Association of XRCC1 Arg399Gln Polymorphism with Colorectal Cancer Risk: A HuGE Meta Analysis of 35 Studies

Mohammad Forat-Yazdi¹, Mohsen Gholi-Nataj¹*, Hossein Neamatzadeh², Parisa Nourbakhsh³, Hossein Shaker-Ardakani⁴

Abstract

Background: Non-synonymous polymorphisms in XRCC1 have been shown to reduce effectiveness of DNA repair and be associated with risk of certain cancers. In this study we aimed to clarify any association between XRCC1 Arg399Gln and colorectal cancer (CRC) risk by performing a meta-analysis of published case-control studies. Materials and Methods: PubMed and Google Scholar were searched to explore the association between XRCC1 and CRC. Odds ratios (ORs) and 95% confidence intervals (CIs) were calculated to estimate the association strength. Publication bias was assessed by Egger’s and Begg’s tests. Results: Up to January 2015, 35 case control studies involving 9,114 CRC cases and 13,948 controls were included in the present meta-analysis. The results showed that the Arg399Gln polymorphism only under an allele genetic model was associated with CRC risk (A vs. G: OR 0.128, 95% CI 0.119-0.138, p<0.001). Also, this meta-analysis suggested that the XRCC1 Arg399Gln polymorphism might associated with susceptibility to CRC in Asians (A vs G: OR 0.124, 95% CI 0.112-0.138, p<0.001) and Caucasian (A vs G: OR 0.132, 95% CI 0.119-0.146, p<0.001) only under an allele genetic model. Conclusions: This meta-analysis confirms the association between XRCC1 Arg399Gln polymorphism and CRC risk and suggests that the heterogeneity is not strongly modified by ethnicity and deviation from the Hardy-Weinberg equilibrium.

Keywords: Colorectal cancer - XRCC1 - Arg399Gln - polymorphism - meta-analysis.

Introduction

Colorectal cancer is the leading cause of cancer-related death worldwide. Overall, it ranks as the third most frequent cancer worldwide, and the third and second most frequent cancer in men and women respectively (Magaji et al., 2014). It remains an enormous financial burden on the health care system. Although many new and advanced techniques have been introduced for the management and surveillance of CRC, but local recurrence and distant metastasis are still considered major complications (Mehrabani et al., 2014; Omranipour et al., 2014). Amongst the known genetic susceptibility to CRC, the x-ray cross-complementing group 1 and 3 (XRCC1 and XRCC3) have been studied most commonly (Gao et al., 2014). The X-ray repair cross-complementing group 1 (XRCC1) protein, which is encoded by the XRCC1 gene, is an important component of the base excision repair (BER) pathway. The XRCC1 gene is located on chromosome 19q13.2-13.3, spans a genetic distance of 33 kb, comprises of 17 exons and encodes a 70-kDa protein consisting of 633 amino acids. XRCC1 has been shown to have a large number of SNPs, and several have been extensively evaluated in cancer epidemiology association investigations because of their relative high frequency in the population (Ladiges et al., 2006). Although there are more than 300 validated polymorphisms in the XRCC1 gene only three of XRCC1 are most studied and lead to amino acid substitutions in XRCC1 at codon 194, codon 280 and codon 399, these non-conservative amino acid changes may alter XRCC1 protein function (Li et al., 2014).

The XRCC1 Arg399Gln polymorphism has been the most studied of the XRCC1 variations and one of the most frequently studied SNPs among all DNA repair gene variations. XRCC1 Arg399Gln showed associations in different directions for different cancers (Ladiges et al., 2006). So, the XRCC1 Arg399Gln polymorphism is associated with an increased risk for CRC (Wang et al., 2010; Liu et al., 2013). Other studies found no relationship between this polymorphism and CRC risk. Limited and controversial results were obtained regarding the association between colorectal cancer risk and XRCC1 Arg399Gln polymorphism. To provide a comprehensive and objective assessment of the association between the XRCC1 gene Arg399Gln polymorphism and CRC risk, a meta-analysis of all eligible case-control studies was performed.
Mohammad Forat-Yazdi et al.

Materials and Methods

Study identification and selection

A comprehensive literature search was performed using PubMed and Google scholar to identify studies that evaluated the association between XRCC1 Arg399Gln polymorphism and the risk of CRC up to February 1, 2015. The following key words were used: ‘Colorectal cancer’ or ‘Colon cancer,’ ‘X-ray repair cross - complementing group 1’ or ‘XRCC1,’ Arg399Gln and ‘polymorphism’ or ‘variant’. The search was restricted to English and Chinese. The reference lists of reviews and retrieved articles were hand searched at the same time. Abstracts or unpublished reports were not considered. If more than one article was published by the same author using the same case series, we selected the study where the most individuals were investigated. The following criteria were used for the study selection: 1) only case-control studies; 2) studies should concern the association between XRCC1 Arg399Gln polymorphism and CRC risk; 3) papers should offer the sample sizes and the genetic distribution or the information that can help infer the results; 4) no overlapping data. If studies had the same or overlapping data, only the largest study should be included in the final analysis.

Data extraction

Necessary information was carefully extracted from all the eligible studies independently by 2 investigators according to the inclusion criteria. The following data were collected from each study: first author, publication year, country, racial descent (categorized as Asian, Caucasian, or mixed descent), numbers of cases and controls, genotype frequency of cases and controls, and the result of Hardy-Weinberg equilibrium test. If a consensus was not reached, another author was consulted to resolve the dispute; then, a final decision was made by the majority of the votes. We did not define any minimum number of patients for inclusion in our meta-analysis.

Statistical methods

The strength of associations between XRCC1 Arg399Gln polymorphism and CRC risk were evaluated by crude ORs together with their corresponding 95% CIs. Also, the pooled ORs and 95% CIs for XRCC1 Arg399Gln polymorphism was calculated by homozygous model

Table 1. Main Characteristics of All Studies Included in the Meta-analysis

| Author          | Country | Case | Control | Genotypes | Genotypes | Alleles | Alleles | HWE |
|-----------------|---------|------|---------|-----------|-----------|---------|---------|-----|
| Poomphakwaen    | Thailand| 230  | 230     | 102       | 101       | 27      | 305     | 155 | 0.0213 |
| Zhang           | China   | 247  | 300     | 131       | 91        | 25      | 353     | 141 | 0.5478 |
| Gil             | Poland  | 133  | 100     | 52        | 67        | 14      | 171     | 95  | 0.3789 |
| Przybylowska    | Poland  | 152  | 170     | 41        | 69        | 40      | 151     | 149 | 0.6146 |
| Procopciuc      | Thailand| 150  | 162     | 42        | 80        | 28      | 164     | 136 | 0.7161 |
| Parveen Khan    | Kashmir | 120  | 146     | 34        | 80        | 6       | 148     | 92  | 0.0899 |
| Nissar          | Kashmir | 130  | 146     | 34        | 80        | 6       | 148     | 92  | 0.0899 |
| Li              | China   | 451  | 630     | 207       | 215       | 29      | 629     | 273 | 0.2206 |
| Zhao            | China   | 485  | 970     | 239       | 188       | 59      | 666     | 306 | 0.7158 |
| Muniz-Mendoza   | Mexico  | 103  | 103     | 48        | 48        | 8       | 144     | 62  | 0.8992 |
| Yin             | Japan   | 685  | 776     | 356       | 275       | 54      | 987     | 383 | 0.2638 |
| Engin           | Turkey  | 96   | 108     | 47        | 37        | 12      | 131     | 61  | 0.5316 |
| Gsur            | Austria | 85   | 1663    | 35        | 31        | 19      | 101     | 69  | 0.5322 |
| Canbay          | Turkey  | 79   | 247     | 63        | 16        | 0       | 142     | 16  | 0.8616 |
| Zhu             | China   | 250  | 213     | 121       | 112       | 17      | 354     | 146 | 0.1376 |
| Brevik          | USA     | 305  | 360     | 120       | 144       | 41      | 384     | 226 | 0.1416 |
| Jelonek         | Poland  | 113  | 295     | 35        | 49        | 29      | 119     | 107 | 0.2031 |
| Wang            | India   | 302  | 291     | 124       | 134       | 40      | 386     | 218 | 0.0417 |
| Huang           | China   | 120  | 150     | 63        | 46        | 11      | 172     | 68  | 0.476  |
| Curtin          | USA     | 1582 | 1950    | 679       | 725       | 178     | 2083    | 1081| 0.3585 |
| Improta         | Italy   | 109  | 121     | 46        | 54        | 9       | 146     | 72  | 0.0495 |
| Slivinski       | Poland  | 100  | 100     | 47        | 37        | 16      | 131     | 69  | 0.619  |
| Song            | China   | 207  | 255     | 92        | 74        | 12      | 258     | 98  | 0.0013 |
| Kasahara        | Japan   | 68   | 121     | 42        | 23        | 3       | 107     | 29  | 0.698  |
| Pardini         | Czech   | 530  | 532     | 229       | 233       | 68      | 691     | 369 | 0.5758 |
| Jin             | China   | 202  | 616     | 109       | 72        | 21      | 290     | 114 | 0.0231 |
| Stern           | Singapore| 294 | 1120    | 167       | 112       | 15      | 446     | 142 | 0.4292 |
| Yeh             | Taiwan  | 718  | 729     | 407       | 260       | 51      | 1074    | 362 | 0.9116 |
| Martinez-Balibrea| Spain   | 70   | 82      | 30        | 33        | 7       | 93      | 47  | 0.2915 |
| Ren             | China   | 178  | 180     | 92        | 74        | 12      | 258     | 98  | 0.0013 |
| Moreno          | Spain   | 355  | 322     | 154       | 160       | 41      | 468     | 242 | 0.8647 |
| Skjelbred       | Norway  | 157  | 399     | 63        | 70        | 24      | 196     | 118 | 0.7015 |
| Hong            | Korea   | 209  | 209     | 112       | 88        | 9       | 312     | 106 | 0.6747 |
| Krupa and Blasiak| Poland | 51   | 100     | 23        | 19        | 9       | 65      | 37  | 0.619  |
| Abdel-Rahman    | Egypt   | 48   | 48      | 22        | 21        | 5       | 65      | 31  | 0.1674 |
Association of XRCC1 Arg399Gln Polymorphism and Colorectal Cancer Risk: A HuGE Meta Analysis of 35 Studies

Results

Thirty-five studies were included based on the search criteria for CRC susceptibility related to the XRCC1 Arg399Gln polymorphisms (Abdel-Rahman et al., 2000; Krupa et al., 2004; Hong et al., 2005; Skjelbred et al., 2006; Ren et al; Moreno et al., 2006; Jin et al., 2007; Stern et al., 2007; Yeh et al., 2007; Martinez-Balibrea et al., 2008; Pardini et al., 2008; Kasahara et al., 2008;

Table 2. Results of Meta-analysis for XRCC1 Arg399Gln Polymorphism and the Risk of Colorectal Cancer

| Test of association | 95% CI | Test of heterogeneity |
|---------------------|-------|-----------------------|
|                     | OR    | Lower     | Upper     | p value | F     | p value |
| A vs G              |       |           |           |         |       |         |
| Overall             | 0.128 | 0.119     | 0.138     | <0.001  | 72.00 | <0.001  |
| Asian               | 0.124 | 0.112     | 0.138     | <0.001  | 0.897 | <0.001  |
| Caucasian           | 0.132 | 0.119     | 0.146     | <0.001  | 66.64 | <0.001  |
| GA vs GG            |       |           |           |         |       |         |
| Overall             | 1.022 | 0.916     | 1.140     | 0.703   | 64.90 | <0.001  |
| Asian               | 1.023 | 0.857     | 1.221     | 0.805   | 78.25 | <0.001  |
| Caucasian           | 0.977 | 0.892     | 1.070     | 0.613   | <0.001| 0.897   |
| AA vs GG            |       |           |           |         |       |         |
| Overall             | 1.112 | 0.917     | 1.347     | 0.281   | 68.85 | <0.001  |
| Asian               | 1.016 | 0.737     | 1.400     | 0.922   | 78.74 | <0.001  |
| Caucasian           | 1.054 | 0.920     | 1.207     | 0.448   | 49.14 | 0.010   |
| AA vs GA+GG         |       |           |           |         |       |         |
| Overall             | 1.100 | 0.929     | 1.303     | 0.268   | 63.53 | <0.001  |
| Asian               | 1.067 | 0.922     | 1.403     | 0.672   | 69.15 | <0.001  |
| Caucasian           | 1.031 | 0.901     | 1.181     | 0.656   | 73.32 | <0.001  |
| GA+AA vs GG         |       |           |           |         |       |         |
| OverallS            | 1.041 | 0.942     | 1.152     | 0.430   | 63.12 | <0.001  |
| Asian               | 1.046 | 0.891     | 1.227     | 0.583   | 76.27 | <0.001  |
| Caucasian           | 0.984 | 0.903     | 1.072     | 0.707   | 68.21 | <0.001  |

Figure 1. Forest Plots Showing the Association of the XRCC1 Arg399Gln Polymorphism with Risk of CRC (A: A vs G; B: GA vs GG; C: AA vs GG; D: AA vs GA+GG; E: GA+AA vs GG)
Meta-analysis results

Table 2 listed the main results of the meta-analysis for XRCC1 Arg399Gln polymorphism. The overall analysis investigating the allele model (OR=0.128 CI 90% 0.119-0.138 p=0.00) showed significant association between XRCC1 Arg399Gln polymorphism and increased CRC risk, although no evidence of associations was detected in the additive (OR=1.022 CI 90% 0.916-1.140 p=0.703), recessive (OR=1.112 CI 90% 0.917-1.347 p=0.281) and dominant (OR=1.100 CI 90% 0.929-1.303 p=0.268), and (OR=1.041 CI 90% 0.942-1.152 p=0.430) models. Next, stratified analyses by ethnicity were performed between XRCC1 Arg399Gln polymorphism and CRC risk. A significant association between XRCC1 Arg399Gln polymorphism and CRC susceptibility was found in Asian and Caucasian populations only in the allele model (Asians: OR=0.124 CI 90% 0.112-0.138, p=0.00; Caucasians: OR=0.132 95% CI 0.119-0.146 p=0.00), (Table 2).

Sensitivity analysis

In the sensitivity analysis, the influence of each study on the pooled OR was examined by repeating the meta-analysis while omitting each study, one at a time. This procedure confirmed the stability of the overall results. In addition, when excluding 5 study in Asian population that did not follow Hardy-Weinberg equilibrium, the estimated pooled OR still did not significantly change at all (data not shown).

Publication bias

Both Begg’s funnel plot and Egger’s test were performed to assess the publication bias of literatures. All these five genetic models for XRCC1 Arg399Gln polymorphism showed consistent results, indicating no publication biases. The shapes of the funnel plot did not indicate any evidence of obvious asymmetry in genetic models model (Figure 4), and the Egger’s test suggested the absence of publication bias (A vs G: p=0.379; GA vs GG: p=0.346; AA vs GG: p=0.324; AA vs GA+GG: p=0.329; GA+AA vs GG: p=0.283).

Discussion

XRCC1 plays an important role in the DNA damage repair pathway for the processing of small base lesions (Improtta et al., 2008). To date more than 300 single nucleotide polymorphisms (SNPs) have been identified and described in the XRCC1 gene, only three SNPs have been extensively studied, which are 194 (Arg to Trp), 280 (Arg to His), and 399 (Arg to Gln). The XRCC1 polymorphisms have been implicated in the risk of various cancers such as esophageal, gastric, lung, breast and other types of cancer (Li et al., 2014). The relationship between the XRCC1 Arg399Gln polymorphisms and CRC risk has been examined in some case–control studies, but the results of these studies were contradictory and inconclusive.

The contradictory findings among case-control studies might be attributed to different sample size, source of controls, genotyping method and matching criteria of subjects, and so on. In addition, the potential gene–gene and gene-environment interactions may also play vital roles in the pathogenesis of CRC. Single study especially the one with relatively sample size may have not enough statistical power to identify a mild genetic association and introduce random errors. Inversely, meta-analysis by pooling all available data from eligible publications takes the advantage of achieving a more precise estimation for potential genetic associations (Guo et al., 2012). The advantages of this meta-analysis are that it is the most complete and the information from the eligible studies is utilized as much as possible through genetic model and stratified analysis. To help resolve the conflicting results this meta-analysis of published studies was conducted using a larger sample size. In this meta-analysis, it was focused on XRCC1 genetic polymorphism and provides the most comprehensive assessment of its association with CRC risk, by critically reviewing 35 studies on XRCC1 Arg399Gln polymorphism (a total of 9,114 cases and 13,948 controls).

Five meta-analyses previously have estimated the association between XRCC1 Arg399Gln polymorphism and CRC susceptibility (Liu et al., 2010; Wang et al., 2010; Wu et al., 2013; Zeng et al., 2013; Qin et al., 2015). However, the association remains not fully understood.
because of inconsistent results across independent studies. Compared with the previous meta-analyses, our meta-analysis involved a remarkably larger number of studies (35 studies) and provided a more comprehensive and reliable conclusion. We have found that the Arg399Gln polymorphism led to an increased risk in allele comparison (Table 2), which was in consistent with a previous meta-analysis among Chinese (Qin et al., 2015).

Present meta-analysis results were not consistent with a previous meta-analysis (81-86) on XRCC1 Arg399Gln polymorphism with CRC risk. Liu et al. (Liu et al., 2010) included 22 case-control studies with a total of 6,291 CRC cases and 10,289 controls concerning the XRCC1 Arg399Gln polymorphism. Their results suggested that XRCC1 Arg399Gln polymorphism was not associated with increased CRC risk and by ethnicity. In a meta-analysis, Qin et al retrieved 11 case-control studies with a total of 3194 CRC cases and 4472 controls in the Chinese Han population. They have not found a significant association between the XRCC1 Arg399Gln polymorphism and CRC risk in the population (Qin et al., 2015). Our results are inconsistent with the meta-analysis performed by Zeng et al., which 26 case-control studies with 6,979 cases and 11,470 controls were pooled in the meta-analysis. They have suggested that the XRCC1 Arg399Gln polymorphism was significantly associated with increased risk of CRC in among high quality studies and in Asians, but not in Caucasians (Zeng et al., 2013). Lu et al, in a meta-analysis suggests that there is an obvious association between the XRCC1 Arg399Gln polymorphism and increased risk of CRC in East Asians (Lu et al., 2013). Wu et al, in an update meta-analysis suggested that the XRCC1 Arg399Gln polymorphism was significantly associated with increased CRC risk (Wu et al., 2014).

Three polymorphisms in XRCC1 (Arg194Trp, Arg280His and Arg399Gln) have been frequently examined in the studies on cancer susceptibility. Liu et al. (Liu et al., 2013) included 22 case-control studies with a total of 6,291 CRC cases and 10,289 controls concerning the XRCC1 Arg399Gln polymorphism, 14 studies with a total of 4,814 CRC cases and 8,357 controls for Arg194Trp, seven studies with a total of 3,505 CRC cases and 4,636 controls for Arg280His. Their results suggested that these three SNPs evaluated are not associated with risk of CRC.

The statistically significant association between the XRCC1 Arg399Gln polymorphism and CRC risk was observed among studies with high quality and in all ethnicity. Sensitivity analyses by sequential omission of any individual studies not identified the significant association. Obviously, in all genetic models there were potential to moderate level heterogeneity. When we deleted 5 Asian studies which were not according to HWE any more, the heterogeneity of all genetic models was not decreased. Since the subjects came from different populations that perhaps have genetic heterogeneity, subgroup analyses were conducted on ethnicity. However, we found that ethnicity might not be the source of heterogeneity (Table 2). This further indicated that ethnicity and deviations from HWE might not be one source of heterogeneity. Other factors such as the sample sizes, diversity in study designs, inclusion criteria, and genotyping methods might be source of heterogeneity (Salanti et al., 2005).

Compared with two previous meta-analyses, our meta-analysis involved a remarkably larger number of studies and provided a more comprehensive and reliable conclusion. However, there are still some limitations in this meta-analysis. First, our meta-analysis included only studies with accessible full-text articles in English. Therefore, missing some otherwise eligible studies that were reported in other languages could lead to publication bias in the results. Second, lacking the original data for the included studies limited our further evaluation of potential interactions among gene-gene, gene-environment, or even different polymorphism loci of the same gene, which all may affect cancer risk. The joint effect between XRCC1 Arg399Gln and other repair genes genotypes on the risk of cancer was not addressed in the present study. However, the lack of individual data from the included studies limited the further evaluation of other potential interactions, as in other genes and environment factors. For instance, only two studies have reported the combined effect of XRCC1 Arg399Gln and other repair genes genotypes on the risk of cancer (Krupa et al., 2004; Kasahara et al., 2008; Wang et al., 2010). Third, due to the lack of detailed data in the primary articles, our results were based on single-factor estimates without adjustment for other risk factors such as age, gender, environmental factors and other variables, which might have caused serious confounding bias.

In summary, the meta-analysis suggested that the XRCC1 Arg399Gln polymorphism was significantly associated with increased CRC, and the G allele probably acts as an important CRC risk factor.

References
Abdel-Rahman SZ, Soliman AS, Bondy ML, et al (2000). Inheritance of the 194Trp and the 399Gln variant alleles of the DNA repair gene XRCC1 are associated with increased risk of early onset colorectal carcinoma in Egypt. Cancer Lett., 159, 79-86.
Brevik A, Joshi AD, Corral R, et al (2010). Polymorphisms in base excision repair genes as colorectal cancer risk factors and modifiers of the effect of diets high in red meat. Cancer Epidemiol Biomarkers Prev, 19, 3167-73.
Canbay E, Cakmakoglu B, Zeybek U, et al (2011). Association of APE1 and hOGG1 polymorphisms with colorectal cancer risk in a Turkish population. Curr Med Res Opin, 27, 1295-302.
Curtin K, Samowitz WS, Wolff RK, et al (2009). Assessing tumor mutations to gain insight into base excision repair sequence polymorphisms and smoking in colon cancer. Cancer Epidemiol Biomarkers Prev, 18, 3384-8.
Engin AB, Karahalil B, Karakaya AE, et al (2011) Association between XRCC1 ARG399Gln and PS3 ARG72Pro polymorphisms and the risk of gastric and colorectal cancer in Turkish population. Arq Hig Rada Toksikol, 62, 207-214.
Gao CM, Ding JH, Li SP, et al (2014). Polymorphisms in XRC1 gene, alcohol drinking, and risk of colorectal cancer: a case-control study in Jiangsu Province of China. Asian Pac J Cancer Prev, 14, 6613-8.
Gil J, Ramsey D, Stembalska A, et al (2012). The C/A
polymorphism in intron 11 of the XPC gene plays a crucial role in the modulation of an individual’s susceptibility to sporadic colorectal cancer. Mol Biol Rep, 39, 527-534.

Gsur A, Bernhart K, Baierl A, et al (2011). No association of XRCC1 polymorphisms Arg194Trp and Arg399Gln with colorectal cancer risk. Cancer Epidemiol, 35, 38-41.

Guo LY, Jin XF, Niu W, et al (2012). Association of XPD and XRCC1 Genetic Polymorphisms with Hepatocellular Carcinoma Risk. Asian Pac J Cancer Prev, 13, 4423-6.

Hong YC, Lee KH, Kim WC, et al (2005). Polymorphisms of XRCC1 gene, alcohol consumption and colorectal cancer. Int J Cancer, 116, 428-32.

Improta G, Sgambato A, Bianchino G, et al (2008). Polymorphisms of the DNA repair genes XRCC1 and XRCC3 and risk of lung and colorectal cancer: a case-control study in a Southern Italian population. Anticancer Res, 28, 2941-6.

Jin MJ, Chen K, Zhang Y, et al (2007). Correlations of single nucleotide polymorphisms of DNA repair gene XRCC1 to risk of colorectal cancer. Ai Zheng, 26, 274-279.

Jelonek K, Gdowicz-Klosok A, Pietrowska M, et al (2010). Association between single-nucleotide polymorphisms of selected genes involved in the response to DNA damage and risk of colon, head and neck, and breast cancers in a Polish population. J Appl Genet, 51, 343-52.

Khan NP, Pandith AA, Yousuf A, et al (2013). The XRCC1 Arg399Gln gene polymorphism and risk of colorectal cancer: a study in Kashmir. Asian Pac J Cancer Prev, 14, 6779-82.

Kasahara M, Osawa K, Yoshida K, et al (2008). Association of MUTYH Gln324His and APEX1 Asp148Glu with colorectal cancer and smoking in a Japanese population. J Exp Clin Cancer Res, 27, 49.

Krupa R, Blasiak J (2004). An association of polymorphism of DNA repair genes XRCC1 and XRCC3 with colorectal cancer. J Exp Clin Cancer Res, 23, 285-294.

Ladiges WC (2006). Mouse models of XRCC1 DNA repair polymorphisms and cancer. Oncogene, 25, 1612-19.

Li W, Yang F, Gui Y, Bian J (2014). DNA repair gene XRCC1 Arg194Trp polymorphism and susceptibility to hepatocellular carcinoma: A meta-analysis. Oncol Lett, 8, 1725-30.

Liu L, Mao L, Li G, et al (2013). Association between XRCC1 and XRCC3 polymorphisms and colorectal cancer risk: a meta-analysis of 23 case-control studies. Mol Biol Rep, 40, 3943-52.

Lu M, Sun L, Yang J, (2013). Letter to the editor: Obvious association between XRCC1 Arg399Gln polymorphism and colorectal cancer in East Asians. Int J Colorectal Dis, 28, 1449-50.

Magaji BA, Moy FM, Rosiani C, et al (2014). Descriptive epidemiology of colorectal cancer in university Malaya medical centre, 2001 to 2010. Asian Pac J Cancer Prev, 15, 6059-64.

Mao D, Zhang Y, Lu H, et al (2013). Association between X-ray repair cross-complementing group 1 Arg194Trp polymorphism and colorectal cancer risk. Tumour Biol, 34, 2529-38.

Martinez-Balibrea E, Abad A, Aranda E, et al (2008). Pharmacogenetic approach for capetitumine or 5-fluorouracil selection to be combined with oxaliplatin as first-line chemotherapy in advanced colorectal cancer. Eur J Cancer, 44, 1229-37.

Mehrabanl D, Shamsdin SA, Dehghan A, et al (2014). Clinical significance of serum vascular endothelial growth factor and complement 3a levels in patients with colorectal cancer in Southern Iran. Asian Pac J Cancer Prev, 15, 9713-7.

Moreno V, Gemignani F, Landi S, et al (2006). Polymorphisms in genes of nucleotide and base excision repair: risk and prognosis of colorectal cancer. Clin Cancer Res, 2, 2101-8.

Muñiz-Mendoza R, Ayala-Madrigal ML, Partida-Pérez M, et al (2012). MLH1 and XRCC1 polymorphisms in Mexican patients with colorectal cancer. Genet Mol Res, 11, 2315-20.

Nassiri M, Kooshlyar MM, Roudbar Z, et al (2013). Genes and SNPs associated with non-hereditary and hereditary colorectal cancer. Asian Pac J Cancer Prev, 14, 5609-14.

Omarnejad R (2014). Prevalence of Local Recurrence of Colorectal Cancer at the Iranian Cancer Institute. Asian Pac J Cancer Prev, 15, 8587-9.

Tian Z, Li YL, Liu JG (2013). XRCC1 Arg399Gln polymorphism contributes to increased risk of colorectal cancer in Chinese population. Mol Biol Rep, 40, 4147-51.

Pardini B, Naccarati A, Novotny J, et al (2008). DNA repair genetic polymorphisms and risk of colorectal cancer in the Czech Republic. Mutat Res, 638, 146-53.

Poomphakwaen K, Promthet S, Suwanrungnuang K, et al (2014). XRCC1 gene polymorphism, diet and risk of colorectal cancer in Thailand. Asian Pac J Cancer Prev, 15, 7479-86.

Procopciuc LM, Osiyan G (2013). Lys751Gln XPD and Arg399Gln XRCC1 in Romanians. Association with sporadic colorectal cancer risk and different stages of carcinomas. Chirurgia (Bucur), 108, 711-8.

Przybylowska K, Kabzinski J, Sygut A, et al (2013). An association selected polymorphisms of XRCC1, OGG1 and MUTYH gene and the level of efficiency oxidative DNA damage repair with a risk of colorectal cancer. Mutat Res, 745, 6-15.

Qin CJ, Xu KW, Chen ZH, et al (2015). XRCC1 R399Q polymorphism and colorectal cancer risk in the Chinese Han population: a meta-analysis. Tumour Biol, [Epub ahead of print]

Salanti G, Sanderson S, Higgins JP (2005). Obstacles and opportunities in meta-analysis of genetic association studies. Genet Med, 7, 13-20.

Santos JC, Funck A, Silva-Fernandes IJ, et al (2014). Effect of APE1 T2197G (Asp148Glu) polymorphism on APE1, XRCC1, PARP1 and OGG1 expression in patients with colorectal cancer. Int J Mol Sci, 15, 17333-43.

Sliwinski T, Krupa R, Wisniewska-Jarosinska M, et al (2008). No association between the Arg194Trp and Arg399Gln polymorphisms of the XRCC1 gene and colorectal cancer risk and progression in a Polish population. Exp Oncol, 30, 253-254.

Skjeldbø CF, Saebø M, Wallin H, et al (2006). Polymorphisms of the XRCC1, XRCC3 and XPD genes and risk of colorectal adenoma and carcinoma, in a Norwegian cohort: a case control study. BMC Cancer, 6, 67.

Song HN, Liu XL, Er XY, et al (2008). The correlative study of the XRCC1 gene haplotype and risk of colorectal cancer in China. J Qigihar Med Coll, 29, 2957-60.

Stern MC, Conti DV, Siegmund KD, et al (2007). DNA repair single-nucleotide polymorphisms in colorectal cancer and their role as modifiers of the effect of cigarette smoking and alcohol in the Singapore Chinese Health Study. Cancer Epidemiol Biomarkers Prev, 16, 2363-2372.

Wang J, Zhao Y, Jiang J, et al (2010). Polymorphisms in DNA repair genes XRC1, XRC3 and XPD, and colorectal cancer risk: a case-control study in an Indian population. J Cancer Res Clin Oncol, 136, 1517-25.

Wang B, Wang D, Huang G, et al (2010). XRC1 polymorphisms and risk of colorectal cancer: a meta-analysis. Int J Colorectal Dis, 25, 313-21.

Wu W, Wu Y, Wang M, et al (2013). Meta-analysis of the association between the XRC1 gene R399Q polymorphism and colorectal cancer: an update. Int J Colorectal Dis, 28, 1453-4.
Yeh CC, Hsieh LL, Tang R, et al (2005). MS-920: DNA repair gene polymorphisms, diet and colorectal cancer risk in Taiwan. *Cancer Lett.*, **224**, 279-288.

Yin G, Morita M, Ohnaka K, et al (2012). Genetic polymorphisms of XRCC1, alcohol consumption, and the risk of colorectal cancer in Japan. *J Epidemiol.*, **22**, 64-71.

Zeng FR, Ling Y, Yang J, et al (2013). X-ray repair cross-complementing group 1 Arg399Gln gene polymorphism and susceptibility to colorectal cancer: a meta-analysis. *Tumour Biol.*, **34**, 555-63.

Zhao Y, Deng X, Wang Z, et al (2012). Genetic polymorphisms of DNA repair genes XRCC1 and XRCC3 and risk of colorectal cancer in Chinese population. *Asian Pac J Cancer Prev.*, **13**, 665-9.

Zhang SH, Wang LA, Li Z, et al (2014). APE1 polymorphisms are associated with colorectal cancer susceptibility in Chinese Hans. *World J Gastroenterol.*, **20**, 8700-8.

Zhu C, Zhang Y, Bao Q, et al (2011). The study on the relationship between XRCC1 gene polymorphisms and the susceptibility of colorectal cancer. *Chin J Dig.*, **31**, 450-4.