wu K, Su D, Li K, Luo J, Au WW (2011) XRCC1 Arg399Gln gene polymorphism and breast cancer risk: a meta-analysis based on case-control studies. Asian Pac J Cancer Prev 12: 2237–2243.

30. Saadat M, Ansari-Lari M (2009) Polymorphism of XRCC1 (at codon 399) and susceptibility to breast cancer, a meta-analysis of the literatures. Breast cancer research and treatment 115: 137–144.

31. Mohrer D, Liberati A, Tetzlaff J, Altman DG (2009) Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Annals of internal medicine 151: 264–269.

32. Higgins J, Thompson SG (2002) Quantifying heterogeneity in a meta-analysis. Statistics in medicine 21: 1539–1558.

33. Egger M, Smith GD, Schneider M, Minder C (1997) Bias in meta-analysis detected by a simple, graphical test. Bmj 315: 629–634.

34. Chou W, Wang H, Wong F, Ding S, Wu P, et al. (2006) Chk2-dependent phosphorylation of XRCC1 in the DNA damage response promotes base excision repair. The EMBO journal 27: 3140–3150.

35. Hung RJ, Hall J, Brennan P, Boffetta P (2005) Genetic polymorphisms in the base excision repair pathway and cancer risk: a HuGE review. American journal of epidemiology 162: 925–942.

36. Shen MR, Jones IM, Mohrenweiser H (1998) Nonconservative amino acid substitution variants exist at polymorphic frequency in DNA repair genes in healthy humans. Cancer research 58: 604–608.

37. Masson M, Niedergang C, Schreiber VER, Muller S, Menissier-de Murcia J, et al. (1998) XRCC1 is specifically associated with poly (ADP-ribose) polymerase and negatively regulates its activity following DNA damage. Molecular and Cellular Biology 18: 3563–3571.

38. Liu L, Yuan P, Liu L, Wu C, Zhang X, et al. (2011) A functional -77T>C polymorphism in XRCC1 is associated with risk of breast cancer. Breast Cancer Res Treat 125: 479–487.

39. Liu L, Yuan P, Wu C, Zhang X, Wang F, et al. (2011) Assessment of XPD Lys751Gln and XRCC1 T-77C polymorphisms in advanced non-small-cell lung cancer patients treated with platinum-based chemotherapy. Lung Cancer 73: 110–115.

40. Zhong R, Liu L, Zou L, Sheng W, Zhu B, et al. (2013) Genetic variations in the TGFbeta signaling pathway, smoking and risk of colorectal cancer in a Chinese population. Carcinogenesis 34: 936–942.

41. Liu L, Wu C, Wang Y, Zhong R, Wang F, et al. (2011) Association of candidate genetic variations with gastric cardia adenocarcinoma in Chinese population: a multiple interaction analysis. Carcinogenesis 32: 336–342.