REVIEW

Association of XRCC2 rs3218536 Polymorphism with Susceptibility of Breast and Ovarian Cancer: A Systematic Review and Meta-Analysis

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Abstract

Background: Previous studies have investigated the association of X-Ray Repair Cross-Complementing Group 2 (XRCC2) rs3218536 polymorphism with breast and ovarian cancer. However, this association remains conflicting. Therefore, we have performed the current systematic review and meta-analysis to clarify the association between XRCC2 rs3218536 polymorphism with risk of breast and ovarian cancer. Methods: We conducted a search in PubMed, Google Scholar and ISI Web of Science to select relevant studies on the association of XRCC2 rs3218536 polymorphism with breast and ovarian cancer susceptibility. We calculated the odds ratios (OR) and 95% confidence intervals (CI) for five genetic contrasts. In addition, a stratified analysis was conducted cancer type, ethnicity and HWE status. Results: A total of 17 studies with 5694 cases and 6450 controls for breast cancer and nine case-control studies with 4464 cases and 6353 controls for ovarian cancer were identified for the analysis of the association with XRCC2 rs3218536 polymorphism. The pooled ORs revealed that XRCC2 rs3218536 polymorphism was associated with breast cancer under the heterozygote contrast (AG vs. GG: OR = 0.929, 95% CI = 0.873-0.987, p=0.018) and ovarian cancer under dominant contrast (AA+AG vs. GG: OR = 0.725, 95% CI = 0.537-0.979, p=0.036) in the overall population. The stratified analysis indicated a significant association of XRCC2 rs3218536 polymorphism with breast and ovarian cancer risk among Caucasians. Conclusion: Inconsistent with previous meta-analysis, this meta-analysis shows that the XRCC2 rs3218536 polymorphism was associated with breast and ovarian cancer risk in overall population, especially among Caucasians.

Keywords: Breast cancer- ovarian cancer- XRCC2 rs3218536- polymorphism- meta-analysis

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Introduction

Breast cancer is the most frequently diagnosed cancer among women, which contributed to 25 % of all cancer cases in women worldwide (Shiryazdi et al., 2015; Yazdi et al., 2015). A hereditary component accounts for 10-15% of all breast and ovarian cancer cases. It is estimated that 30% of hereditary breast cancer cases are due to mutations in one of the BRCA1 and BRCA2 genes (Forat-Yazdi et al., 2015; Neamatzadeh et al., 2015). Ovarian cancer is the fifth leading cause of cancer deaths occurring in women and leading cause of mortality from gynecologic cancer (Stewart et al., 2013). It is estimated that familial ovarian cancer accounts for 5-15% of the total cases of ovarian cancer (Lynch et al., 2009). It is known that family history is one of the most important risk factors in ovarian cancer development. A possible genetic contribution to both breast and ovarian cancer risk is indicated by the increased incidence of these cancers among women with a family history (National Comprehensive Cancer Network). The mechanism of breast and ovarian carcinogenesis is still not well understood (Yoneda et al., 2012). It has been reported that several potential genes (with low, medium and high penetrance) and combining with environmental factors may be important in the development of these malignancies (Xu et al., 2014; Yoneda et al., 2012).

The X-Ray Repair Cross-Complementing Group 2 (XRCC2) gene encodes a member of the Rad51 family of related proteins that maintains chromosome stability by participating in homologous recombination and repairs DNA damage. The XRCC2 and XRCC3 are two of the members of RAD51-related proteins (Michalska et al.,

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through consensus with a third investigator. In this meta-analysis the subject’s (cases and controls) ethnicities were categorized as Caucasian, Asian, or African.

**Materials and Methods**

**Literature and Search Strategy**

We have conducted a systematic literature search using the PubMed, Gene, Google scholar, Web of Science and EMBASE database to find studies assessing the association between XRCC2 rs3218536 polymorphism and breast and ovarian cancer up to January 20, 2017. We sought publication with the following key words: “breast cancer”, “ovarian cancer”, “X-Ray Repair Cross Complementing 2”, “DNA repair protein XRCC2”, “XRCC2”, “rs3218536”, “single nucleotide polymorphism”, “polymorphism”, “SNP”, “mutation”, and “variation”. In addition, we have identified related studies by hand screening of included studies. The search was limited to human studies were published only in English language.

**Inclusion Criteria and Data Extraction**

The studies included in the current meta-analysis meet the following criteria: (1) evaluates the association between XRCC2 rs3218536 polymorphism and breast and ovarian cancer risk; (2) used case–control or prospective cohort design; and (3) containing at least genotype frequencies for estimating an odds ratio (OR) with 95% confidence interval (95% CI). In addition, the exclusion criteria were as the follows: (1) not conducted on human subjects, (2) not breast and ovarian cancer research (3) only included patients or healthy subjects, (4) duplicate of previous publications (completely or partially), and (5) above all, have not sufficient data about frequency of genotypes.

**Data extraction**

For each study, we have extracted carefully (two authors independently) the following data: First author, publication year, country of origin, ethnicity, number of cases and controls, and Hardy–Weinberg Equilibrium (HWE). Any disagreements were discussed and resolved statistically significant.

**Results**

**Characteristics of the included studies**

Based on the established search criteria, articles were retrieved for the association of XRCC2 rs3218536 polymorphism with breast and ovarian cancer susceptibility. Twenty publications (26 studies) met the inclusion criteria, the characteristics of which are showed in Table 1 and 2. Of these 20 publications, 16 publications (17 studies) with 5694 cases and 6450 controls evaluate the association of XRCC2 rs3218536 polymorphism with breast cancer risk. Two out of the 17 studies were published in Asians (Ding et al., 2014; Qureshi et al., 2014) and the others were in Caucasians (Rafii et al., 2002; Kuschel et al., 2002, Han et al., 2004; Webb et al., 2005; Millikan et al., 2005; García-Closas et al., 2006; Brooks et al., 2008; Loizidou et al., 2008; Pooley et al., 2008; Silva et al., 2010; Jakubowska et al., 2010; Makowska et al., 2012; Smolarz et al., 2014; Shadrina et al., 2014). There were 15 studies of Caucasian descendants (USA, UK, Poland, Australia, Portugal, Russia and Cyprus) and 2 studies of East Asian descendants communities (China and Pakistan). In addition, of these 20 publications, 5 publications (9 case-control studies) with 4464 cases and 6353 controls for association between XRCC2 rs3218536 polymorphism and ovarian cancer. The populations came from different ethnic backgrounds.

**Statistical analysis**

The strength of association was assessed by calculating the odds ratios and 95% confidence intervals and the Z-test was used to evaluate statistical significance with P-values less than 0.01 considered as statistically significant. Pooled ORs were estimated for five genetic contrast including allele (A vs. G), heterozygote (AG vs. GG), homozygote (AA vs. GG), dominant (AA+AG vs. GG) and recessive (AA vs. AG+GG) contrasts. In the current meta-analysis, the heterogeneity among studies was calculated by X2-based Q test and I2. The heterogeneity were considered significant when p value was less than 0.05 for the Q test or I2>25% in I2 statistics. Moreover, a random effects model using the DerSimonian was utilized to calculate the OR and 95% CI for comparisons with moderate to high heterogeneity (P-value > 0.1 and I2 > 25%) (DerSimonian et al., 1986). Otherwise, a fixed-effects model using the Mantel–Haenszel method was used. Sensitivity analysis was performed by sequential omission of individual studies (leave-one-out analysis) for various genetic models in the overall population and for subgroup analysis by ethnicity and HWE status. We have evaluated publication bias graphically using the Begg’s funnel plot and statistically using the method of Egger’s linear regression test (Egger et al., 1997). P<0.05 indicated that the result was statistically significant. We have used comprehensive meta-analysis (CMA) V2.0 software (Biostat, USA) to perform all the statistical analyses. Two-sided P values < 0.05 were considered statistically significant.
countries, including UK, Denmark, USA, Australia, Egypt and Poland. There were 8 studies (Auranen et al., 2005; Webb et al., 2005; Beesley et al., 2007; Michalska et al., 2016) of Caucasian descendants and 1 study (Mohamed et al., 2013) of African descendant. Genotype distributions in the controls of two studies for breast cancer (Loizidou et al., 2008; Silva et al., 2010) and two studies for ovarian cancer (Mohamed et al., 2013; Michalska et al., 2016) were not in agreement with HWE (p < 0.05).

**Meta-analysis**

**Association of XRCC2 rs3218536 polymorphism and breast cancer**

The meta-analysis of a possible association between XRCC2 rs3218536 polymorphism and breast cancer is summarized in Tables 3. Based on the total study population, a strong association was found between XRCC2 rs3218536 polymorphism and breast cancer under the heterozygote contrast (AG vs. GG: OR = 0.929, 95% CI = 0.873-0.987, p=0.018) in the overall population (Figure 2E). Considering the limited number of qualified studies in the Asian and other descendant populations, the stratified analyses was only presented for Caucasians. In the subgroup analyses of ethnicity, the meta-analysis results indicated a strong association between the XRCC2 rs3218536 polymorphism and breast cancer susceptibility among Caucasians only under the heterozygote contrast (AG vs. GG: OR = 0.920, 95% CI = 0.861-0.980, p=0.009). Additionally, significant associations between the XRCC2 rs3218536 polymorphism and breast cancer under the recessive contrast (AG vs. GG: OR = 1.635, 95% CI = 1.109-2.413, p=0.013) was found according to the HWE.

**Association of XRCC2 rs3218536 polymorphism and ovarian cancer**

The meta-analysis of a possible association between the XRCC2 rs3218536 polymorphism and risk of ovarian cancer.
cancer is summarized in Table 4. The pooled analysis for XRCC2 rs3218536 polymorphism and risk of ovarian cancer involved 5 publications (9 case-control studies) with 4,464 cases and 6,353 controls. The pooled ORs revealed that XRCC2 rs3218536 polymorphism was associated with risk of ovarian cancer only under dominant genetic model (AA+AG vs. GG: OR = 0.725, 95% CI = 0.537-0.979, p=0.036) in the overall (Table 4). Stratification analysis by ethnicity showed significant association between XRCC2 rs3218536 polymorphism and ovarian cancer in Caucasian under heterozygote contrast (AG vs. GG: OR = 0.710, 95% CI = 0.517-0.975, p=0.034) and dominant contrast (AA+AG vs. GG: OR = 0.666, 95% CI = 0.502-0.884, p=0.005, Table 2, Figure 2a). And we also observed association between this polymorphism and ovarian cancer according to the HWE under allele contrast (A vs. G: OR = 0.685, 95% CI =

Table 3. Meta-Analysis of the Association of XRCC2 Rs3218536 Polymorphism and Breast Cancer

| Genetic model | Type of model | Heterogeneity | Odds ratio | 95% CI | P_{H} | P_{OR} | P_{Begg} | P_{Egger} |
|---------------|---------------|---------------|------------|--------|-------|--------|----------|----------|
| Overall       | A vs. G       | Random        | <0.001     | 1.027  | 0.904-1.167 | 0.681 | 0.387 | 0.142 |
|               | AG vs. GG     | Fixed         | 0.113      | 0.929  | 0.873-0.987 | 0.018 | 0.592 | 0.412 |
|               | AA vs. AG     | Random        | <0.001     | 1.125  | 0.770-1.643 | 0.542 | 1     | 0.868 |
|               | AA+AG vs. GG  | Random        | <0.001     | 1.118  | 0.923-1.353 | 0.255 | 0.108 | 0.016 |
|               | AA vs. AG+GG  | Random        | <0.001     | 1.443  | 0.945-2.203 | 0.089 | 0.742 | 0.695 |
| Caucasian     | A vs. G       | Random        | <0.001     | 0.998  | 0.872-1.143 | 0.979 | 0.552 | 0.216 |
|               | AG vs. GG     | Fixed         | 0.137      | 0.92   | 0.861-0.980 | 0.009 | 1     | 0.779 |
|               | AA vs. AG     | Random        | <0.001     | 1.038  | 0.647-1.665 | 0.878 | 0.631 | 0.76  |
|               | AA+AG vs. GG  | Random        | <0.001     | 1.098  | 0.892-1.352 | 0.377 | 0.165 | 0.033 |
|               | AA vs. AG+GG  | Random        | <0.001     | 1.354  | 0.774-2.371 | 0.289 | 0.45  | 0.856 |
| HWE           | A vs. G       | Random        | <0.001     | 1.077  | 0.956-1.213 | 0.225 | 0.165 | 0.033 |
|               | AG vs. GG     | Fixed         | 0.116      | 0.943  | 0.885-1.006 | 0.074 | 0.428 | 0.312 |
|               | AA vs. AG     | Random        | 0.01       | 1.232  | 0.892-1.701 | 0.206 | 0.582 | 0.555 |
|               | AA+AG vs. GG  | Random        | <0.001     | 1.196  | 0.973-1.471 | 0.089 | 0.047 | 0.009 |
|               | AA vs. AG+GG  | Random        | <0.001     | 1.635  | 1.109-2.413 | 0.013 | 0.854 | 0.28  |
0.496-0.947, p=0.034), heterozygote contrast (AG vs. GG: OR = 0.710, 95% CI = 0.517-0.975, p=0.034) and dominant contrast (AA+AG vs. GG: OR = 0.666, 95% CI = 0.502-0.884, p=0.005, Table 2, Figure 2a).

**Test of heterogeneity**

For XRCC2 rs3218536 polymorphism and breast cancer, when the data pooled a significant heterogeneity observed in allele (I²=79.49%, P=0.001), homozygote (I²=66.50%, P=0.042), dominant (I²=86.39%, P=0.001) and recessive (I²=78.06%, P=0.001) contrasts (Table 3). After subjects stratified by ethnicity and HWE status, the heterogeneity not disappeared obviously (Table 3). For XRCC2 rs3218536 polymorphism and ovarian cancer, when the data pooled a significant heterogeneity observed in allele (I²=97.33%, P=0.001), heterozygote (I²=82.27%, P=0.001), homozygote (I²=82.73%, P=0.001), dominant (I²=80.96%, P=0.001) and recessive (I²=92.22%, P=0.001) contrasts (Table 4).

After subjects stratified by ethnicity and HWE status, the heterogeneity not disappeared obviously Caucasian. However, by HWE status the heterogeneity disappeared obviously in heterozygote (I²=12.14%, P=0.337), homozygote (I²=0.00%, P=0.629) and recessive (I²=10.04%, P=0.352) contrasts (Table 4).

**Publication bias**

Both Begg’s funnel plot and Egger’s test were performed to assess the publication bias of literatures. The shapes of the funnel plots revealed no obvious asymmetry for association of XRCC2 rs3218536 polymorphism with breast cancer in the overall analyses (Figure 2A). However, the results of Egger’s regression test provided sufficient evidence for publication bias in dominant contrast (P_{Begg}=0.108, P_{Egger}=0.016), suggesting that there was obvious publication bias in the genetic contrast. In addition, the publication bias has seen in the meta-analysis XRCC2 rs3218536 polymorphism in Caucasians (dominant contrast: P_{Begg}=0.108, P_{Egger}=0.016) and by HWE status (allele contrast: P_{Begg}=0.165, P_{Egger}=0.033; dominant contrast: P_{Begg}=0.047, P_{Egger}=0.009). Moreover, the results of Egger’s regression test provided evidence of publication bias for association of XRCC2 rs3218536 polymorphism with ovarian cancer in allele (P_{Begg}=0.001, P_{Egger}=0.033), homozygote (P_{Begg}=0.465, P_{Egger}=0.002) and recessive contrasts (P_{Begg}=0.916, P_{Egger}=0.002) in overall analysis. In addition, the publication bias has seen in the meta-analysis XRCC2 rs3218536 polymorphism and ovarian cancer in Caucasians (allele: P_{Begg}=1.000, P_{Egger}=0.045; homozygote: P_{Begg}=0.901, P_{Egger}=0.002 and recessive contrasts: P_{Begg}=0.901, P_{Egger}=0.001).

**Discussion**

In this meta-analysis, we have evaluated the associations of XRCC2 rs3218536 polymorphism with breast and ovarian cancer susceptibility. To the best knowledge, our data suggested a significant association between the XRCC2 rs3218536 polymorphism and increased risk for breast cancer under heterozygote contrast. Additionally, the dominant contrast for the XRCC2 rs3218536 polymorphism indicated increased risk for OC.

Several meta-analyses have estimated the association between XRCC2 rs3218536 polymorphism and breast cancer risk (Yu et al., 2010; He et al., 2014; Kong et al., 2015; Zhang et al., 2016). He et al., (2014) in a meta-analysis of 45 case-control studies from 26
publications with 30868 cases and 38656 controls have evaluated XRCC2 rs3218536 polymorphism association with breast and ovarian cancer risk. According to their results, this polymorphism might be had different roles in development breast and ovarian cancer. Their findings not confer the association between XRCC2 rs3218536 polymorphism and breast cancer. While, they have showed this polymorphism might contribute to decreased ovarian cancer susceptibility. Actually, their findings suggested a protective role of the XRCC2 rs3218536 polymorphism in formation of ovarian cancer. Similarly to the He et al., (2014) results, in another meta-analysis of 16 studies involving 18,341 cases and 19,028 controls, Yu et al., (2010) not found evidence of a significant association between XRCC2 rs3218536 and breast cancer susceptibility in all five genetic contrasts. Also, in the recent meta-analysis by Kong et al., (2015) they have reported the same results to the two meta-analyses. However, inconsistent to the previous meta-analyses, we have found that the XRCC2 rs3218536 polymorphism positively confer the risk of development both breast cancer in the overall population and Caucasians. Interestingly, Zhang et al., (2016) in a meta-analysis of 15 case-control studies with 4,757 cases and 8,431 controls not found a significant association between XRCC2 rs3218536 polymorphism and ovarian cancer risk. In addition, in the stratified analyses by HWE status they have seen that rs3218536 polymorphism was associated with the decreased risk of ovarian cancer. However, in the current meta-analysis, we have found that this polymorphism significantly associated with risk of ovarian cancer in overall and by subgroup analysis in Caucasians and HWE status.

Many factors may contribute to the strong heterogeneity among overall analysis (Mehdinejad et al., 2017; Jafari Nedooshan et al., 2017). In the meta-analysis of XRCC2 rs3218536 polymorphism and breast cancer, the heterogeneity between studies was not significantly reduced in the subgroup analysis by the ethnicity and HWE, which indicating that the effect of XRCC2 rs3218536 in development breast cancer may not be modified by ethnicity and HWE. However, the heterogeneity between studies in the meta-analysis of XRCC2 rs3218536 polymorphism and ovarian cancer was significantly reduced by HWE status.

To the best knowledge, current meta-analysis is by far the most comprehensive and convincing on the association of the XRCC2 rs3218536 polymorphism with breast and ovarian cancer susceptibility to date. This meta-analysis has two strengths compared with previous meta-analysis as follow; first, in this meta-analysis, relatively all eligible studies with large sample sizes were included, which would decrease the risk of random error. Second, the quality of eligible publications included in meta-analysis was more satisfactory and met mostly the inclusion criteria. However, some limitations should be taken into consideration when explaining the results as follow: first, most of the studies included in the meta-analysis were performed in the Caucasian population, the limited number was from Asians (only two publications) and there was no relevant study from Africans. However, most subjects were from Caucasian, but limited to the UK, Poland and USA. Thus, to obtain more precise meta-analysis of XRCC2 rs3218536 polymorphism on breast and ovarian cancer susceptibility, additional studies with larger sample size and involving different ethnicities especially Asians and African are required. Second, because we have included only relevant published articles and written in English language in the meta-analysis, publication bias may have occurred, even though it was not found by making use of statistical tests. Third, the overall outcomes were based on individual unadjusted ORs without adjustment for other risk factors such as age, histological subtypes, clinical stages, menstrual status, environmental and other confounding lifestyle factors. Finally, this meta-analysis could not address the gene-gene and gene-environmental interactions in the association between XRCC2 rs3218536 polymorphism and risk of breast and ovarian cancer. Therefore, future studies that include detailed information on exposures to environmental factors to assess the possible gene-gene and gene-environmental interactions in the association between XRCC2 rs3218536 polymorphism and risk of breast and ovarian cancer are required.

In summary, this systematic review and meta-analysis shows that the XRCC2 rs3218536 polymorphism was associated with breast and ovarian cancer susceptibility in overall population and Caucasians. According to the limitations listed above, Asian and African descendant studies should be similarly performed.

References

Auranen A, Song H, Waterfall C, et al. (2005). Polymorphisms in DNA repair genes and epithelial ovarian cancer risk. Int J Cancer, 117, 611-18.

Beesley J, Jordan SJ, Spurdle AB, et al. (2007) Association between single-nucleotide polymorphisms in hormone metabolism and DNA repair genes and epithelial ovarian cancer: results from two Australian studies and an additional validation set. Cancer Epidemiol Biomarkers Prev, 16, 2557–65.

Brooks J, Shore RE, Zeleniuch-Jacquotte A, et al. (2008). Polymorphisms in RAD51, XRCC2, and XRCC3 are not related to breast cancer risk. Cancer Epidemiol Biomarkers Prev, 17, 1016–19.

Ding P, Yang Y, Cheng L, et al. (2014). The relationship between seven common polymorphisms from five DNA repair genes and the risk for breast cancer in northern Chinese women. PLoS One, 9, e92083.

DerSimonian R, Laird N (1986). Meta-analysis in clinical trials. Control Clin Trials, 7, 177-88.

Egger M, Davey Smith G, Schneider M, et al. (1997). Bias in meta-analysis detected by a simple, graphical test. BMJ, 315, 629-34.

Han J, Hankinson SE, Ranu H, et al. (2004). Polymorphisms in DNA double-strand break repair genes and breast cancer risk in the nurses’ health study. Carcinogenesis, 25, 189-95.

He Y, Zhang Y, Jin C, et al. (2014). Impact of XRCC2 Arg188His polymorphism on cancer susceptibility: A meta-analysis. PLoS One, 9, e91202.

Forat-Yazdi M, Neamatzadeh H, Sheikhha M, et al. (2015). BRCAl and BRCAl2 Common Mutations in Iranian Breast Cancer Patients: a meta-analysis. Asian Pac J Cancer Prev, 16, 1219-24.

Garcia-Closas M, Egan KM, Newcomb PA, et al. (2006). Polymorphisms in DNA double-strand break repair genes
and risk of breast cancer: two population-based studies in USA and Poland, and meta-analyses. Hum Genet, 119, 376-88.

Jafari Nedooshan J, Forat Yazdi M, Neamatzadeh H, et al (2017). Genetic association of XRCC1 gene rs1799782, rs25487 and rs25489 polymorphisms with risk of thyroid cancer: a Systematic review and meta-analysis. Asian Pac J Cancer Prev, 18, 263-70.

Jakubowska A, Gronwald J, Menkiszak J, et al (2010). BRCA1-associated breast and ovarian cancer risks in Poland: with no association with commonly studied polymorphisms. Breast Cancer Res Treat, 119, 201-11.

Kong B, Lv ZD, Chen L, et al (2015). Lack of an association between XRCC2 R188Hpolymorphisms and breast cancer: an updatemeta-analysis involving 35,422 subjects. Int J Clin Exp Med, 8, 15805-14.

Kuschel B, Auranen A, McBride S (2002). Variants in DNA doublestrand break repair genes and breast cancer susceptibility. Hum Mol Genet, 11, 1399-40272.

Loizidou MA, Michael T, Neuhausen SL, et al (2008). Genetic polymorphisms in the DNA repair genes XRCRC1, XRCRC2 and XRCRC3 and risk of breast cancer in Cyprus. Breast Cancer Res Treat, 112, 575-9.

Lynch HT, Casey MJ, Snyder CL, et al (2009). Hereditary ovarian carcinoma: heterogeneity, molecular genetics, pathology, and management. Mol Oncol, 3, 97-137.

Mehdinejad M, Sobhan MR, Mazaheri M, et al (2017). Genetic association between ERCC2, NBN, RAD51 gene variants and osteosarcoma risk: a systematic review and meta-analysis. Asian Pac J Cancer Prev, 18, 1315-21.

Michalska MM, Samulak D, Romanowicz H, et al (2016). Association between single nucleotide polymorphisms (SNPs) of XRCRC2 and XRCRC3 homologous recombination repair genes and ovarian cancer in Polish women. Exp Mol Pathol, 100, 243-7.

Millikan RC, Player JS, Decotret AR, et al (2005). Polymorphisms in DNA repair genes, medical exposure to ionizing radiation, and breast cancer risk. Cancer Epidemiol Biomarkers Prev, 14, 2326-34.

Mohamed FZ, Hussien YM, AIBakry MM, et al (2013). Role of DNA repair and cell cycle control genes in ovarian cancer susceptibility. Mol Biol Rep, 40, 3757-68.

National comprehensive cancer network (2014). NCCN guidelines version 2.2014 genetics/familial high-risk assessment: Breast and ovarian, MS3-8.

Neamatzadeh H, Shiryazdi SM, Kalantar SM (2015). BRCA1 and BRCA2 mutations in Iranian breast cancer patients: A systematic review. J Res Med Sci, 20, 284-93.

Pooley KA, Baynes C, Driver KE, et al (2008). Common single-nucleotide polymorphisms in DNA double-strand break repair genes and breast cancer risk. Cancer Epidemiol Biomarkers Prev, 17, 3482-9.

Qureshi Z, Mahjabeen I, Baig R, et al (2014). Correlation between selected XRCRC2, XRCRC3 and RAD51 gene polymorphisms and primary breast cancer in women in Pakistan. Asian Pac J Cancer Prev, 15, 10225-9.

Rafii S, O’Regan P, Xinarianos G, et al (2002). A potential role for the XRCRC2 R188H polymorphic site in DNA-damage repair and breast cancer. Hum Mol Genet, 11, 1433-8.

Romanowicz-Makowska H, Smolarz B, Zadrozyń M, et al (2012). The association between polymorphisms of the RAD51 - G135C, XRCRC2-A arg188His and XRCRC3-Thr241Met genes and clinicopathologic features in breast cancer in Poland. Eur J Gynaecol Oncol, 33, 145–50.

Satwar R, Bashir K, Saeed S, et al (2016). Association of promoter polymorphisms in Xrcrc2 gene involved in DNA double strand break repair and increased susceptibility to thyroid cancer risk in Pakistani population. J Carcinog Mutagen, 7, 265.

Shadrina AS, Ermolenko NA, Boyarskikh UA, et al (2016). Polymorphisms in DNA repair genes and breast cancer risk in Russian population: a case–control study. Clin Exp Med, 16, 21–8.

Shiryazdi SM, Kargar S, Nasaj H, et al (2015). The accuracy of Breastlight in detection of breast lesions. Indian J of Cancer, 52, 513.

Silva SN, Tomar M, Paulo C, et al (2010). Breast cancer risk and common single nucleotide polymorphisms in homologous recombination DNA repair pathway genes XRCRC2, XRCRC3, NBS1 and RAD51. Cancer Epidemiol, 34, 85-92.

Smolarz B, Makowska M, Samulak D, et al (2015). Association between single nucleotide polymorphisms (SNPs) of XRCRC2 and XRCRC3 homologous recombination repair genes and triple-negative breast cancer in Polish women. Clin Exp Med, 15, 151-7.

Sobhan MR, Forat Yazdi M, Mazaheri M, et al (2017). Association between the DNA repair gene XRCRC3 rs861539 polymorphism and risk of osteosarcoma: a systematic review and meta-analysis. Asian Pac J Cancer Prev, 18, 549-55.

Stewart SL, Lakhani N, Brown PM, et al (2013). Gynecologic cancer prevention and control in the national comprehensive cancer control program: progress, current activities, and future directions. J Womens Health (Larchmt), 22, 651-7.

Webb PM, Hopper JL, Newman B, et al (2005). Double strand break repair gene polymorphisms and risk of breast or ovarian cancer. Cancer Epidemiol Biomarkers Prev, 14, 319-23.

Xu K, Song X, Chen Z, et al (2014). XRCRC2 rs3218536 polymorphism decreases the sensitivity of colorectal cancer cells to poly (ADP-ribose) polymerase 1 inhibitor. Oncol Lett, 8, 1222-8.

Yazdi MF, Rafieian S, Gholi-Nataj M, et al (2015). CYP2D6 Genotype and risk of recurrence in tamoxifen treated breast cancer patients. Asian Pac J Cancer Prev, 16, 6783-7.

Yoneda A, Lendorf ME, Couchman JR, et al (2012). Breast and ovarian cancers: a survey and possible roles for the cell surface heparan sulfate proteoglycans. J Histochem Cytochem, 60, 9-21.

Yu KD, Chen AX, Qiu LX, et al (2010). XRCRC2 Arg188His polymorphism is not directly associated with breast cancer risk: evidence from 37,369 subjects. Breast Cancer Res Treat, 123, 219–25.

Zhang W, Zhang Z (2016). Associations between XRCC2 rs3218536 and Breast and Ovarian Cancer.