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Meta-analysis of Genetic Polymorphisms and Ophthalmologic Disease Risk in Asian Populations: a Case of DNA Repair XRCC1 Gene

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Abstract: This study aimed to assess a meta-analysis of the association of XRCC1 polymorphisms with the risk of various ophthalmologic diseases in Asian population. This meta-analysis was performed by critically reviewing reveals 38 studies involving 1373 cases and 1745 controls. Among all the eligible studies, one focused on Arg194Trp polymorphism, nine described the Arg399Gln and no article investigated on Arg280His. There was a large between-study heterogeneity in ORs of individual studies of the dominant model (χ^2 = 74.18, I^2 =58.9%, p = 0.013) and the additive (χ^2 = 56.18, I^2 = 41.4%, p = 0.091) models, but a moderate heterogeneity in the recessive model (χ^2 = 72.27, I^2=78.8%, p = 0.000) was observed. So, we pooled the results using the random-effect analysis and found that Arg399Gln has a weak relation with ophthalmologic disease in the recessive (OR = 0.96, 95% CI: 0.64-1.44), the dominant (OR = 1.05, 95% CI: 0.82-1.33) and the additive (OR = 1.15, 95% CI: 0.77-1.70) and models. 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 of XRCC1 genes in the pathogenesis of ophthalmologic diseases. Finally, our meta-analysis showed Arg399Gln variant was not associated with increased ophthalmologic diseases risk via dominant and recessive modes among Asian population.

Key words: XRCC1 gene, polymorphisms, Arg194Trp, Arg399Gln, ophthalmologic diseases, ethnicity

INTRODUCTION

There is increasing evidence suggests that damage to human DNA might initiate the cancer, which caused by external agents such as chemical agents, ionizing radiation and UV (Carpenter *et al*., 1998; Okayasu, 2012; Rastogi *et al*., 2010; Yanez *et al*., 2002). 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 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) up to now (Shen *et al*., 1998), which were predicted to be possibly damaging the XRCC1 function (Metsola *et al*., 2005). 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 (Caldecott *et al*., 1996). 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 cancer risk (Loizidou *et al*., 2008; Saadat *et al*., 2008) and reports showed a possible protective effect (Costa *et al*., 2007), while many studies observed no significant association between these polymorphisms and the cancer

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(Thyagarajan *et al*.,2006). Besides it was reported that XRCC1 gene polymorphism is associated with several cancers including lung, esophageal and prostate cancers, among different population (Hao *et al*., 2004; Lee *et al*., 2001, 2002; Misra *et al*., 2003; Moullan *et al*., 2003; Van Gils *et al*., 2002). Moreover, no evidence of any associations between Arg399Gln polymorphism and bladder cancer susceptibility has not shown (Wang *et al*., 2008), hence other researchers reported that 399 Gln/Gln genotype is associated with a risk of lung cancer among Asians ethnicity (Kiyohara *et al*., 2006). Although, large numbers of epidemiologic studies have been evaluated the role of XRCC1 polymorphisms on various ophthalmologic diseases, such as liver cirrhosis, Alzheimer, glaucoma, cataract, HIV-1/AIDS, schizophrenia, type 2 diabetes (Attar *et al*., 2010; Bau *et al*., 2007; Bazo *et al*., 2011; Chen *et al*., 2010; Chiang *et al*., 2010; Gorgun *et al*., 2010; Gu *et al*., 2007; Guven *et al*., 2007a, b; Kasznicki *et al*., 2009; Lin *et al*., 2009; Luo *et al*., 2011; Padma *et al*., 2011; Parildar-Karpuzoglu *et al*., 2008; Qian *et al*., 2010; Rossit *et al*., 2002; Sobti *et al*., 2009; Sterpone *et al*., 2009; Unal *et al*., 2007; Vural *et al*., 2009; Warchol *et al*., 2012; Yang *et al*., 2009; Yousaf *et al*., 2011; Zhao *et al*., 2012) and cancers, but no such comprehensive analysis in the field of ophthalmologic 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 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 ophthalmologic diseases in different Asian 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 OCT 12, 2012). In addition, all publications in other databases such as IranMedex, SID (Scientific Information Database) were searched. In a total of 383 retrieved relevant references, nine publications were identified to be eligible for the inclusion in the meta-analysis (Fig. 1). These studies had a case-control study design that assessed the association between the XRCC1 Arg194Trp, the Arg399Gln and Arg280His polymorphisms and risk of ophthalmologic 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 ophthalmologic 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 ophthalmologic 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% Confidence Intervals (CI) to estimate ophthalmologic diseases 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 ophthalmologic diseases compare to that of allele Arg, as well as using additive (Trp/Trp vs. Arg/Arg), recessive

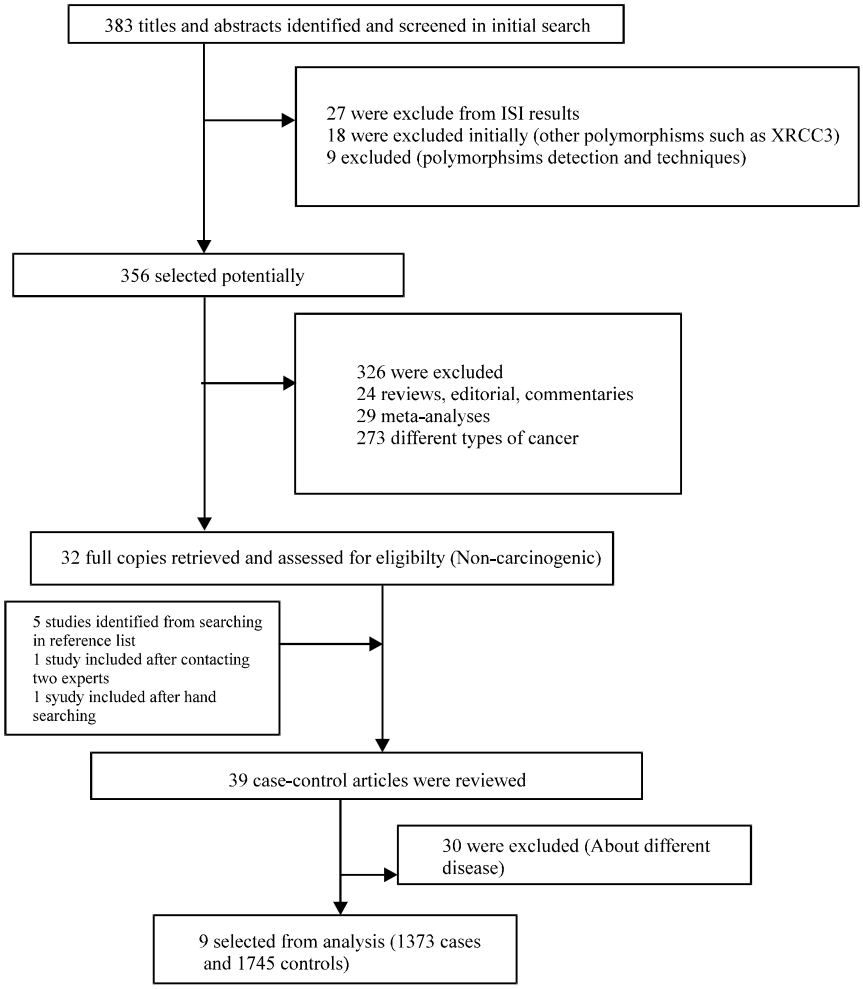

Fig. 1: Flowchart of eligible studies

(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 polymorphism. 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 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 (Ioannidis *et al*., 2008). So the heterogeneity was considered significant, if the p-value<0.10 and I^2>25, a random-effect model was suitable, otherwise if the p-value = 0.10 and I^2 = 25, a fixed-effect 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 = 0.05 suggests no bias).All analyses were done using STATA 11.0 software. All the p-values were two-sided.

RESULTS

Eligible studies: Nine reports focused on the role of any polymorphism of the XRCC1 gene in the ophthalmologic diseases risk were reviewed. Thus the present meta-analysis reveals 9 studies involving 1373 cases and 1745 controls (Table 1). Each sub-population study has treated

Table 1: Studies included in the meta-analysis

			Age (Mean±SD)				Study characteristics		
Source	Country	Disease type	Case	Control	Cases/control	Genotype studied	Method	Population	Design	Control
Yousaf *et al.* (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 *et al.* (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
Guven *et al.* (2007a)	Turkey	Glaucoma	61.3±6.9	59.1±5.8	144/121	Codon 399	PCR-RFLP	Turkish	Population-based	Disease-free
Luo *et al.* (2011)	China	Cataract	68±8	61.5±7	180/174	Codon 399	PCR-RFLP	Chinese	Hospital-based	Disease-free
Unal *et al.* (2007)	Turkey	Cataract	64±8	63±8	195/194	Codon 399	PCR-RFLP	Turkish	Population-based	Disease-free
Padma *et al.* (2011)	India	Cataract	58.6±0.40	49.1±0.55	208/151	Codon 399	PCR-RFLP	Indian	Hospital-based	Healthy subjects
Gorgun *et al.* (2010)	Turkey	Macular degeneration	75±8	73±10	120/205	Codon 399 codon 194	PCR-RFLP	Turkish	Population-based	Disease-free
Chiang *et al.* (2010)	Taiwan	Pterygium	64.6	64.2	127/103	Codon 399	PCR-RFLP	Taiwanese	Hospital-based	Healthy subjects
Chen *et al.* (2010)	Taiwan	Pterygium	57	62	83/206	Codon 399	PCR-RFLP	Chinese	Hospital-based	Disease-free

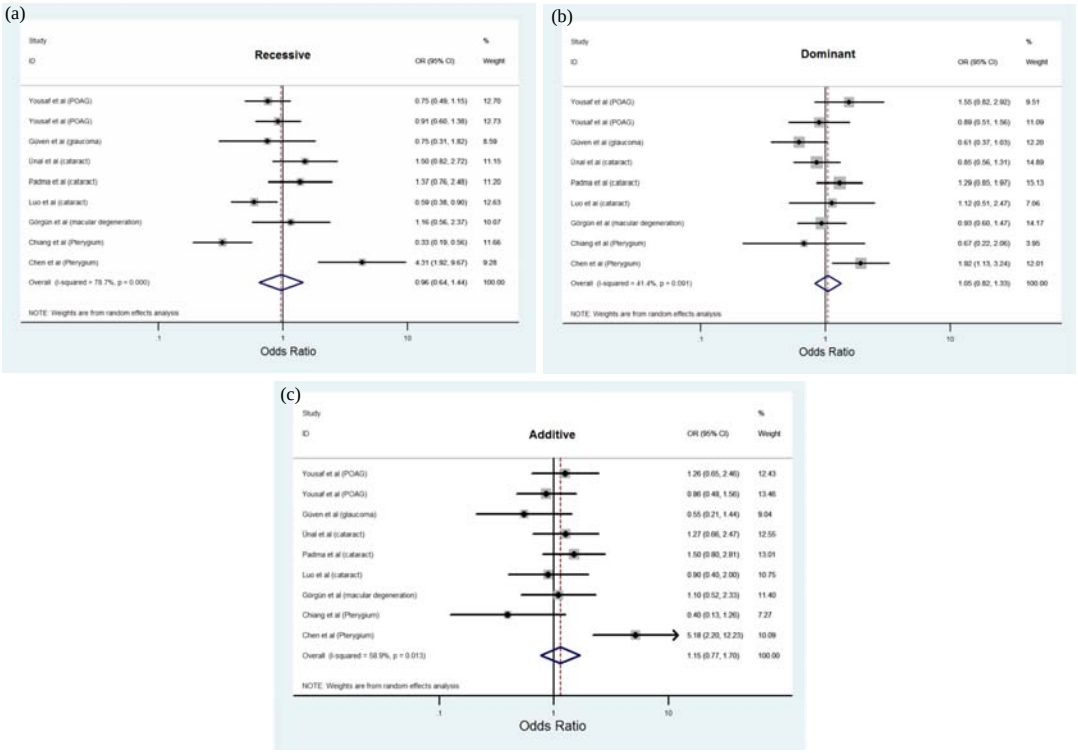

Fig. 2(a-c): Forest plots of ORs with 95% CI for XRCC1 polymorphisms and risk of Ophthalmologic disease. Recessive model of (a) Arg194Trp (Trp/Trp vs. Arg/Arg), (b) Dominant model (Trp/Trp vs. Arg/Arg+Arg/Trp) and (c) Additive model (Trp/Trp +Arg/Trp vs. Arg/Arg)

as a separate in the analysis. Among all the eligible studies, one focused on Arg194Trp polymorphism, nine described the Arg399Gln and no article investigated on Arg280His.

Arg399Gln: We examined the association between Arg399Gln XRCC1 polymorphism and ophthalmologic diseases risk, assuming various inheritance models of the 399Gln allele for each individual study (Table 2). There was a large between-study heterogeneity in ORs of individual studies of the dominant model (χ^2 = 74.18, I^2 = 58.9%, p = 0.013) and the additive (χ^2 = 56.18, I^2 = 41.4%, p = 0.091) models, but a moderate heterogeneity in the recessive (χ^2 = 72.27, I^2 = 78.8%, p = 0.000) was observed. So we pooled the results using the random-effect analysis and found that Arg399Gln has a weak relation with ophthalmologic disease in the recessive (OR = 0.96, 95% CI: 0.64-1.44, Fig. 2A and 3A), the dominant (OR = 1.05, 95% CI: 0.82-1.33, Fig. 2B and 3B) and the additive (OR = 1.15, 95% CI: 0.77-1.70, Fig. 2C and 3C) and models.

Sensitivity analysis: We implemented sensitivity analyses to assess the effect of those studies that are not in HWE. The results stayed similar when eliminating those studies. The present analyses of hospital based and population-based studies individually also did not lead to different conclusion. Moreover, meta-regression did not find 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 = 1.45, p = 0.19, Fig. 4a), dominant (t = -0.1, p = 0.92, Fig, 4b) and additive (t = -0.58, p = 0.57, Fig. 4c) models (Table 3). However, when we stratified Arg399Gln, Arg194Trp polymorphisms, according to different ethnic subgroups include Asian population; there was no public bias in each subgroup (Table 4).

DISCUSSION

Large and unbiased molecular and genetic epidemiologic studies of SNPs such as DNA repair genes, may provide insight into the *in vivo* relations between the candidate genes and ophthalmologic and cancer risk. XRCC1 is very important repair gene for efficient base

Table 2: Genotyping frequencies of Arg194Trp and Arg399Gln polymorphisms

		Cases				Control					
		Genotypes				Genotypes					
Source	Total	Arg/Arg	Arg/Gln	Gln/Gln	% with Arg allele	Total	Arg/Arg	Arg/Gln	Gln/Gln	% with Arg allele	Matched
Arg194Trp polymorphism											
Gorgun *et al.* (2010)	120	98	21	1	90	205	180	25	0	94	Age, sex and ethnicity
Arg399Gln polymorphism											
Chiang *et al.* (2010)	127	9	70	48	65	103	5	31	67	80	Age
Guven *et al.* (2007a)	195	65	100	30	59	194	58	115	21	60	Age, sex and ethnicity
Chen *et al.* (2010)	83	31	35	17	68	206	104	80	22	69	
Padma *et al.* (2011)	208	90	82	36	63	151	75	56	20	68	Age and sex
Yousaf *et al.* (2011)	160	17	73	70	67	193	30	65	98	68	Age and sex
Yousaf *et al.* (2011)	163	28	56	79	66	193	30	65	98	68	Age and sex
Luo *et al.* (2011)	180	13	71	96	73	174	14	45	115	79	Age and sex
Guven *et al.* (2007a)	144	56	78	10	65	121	34	76	11	60	Age and sex
Gorgun *et al.* (2010)	120	60	46	14	69	205	99	85	21	69	Age, sex and ethnicity

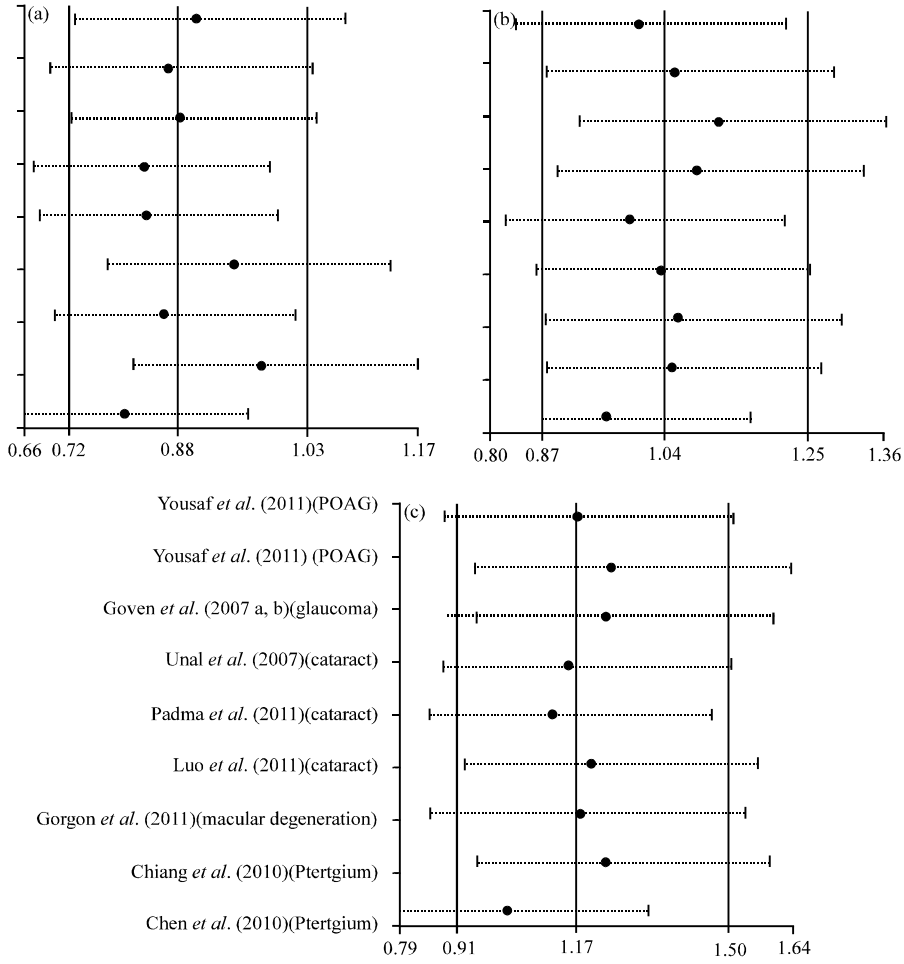

Fig. 3(a-c): Cumulative meta-analysis of Arg399Gln, (a) Recessive model of (Gln/Gln vs. Arg/Arg), (b) Dominant model (Gln/Gln vs. Arg/Arg +Arg/Gln) and (c) Additive model (Gln/Gln+Arg/Gln vs. Arg/Arg)

excision and single-strand break in DNA. The present meta-analysis observed Arg194Trp and Arg399Gln polymorphisms of the XRCC1 gene and their associations with ophthalmologic disease risk in Asian populations and ethnicity, by critically reviewing nine studies.

Many studies indicated the association between the oxidative or UV light DNA damage and cataract development (Kleiman *et al*., 1990; Pendergrass *et al*., 2005; Reddy *et al*., 1998; Risa *et al*., 2004; Spector, 1995), 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 (McCarty and Taylor, 2002). Previous studies showed no association between Arg194Trp polymorphism and the indicators of DNA repair capacity, such as, sensitivity to ionizing radiation or DNA-adduct levels (Tuimala *et al*., 2002, 2004). Our meta-analysis also found evidence that 194Trp variant did not alter the ophthalmologic 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 (Patel *et al*., 2005; Wang *et al*., 2003). Studies suggest that Arg194Trp polymorphism does not modify the risk for diseases including alcoholic cirrhosis, pre-eclampsia (PE) and idiopathic azoospermia in Asian population (Gu *et al*., 2007; Qian *et al*., 2010; Vural *et al*., 2009), while some studies showed a protective effect against other disease such as Chronic Obstructive Pulmonary Disease (COPD) and pterygium in Asian population (Chiang *et al*., 2010; Xie *et al*., 2009). In some meta-analysis about the association between Arg194Trp and risk of cancer considering different genetic models, no evidence of protective effect against bladder and breast cancer has

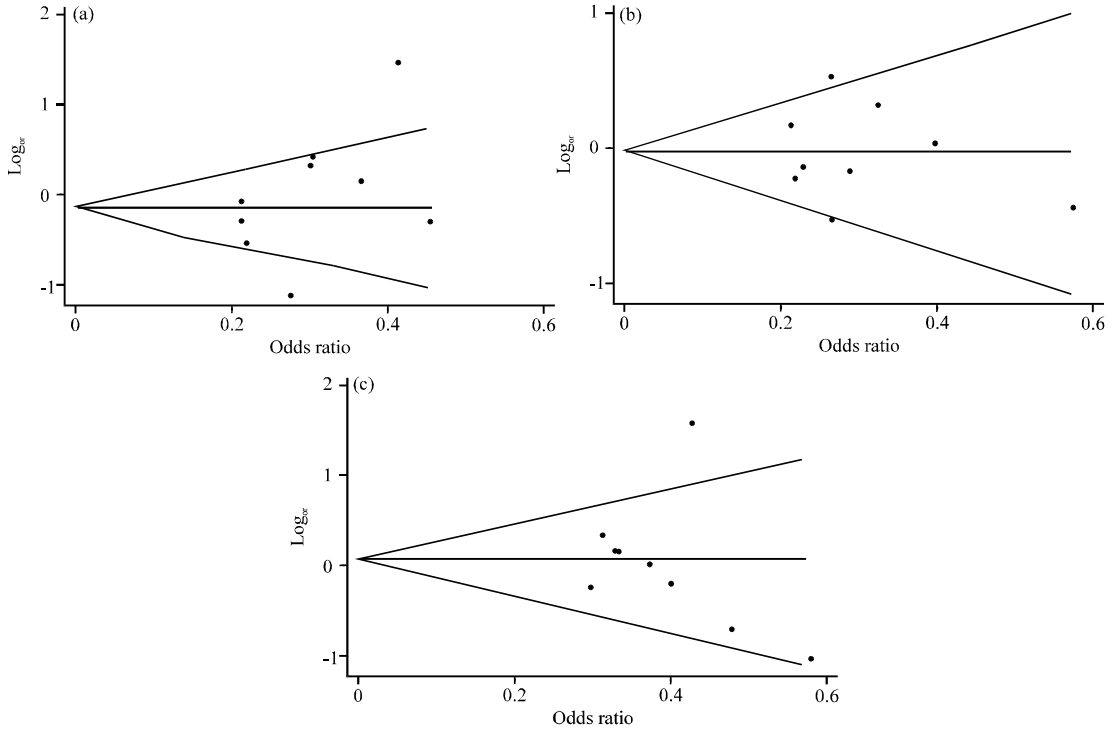

Fig. 4(a-c): Forest plots of ORs with 95% CI for XRCC1 polymorphisms and risk of Ophthalmologic disease, (a) Recessive model of Arg280His (His/His vs. Arg/Arg), (b) Dominant model (His/His vs. Arg/Arg+Arg/His) and (c) Additive model (His/His+Arg/His vs. Arg/Arg)

Table 3: Egger's test variables to assess publication bias and comparison of 399Gln vs. 399Arg

	XRCC1 polymorphisms					
	Genetic models					
	Recessive		Dominant		Additive	
Different diseases	t	p-value	t	p-value	t	p-value
All diseases	1.45	0.19	-0.1	0.92	-0.58	0.57

*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)

Table 4: The association of XRCC1 gene polymorphisms and ophthalmologic risk by assuming different population

Variables	XRCC1 Polymorphism OR(95%CI) Arg399Gln
All diseases	
Recessive model	0.96 (0.64-1.44)
Dominant model	1.04 (0.82-1.33)
Additive model	1.14 (0.77-1.70)

been found in Asian and Caucasian (Chen *et al*., 2011; Huang *et al*., 2009; Lao *et al*., 2008; Wang *et al*., 2008). However, others showed Arg280His genotype increased risk for Differentiated Thyroid Carcinoma (DTC) and Gastric Cardiac Adenocarcinoma (GCA) in dominant model, while mildly reduced the risk for this cancer in Asian population (Fard-Esfahani *et al*., 2011; Yan *et al*., 2009). 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 ophthalmologic disease including alcoholic cirrhosis, pre-eclampsia (PE), Alzheimer's disease (AD), ocular diseases include Primary Open Angle Glaucoma (POAG), cataract, Pterygium, severe chronic atrophic gastritis and idiopathic azoospermia in Asian population (Chiang *et al*., 2010; Gu *et al*., 2007; Padma *et al*., 2011; Qian *et al*., 2010; Rossit *et al*., 2002; Unal *et al*., 2007), while some studies showed no association with other disease such as Chronic Obstructive Pulmonary Disease (COPD) and endometriosis in such ethnicity (Attar *et al*., 2010; Bazo *et al*., 2011). Several well-known atherosclerotic risk factors, such as dyslipidemia and diabetes mellitus, lead to DNA damage (Andreassi 2003), thus the effects of this risk factors on DNA damage in Coronary Artery Disease (CAD) have been demonstrated formerly (Dincer *et al*., 2003; Duell *et al*., 2000) and found no associations between CAD and Arg399Gln

polymorphism in Asian (Turkish) population (Guven *et al*., 2007a), whereas, other study showed a relationship between CAD and Arg399Gln, polymorphisms in Caucasian (Bazo *et al*., 2011). In Cystic Fibrosis (CF), there was slight correlation between Arg399Gln polymorphism with liver status and pancreatic insufficiency in Caucasian, but this correlation was not significant (Sterpone *et al*., 2009). 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 (SLE) incidence (Warchol *et al*., 2012). Furthermore, the XRCC1 (Arg399Gln polymorphism) may affect risk of two major birth defects including spina bifida and oral clefts in Caucasian (USA) population (Olshan *et al*., 2005). The majority of studies have reported that there was no association between the XRCC1 (codon 399) polymorphism and cancer (Fard-Esfahani *et al*., 2011; Goode *et al*., 2002; Huang *et al*., 2009; Hung *et al*., 2005; Lao *et al*., 2008; Yan *et al*., 2009). In the minority of researches, a weak but statistically significant association has been found in Asian countries, entirely (Garte, 1998; Hu *et al*., 2005; Kiyohara *et al*., 2006; Qu and Morimoto, 2005). The present meta-analysis suggests that 399Gln may increases the ophthalmologic 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 the 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 (Garte, 1998).

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 of XRCC1 genes in the pathogenesis of ophthalmologic diseases.

Finally, our meta-analysis showed Arg399Gln variant was not associated with increased ophthalmologic diseases risk via dominant and recessive modes among Asian population.

REFERENCES

Andreassi, M.G., 2003. Coronary atherosclerosis and somatic mutations: An overview of the contributive factors for oxidative DNA damage. Mutation Res./Rev. Mutation Res., 543: 67-86.

Attar, R., C. Cacina, S. Sozen, E. Attar and B. Agachan, 2010. DNA repair genes in endometriosis. Genet. Mol. Res., 9: 629-636.

Bau, D.T., Y.Y. Hsieh, L. Wan, R.F. Wang and C.C. Liao *et al*., 2007. Polymorphism of XRCC1 codon Arg 399 Gln is associated with higher susceptibility to endometriosis. Chin. J. Physiol., 50: 326-329.

Bazo, A.P., D. Salvadori Jr., R.A.F. Salvadori, L.P. Sodre and G.N. da Silva *et al*., 2011. DNA repair gene polymorphism is associated with the genetic basis of atherosclerotic coronary artery disease. Cardiovasc. Pathol., 20: e9-e15.

Caldecott, K.W., S. Aoufouchi, P. Johnson and S. Shall, 1996. XRCC1 polypeptide interacts with DNA polymerase b and possibly poly (ADP-ribose) polymerase and DNA ligase III is a novel molecular nick-sensor *in vitro*. Nucleic Acids Res., 24: 4387-4394.

Carpenter, D.O., K.F. Arcaro, B. Bush, W.D. Niemi, S. Pang and D.D. Vakharia, 1998. Human health and chemical mixtures: An overview. Environ. Health Perspect., 106: 1263-1270.

Chen, M.B., C. Li, M.X. Wei, W. Shen and P.H. Lu, 2011. Re: XRCC1 Arg399Gln, Arg194Trp and Arg280His polymorphisms in breast cancer risk: A meta-analysis (Mutagenesis, 24, 331-339, 2009). Mutagenesis, 26: 675-676.

Chen, P.L., K.T. Yeh, Y.Y. Tsai, H. Koeh, Y.L. Liu, H. Lee and Y.W. Cheng, 2010. XRCC1, but not APE1 and hOGG1 gene polymorphisms is a risk factor for pterygium. Mol. Vis., 16: 991-996.

Chiang, C.C., Y.Y. Tsai, D.T. Bau, Y.W. Cheng, S.H. Tseng, R.F. Wang and F.J. Tsai, 2010. Pterygium and genetic polymorphisms of the DNA repair enzymes XRCC1, XPA and XPD. Mol. Vision, 16: 698-704.

Costa, S., D. Pinto, D. Pereira, H. Rodrigues, J. Cameselle-Teijeiro, R. Medeiros and F. Schmitt, 2007. DNA repair polymorphisms might contribute differentially on familial and sporadic breast cancer susceptibility: A study on a Portuguese population. Breast Cancer Res. Treat., 103: 209-217.

Dincer, Y., T. Akcay, H. Ilkova, Z. Alademir and G. Ozbay, 2003. DNA damage and antioxidant defense in peripheral leukocytes of patients with type I diabetes mellitus. Mutation Res./Fundam. Mol. Mech. Mutagenesis, 527: 49-55.

Duell, E.J., J.W. Wiencke, T.J. Cheng, A. Varkonyi and Z.F. Zuo *et al*., 2000. Polymorphisms in the DNA repair genes XRCC1 and ERCC2 and biomarkers of DNA damage in human blood mononuclear cells. Carcinogenesis (Lond.), 21: 965-971.

Fard-Esfahani, P., A. Fard-Esfahani, S. Fayaz, B. Ghanbarzadeh and P. Saidi *et al*., 2011. Association of Arg194Trp, Arg280His and Arg399Gln polymorphisms in X-ray repair cross-complementing group 1 gene and risk of differentiated thyroid carcinoma in Iran. Iran. Biomed. J., 15: 73-78.

Garte, S., 1998. The role of ethnicity in cancer susceptibility gene polymorphisms: The example of CYP1A1. Carcinogenesis, 19: 1329-1332.

Goode, E.L., C.M. Ulrich and J.D. Potter, 2002. Polymorphisms in DNA repair genes and associations with cancer risk. Cancer Epidemiol. Biomarkers Prev., 11: 1513-1530.

Gorgun, E., M. Guven, M. Unal, B. Batar and G.S. Guven *et al*., 2010. Polymorphisms of the DNA repair genes XPD and XRCC1 and the risk of age-related macular degeneration. Invest. Ophthalmol. Vision Sci., 51: 4732-4737.

Gu, A., G. Ji, J. Liang, Y. Xia and N. Lu *et al*., 2007. DNA repair gene XRCC1 and XPD polymorphisms and the risk of idiopathic azoospermia in a Chinese population. Int. J. Mol. Med., 20: 743-747.

Guven, M., G.S. Guven, E. Oz, A. Ozaydin and B. Batar *et al*., 2007a. DNA repair gene XRCC1 and XPD polymorphisms and their association with coronary artery disease risks and micronucleus frequency. Heart Vessels, 22: 355-360.

Guven, M., M. Unal, B. Batar, E. Eroglu and K. Devarnoglu *et al*., 2007b. Polymorphisms of DNA repair genes XRCC1 and XPD and risk of Primary Open Angle Glaucoma (POAG). Mol. Vision, 13: 12-17.

Hao, B., H. Wang, K. Zhou, Y. Li and X. Chen *et al*., 2004. Identification of genetic variants in base excision repair pathway and their associations with risk of esophageal squamous cell carcinoma. Cancer Res., 64: 4378-4384.

Hu, Z., H. Ma, F. Chen, Q. Wei and H. Shen, 2005. XRCC1 polymorphisms and cancer risk: A meta-analysis of 38 case-control studies. Cancer Epidemiol. Biomarkers Prev., 143: 1810-1818.

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

Hung, R.J., J. Hall, P. Brennan and P. Boffetta, 2005. Genetic polymorphisms in the base excision repair pathway and cancer risk: A HuGE review. Am. J. Epidemiol., 162: 925-942.

Ioannidis, J.P.A., P. Boffetta, J. Little, T.R. O'Brien and A.G. Uitterlinden *et al*., 2008. Assessment of cumulative evidence on genetic associations: Interim guidelines. Int. J. Epidemiol., 37: 120-132.

Kasznicki, J., R. Krupa, J. Blasiak and J. Drzewoski, 2009. Association between polymorphisms of the DNA repair genes XRCC1 and hOGG1 and type 2 diabetes mellitus in the Polish population. Polskie Archiwum Medycyny Wewnetrznej, 119: 122-127.

Kiyohara, C., K. Takayama and Y. Nakanishi, 2006. Association of genetic polymorphisms in the base excision repair pathway with lung cancer risk: A meta-analysis. Lung Cancer, 54: 267-283.

Kleiman, N.J., R.R. Wang and A. Spector, 1990. Hydrogen peroxide-induced DNA damage in bovine lens epithelial cells. Mutation Res./Genet. Toxicol., 240: 35-45.

Lao, T., W. Gu and Q. Huang, 2008. A meta-analysis on XRCC1 R399Q and R194W polymorphisms, smoking and bladder cancer risk. Mutagenesis, 23: 523-532.

Lee, J.M., Y.C. Lee, S.Y. Yang, P.W. Yang and S.P. Luh *et al*., 2001. Genetic polymorphisms of XRCC1 and risk of the esophageal cancer. Int. J. Cancer, 95: 240-246.

Lee, S.G., B. Kim, J. Choi, C. Kim, I. Lee and K. Song, 2002. Genetic polymorphisms of XRCC1 and risk of gastric cancer. Cancer Lett., 187: 53-60.

Lin, Y.J., L. Wan, C.M. Huang, S.Y. Chen and Y.C. Huang *et al*., 2009. Polymorphisms in the DNA repair gene XRCC1 and associations with systemic lupus erythematosus risk in the Taiwanese Han Chinese population. Lupus, 18: 1246-1251.

Loizidou, M.A., T. Michael, S.L. Neuhausen, R.F. Newbold and Y. Marcou *et al*., 2008. Genetic polymorphisms in the DNA repair genes XRCC1, XRCC2 and XRCC3 and risk of breast cancer in Cyprus. Breast Cancer Res. Treat., 112: 575-579.

Luo, Y.F., B.B. Wang, Z. Zhou, X.C. Ding and S.S. Hu *et al*., 2011. Polymorphisms of the DNA repair genes XPD and XRCC1 and the risk of age-related cataract development in Han Chinese. Curr. Eye Res., 36: 632-636.

McCarty, C.A. and H.R. Taylor, 2002. A review of the epidemiologic evidence linking ultraviolet radiation and cataracts. Dev. Ophthalmol., 35: 21-31.

Metsola, K., V. Kataja, P. Sillanpaa, P. Siivola and L. Heikinheimo *et al*., 2005. XRCC1 and XPD genetic polymorphisms, smoking and breast cancer risk in a Finnish case-control study. Breast Cancer Res., 7: R987-R997.

Misra, R.R., D. Ratnasinghe, J.A. Tangrea, J. Virtamo and M.R. Andersen *et al*., 2003. Polymorphisms in the DNA repair genes XPD, XRCC1, XRCC3 and APE/ref-1 and the risk of lung cancer amongmale smokers in Finland. Cancer Lett., 191: 171-178.

Moullan, N., D.G. Cox, S. Angele, P. Romestaing, J.P. Gerard and J. Hall, 2003. Polymorphisms in the DNA repair gene XRCC1, breast cancer risk and response to radiotherapy. Cancer Epidemiol. Biomarkers Prev., 12: 1168-1174.

Okayasu, R., 2012. Repair of DNA damage induced by accelerated heavy ions: A mini review. Int. J. Cancer, 130: 991-1000.

Olshan, A.F., G.M. Shaw, R.C. Millikan, C. Laurent and R.H. Finnell, 2005. Polymorphisms in DNA repair genes as risk factors for spina bifida and orofacial clefts. Am. J. Med. Genet. Part A, 135: 268-273.

Padma, G., M. Mamata, K.R. Reddy and T. Padma, 2011. Polymorphisms in two DNA repair genes (XPD and XRCC1)-association with age related cataracts. Mol. Vision, 17: 127-133.

Parildar-Karpuzoglu, H., S. Dogru-Abbasoglu, H.A. Hanagasi, B. Karadag, H. Gurvit, M. Emre and M. Uysal, 2008. Single nucleotide polymorphisms in base-excision repair genes hOGG1, APE1 and XRCC1 do not alter risk of Alzheimer's disease. Neurosci. Lett., 442: 287-291.

Patel, A.V., E.E. Calle, A.L. Pavluck, H.S. Feigelson, M.J. Thun and C. Rodriguez, 2005. A prospective study of XRCC1 (X-ray cross-complementing group 1) polymorphisms and breast cancer risk. Breast Cancer Res., 7: R1168-R1173.

Pendergrass, W., P. Penn, D. Possin and N. Wolf, 2005. Accumulation of DNA, nuclear and mitochondrial debris and ROS at sites of age-related cortical cataract in mice. Invest. Ophthalmol. Vision Sci., 46: 4661-4670.

Qian, Y., W. Chen, J. Wu, T. Tao and L. Bi *et al*., 2010. Association of polymorphism of DNA repair gene XRCC1 with sporadic late-ons*et al*zheimer's disease and age of onset in elderly Han Chinese. J. Neurol. Sci., 295: 62-65.

Qu, T. and K. Morimoto, 2005. X-ray repair cross-complementing group 1 polymorphisms and cancer risks in Asian populations: A mini review. Cancer Detection Prev., 29: 215-220.

Rastogi, R.P., Richa, A. Kumar, M.B. Tyagi and R.P. Sinha, 2010. Molecular mechanisms of ultraviolet radiation-induced DNA damage and repair. J. Nucleic Acids, 10.4061/2010/592980

Reddy, V.N., F.J. Giblin, L.R. Lin and B. Chakrapani, 1998. The effect of aqueous humor ascorbate on ultraviolet-B-induced DNA damage in lens epithelium. Invest. Ophthalmol. Vision Sci., 39: 344-350.

Risa, O., O. Saether, S. Lofgren, P.G. Soderberg, J. Krane and A. Midelfart, 2004. Metabolic changes in rat lens after *in vivo* exposure to ultraviolet irradiation: Measurements by high resolution MAS ^{1}H NMR spectroscopy. Invest. Ophthalmol. Vision Sci., 45: 1916-1921.

Rossit, A.R.B., I.R. Cabral, C. Hackel, R.C.M.A. da Silva, N.D.T.C. Froes and S.Z. Abdel-Rahman, 2002. Polymorphisms in the DNA repair gene XRCC1 and susceptibility to alcoholic liver cirrhosis in older Southeastern Brazilians. Cancer Lett., 180: 173-182.

Saadat, M., L. Kohan and S. Omidvari, 2008. Genetic polymorphisms of XRCC1 (codon 399) and susceptibility to breast cancer in Iranian women, a case-control study. Breast Cancer Res. Treat., 111: 549-553.

Shen, M.R., I.M. Jones and H. Mohrenweiser, 1998. Nonconservative amino acid substitution variants exist at polymorphic frequency in DNA repair genes in healthy humans. Cancer Res., 58: 604-608.

Sobti, R.C., S.A. Mahdi, N. Berhane, S.A. Hosseini, R. Kler, V. Kuttiat and A. Wanchu, 2009. The influence of variations in the DNA repair (XRCC1) gene on HIV-1/AIDS among Indian population. Folia Biologica, 55: 183-186.

Spector, A., 1995. Oxidative stress-induced cataract: Mechanism of action. FASEB J., 9: 1173-1182.

Sterpone, S., T. Cornetta, A. Angioni, E. Fiscarelli, V. Lucidi, A. Testa and R. Cozzi, 2009. DNA damage and related modifier genes in Italian cystic fibrosis patients. Biol. Res., 42: 477-486.

Thyagarajan, B., K.E. Anderson, A.R. Folsom, D.R. Jacobs Jr. and C.F. Lynch *et al*., 2006. No association between XRCC1 and XRCC3 gene polymorphisms and breast cancer risk: Iowa Women's health study. Cancer Detection Prev., 30: 313-321.

Tuimala, J., G. Szekely, S. Gundy, G. Sarolta and H. Ari *et al*., 2002. Genetic polymorphisms of DNA repair and xenobiotic-metabolizing enzymes: Role in mutagen sensitivity. Carcinogenesis, 23: 1003-1008.

Tuimala, J., G. Szekely, H. Wikman, H. Jarventaus, A. Hirvonen, S. Gundy and H. Norppa, 2004. Genetic polymorphisms of DNA repair and xenobiotic-metabolizing enzymes: Effects on levels of sister chromatid exchanges and chromosomal aberrations. Mutation Res./Fundam. Mol. Mech. Mutagen., 554: 319-333.

Unal, M., M. Guven, B. Batar, A. Ozaydin, A. Sarici and K. Devranoglu, 2007. Polymorphisms of DNA repair genes XPD and XRCC1 and risk of cataract development. Exp. Eye Res., 85: 328-334.

Van Gils, C.H., R.M. Bostick, M.C. Stern and J.A. Taylor, 2002. Differences in base excision repair capacity may modulate the effect of dietary antioxidant intake on prostate cancer risk: An example of polymorphisms in the XRCC1 gene. Cancer Epidemiol. Biomarkers Prev., 11: 1279-1284.

Vural, P., S. Degirmencioglu, S. Dogru-Abbasoglu, N.Y. Saral, C. Akgul and M. Uysal, 2009. Genetic polymorphisms in DNA repair gene APE1, XRCC1 and XPD and the risk of pre-eclampsia. Eur. J. Obstetrics Gynecol. Reprod. Biol., 146: 160-164.

Wang, C., Y. Sun and R. Han, 2008. XRCC1 genetic polymorphisms and bladder cancer susceptibility: A meta-analysis. Urology, 72: 869-872.

Wang, Y., M.R. Spitz, Y. Zhu, Q. Dong, S. Shete and X. Wu, 2003. From genotype to phenotype: Correlating XRCC1 polymorphisms with mutagen sensitivity. DNA Repair, 2: 901-908.

Warchol, T., A. Mostowska, M. Lianeri, J.K. Lacki and P.P. Jagodzinski, 2012. XRCC1 Arg399Gln gene polymorphism and the risk of systemic lupus erythematosus in the Polish population. DNA Cell Biol., 31: 50-56.

Xie, J., S. Yang, Y. Xu and Z. Zhang, 2009. XRCC1 Arg194Trp polymorphism and risk of chronic obstructive pulmonary disease. J. Huazhong Univ. Sci. Technol. (Med. Sci.), 29: 551-556.

Yan, L., D. Yanan, S. Donglan, W. Na, Z. Rongmiao and C. Zhifeng, 2009. Polymorphisms of XRCC1 gene and risk of gastric cardiac adenocarcinoma. Dis. Esophagus, 22: 396-401.

Yanez, L., D. Ortiz, J. Calderon, L. Batres and L. Carrizales *et al*., 2002. Overview of human health and chemical mixtures: Problems facing developing countries. Environ. Health Perspect., 110: 901-909.

Yang, S.F., Y.J. Xu, J.G. Xie and Z.X. Zhang, 2009. hOGG1 Ser326Cys and XRCC1 Arg399Gln polymorphisms associated with chronic obstructive pulmonary disease. Chin. Med. J., 122: 960-966.

Yousaf, S., M.I. Khan, S. Micheal, F. Akhtar and S.H. Ali *et al*., 2011. XRCC1 and XPD DNA repair gene polymorphisms: A potential risk factor for glaucoma in the Pakistani population. Mol. Vision, 17: 1153-1163.

Zhao, Y., X. Deng, Z. Wang, Q. Wang and Y. Liu, 2012. Genetic polymorphisms of DNA repair genes XRCC1 and XRCC3 and risk of colorectal cancer in Chinese population. Asian Pac. J. Cancer Prev., 13: 665-669.