Genetic Variant Arg399Gln G>A of XRCC1 DNA Repair Gene Enhanced Cancer Risk Among Indian Population: Evidence from Meta-analysis and Trial Sequence Analyses

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Abstract The X-ray repair cross-complementation group 1 (*XRCC1*) gene plays an important role in base excision repair pathway. Several studies have reported contradictory results for *XRCC1* exon 10 (Arg399Gln, G23990A, rs25487) gene polymorphism and cancer risk in Indian population, making it difficult to interpret them. Therefore, we have conducted a meta-analysis to evaluate the more precise association between *XRCC1* exon 10 G>A gene polymorphism and risk of cancer by published studies. We searched PubMed (Medline) and Google scholar web databases to cover all studies published on association between *XRCC1* exon 10 G>A gene polymorphism and cancer risk until August 2016. Pooled odds ratios (ORs) and 95% confidence intervals (95% CIs) were used to appraise the strength of association. Heterogeneity, publication bias and sensitivity analysis were also assessed. Twenty-five published studies had fulfilled the inclusion criteria comprising 4131 confirmed cancer cases and 5013 controls. When all studies were pooled together, overall significant association was found between *XRCC1* exon 10 G>A polymorphism and cancer risk in variant allele carrier (A vs. G: OR 1.217, 95% CI 1.056–1.402, $p = 0.007$), homozygous (AA vs. GG: OR 1.359, 95% CI 1.036–1.783, $p = 0.027$), dominant (AA+AG vs. GG OR 1.208, 95% CI 1.006–1.450, $p = 0.043$) and recessive (AA vs. AG+GG: OR 1.315, 95% CI 1.029–1.680, $p = 0.029$) genetic models. Further sensitivity analysis supported the stability of our result by showing similar ORs before and after removal

of a single study. The present meta-analysis suggested that the *XRCC1* exon 10 G>A polymorphism contribute cancer risk in Indian population, and supports that individuals with risk allele A and AA genotype are at higher risk of developing cancer.

Keywords Cancer · Meta-analysis · *XRCC1* gene · Polymorphism · Meta-analysis · Risk factor

Introduction

Cancer remains a major health problem leading to increased morbidity and mortality around the world [1]. The issue is major concern especially in developing country like India, where cancer incidence is predicted to reach 1148,757 cases in the year 2020 [2]. The precise mechanism of carcinogenesis is still complicated and largely unknown. Epidemiological studies reported that interaction between genetic and environmental factors play an important role in cancer development [3].

Recent genome-wide association studies (GWAS) have clearly unveiled that single-nucleotide polymorphisms (SNPs) is the most common forms of human genetic variation have important role in defining individual susceptibility to cancer [4]. This clearly indicated that SNPs can be used as promising biomarker in the near future for the assessment of individual genetic background for cancer prognosis and signify an interesting field of cancer research. Knowledge of cancer genetics is rapidly improving and helping us to identify individuals at risk and provide new possibilities for the diagnosis and treatment of cancer.

Human genome is constantly damaged by endogenous and exogenous sources, and the repair of damaged DNA is

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essential to protect cells against cancer [5]. Different DNA repair pathways and genes system have evolved to repair the specific type of DNA lesion and maintain the genomic integrity. SNPs in DNA repair genes may influence DNA repair capacity and can lead to genomic instability and modulation of cancer susceptibility [6].

Base damage and DNA single strand breaks are repaired through the base excision repair (BER) pathway. X-ray Repair Cross Complementing Group 1 (*XRCC1*, located on chromosome 19q13.2), is a DNA repair protein mainly repair DNA damage caused by active oxygen, ionization and alkylating agents [7]. *XRCC1* acts as a scaffolding protein with DNA polymerase β via the NH2 terminus domain and with DNA ligase III BRCT domain in detection and protection of DNA strand breaks and subsequent targeting of BER complex to the damaged site [8]. Several polymorphism have been identified in *XRCC1* gene, among them codon 399 (Arg to Gln substitution, G23990A, rs25487) is located in the non conserved region between conserved residues of the BRCT-I interaction domain. Variant allele 399Gln demonstrated association with higher levels of mutation, reduced DNA repair capacity and prolonged cell cycle delay thereby influence susceptibility to cancer [9].

Considering their significant role of *XRCC1* gene in DNA repair and mutation, numerous epidemiological case–control studies have been performed to evaluate the association between the *XRCC1* exon 10 G>A gene polymorphism and cancer susceptibility in Indian populations, but the results have been inconclusive [10–34].

Researchers of the reported studies have not yet come up with a concrete agreement, because up to now, there has been no comprehensive research conducted to combine the data of various cancer studies. However, they have shown the *XRCC1* polymorphism have role in different types of cancer in Indian population, but single study is always underpowered to reflect the reliable results. Therefore, we conducted this meta-analysis with rigorous statistical method to derive the more precise results of the association between *XRCC1* exon 10 G>A gene polymorphism and overall cancer risk among Indian population.

Materials and Methods

Literature Search Strategy

A systematic literature search was conducted on PubMed (Medline) and Google scholar to identify studies that had investigated the association of *XRCC1* gene polymorphisms and cancer risk in Indian population, last updated searched was performed on August 2016. The search key were used *XRCC1* OR *X-ray repair cross complementing group 1* and “polymorphism OR mutation OR variant” and “Cancer OR malignancy OR tumor” and “Indian OR India”. The search was focused on studies that had been carried out in humans. We also did manual search of reference list from the retrieve articles for other additional eligible studies.

Fig. 1 Prisma flow chart with inclusion and exclusion criteria for eligible studies

Inclusion and Exclusion Criteria

Articles included in the current meta-analysis had to meet all the following criteria: (1) must evaluated the association between *XRCC1* exon 10 polymorphism and cancer risk, (2) use a case–control design, (3) recruited histologically confirmed cancer patients and healthy controls, (4) have available genotype frequency in case and control. In addition, the following exclusion criteria were also used: (1) repeated or overlapping studies, (2) case only studies, (3) review articles, (4) animal studies, (5) no usable data reported.

Data Extraction and Quality Assessment

To minimize the bias and improve the reliability, the methodological quality assessment and data extraction were independently abstracted by two independent researchers by strictly following the inclusion–exclusion criteria mentioned above. The major characteristics abstracted from the retrieved studies included the name of

the first author, year of publication, the number of cases and controls, type of cancer, genotype frequencies for cases and controls and source of genotyping. An agreement was reached by fully discussion between the two researchers whenever there was a conflict.

Statistical Analysis

The strength of the association between *XRCC1* exon 10 G>A polymorphism and cancer risk was measured by their corresponding 95% CIs and ORs. Heterogeneity assumption between studies was performed by the Chi square based Q-test and considered significant at p value < 0.05 [35]. A fixed effect model (if $p > 0.05$) OR a random effect model (if $p < 0.05$) was used for pooling the results [36, 37]. Moreover, I^2 statistics was also employed to efficiently test the heterogeneity. Hardy–Weinberg equilibrium (HWE) in the controls was measured via Chi square test. Funnel plot asymmetry was estimated by Egger's linear regression test which is a type of linear regression approach to estimate the funnel plot asymmetry

Table 1 Main characteristics of all studies included in the meta-analysis

First authors and year	Cancer	Association	Control	Cases	Source
Ghosh et al. [10]	Gastric	Increased	82	70	Blood
Bajpai et al. [11]	Cervical	Increased	68	65	Blood, Tissue
Saikia et al. 2014 [12]	Lung	No	544	272	Blood
Choudhury et al. [13]	HNSC	Increased	140	110	Blood
Uppal et al. [14]	Lung	Increased	100	100	Blood
Natukula et al. [15]	Lung	Increased	101	100	Blood
Devi et al. [16]	HCC	No	93	93	Blood
Bose et al. [17]	HCC	No	210	55	Blood
Annamaneni et al. [18]	CML	Increased	350	350	Blood
Khan et al. [19]	Colorectal	Protective	146	120	Blood
Nissar et al. [20]	Colorectal	Increased	150	130	Blood
Berhane et al. [21]	Prostate	Increased	150	150	Blood
Kumar et al. [22]	SCCHN	Reduced	278	278	Blood
Mittal et al. [23]	Bladder	Increased	250	212	Blood
Mittal et al. [23]	Prostate	No	250	195	Blood
Wang et al. [24]	Colorectal	No	291	302	Blood
Srivastava et al. [25]	Gallbladder	Reduced	204	173	Blood
Syamala et al. [26]	Breast	Increased	367	359	Blood
Kiran et al. [27]	Hepatocellular carcinoma	Reduced	171	63	Blood
Mitra et al. [28]	Breast	Increased	225	150	Blood
Sreeja et al. [29]	Lung	Increased	211	211	Blood
Sobti et al. [30]	Esophageal	Reduced	160	120	Blood
Pachouri et al. [31]	Lung	Reduced	122	103	Blood
Ramachandran et al. [32]	Oral	Increased	110	110	Blood
Joseph et al. [33]	Leukemia	Increased	117	117	Blood
Chacko et al. [34]	Breast	Increased	123	123	Blood

SCCHN squamous cell cancer of the head and neck, HCC hepatocellular carcinoma

on the natural logarithm scale of the OR. The significance of the intercept was determined by the t-test (p value < 0.05 was considered as representation of statistically significant publication bias level) [38]. The statistical analysis involved in this meta-analysis was performed by Comprehensive Meta-Analysis (CMA)

Version 2 software program (Biostat Inc., USA). All p values were two sided and statistical significance level was considered as p value < 0.05 for this meta-analysis. To ensure the reliability and accuracy of the statistical analysis, independently entered the data into the software program and reached a consensus.

Table 2 Genotypic distribution of XRCC1 exon 10 G>A gene polymorphism included in meta-analysis

Authors and year	Controls				Cancer cases				HWE	
	Genotype			Minor allele MAF	Genotype			Minor allele MAF	p value	
	GG	GA	AA		GG	GA	AA			
Ghosh et al. [10]	48	30	4	0.231	28	33	9	0.364	0.802	
Bajpai et al. [11]	23	33	12	0.419	12	22	31	0.646	0.978	
Saikia et al. [12]	322	188	34	0.235	146	103	23	0.273	0.354	
Choudhury et al. [13]	62	63	15	0.332	36	55	19	0.422	0.865	
Uppal et al. [14]	12	65	23	0.555	18	32	50	0.66	0.001	
Natukula et al. [15]	55	36	10	0.277	40	41	19	0.395	0.266	
Devi et al. [16]	32	51	10	0.381	36	45	12	0.370	0.118	
Bose et al. [17]	46	88	75	0.569	4	29	22	0.663	0.040	
Annamaneni et al. [18]	61	235	54	0.49	79	191	80	0.501	0.001	
Khan et al. [19]	50	62	34	0.445	34	80	6	0.383	0.089	
Nissar et al. [20]	75	30	45	0.4	63	37	30	0.373	0.001	
Berhane et al. [21]	62	64	24	0.373	50	60	40	0.466	0.280	
Kumar et al. [22]	98	144	36	0.388	128	124	26	0.316	0.132	
Mittal et al. [23]	102	109	39	0.374	67	106	39	0.433	0.276	
Mittal et al. [23]	105	102	43	0.376	84	62	49	0.410	0.039	
Wang et al. [24]	139	113	39	0.328	124	138	40	0.360	0.041	
Srivastava et al. [25]	65	99	40	0.438	80	74	19	0.323	0.834	
Syamala et al. [26]	193	126	48	0.302	147	154	58	0.376	0.000	
Kiran et al. [27]	45	70	27	0.436	25	33	5	0.341	0.980	
Mitra et al. [28]	83	107	35	0.393	44	52	54	0.533	0.957	
Sreeja et al. [29]	102	80	29	0.327	78	86	47	0.426	0.044	
Sobti et al. [30]	58	73	29	0.409	50	58	12	0.341	0.474	
Pachouri et al. [31]	35	70	17	0.426	53	38	12	0.300	0.055	
Ramachandran et al. [32]	73	33	4	0.186	46	48	16	0.363	0.910	
Joseph et al. [33]	75	33	9	0.217	55	46	16	0.333	0.061	
Chacko et al. [34]	79	35	9	0.215	56	50	17	0.341	0.079	

MAF Minor allele frequency, HWE Hardy–Weinberg equilibrium

Table 3 Statistics to test publication bias and heterogeneity in meta-analysis

Comparisons	Egger's regression analysis			Heterogeneity analysis			Model used for meta-analysis
	Intercept	95% Confidence interval	p value	Q value	$P_{\text{heterogeneity}}$	I^2 (%)	
A versus G	1.99	−1.55 to 5.53	0.25	124.57	0.01	79.93	Random
AA versus GG	0.66	−2.16 to 3.48	0.63	98.22	0.01	74.54	Random
AG versus GG	0.52	−2.26 to 3.31	0.70	90.47	0.01	72.36	Random
AA+AG versus GG	0.93	−1.99 to 3.87	0.51	100.54	0.01	75.13	Random
AA versus AG+GG	−0.33	−3.22 to 2.56	0.81	99.85	0.01	74.96	Random

Fig. 2 Forest plot of allele model for overall cancer risk associated with *XRCC1* exon 10 G>A polymorphism. The *squares* and *horizontal lines* correspond to the study specific OR and 95% CI

Trial Sequential Analysis (TSA)

According to Cochrane handbook, meta- analyses are considered to be the best if all eligible trials are included in the analysis. However, it may not be sufficient evidence. Sometimes meta-analysis may lead to systematic errors (bias) or random errors (play of chance). To minimize error novel statistical analysis software, TSA (Trial sequential analysis tool from Copenhagen Trial Unit, Center for Clinical Intervention Research, Denmark) has been introduced which estimate required information size and an adjusted threshold for statistical significance and estimate power of current conclusion [39–41]. If a TSA monitoring boundary is crossed with Z curve before the required information size is reached, robust evidence might have been confirmed and further trails are unnecessary. In contrast, if the Z curve does not cross monitoring boundaries and the required information size has not been reached, it is necessary to continue doing trials. In the present investigation, we used Trial Sequential Analysis (version 0.9, <http://www.ctu.dk/tsa/>).

Results

Literature Search and Meta-Analysis Databases

We identified a total of fifty-two studies by scrupulous literature search from the PubMed (Medline) and Google scholar. As per the pre-set selection (inclusion–exclusion) criteria, a total of twenty-five research articles were finally included (Fig. 1). Studies showing *XRCC1* polymorphism to predict survival OR as an indicator for response to therapy of patients were excluded straight-away. Similarly, research articles investigating the levels of *XRCC1* mRNA or protein expression and relevant review articles were also excluded. We included only case–control or cohort design studies having frequency of all three genotypes. Eligible included studies, cancer types, publication year, distribution of genotypes and minor allele frequency (MAF) in the controls and cases have been shown in Tables 1 and 2.

Fig. 3 Forest plot of homozygous model for overall cancer risk associated with *XRCC1* exon 10 G>A polymorphism. The squares and horizontal lines correspond to the study specific OR and 95% CI

Publication Bias

The Begg's funnel plot and Egger's test were performed to examine the publication bias among the included studies for this meta-analysis. The shape of funnel plot did not elucidate any asymmetry in all comparison models. Egger's test, a linear regression approach for measuring funnel plot on the natural logarithm scale of the OR, also showed no evidence of publication bias (Table 3).

Evaluation of Heterogeneity

In order to test heterogeneity among the selected studies, Q-test and I^2 statistics were employed. Heterogeneity was observed in all genetic models, i.e. allele (A vs. G), homozygous (AA vs. GG), heterozygous (AG vs. GG), dominant (AA+AG vs. GG) and recessive (AA vs. AG+GG). Thus, random effect model was applied to synthesize the data for above models (Table 3).

Overall Association of *XRCC1* Exon 10 G>A Polymorphism and Cancer

We pooled all twenty-five studies together and it resulted into 4131 confirmed cancer cases and 5013 healthy controls to examining the overall association between *XRCC1* exon 10 G>A gene polymorphism and cancer risk. The pooled OR from all eligible studies indicated significant risk of cancer susceptibility with variant allele (A vs. G: OR 1.217, 95% CI 1.056–1.402, $p = 0.007$), homozygous (AA vs. GG: OR 1.359, 95% CI 1.036–1.783, $p = 0.027$), dominant (AA+AG vs. GG OR 1.208, 95% CI 1.006–1.450, $p = 0.043$) and recessive (AA vs. AG+GG: OR 1.315, 95% CI 1.029–1.680, $p = 0.029$) genetic models compared with wild type GG genotype. Whereas, no significant association was found in heterozygous (AG vs. GG: OR 1.135, 95% CI 0.942–1.368, $p = 0.183$) model (Figs. 2, 3, 4, 5 and 6).

Sensitivity Analysis

We have performed sensitivity analysis by sequentially omitting individual study to evaluate the stability of the

Fig. 4 Forest plot of heterozygous model for overall cancer risk associated with *XRCC1* exon 10 G>A polymorphism. The squares and horizontal lines correspond to the study specific OR and 95% CI

present meta-analysis. The results of sensitivity analysis indicated that pooled OR before and after exclusion of the study which probably contribute the heterogeneity were generally similar. Hence, the results of this meta-analysis were stable and convincing (Figures not shown).

Trial Sequence Analysis (TSA) of *XRCC1* Exon 10 G>A Polymorphism and Cancer

The results of TSA were consistent with present meta-analysis. TSA analysis used allele genetic model (A vs. G) revealed that cumulative Z curve crossed with TSA monitoring boundary before reaching the required information size, confirmed that this polymorphism is associated with increased risk and further relevant trials are unnecessary (Fig. 7).

Discussion

DNA repair mechanisms play an important role in protection against damage and mutation. Genetic polymorphism in DNA repair genes may be the underlying molecular mechanism of the individual variation in DNA repair capacity. Several studies have supported an important role for genetics in determining the risk for cancer, and

association studies are apposite for searching susceptibility genes involved in cancer [42]. Hence, it is more reasonable to identify the key gene polymorphisms that are associated with cancer risk is essential for predicting individual at risk.

The *XRCC1* protein has shown the importance of early development in mouse models, presumably for repair of endogenous DNA [43]. *XRCC1* interacts with poly (ADP-ribose) polymerase, a nuclear zinc-finger DNA-binding protein that detects single strand breaks and polynucleotide kinase and thereby accelerates the overall repair process. This novel pathway for mammalian single-strand break repair reveals a concerted role for *XRCC1* gene in the initial step of processing damaged DNA ends [44].

In the present meta-analysis, our main focus was to estimate the more precise results to understand the contribution of *XRCC1* exon 10 G>A gene polymorphism in overall cancer susceptibility. Meta-analysis is a powerful statistical tool for deriving results from pooled data because it combines the data from individual studies where individual sample sizes are small and lower statistical power and resolve discrepancy in genetic association studies [45]. Currently, it is broadly cited and accepted as the highest level of evidence in epidemiological studies and medical science.

Fig. 5 Forest plot of dominant model for overall cancer risk associated with *XRCC1* exon 10 G>A polymorphism. The squares and horizontal lines correspond to the study specific OR and 95% CI

Fig. 6 Forest plot of recessive model for overall cancer risk associated with *XRCC1* exon 10 G>A polymorphism. The squares and horizontal lines correspond to the study specific OR and 95% CI

Fig. 7 Trial sequence analysis of all studies on *XRCC1* exon 10 G>A gene polymorphism based on allelic genetic model

To our knowledge, this is the first meta-analysis to assess the relationship between *XRCC1* exon 10 G>A gene polymorphism and overall cancer risk among Indian population. The associations for the allele contrast, homozygous, heterozygous, dominant and recessive models were examined. After rigorous statistical analysis, we found that A allele and homozygous AA genotype of *XRCC1* gene was associated with a significant increased risk of cancer susceptibility in all four genetic models. Our meta-analysis serves as a preliminary overview of the involvement of *XRCC1* exon 10 G>A gene polymorphism as a potential etiological factor in carcinogenesis and sheds some light on the pathogenesis of its deadly disease. The codon 399 G>A polymorphism could influence the function of *XRCC1* gene and may influence DNA repair capacity and consequently increase the risk of developing cancer. Experimental evidence suggested that 399Gln allele have higher number of chromosomal breaks, DNA adducts per cell than those with other genotypes, and these type of subjects are more prone to chemically induced genetic damage [46]. Cells lacking the *XRCC1* protein are hypersensitive to damage from ionizing radiation and alkylating agents and that *XRCC1* is

required for the efficient repair of single strand DNA damage [47].

Genetically complex diseases differ from simple Mendelian diseases and cancer etiology is polygenic, a single genetic variant is usually inadequate to predict the risk of this deadly disease. Though, we interpreted our findings with full caution, but, some limitation of our meta-analysis should be addressed. Heterogeneity is an important issue while interpreting the results of meta-analysis, although, it can be minimized by applying random-effects model (45). In the present study we detected inter-study heterogeneity. The source of heterogeneity may arise possibly due to regional lifestyle varied among populations from different parts of India [48], another point could be recruitment of control subjects. Gene environment interaction and adjusted ORs have not been performed due to the limited number of data.

In spite of this, the current study has some advantages. First, this meta-analysis involved large set of individual data from twenty-five independent studies, which provide enough statistical power to authenticate our results. Second, publication bias was not found by funnel plot and

Egger linear regression test, thus the all results are statistically robust. Third, Sensitivity analysis showed that the results were not influenced by any single study. Fourth, TSA also showed that the conclusions are robust. Moreover, we used explicit criteria for present study's inclusion and performed strict data extraction and analysis to make satisfactory and robust conclusion.

Conclusion

In summary, our meta-analysis indicated that the variant allele and genotypes of *XRCC1* exon 10 G>A gene polymorphism was associated with a cancer risk in Indian population. This finding may useful for screening high risk individual for primary preventing and early detection as treatment of cancer for both researchers and clinicians. Further, more intensive and deeper studies will be required to understand the effect of *XRCC1* gene polymorphisms on cancer risk in Indian population.

Compliance with Ethical Standards

Conflict of interest Authors declare that they have no conflict of interest.

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