Meta Analysis

# Deoxyribonucleic acid repair gene X-ray repair cross-complementing group 1 polymorphisms and non-carcinogenic disease risk in different populations: A meta-analysis

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**PURPOSE:** This study aims to assess a meta-analysis of the association of X-ray repair cross-complementing group 1 (XRCC1) polymorphisms with the risk of various non-carcinogenic diseases in different population.
**MATERIALS AND METHODS:** This meta-analysis was performed by critically reviewing reveals 38 studies involving 10043 cases and 11037 controls. Among all the eligible studies, 14 focused on Arg194Trp polymorphism, 33 described the Arg399Gln and three articles investigated on Arg280His. Populations were divided into three different ethnic subgroups include Caucasians, Asians and other (Turkish and Iranian).
**RESULTS:** Pooled results showed no correlation between Arg194Trp and non-carcinogenic disease. There was only weak relation in the recessive (odds ratio [OR] =1.11, 95% confidence interval [CI]: 0.86-1.44) model in Asian population and dominant (OR = 1.04, 95% CI: 0.66-1.63) model of other populations. In Arg399Gln polymorphism, there was no relation with diseases of interest generally. In the pooled analysis, there were weak relation in the dominant (OR = 1.08, 95% CI: 0.86-1.35) model of Asian population and quite well-correlation with recessive (OR = 1.49, 95% CI: 1.19-1.88), dominant (OR = 1.23, 95% CI: 0.94-1.62), and additive (OR = 1.23, 95% CI: 0.94-1.62) models of other subgroup. For Arg280His, there was a weak relation only in the dominant model (OR = 1.06, 95% CI: 0.74-1.51).
**CONCLUSION:** The present meta-analysis correspondingly shows that Arg399Gln variant to be associated with increased non-carcinogenic diseases risk through dominant and recessive modes among Iranian and Turkish population. It also suggests a trend of dominant and recessive effect of Arg280His variant in all population and its possible protective effect on non-carcinogenic diseases.

**Key words:** Arg194Trp, Arg280His, Arg399Gln, ethnicity, non-carcinogenic diseases, polymorphisms, X-ray repair cross-complementing group 1 gene

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## Introduction

There is increasing evidence suggests that damage to human deoxyribonucleic acid (DNA) might initiate the cancer, which caused by external agents such as chemical agents, ionizing radiation and ultraviolet (UV).[1-3] The X-ray repair cross-complementing group 1 (XRCC1) is a DNA repair gene and a number of its single nucleotide polymorphisms (SNPs) have been considered as a modifying risk factor for a variety of cancer types. Three different polymorphisms in XRCC1 gene have been identified at codon 399 (Arg to Gln), 194 (Arg to Trp) and 280 (Arg to His) until now,[4] which were predicted to be possibly damaging the XRCC1 function.[5]

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The interactions of XRCC1 and its substrate result in assembly of the repair complex at the site of damage and regulate the activity of several repair enzymes.[6] The polymorphism Arg399Gln changes XRCC1's structure and maybe disrupt the combination of several repair enzymes, particularly poly (ADP-ribose) polymerase 1 (PARP1). Arg194Trp and Arg280His also change XRCC1's structure, but maybe not influence the function of XRCC1.

Previous analysis of case-control reports is the most predominant method of exploring the association between a specific gene and a disease. However, studies on XRCC1 polymorphisms in cancer have provided challenging and controversial results so far. Although other studies have found that the XRCC1 increase in breast cancer risk,[7,8] and reports showed a possible protective effect,[9] while many studies observed no significant association between these polymorphisms and the disease.[10] Besides it was reported thatXRCC1 gene polymorphism is associated with several cancers including lung, esophageal, and prostate cancers, among different population.[11-16]

Moreover, no evidence of any associations between Arg399Gln polymorphism and bladder cancer susceptibility has not shown,[17] hence other researchers reported that 399 Gln/Gln genotype is associated with a risk of lung cancer among Asians ethnicity,[18] and breast cancer in African Americans.[19] There are fairly few studies lead to observe the relationship between cancer risk and Arg280His variant up to the present time, only a single study revealed this association.[20,21] Although, large numbers of epidemiologic studies have been evaluated the role of XRCC1 polymorphisms on various non-carcinogenic diseases, such as liver cirrhosis, Alzheimer, glaucoma, cataract, human immunodeficiency virus-1/acquired immunodeficiency syndrome, schizophrenia, type 2 diabetes[22-56] and cancers, but no such comprehensive analysis in the field of non-carcinogenic disease, is reported so far.

Nevertheless, a meta-analysis of all existing reports will help to create a more convincing result, because some of these studies were based on a small sample size, thus, subgroup analysis based on ethnic and other factors may also yield more meaningful results. It is important to perform a quantitative synthesis of the available evidence using more rigorous methods on the amounts of evidence have been accumulated so far. Therefore, we performed a meta-analysis of all eligible case-control studies published to date, to assess the association of XRCC1 polymorphisms with the risk of various non-carcinogenic diseases in different population.

## Materials and Methods

### *Study selection*

Relevant studies were identified in the PubMed, ISI web of science and Scopus using combinations of the search phrases "X-ray cross-complementing group 1," "polymorphism,'' "DNA repair gene" and all possible combination (the last search update on October 12, 2012). In addition, all publications in other databases such as IranMedex, scientific information database were searched. In a total of 383 retrieved relevant references, 38 publications were identified to be eligible for inclusion in the meta-analysis. These studies had a case-control study design that assessed the association between the XRCC1 Arg194Trp, the Arg399Gln and Arg280His polymorphisms and risk of non-carcinogenic diseases using human genomic DNA samples.

### *Inclusion criteria*

#### Study design

Case-control studies were included in the evaluation, since this study design allows a comparison to be made between the affected individuals and healthy or disease-free ones, which is essential for the meta-analysis model.

#### Participants

Studies that included patients with any non-tumorigenic or non-carcinogenic condition were included in the evaluation.

### *Exclusion criteria*

Studies that were not representative or not case-control were excluded. The studies that showed not enough data for analysis were excluded after contacting corresponding author twice.

### *Data extraction*

Two reviewers independently screened all titles and abstracts. Full paper manuscripts of any titles/abstracts

that appeared to be relevant were obtained where possible and the relevance of each study independently assessed by two reviewers according to the inclusion and exclusion criteria. Two authors (FR and NS) mined data and reached an agreement on all of the eligibility items, including author, journal and year of publication, location of study, selection and characteristics of cases and controls, control source, demographics, ethnicity and genotyping information.

### *Meta-analysis*

The odds ratios (OR) of selected non-carcinogenic diseases associated with the XRCC1 Arg194Trp, the Arg399Gln and Arg280His polymorphisms were estimated for each study independently. We estimated the risk first for the variant homozygous genotypes, compared with the wild-type homozygous genotypes, assuming recessive and dominant effect models, respectively.

### *Statistical analysis*

We calculated OR and 95% of confidence intervals (CI) to estimate non-carcinogenic risk associated with the XRCC1 polymorphism for each study. Inevitably, studies included in the meta-analysis differed in the variables of interest and thus, any kind of variability among studies may be termed heterogeneity. In meta-analysis, we examined the association between allele Trp of Arg194Trp and the risk of non-carcinogenic diseases compare with that of allele Arg, as well as using additive (Trp/Trp vs. Arg/Arg), recessive (Trp/Trp vs. [Arg/Trp + Arg/Arg]) and dominant ([Trp/Trp + Arg/Trp] vs. Arg/Arg) genetic models. The same method was applied to the other two polymorphisms. We evaluated the deviations from the Hardy-Weinberg equilibrium for the control group in each study by Chi-square test using a web-based program (http://www.ihg.gsf.de/cgi-bin/hw/hwa1.pl) for goodness of fit.

In the present study, both Der Simonian and Laird's random-effects method and Mantel-Haenszel's fixed-effects (FEs) method were used. In the meta-analysis, to evaluate the between-study heterogeneity both Chi-square-based Q-statistic and I-squared ($I^2$) tests were performed. Furthermore, according to Venice criteria, for the $I^2$ test included: <25% represents no heterogeneity, =25-50% represents moderate heterogeneity, =50-75% represents large heterogeneity and > 75% represents extreme heterogeneity.[57] So the heterogeneity was considered significant, if the $P < 0.10$ and $I^2 > 25$, a random-effect model was suitable, otherwise if the $P \geq 0.10$and $I^2 \leq 25$, a FE model was then used to estimate summary ORs and 95% CIs. Publication bias was assessed by a funnel plot based on the Egger's regression test and a *t*-test was implemented to determine the significance of the asymmetry. An asymmetric plot suggested possible publication bias ($P \geq 0.05$ suggests no bias). All analyses were performed using STATA 11.0 (StataCorp LP, Lakeway Drive, College Station, Texas, USA). All the *P* values were two-sided.

## Results

### *Eligible studies*

Thirty-nine reports focused on the role of any polymorphism of the XRCC1 gene in the non-carcinogenic risk were reviewed [Figure 1]. Four combined analysis include 3 individual case-control studies, two of which were also reported by Yousaf *et al.*,[26] Ferguson *et al.*,[45] and Olshan *et al.*,[49] respectively. Thus, the present meta-analysis reveals 38 studies from 35 published papers involving 10043 cases and 11037 controls [Table 1]. Each sub-population study has treated as a separate in the analysis. Among all the eligible studies, 14 focused on Arg194Trp polymorphism, 33 described the Arg399Gln and 3 articles investigated on Arg280His. Populations were divided into three different ethnic subgroups include Caucasians, Asians, and other (Turkish and Iranian) [Table 1]. Considering each polymorphism, the overall genotype distributions in controls were significantly different (all $P < 0.001$) between Caucasian with Asian populations and other subgroup with Asian, but were not significant between Caucasian with other populations.

### *Arg194Trp*

A total of 14 (3 Caucasian, 6 Asian, 5 other include Turkish) studies involving 3173 cases and 3863 controls addressed the association between Arg194Trp polymorphism and non-carcinogenic risk were reviewed [Table 2]. There was no between-study heterogeneity in ORs of individual

**Table 1: Studies included in the meta-analysis**

| Authors, year | Country | Disease type | Age (mean±SD) | | Cases/ control | Genotype studied | Method | Study characteristics | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Case | Control | | | | Population | Design | Control |
| Rossit, 2002 | Brazil | Alcoholic liver cirrhosis | 47.6±10 | 44.7±12 | 97/96 | Codon 399 Codon 194 | Multiplex PCR | Brazilian | Population-based | Healthy subjects |
| Parildar-Karpuzoğlu, 2008 | Turkey | Alzheimer's disease | 73.8±6.8 | 76.1±6.7 | 91/93 | Codon 399 Codon 280 | PCR-RFLP | Turkish | Population-based | Any illness-free |
| Qian, 2010 | China | Alzheimer's disease | 82.1±5.8 | 83.0±4.6 | 212/203 | Codon 194 | PCR-RFLP | Chinese | Hospital-based | Healthy subjects |
| Zhao, 2006 | China | Asbestosis | - | - | 104/101 | Codon 399 | PCR-RFLP | Chinese | Population-based | Healthy subjects |
| Yousaf, 2011 | Pakistan | Primary open angle glaucoma | 41.3±13.7 | 39.7±11.9 | 160/193 | Codon 399 | PCR-RFLP | Punjabi Pakistani | Population-based | Disease-free |
| Yousaf, 2011 | Pakistan | Primary close angle glaucoma | 43.6±15.8 | 39.7±11.9 | 163/193 | Codon 399 | PCR-RFLP | Punjabi Pakistani | Population-based | Disease-free |
| Güven, 2007 | Turkey | Glaucoma | 61.3±6.9 | 59.1±5.8 | 144/121 | Codon 399 | PCR-RFLP | Turkish | Population-based | Disease-free |
| Luo, 2011 | China | Cataract | 68±8 | 61.5±7 | 180/174 | Codon 399 | PCR-RFLP | Chinese | Hospital-based | Disease-free |
| Unal, 2007 | Turkey | Cataract | 64±8 | 63±8 | 195/194 | Codon 399 | PCR-RFLP | Turkish | Population-based | Disease-free |
| Padma, 2011 | India | Cataract | 58.6±0.40 | 49.1±0.55 | 208/151 | Codon 399 | PCR-RFLP | Indian | Hospital-based | Healthy subjects |
| Attar, 2010 | Turkey | Endometriosis | 35.20±9.04 | 38.43±7.23 | 52/101 | Codon 399 | PCR-RFLP | Turkish | Population-based | Disease-free |
| Gu, 2007 | China | Male infertility | - | - | 171/247 | Codon 399 Codon 194 | PCR-RFLP | Chinese | Population-based | Healthy subjects |
| Yang, 2009 | China (Chinese) | COPD | 65±11 | 64±11 | 201/309 | Codon 399 | PCR-RFLP | Chinese | Hospital-based | COPD-disease-free |
| Guven, 2007 | Turkey | Coronary artery disease | 59.9±12.2 | 55.3±14.9 | 147/48 | Codon 399 | PCR-RFLP | Turkish | Population-based | CAD-disease-free |
| Bazo, 2011 | Brazil | Coronary artery disease | 61.6±10.0 | 58.5±11.1 | 299/101 | Codon 399 Codon 194 | PCR-RFLP | Brazilian | Hospital-based | CAD-disease-free |
| Sterpone, 2009 | Italia | Cystic fibrosis | 14±2.8 | - | 93/63 | Codon 399 | PCR-RFLP | Caucasian | Hospital-based | Healthy subjects |
| Bau, 2007 | Taiwan | Endometriosis | 31.4±4.5 | 30.7±5.4 | 141/100 | Codon 399 | PCR-RFLP | Taiwanese Chinese (mixed) | Hospital-based | Disease-free |
| Attar, 2010 | Turkey | Endometriosis | 38.4±7.23 | 35.2±9.04 | 153/101 | Codon 399 | PCR-RFLP | Turkish | Hospital-based | Disease-free |
| Lin, 2009 | Taiwan | Systemic lupuserythematosus | - | - | 172/160 | Codon 399 Codon 194 | PCR-RFLP | Taiwanese | Population-based | Healthy subjects |
| Sobti, 2009 | India | HIV-1/AIDS | 35.23±8.04 | 36.17±10.49 | 300/300 | Codon 399 | PCR-RFLP | Indian | Population-based | Disease-free |
| Warchoł, 2011 | Poland | Systemic lupus erythematosus | 37±12 | 36±11 | 265/360 | Codon 399 | PCR-RFLP | Polish | Hospital-based | Healthy subjects |
| Görgün, 2010 | Turkey | Macular degeneration | 75±8 | 73±10 | 120/205 | Codon 399 Codon 194 | PCR-RFLP | Turkish | Population-based | Disease-free |
| Vural, 2009 | Turkey | Pre-eclampsia | 26.7±5 | 28.2±4.1 | 101/107 | Codon 399 Codon 194 | PCR-RFLP | Turkish | Population-based | Disease-free |
| Chiang, 2010 | Taiwan | Pterygium | 64.6 | 64.2 | 127/103 | Codon 399 | PCR-RFLP | Taiwanese | Hospital-based | Healthy subjects |
| Chen, 2010 | Taiwan | Pterygium | 57 | 62 | 83/206 | Codon 399 | PCR-RFLP | Chinese | Hospital-based | Disease-free |
| Ferguson, 2008 | Ireland | Barrett's esophagus | 62.4 | 63.0 | 212/220 | Codon 399 | PCR-RFLP | Caucasian | Population-based | Disease-free |
| Ferguson, 2008 | Ireland | Reflux esophagitis | 61.7 | 63.0 | 230/220 | Codon 399 | PCR-RFLP | Caucasian | Population-based | Disease-free |
| Koyama, 2006 | Japan | Rheumatoid arthritis | 58.7±11.1 | 23.6±4.7 | 40/102 | Codon 399 Codon 194 Codon 280 | PCR-RFLP | Japanese | Population-based | Healthy subjects |
| Derakhshandeh, 2009 | Iran | Schizophrenia | 41.9±13.5 | 40.6±13.2 | 303/303 | Codon 194 | PCR-RFLP | Iranian | Hospital-based | Healthy subjects |

*Contd...*

**Table 1: Contd**

| Authors, year | Country | Disease type | Age (mean±SD) | | Cases/ control | Genotype studied | Method | Study characteristics | | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | | Case | Control | | | | Population | Design | Control |
| Saadat, 2008 | Iran | Schizophrenia | 41.9±13.5 | 40.6±13.2 | 303/303 | Codon 399 | PCR-RFLP | Iranian | Hospital-based | Healthy subjects |
| Olshan, 2005 | USA | Oral clefts | - | - | 481/350 | Codon 399 | PCR-RFLP | Caucasian | Population-based | Disease-free |
| Olshan, 2005 | USA | Spina bifida | - | - | 380/350 | Codon 399 | PCR-RFLP | Caucasian | Population-based | Disease-free |
| Kasznicki, 2009 | Poland | Type 2 diabetes | 67.58±11.27 | 61.60±16.88 | 94/101 | Codon 399 | PCR-RFLP | Caucasian | Population-based | Disease-free |
| Batar, 2010 | Turkey | Asthma | 44.8±14.0 | 41.4±13.6 | 116/180 | Codon 399<br>Codon 194 | PCR-RFLP | Turkish | Population-based | Healthy-subjects |
| Xie, 2009 | China | COPD | 64.77±11.43 | 64.48±11.01 | 201/309 | Codon 399<br>Codon 194 | PCR-RFLP | Chinese | Hospital-based | COPD and non-tobacco-related disease-free |
| Ji, 2010 | China | Male infertility | - | - | 620/273 | codon 399<br>Codon 194<br>Codon 280 | PCR-RFLP | Chinese | Population-based | Healthy-subjects |
| Frank, 2011 | Germany | Chronic Atrophic Gastritis | - | - | 535/1054 | Codon 399 | PCR-RFLP | Caucasian | Population-based | Disease-free |
| Bassi, 2008 | Brazil | Systemic lupus erythematous | 41.7 | 38.7 | 163/125 | Codon 399 | PCR-RFLP | Caucasian | Hospital-based | Healthy-subjects |
| Dog˘ru-Abbasog˘lu, 2007 | Turkey | Sporadic Alzheimer's disease | 76.12±6.32 | 74.62±6.76 | 98/95 | Codon 194 | PCR-RFLP | Turkish | Hospital-based | Disease-free |

PCR: Polymerase chain reaction, RFLP: Restriction fragment length polymorphism, COPD: Chronic obstructive pulmonary disease, HIV: Human immunodeficiency virus, AIDS: Acquired immunodeficiency syndrome, SD: Standard deviation

studies of the recessive ($\chi^2$ = 9.21, $I^2$ = 0%, $P$ = 0.757) and the additive ($\chi^2$ = 10.12, $I^2$ = 0%, $P$ = 0.684) models, hence there was a moderate heterogeneity in the dominant model ($\chi^2$ = 19.80, $I^2$ = 34.4%, $P$ = 0.100). Accordingly, we pooled the results using the FE model and found that TrpArg194Trp had a weak relation with non-carcinogenic disease in the recessive model [OR = 1.03, 95% CI: 0.88-1.22, Figure 2a], while used a FE model for the additive model [OR = 0.96, 95% CI: 0.79-1.17, Figure 2c] and a random-effects model for the dominant type [OR = 0.94, 95% CI: 0.81-1.11, Figure 2c] that showed no correlation likewise.

Although we analyzing TrpArg194Trp polymorphism in stratified ethnic subgroups, there was no between-study heterogeneity in ORs of individual studies of the Caucasian subgroups in the recessive ($\chi^2$ = 0.82, $I^2$ = 0%, $P$ = 0.664), the dominant ($\chi^2$ = 1.99, $I^2$ = 0%, $P$ = 0.369) and the additive ($\chi^2$ = 0.95, $I^2$ = 0%, $P$ = 0.621) models. Hence, we pooled the results using the FE analysis and found that TrpArg194Trp was not related with non-carcinogenic disease in the recessive (OR = 0.99, 95% CI: 0.79-1.23, Figure 3a), dominant (OR = 0.85, 95% CI: 0.67-1.08, Figure 3b) and additive (OR = 0.90, 95% CI: 0.67-1.21, Figure 3c) models. Meanwhile, when we analyzed the Asian subgroups, there was no between-study heterogeneity in ORs of individual studies of the recessive ($\chi^2$ = 5.11, $I^2$ = 2.2%, $P$ = 0.402), the dominant ($\chi^2$ = 5.75, $I^2$ = 13.1%, $P$ = 0.331) and the additive ($\chi^2$ = 5.64, $I^2$ = 11.3%, $P$ = 0.343) models. Thus, we pooled the results using the FE analysis and found that TrpArg194Trp was not related with non-carcinogenic disease in dominant (OR = 0.95, 95% CI: 0.81-1.11, Figure 3e), but had a weak correlation with the recessive (OR = 1.11, 95% CI: 0.86-1.44, Figure 3d) and the additive (OR = 1.04, 95% CI: 0.79-1.37, Figure 3f) models. Then in the analysis of the other subgroups, there was no between-study heterogeneity in ORs of individual studies of the recessive ($\chi^2$ = 2.75, $I^2$ = 0%, $P$ = 0.600), and the additive ($\chi^2$ = 3.09, $I^2$ = 0%, $P$ = 0.543) models, but there was a large heterogeneity in the dominant ($\chi^2$ = 10.78, $I^2$ = 62.9%, $P$ = 0.029), so we took a random-effects analysis. Consequently we pooled the results using the FE analysis and found that TrpArg194Trp was not related with non-carcinogenic disease in the recessive [OR = 0.86, 95% CI: 0.36-2.03,

**Table 2: Genotyping frequencies of Arg194Trp polymorphism**

| First authors, year | Cases | | | | | Control | | | | | Matched |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | Genotypes | | | % with Arg allele | Total | Genotypes | | | % with Arg allele | |
| | | Arg/Arg | Arg/Trp | Trp/Trp | | | Arg/Arg | Arg/Trp | Trp/Trp | | |
| Caucasian | | | | | | | | | | | |
| Rossit, 2002 | 97 | 82 | 14 | 1 | 92 | 96 | 79 | 17 | 0 | 91 | Age, sex and ethnicity |
| Bazo, 2009 | 117 | 40 | 6 | 0 | 93 | 52 | 28 | 10 | 1 | 85 | Age and sex |
| Frank, 2011 | 533 | 106 | 246 | 171 | 96 | 1054 | 192 | 506 | 342 | 99 | |
| Subtotal | 650 | 228 | 266 | 172 | - | 1202 | 299 | 533 | 343 | - | |
| Asian | | | | | | | | | | | |
| Koyama, 2006 | 40 | 5 | 13 | 21 | 63 | 102 | 16 | 44 | 42 | 71 | Age and ethnicity |
| Gu, 2007 | 176 | 77 | 74 | 20 | 67 | 248 | 101 | 119 | 27 | 65 | Age and sex |
| XIE, 2009 | 201 | 112 | 72 | 17 | 74 | 309 | 143 | 130 | 36 | 68 | Age and sex |
| Lin, 2009 | 172 | 79 | 67 | 12 | 71 | 160 | 102 | 74 | 16 | 72 | - |
| Ji, 2010 | 984 | 301 | 258 | 61 | 69 | 620 | 140 | 115 | 18 | 72 | Age and sex |
| Qian, 2010 | 212 | 100 | 94 | 18 | 69 | 203 | 94 | 92 | 17 | 69 | Age and sex |
| Subtotal | 1785 | 674 | 578 | 149 | - | 1642 | 596 | 574 | 156 | - | |
| Other populations | | | | | | | | | | | |
| Dog˘ru-Abbasog˘lu, 2007 | 98 | 84 | 11 | 0 | 94.2 | 95 | 78 | 18 | 2 | 88.8 | Age and sex |
| Vural, 2009 | 101 | 89 | 12 | 0 | 94 | 107 | 90 | 15 | 2 | 91 | Age and sex |
| Derakhshandeh, 2009 | 303 | 249 | 50 | 4 | 90 | 303 | 242 | 57 | 4 | 90 | Age and sex |
| Batar, 2010 | 116 | 90 | 26 | 0 | 89 | 309 | 157 | 23 | 0 | 94 | Age and ethnicity |
| Görgün, 2010 | 120 | 98 | 21 | 1 | 90 | 205 | 180 | 25 | 0 | 94 | Age, sex and ethnicity |
| Subtotal | 738 | 610 | 120 | 5 | - | 1019 | 747 | 138 | 8 | - | |
| Total | 3173 | 1512 | 964 | 326 | - | 3863 | 1642 | 1245 | 507 | - | |

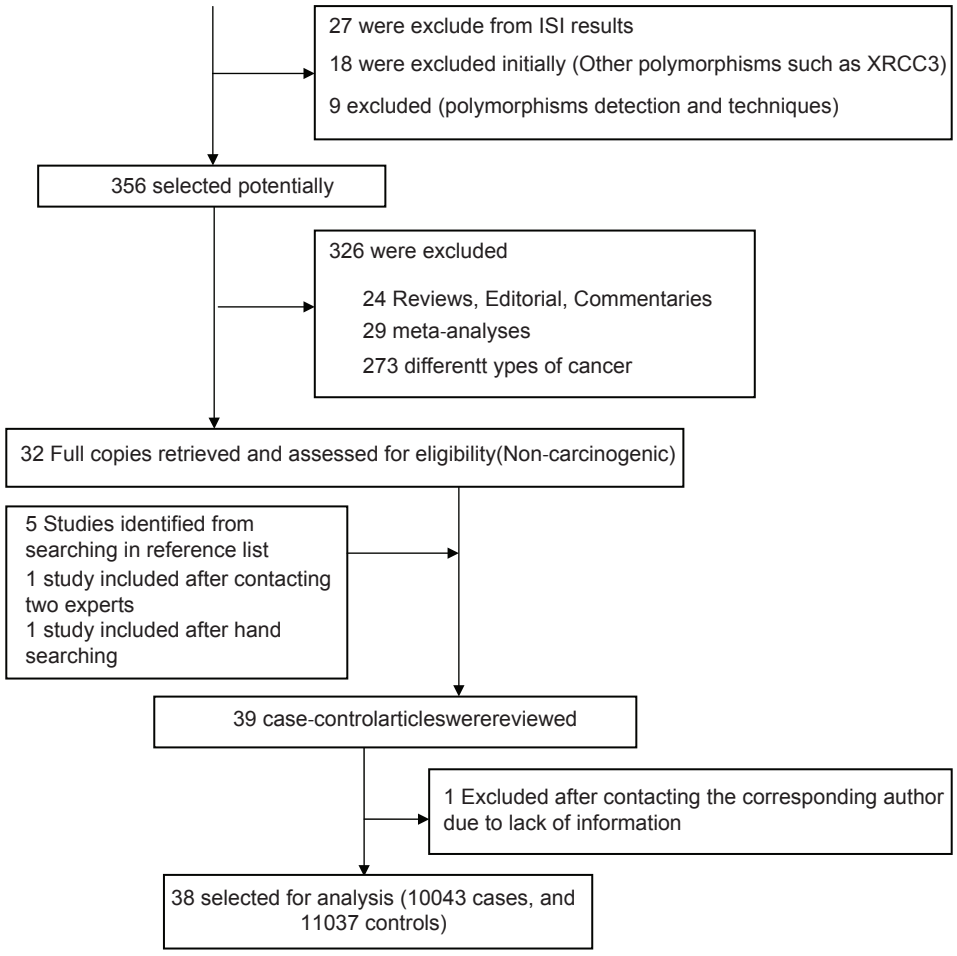


**Figure 1: Flowchart of eligible studies**

Figure 3g] and additive [OR = 0.85, 95% CI: 0.38-2.00, Figure 3i] models, while had a weak relation with the dominant [OR = 1.04, 95% CI: 0.66-1.63, Figure 3h] using random-effect analysis.

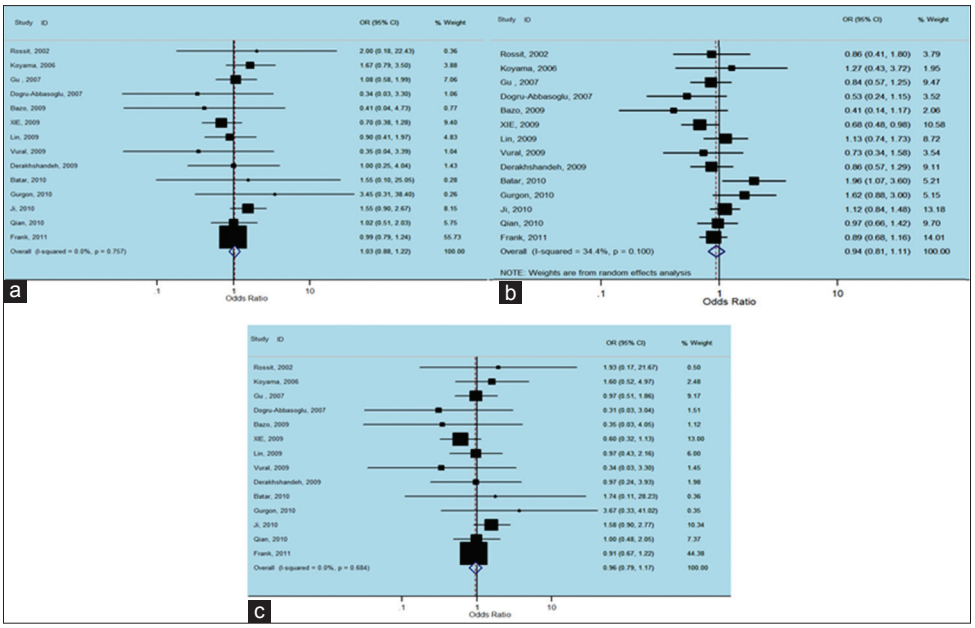


**Figure 2: Forest plots of odds ratios with 95% confidence interval for X-ray repair cross-complementing group 1 polymorphisms and risk of Non-carcinogenic disease. (a) Recessive model of Arg194Trp (Trp/Trp vs. Arg/Arg), (b) dominant model (Trp/Trp vs. Arg/Arg + Arg/Trp) and (c) additive model (Trp/Trp + Arg/Trp vs. Arg/Arg)**

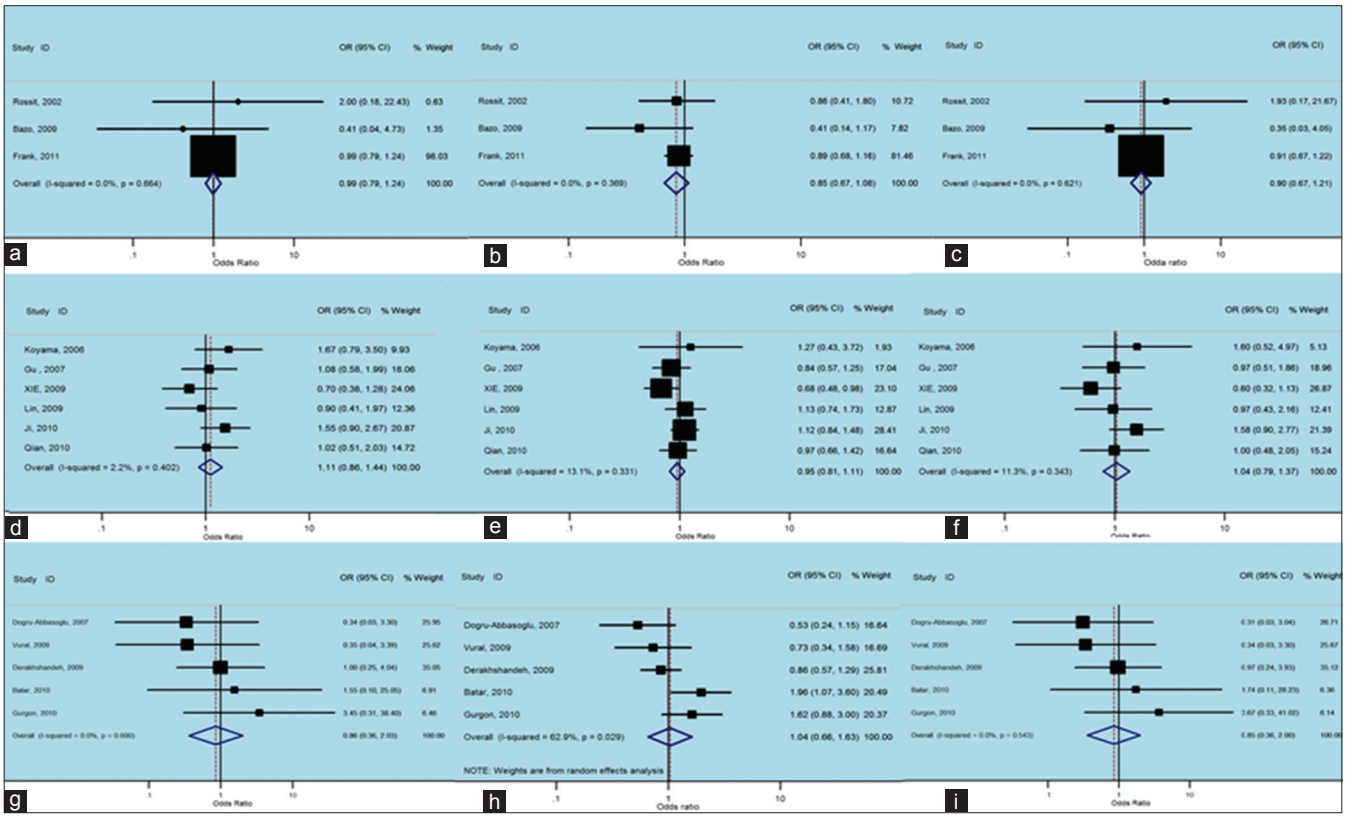


**Figure 3: Forest plots of odds ratios with 95% confidence interval for X-ray repair cross-complementing group 1 polymorphisms and risk of non-carcinogenic disease (right) recessive model of Arg194Trp (Trp/Trp vs. Arg/Arg), (middle) dominant model (Trp/Trp vs. Arg/Arg+ Arg/Trp) and (left) additive model (Trp/Trp + Arg/Trp vs. Arg/Arg); first row is a subgroup analysis in Caucasian population under an fixed-effects (FEs) model (a-c); second row is a subgroup analysis in Asian population under an FEs model (d-f); third row is a subgroup analysis as other population under an FEs model (g and i) and random-effects**

### *Arg399Gln*

There were 33 studies (3099 cases and 3169 controls) concerning eight Caucasian, 14 Asian and 11 other subgroups, which addressed the relation of XRCC1 Arg399Gln polymorphism and the risk of non-carcinogenic diseases. We examined the association between Arg399Gln XRCC1 polymorphism and non-carcinogenic diseases risk, assuming various inheritance models of the399Gln allele for each individual study [Table 3]. There was a large between-study heterogeneity in ORs of individual studies of the recessive ($\chi^2$ = 72.27, $I^2$ = 55.7%, $P$ = 0.000) and the additive ($\chi^2$ = 56.18, $I^2$ = 43.0%, $P$ = 0.005) models, but a moderate heterogeneity in the dominant model ($\chi^2$ = 74.18, $I^2$ = 56.9%, $P$ = 0.000). Hence, we pooled the results using the random-effect analysis and found that Gln Arg399Gln has a weak relation with non-carcinogenic disease in the recessive [OR = 1.02, 95% CI: 0.86-1.21, Figure 4a], additive [OR = 1.15, 95% CI: 0.96-1.39, Figure 4c] and the dominant [OR = 1.10, 95% CI: 0.96-1.26, Figure 4b] models.

There was no between-study heterogeneity in ORs of individual studies of the Caucasian subgroups in the recessive ($\chi^2$ = 0.83, $I^2$ = 0%, $P$ = 0.997), the dominant ($\chi^2$ = 8.73, $I^2$ = 19.8%, $P$ = 0.273) and the additive ($\chi^2$ = 1.92, $I^2$ = 0%, $P$ = 0.964) models. So we pooled the results using the FE analysis and found that Gln Arg399Gln was not related with non-carcinogenic disease in the recessive [OR = 0.93, 95% CI: 0.73-1.20, Figure 5a], dominant [OR = 0.99, 95% CI: 0.84-1.18, Figure 5b] and additive [OR = 0.94, 95%

**Table 3: Genotyping frequencies of Arg399Gln polymorphism**

| First authors, year | Cases | | | | | Control | | | | | Matched |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | Genotypes | | | % with Arg allele | Total | Genotypes | | | % with Arg allele | |
| | | Arg/Arg | Arg/Gln | Gln/Gln | | | Arg/Arg | Arg/Gln | Gln/Gln | | |
| Caucasian | | | | | | | | | | | |
| Rossit, 2002 | 97 | 37 | 48 | 12 | 63 | 96 | 49 | 34 | 13 | 69 | Age, sex and ethnicity |
| Olshan, 2005 | 125 | 58 | 50 | 15 | 68 | 350 | 135 | 155 | 35 | 66 | - |
| Olshan, 2005 | 125 | 53 | 54 | 11 | 68 | 350 | 135 | 155 | 35 | 66 | - |
| Ferguson, 2008 | 230 | 99 | 104 | 27 | 62 | 248 | 100 | 115 | 33 | 63 | Age, sex and ethnicity |
| Ferguson, 2008 | 212 | 73 | 113 | 26 | 62 | 248 | 100 | 115 | 33 | 63 | Age, sex and ethnicity |
| Bazo, 2009 | 117 | 25 | 0 | 0 | 54 | 52 | 20 | 0 | 0 | 85 | Age and sex |
| Sterpone, 2009 | 93 | 36 | 39 | 18 | 60 | 63 | 27 | 25 | 11 | 63 | Age and sex |
| Kasznicki, 2009 | 94 | 35 | 40 | 19 | 59 | 101 | 29 | 49 | 23 | 53 | |
| Subtotal | 1093 | 416 | 448 | 128 | - | 1508 | 595 | 648 | 183 | - | |
| Asian | | | | | | | | | | | |
| Koyama, 2006 | 40 | 5 | 13 | 22 | 74 | 102 | 9 | 34 | 59 | 71 | Age and ethnicity |
| Zhao, 2006 | 104 | 16 | 12 | 23 | 43 | 101 | 19 | 22 | 12 | 57 | |
| Gu, 2007 | 176 | 102 | 64 | 5 | 88 | 248 | 101 | 119 | 27 | 83 | Age and sex |
| XIE, 2009 | 201 | 112 | 72 | 17 | 74 | 309 | 143 | 130 | 36 | 68 | Age and sex |
| Yang, 2009 | 201 | 95 | 91 | 15 | 70 | 309 | 175 | 111 | 23 | 75 | Age, sex and ethnicity |
| Sobti, 2009 | 300 | 111 | 126 | 63 | 58 | 300 | 133 | 125 | 42 | 65 | Age and sex |
| Lin, 2009 | 172 | 10 | 83 | 71 | 69 | 160 | 21 | 78 | 120 | 73 | - |
| Ji, 2010 | 984 | 327 | 239 | 54 | 72 | 620 | 153 | 97 | 23 | 74 | Age and sex |
| Chiang, 2010 | 127 | 9 | 70 | 48 | 65 | 103 | 5 | 31 | 67 | 80 | Age |
| Chen, 2010 | 83 | 31 | 35 | 17 | 68 | 206 | 104 | 80 | 22 | 69 | |
| Padma, 2011 | 208 | 90 | 82 | 36 | 63 | 151 | 75 | 56 | 20 | 68 | Age and sex |
| Yousaf, 2011 | 160 | 17 | 73 | 70 | 67 | 193 | 30 | 65 | 98 | 68 | Age and sex |
| Yousaf, 2011 | 163 | 28 | 56 | 79 | 66 | 193 | 30 | 65 | 98 | 68 | Age and sex |
| Luo, 2011 | 180 | 13 | 71 | 96 | 73 | 174 | 14 | 45 | 115 | 79 | Age and sex |
| Subtotal | 3099 | 966 | 1087 | 616 | - | 3169 | 1012 | 1058 | 762 | - | |
| Other population | | | | | | | | | | | |
| Ünal, 2007 | 195 | 65 | 100 | 30 | 59 | 194 | 58 | 115 | 21 | 60 | Age, sex and ethnicity |
| Güven, 2007 | 147 | 50 | 76 | 21 | 60 | 48 | 12 | 33 | 3 | 59 | Age and sex |
| Güven, 2007 | 144 | 56 | 78 | 10 | 65 | 121 | 34 | 76 | 11 | 60 | Age and sex |
| Bau, 2007 | 141 | 7 | 75 | 59 | 68 | 100 | 15 | 55 | 30 | 58 | Age, sex and BMI |
| Saadat, 2008 | 303 | 100 | 159 | 44 | 60 | 303 | 132 | 142 | 29 | 67 | Age and sex |
| Parildar-Karpuzoğlu, 2008 | 91 | 35 | 49 | 7 | 67 | 93 | 49 | 46 | 8 | 66 | Age and sex |
| Vural, 2009 | 101 | 39 | 48 | 14 | 63 | 107 | 44 | 53 | 10 | 66 | Age and sex |
| Attar, 2010 | 153 | 40 | 12 | 0 | 65 | 101 | 86 | 15 | 0 | 68 | sex |
| Görgün, 2010 | 120 | 60 | 46 | 14 | 69 | 205 | 99 | 85 | 21 | 69 | Age, sex and ethnicity |
| Batar, 2010 | 116 | 39 | 57 | 20 | 58 | 309 | 91 | 71 | 18 | 70 | Age and ethnicity |
| Attar, 2010 | 52 | 40 | 12 | 0 | | 101 | 86 | 15 | 0 | | |
| Subtotal | 1563 | 531 | 712 | 219 | - | 1682 | 706 | 706 | 151 | - | |
| Total | 5755 | 1913 | 2247 | 963 | - | 6359 | 2313 | 2412 | 1096 | - | |

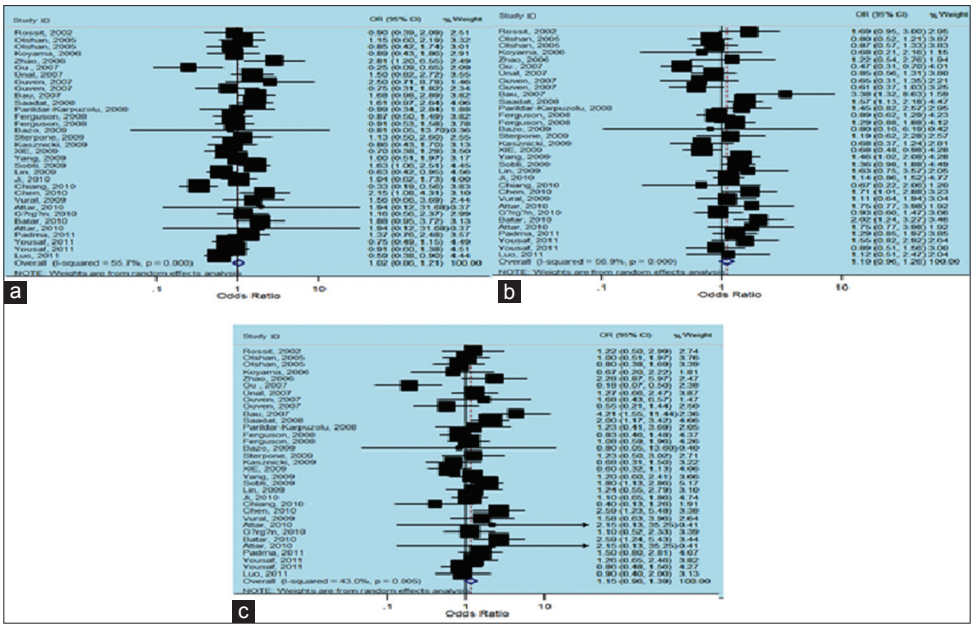


**Figure 4: Forest plots of odds ratios with 95% confidence interval for X-ray repair cross-complementing group 1 polymorphisms and risk of non-carcinogenic disease. (a) Recessive model of Arg399Gln (Gln/Gln vs. Arg/Arg), (b) dominant model (Gln/Gln vs. Arg/Arg + Arg/Gln) and (c) additive model (Gln/Gln + Arg/Gln vs. Arg/Arg)**

CI: 0.72-1.22, Figure 5c] models. Furthermore, when we analyzed the Asian subgroups, there was a large between-study heterogeneity in ORs of individual studies of the recessive ($\chi^2$ = 50.82, $I^2$ = 74.4%, $P$ = 0.000), the dominant ($\chi^2$ = 35.89, $I^2$ = 63.8%, $P$ = 0.001) and the additive ($\chi^2$ = 33.36, $I^2$ = 61.0%, $P$ = 0.002) models. Hence, we pooled the results using the random-effect analysis and found that Gln Arg399Glnwas not related with non-carcinogenic disease in the recessive [OR = 0.88, 95% CI: 0.66-1.18, Figure 5d], while it presented a weak correlation with dominant [OR = 1.08, 95% CI: 0.86-1.35, Figure 5e], and additive [OR = 1.05, 95% CI: 0.77-1.43, Figure 5f] models. Then in the analysis of the other subgroups, there was no between-study heterogeneity in ORs of individual studies of the recessive ($\chi^2$ = 0.40, $I^2$ = 0%, $P$ = 0.819), and the dominant ($\chi^2$ = 0.22, $I^2$ = 0%, $P$ = 0.898) models, but there was a large heterogeneity in the additive ($\chi^2$ = 5.03, $I^2$ = 60.2%, $P$ = 0.081), so we took a random-effects analysis. Therefore, we pooled the results using the FE model and found that TrpArg194Trp was related with non-carcinogenic disease in the recessive [OR = 1.49, 95% CI: 1.19-1.88, Figure 5g], and additive [OR = 1.61, 95% CI: 1.24-2.10, Figure 5i] models, using random-effects analysis, it was correlated with the dominant [OR = 1.23, 95% CI: 0.94-1.62, Figure 5h] model as well.

### *Arg280His*

There were only three studies (1115 cases and 815 controls) involving one Caucasian and 2 Asian reports, that investigating the relation of XRCC1 Arg280His polymorphism and the risk of non-carcinogenic disease. We examined the relationship between Arg280His XRCC1 polymorphism and non-carcinogenic diseases risk, assuming various inheritance models of the 280His allele for each individual study [Table 4]. There was no between-study heterogeneity in ORs of individual studies of the recessive ($\chi^2$ = 0.40, $I^2$ = 0%, $P$ = 0.819) and the additive ($\chi^2$ = 0.22, $I^2$ = 0%, $P$ = 0.898) models, whereas the dominant model has a large heterogeneity ($\chi^2$ = 5.03, $I^2$ = 60.2%, $P$ = 0.081). Accordingly we pooled the results using the FE analysis in the recessive [OR = 0.50, 95% CI: 0.22-1.11, Figure 6a], additive [OR = 0.58, 95% CI: 0.19-1.74, Figure 6c] and using random-effects analysis in the dominant models [OR = 1.06, 95% CI: 0.74-1.51, Figure 6b] and found that His Arg280His was not related with non-carcinogenic disease.

### *Sensitivity analysis*

We implemented sensitivity analyses to assess the effect of those studies that are not in Horner-Wadsworth-Emmons.[28,36,38,44] The results

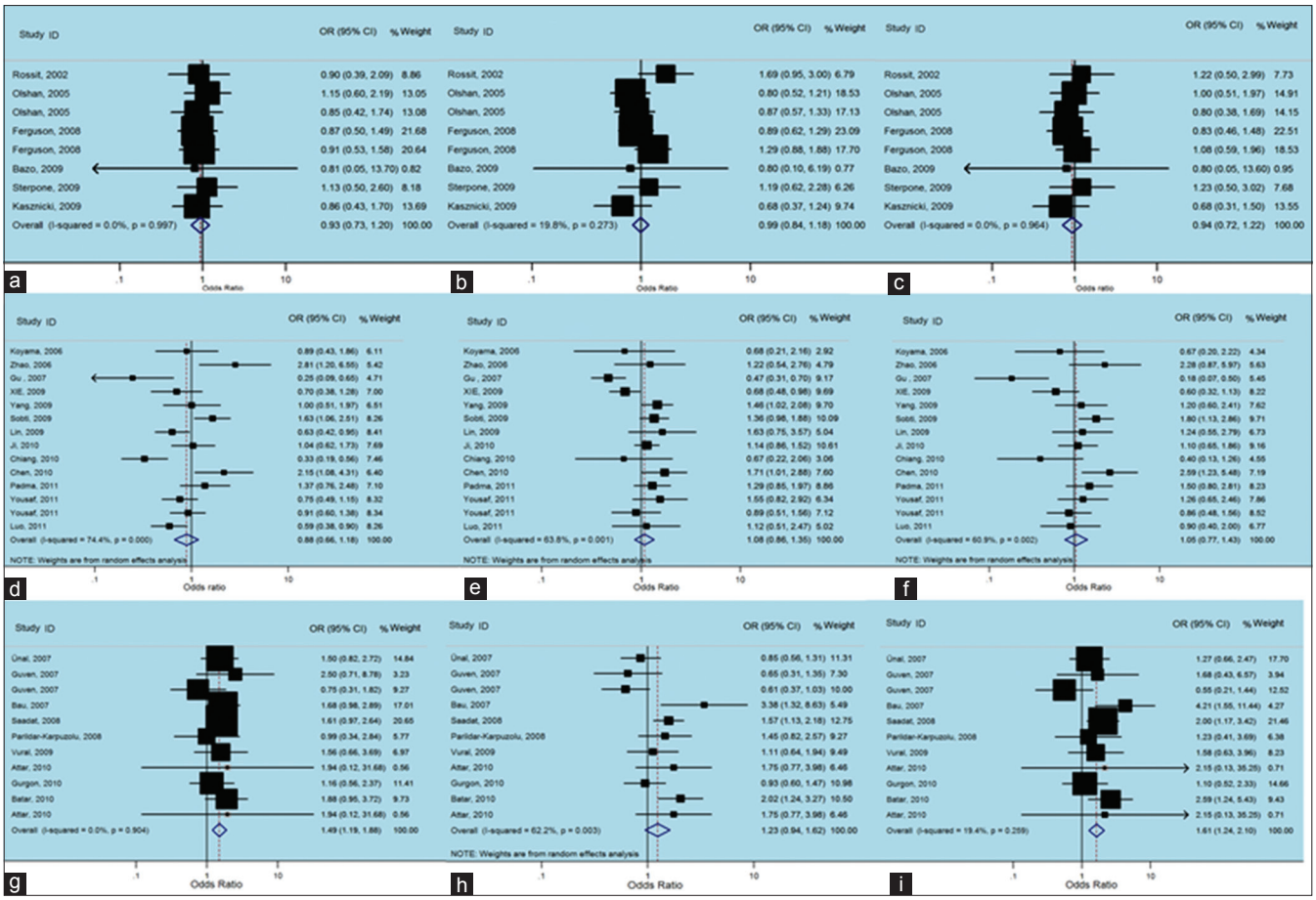

**Figure 5: Forest plots of odds ratios with 95% confidence interval for X-ray repair cross-complementing group 1 polymorphisms and risk of non-carcinogenic disease (right) recessive model of Arg399Gln (Gln/Gln vs. Arg/Arg), (middle) dominant model (Gln/Gln vs. Arg/Arg+ Arg/Gln) and (left) Additive model (Gln/Gln + Arg/Gln vs. Arg/Arg); first row is a subgroup analysis in Caucasian population under an fixed-effects (FEs) model (a-c); second row is a subgroup analysis in Asian population under an FEs model (d-f); third row is a subgroup analysis in other population under an FEs model (g-i)**

**Table 4: Genotyping frequencies of Arg280His polymorphism**

| First authors, year | Cases | | | | | Control | | | | | Matched |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | Total | Genotypes | | | % with Arg allele | Total | Genotypes | | | % with Arg allele | |
| | | Arg/Arg | Arg/His | His/His | | | Arg/Arg | Arg/His | His/His | | |
| Caucasian | | | | | | | | | | | |
| Parildar-Karpuzoğlu, 2008 | 91 | 81 | 9 | 1 | 90 | 93 | 74 | 18 | 1 | 94 | Age and sex |
| Subtotal | 91 | 81 | 9 | 1 | - | 93 | 74 | 18 | 1 | - | |
| Asian | | | | | | | | | | | |
| Koyama, 2006 | 40 | 0 | 6 | 34 | 96 | 102 | 0 | 7 | 95 | 92 | Age and ethnicity |
| Ji, 2010 | 984 | 517 | 98 | 5 | 91 | 620 | 237 | 32 | 4 | 93 | Age and sex |
| Subtotal | 1024 | 517 | 104 | 39 | - | 722 | 237 | 39 | 99 | - | |
| Total | 1115 | 598 | 113 | 40 | - | 815 | 311 | 57 | 100 | - | |

stayed similar when eliminating those studies. The present analyses of hospital based and population-based studies individually also did not lead to a different conclusion. In addition, meta-regression did not find a significant difference between various study designs.

### *Publication bias*

Funnel plots and Egger's test were performed to assess publication bias, which suggested that there were no publication bias for the comparison of Arg399Gln polymorphism, in term of recessive ($t = 1.07$, $P = 0.294$), dominant ($t = 0.39$, $P = 0.701$) and additive ($t = -0.57$,

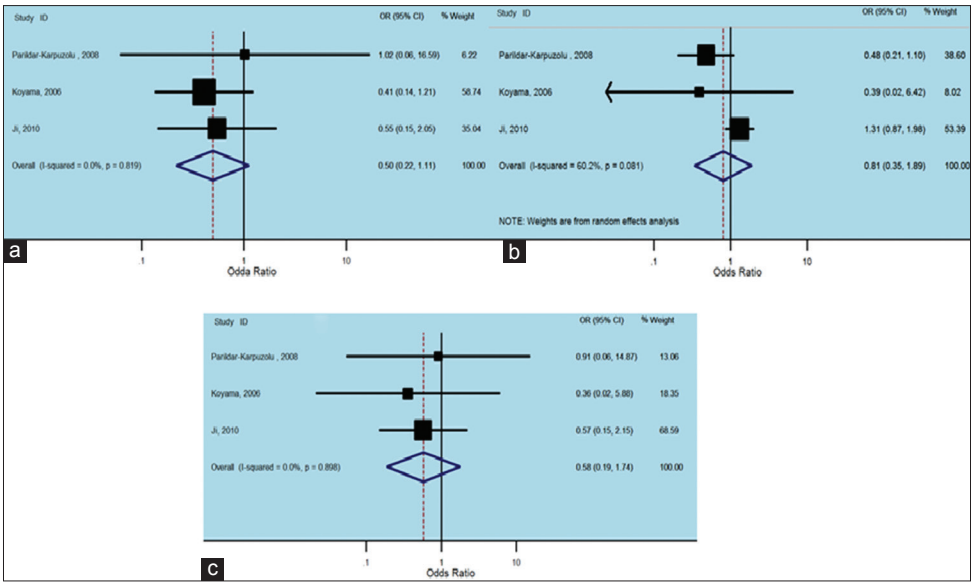


**Figure 6: Forest plots of odds ratios with 95% confidence interval for X-ray repair cross-complementing group 1 polymorphisms and risk of Non-carcinogenic disease. (a) Recessive model of Arg280His (His/His versus Arg/Arg), (b) dominant model (His/His vs. Arg/Arg + Arg/His) and (c) additive model (His/His + Arg/His vs. Arg/Arg)**

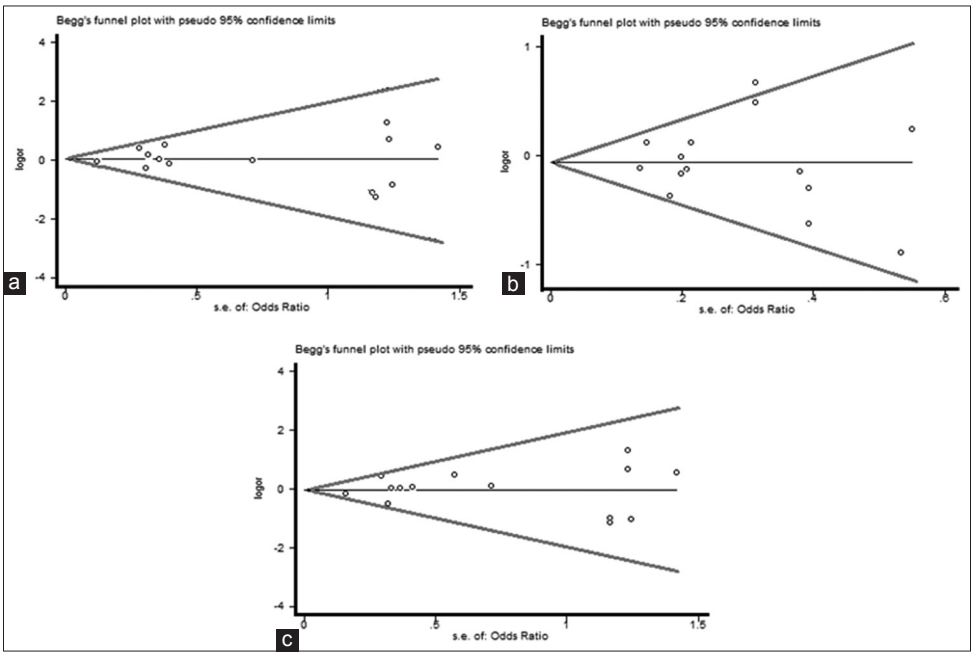


**Figure 7: Begg's funnel plot of the Egger's test of allele comparison for publication bias. (a) Additive model of Arg194Trp (Trp/Trp vs. Arg/Arg), (b) dominant model (Trp/Trp vs. Arg/Arg+ Arg/Trp) and (c) recessive model (Trp/Trp + Arg/Trp vs. Arg/Arg)**

$P = 0.575$) models [Figure 7 and Table 5]. Furthermore, there were no publication bias for the comparison of Arg194Trp polymorphism, in term of recessive ($t = -0.01$, $P = 0.995$), dominant ($t = -0.19$, $P = 0.854$) and additive ($t = -0.12$, $P = 0.910$) models [Figure 9 and Table 5]. Besides, there were no publication bias for the comparison of Arg280His polymorphism, in term of recessive ($t = 3.13$, $P = 0.197$), dominant ($t = -1.08$, $P = 0.475$) and additive ($t = -0.00$, $P = 0.997$) models [Figure 11 and Table 5]. However, when we stratified Arg399Gln, Arg194Trp and Arg280His polymorphisms, according to different ethnic subgroups include Caucasian, Asian and other; there was no public bias in each subgroup [Figures 8, 10, 12 and Table 5 and 6].

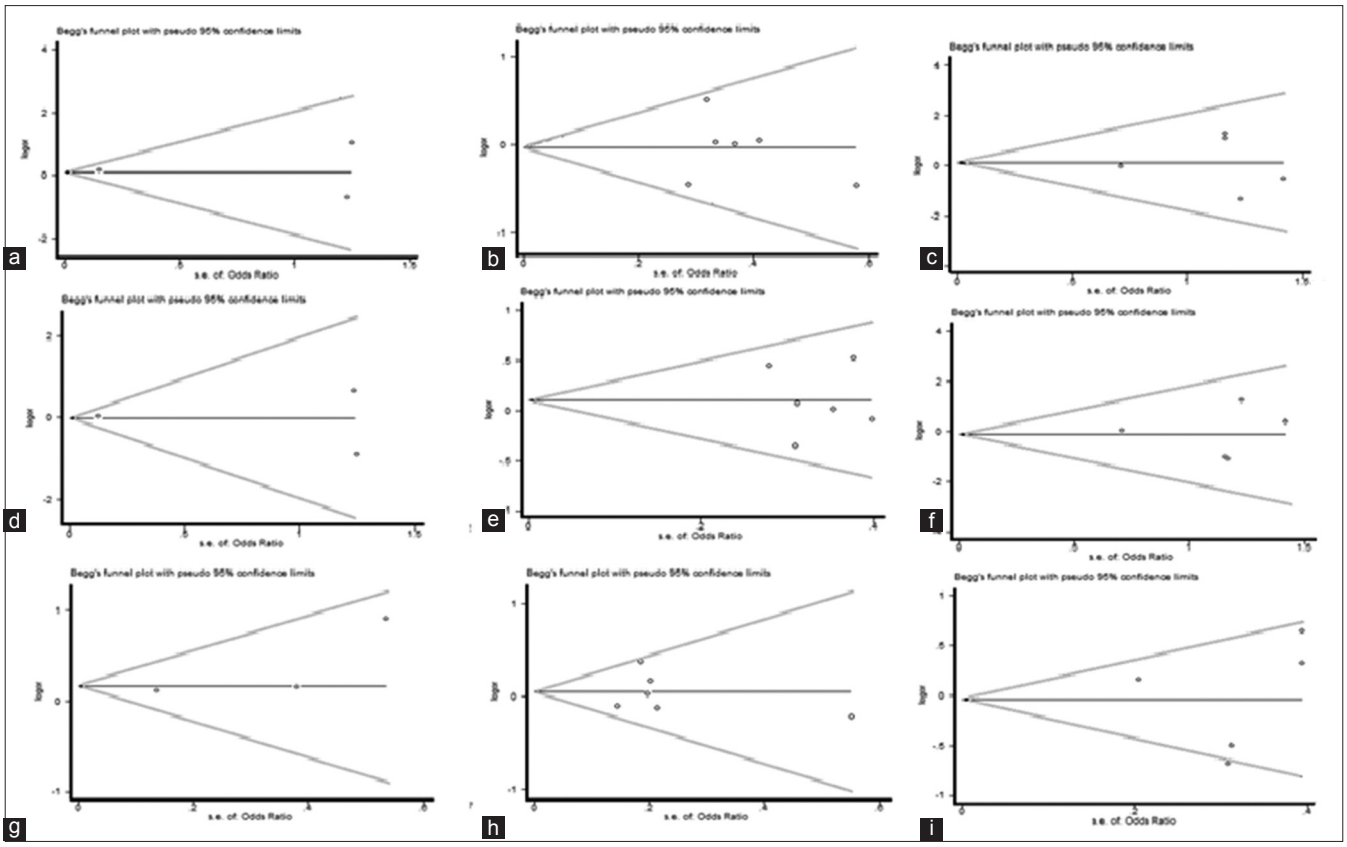


**Figure 8: Begg's funnel plot of the Egger's test of allele comparison for publication bias (top) additive model of Arg194Trp (Trp/Trp vs. Arg/Arg), (middle) dominant model (Trp/Trp vs. Arg/Arg+ Arg/Trp) and (bottom) recessive model (Trp/Trp + Arg/Trp vs. Arg/Arg); first row is a subgroup analysis in Caucasian population (a-c); second row is a subgroup analysis in Asian population (d-f); Third row is a subgroup analysis in other population (g-i)**

**Table 5: Egger's test variables to assess publication bias and comparison of 399Gln versus 399Arg, 194Trp versus 194Arg and 280His versus 280Arg**

| Ethnic subgroups | XRCC1 polymorphisms | | | | | |
|---|---|---|---|---|---|---|
| | Recessive | | Dominant | | Additive | |
| | *t* | *P* value | *t* | *P* value | *t* | *P* value |
| Genetic models of Arg194Trp | | | | | | |
| Caucasian | −0.11 | 0.933 | −1.29 | 0.420 | −0.11 | 0.931 |
| Asian | 0.16 | 0.877 | 0.20 | 0.852 | −0.24 | 0.823 |
| Other | 0.04 | 0.967 | −0.08 | 0.938 | 0.11 | 0.923 |
| Overall | −0.01 | 0.995 | −0.19 | 0.854 | 0.12 | 0.910 |
| Genetic models of Arg194Trp | | | | | | |
| Caucasian | 0.09 | 0.928 | 0.08 | 0.939 | 0.14 | 0.896 |
| Asian | 0.43 | 0.673 | 0.01 | 0.995 | −1.58 | 0.139 |
| Other | −0.21 | 0.839 | 0.38 | 0.712 | −0.06 | 0.935 |
| Overall | 1.07 | 0.297 | 0.39 | 0.701 | −0.57 | 0.575 |
| Genetic models of Arg280His | | | | | | |
| Overall* | 3.13 | 0.197 | −1.08 | 0.475 | −0.00 | 0.997 |

*Ethnicity subgroup analysis was not possible due to very small samples in Arg280His polymorphism (one Caucasian and 2 Asian). Recessive model of Arg194Trp (Trp/Trp vs. Arg/Arg), Dominant model (Trp/Trp vs. Arg/Arg+Arg/Trp) and Additive model (Trp/Trp+Arg/Trp vs. Arg/Arg). Recessive model of Arg399Gln (Gln/Gln vs. Arg/Arg), Dominant model (Gln/Gln vs. Arg/Arg+Arg/Gln) and (C) Additive model (Gln/Gln+Arg/Gln vs. Arg/Arg). Recessive model of Arg280His (His/His vs. Arg/Arg), Dominant model (His/His vs. Arg/Arg+Arg/His) and Additive model (His/His+Arg/His vs. Arg/Arg). XRCC1: X-ray repair cross-complementing group 1

**Table 6: The association of XRCC1 gene polymorphisms and non-carcinogenic risk by assuming different population**

| Variables (models) | XRCC1 polymorphism OR (95%CI) | | |
|---|---|---|---|
| | Arg194Trp | Arg399Gln | Arg280His |
| All population | | | |
| Recessive | 1.03 (0.88-1.22) | 1.02 (0.86-1.21) | 0.50 (0.22-1.11)* |
| Dominant | 0.94 (0.81-1.11) | 1.10 (0.96-1.26)* | 0.81 (0.35-1.89)* |
| Additive | 0.96 (0.79-1.17) | 1.15 (0.96-1.39)* | 0.58 (0.19-1.74)* |
| Caucasian | | | |
| Recessive | 0.99 (0.79-1.24) | 0.93 (0.73-1.20) | - |
| Dominant | 0.85 (0.67-1.08) | 0.99 (0.84-1.18) | - |
| Additive | 0.90 (0.67-1.21) | 0.94 (0.72-1.22) | - |
| Asian | | | |
| Recessive | 1.11 (0.86-1.44)* | 0.88 (0.66-1.18) | - |
| Dominant | 0.95 (0.81-1.11) | 1.08 (0.86-1.35) | - |
| Additive | 1.04 (0.79-1.37) | 1.05 (0.77-1.43) | - |
| Other | | | |
| Recessive | 0.86 (0.36-2.03) | 1.49 (1.19-1.88)* | - |
| Dominant | 1.04 (0.66-1.63) | 1.23 (0.64-1.62)* | - |
| Additive | 0.85 (0.36-2.00) | 1.61 (1.24-2.10)* | - |

*Significant correlation, XRCC1: X-ray repair cross-complementing group 1, OR: Odds ratio, CI: Confidence interval

## Discussion

Large and unbiased molecular and genetic epidemiologic studies of SNPs such as DNA repair

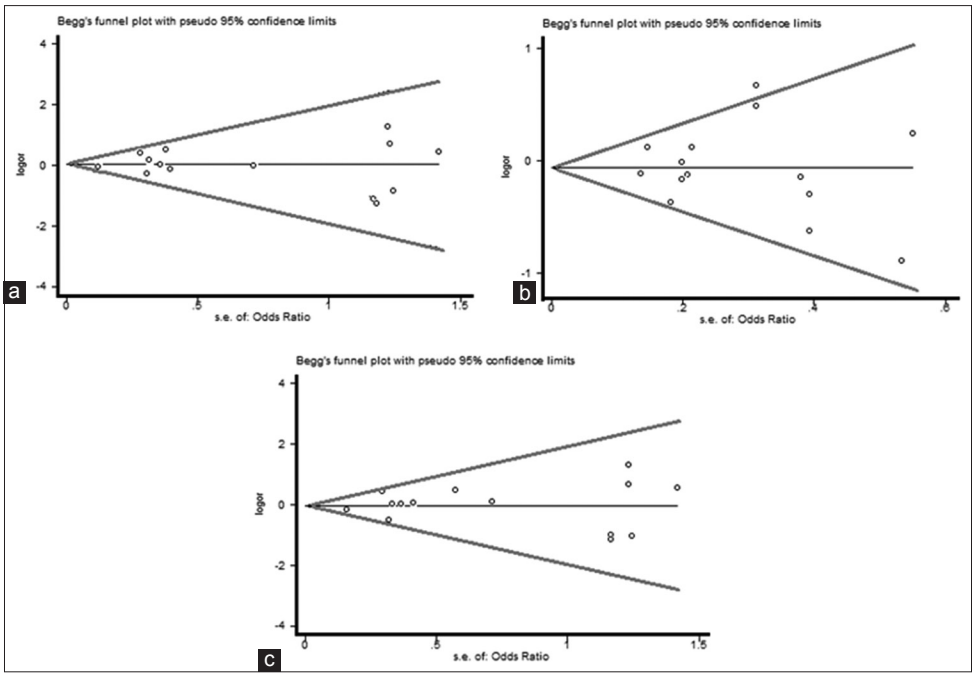


**Figure 9: Begg's funnel plot of the Egger's test of allele comparison for publication bias (top) (right) additive model of Arg399Gln (Gln/Gln vs. Arg/Arg), (middle) dominant model (Gln/Gln vs. Arg/Arg+ Arg/Gln) and (bottom) recessive model (Gln/Gln + Arg/Gln vs. Arg/Arg)**

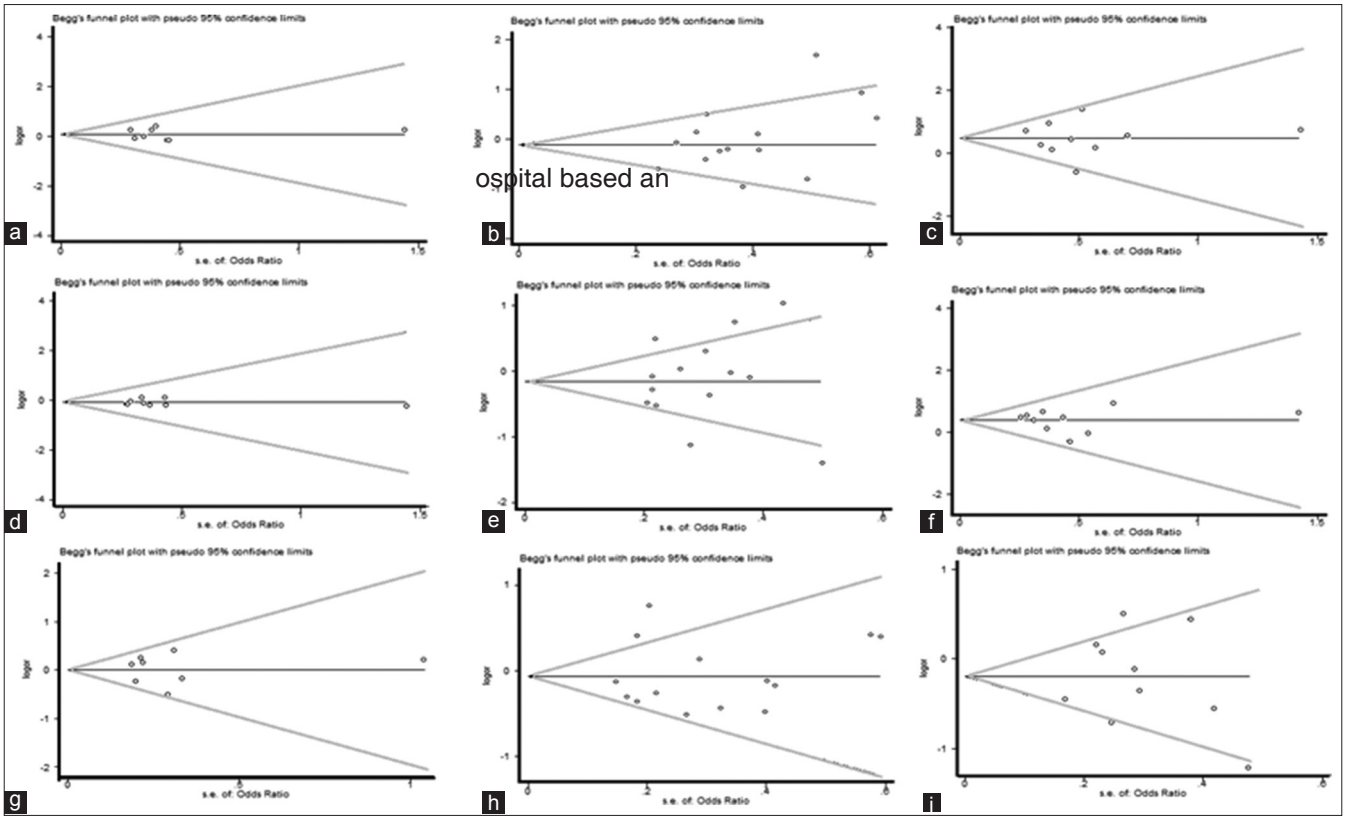


**Figure 10: Begg's funnel plot of the Egger's test of allele comparison for publication bias (top) (right) additive model of Arg399Gln (Gln/Gln vs. Arg/Arg), (middle) dominant model (Gln/Gln vs. Arg/Arg + Arg/Gln) and (bottom) Recessive model (Gln/Gln + Arg/Gln versus Arg/Arg); First row is a subgroup analysis in Caucasian population (a-c); second row is a subgroup analysis in Asian population (d-f); third row is a subgroup analysis in other population (g-i)**

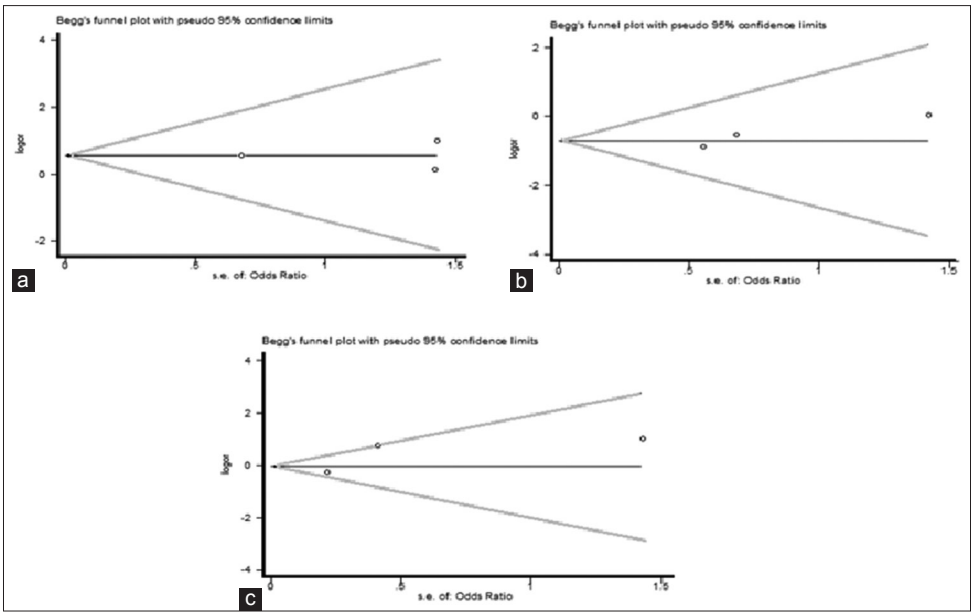


**Figure 11: Begg's funnel plot of the Egger's test of allele comparison for publication bias. (a) Additive model of Arg280His (Gln/Gln vs. Arg/Arg), (His/His vs. Arg/Arg), (b) dominant model (His/His vs. Arg/Arg + Arg/His) and (c) additive model (His/His + Arg/His vs. Arg/Arg)**

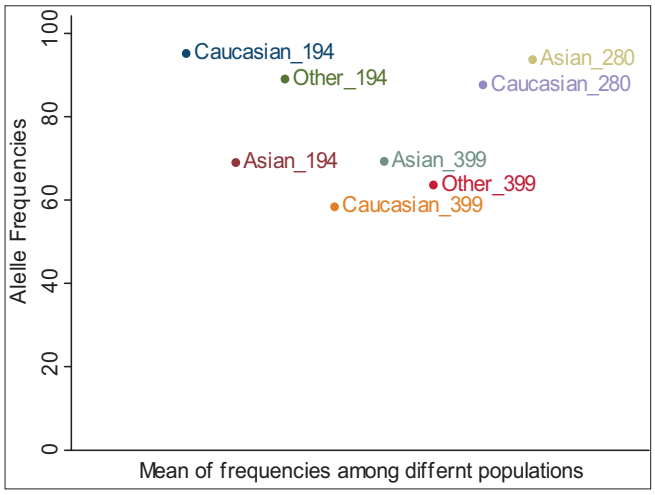


**Figure 12: Mean of Arg allele frequencies for non-carcinogenic diseases between different populations**

genes, may provide insight into the *in vivo* relations between the candidate genes and non-carcinogenic and cancer risk. XRCC1 is very important repair gene for efficient base excision and single-strand break in DNA. The present meta-analysis observed Arg194Trp, Arg280His and Arg399Gln polymorphisms of the XRCC1 gene and their associations with non-carcinogenic disease risk in various populations and ethnicity, by critically reviewing 38 studies.

Many of the studies indicated the association between the oxidative or UV light DNA damage and cataract development,[58-62] that the contribution of DNA damage in cataract pathogenesis indicate the role of DNA repair enzymes such as XRCC1. An epidemiologic study that reviewed twenty-two researches revealed a well-documented risk for cataract and DNA damage due to UV exposure.[63] Previous studies showed no association between Arg194Trp polymorphism and indicators of DNA repair capacity, such as, sensitivity to ionizing radiation or DNA-adduct levels.[64] Hence, our meta-analysis found evidence that 194Trp variant altered non-carcinogenic disease risk among Asian populations. However, other studies showed that this polymorphism exhibited significantly lower values of chromosomal breaks per cell and the protective effect of 194Trp.[65,66] Studies suggest that Arg194Trp polymorphism does not modify the risk for non-carcinogenic disease including alcoholic cirrhosis, pre-eclampsia (PE) and idiopathic azoospermia in Asian, Caucasian and other population,[24,32,42] while some studies showed a protective effect against other disease such as chronic obstructive pulmonary disease (COPD) and Pterygiumin Asian population.[43,53] In some meta-analysis about the association between Arg194Trp and risk of cancer considering different genetic models, no evidence of the protective effect against the bladder and breast cancer has been found in Asian and Caucasian.[17,67-69] However, others showed

Arg280His genotype increased risk for differentiated thyroid carcinoma and gastric cardiac adenocarcinoma in the dominant model, while mildly reduced the risk for this cancer in Asian and Other (Iranian) population.[70,71] Our meta-analysis also recommends a tendency towards recessive mode of risky effect of 194Trp, which suggest that further studies should be performed to evaluate the effect of this polymorphism.

Moreover, for XRCC1-Arg399Gln polymorphism studies showed that this polymorphism may modify the risk for the non-carcinogenic disease including alcoholic cirrhosis, PE, Alzheimer's disease (AD), ocular diseases include primary open angle glaucoma, cataract, Pterygium, severe chronic atrophic gastritis and idiopathic azoospermia in Asian, Caucasian and other population,[23,24,27,29,30,32,42,43,68] while some studies showed no association with other disease such as COPD and endometriosis in Asian and other population.[31,53] Several well-known atherosclerotic risk factors, such as dyslipidemia and diabetes mellitus, lead to DNA damage,[69] thus the effects of this risk factors on DNA damage in coronary artery disease (CAD) have been demonstrated formerly[70,71] and found no associations between CAD and Arg399Gln polymorphism in other (Turkey) population[34] whereas, other study showed a relationship between CAD and Arg399Gln, polymorphisms in Caucasian.[35] In cystic fibrosis, there was slight correlation between Arg399Gln polymorphism with liver status and pancreatic insufficiency in Caucasian, but this correlation was not significant.[36] In a meta-analysis of Asian (Taiwanese Han Chinese) and Caucasian (Brazilian, and Polish) populations showed that the XRCC1 (Arg399Gln polymorphism) was associated with systemic lupus erythematous incidence.[40] Furthermore, the XRCC1 (Arg399Gln polymorphism) may affect risk of two major birth defects including spina bifida and oral clefts in Caucasian (USA) population.[49] The majority of studies have reported that there was no association between the XRCC1 (codon 399) polymorphism and cancer.[72-79] In the minority of researches, a weak but statistically significant association has been found in Asian countries, entirely.[18,72-74] Our meta-analysis suggests that 399Gln increases non-carcinogenic disease risk by 50%, 25% and 60% with recessive, dominant and additive models in other population only, respectively, which indicated that the genotype distributions of Arg399Gln varied with ethnicity. There may be two explanations concerning the difference in results. Genetic, environmental, and ethnic differences in allele frequency for the investigated polymorphisms can affect results in studies. One possible explanation could be differences in ethnicity in term of dietary habits and drinking, health-care access and socioeconomic factors. Another more reasonable clarification may be linked to diversity in linkage or genetic associations between alleles in different populations, which formerly were reported in cancer.[80]

From the Biological point of view, 280His codon is placed in the proliferating cell nuclear antigen-binding region. Previously, it was suggested 280His codon to be associated with higher bleomycin sensitivity, which resulted in a reduced DNA repair capacity produced by bleomycin.[71] Studies showed that XRCC1-Arg280His polymorphism had a protective effect on non-carcinogenic disease such as AD, rheumatoid arthritis in other (Turkish) and Asian (Taiwanese and Japanese) population,[23,46,61] while does not meet the frequency criteria for being considered an important SNP in some non-carcinogenic disease like ocular disease (Pterygium), severe chronic atrophic gastritis, spina bifida and oral clefts among Asian (Chinese) and Caucasian (Irish and American) population.[38,44,45,49] Our meta-analysis suggests a tendency for Asian and Caucasian populations harboring Arg280His to have a protective effect against non-carcinogenic disease through both recessive and dominant effect [Table 5]. These varying effects in Asian and Caucasian populations may be due to the difference in distributions of this SNP, with a lower frequency in Caucasian population (4-6%) when compared with Asian population [Table 4]. As studies of Arg280His among all populations especially Asian and other subgroup are at present in adequate, further studies including a broader variety of Asian and other subgroup subjects should be carried out to approve whether this XRCC1 variant alters non-carcinogenic disease risk differently in Asian and other subgroup populations.

## Conclusion

The present meta-analysis correspondingly shows that comprising diverse population is very important since susceptibility loci might vary indifferent ethnic groups. To ratify our findings, widespread studies with enlarged sample size and various populations are essential to

explain the role of all polymorphism ofXRCC1 genes in the pathogenesis of non-carcinogenic diseases. Finally, our meta-analysis showed Arg399Gln variant to be associated with increased non-carcinogenic diseases risk through dominant and recessive modes among Iranian and Turkish population. It also suggests a trend of dominant and recessive effect of Arg280His variant in all population and its possible protective effect on non-carcinogenic diseases as well.

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