RESEARCH ARTICLE

Editorial Process: Submission:05/14/2025 Acceptance:11/07/2025 Published:11/22/2025

XRCC1 Arg399Gln Genetic Variant Increases Colorectal Cancer Susceptibility: A Comprehensive Meta-Analysis

Praveen Kumar Kampalli[1], Mohan Krishna Ghanta[2], Rishitha Chowdary Mavillapalli[3], Afroz Alam[1], Sujatha Peela[4], LVKS Bhaskar[5]*

Abstract

Introduction: Colorectal cancer (CRC) continues to be a common health condition and one of the most prevalent and lethal cancers worldwide. CRC is the third most leading cancer by incidence and second most common cause of cancer mortality. Emerging evidence showing that inherited genetic variants in genes coding for DNA repair enzymes have potential role in increasing the risk of CRC. Among these, polymorphisms in the *XRCC1* has been widely investigated, although the results have been varied in different populations. **Methods:** The current meta-analysis is aimed to explain the relation between three *XRCC1* polymorphisms and the CRC risk. Meta-analysis included a combined analysis of 52 case-controls studies including 23 Arg194Trp studies, 8 Arg280His studies, and 42 Arg399Gln studies. **Results:** The results of the present study revealed a statistically significant correlation between the Arg399Gln polymorphism and the increased risk of CRC (OR = 1.10, 95% CI = 1.01–1.20, p = 0.038, random effects model). However, subgroup analysis based on ethnicity revealed no statistical significance between CRC risk and *XRCC1* polymorphisms in Asian and Caucasian populations. In addition, no publication bias was found in the current meta-analysis. **Conclusion:** Overall, the data suggest that *XRCC1* Arg399Gln might be associated with increased CRC susceptibility, while Arg194Trp and Arg280His are not significantly associated.

Keywords: Colorectal Cancer- *XRCC1*- Gene- SNP- Meta-analysis

Asian Pac J Cancer Prev, **26 (11)**, 4127-4137

Introduction

Colorectal cancer (CRC) is known to be a global health burden, both in the terms of incidence and mortality [1, 2]. It is one of the three most frequently diagnosed cancers in the world and the second in cancer-related deaths. According to global estimates in 2020, approximately 1.9 million new cases and 930,000 deaths were reported due to CRC [3, 4]. Incidence rates differ geographically, with higher rates in developed nations and increasing rates in developing countries that are adopting Western lifestyles [5]. Risk factors include obesity, sedentary lifestyle, red meat consumption, alcohol, and tobacco use. Recent data indicate that approximately one in ten CRC cases occurs in individuals aged 50 years or younger, which is a concerning trend [6]. Early detection through screening programs has contributed to reduced mortality in developed countries [7]. Several biomarkers, such as Carcinoembryonic antigen, CA 19-9, microsatellite instability, K-RAS mutations, and BRAF mutations, are used to monitor treatment response, recurrence, and prognosis of colorectal cancer [8]. Treatment options include surgery, chemotherapy, radiation therapy, and targeted therapies.

Improvements in the treatment of metastatic CRC have come a long way over the last few decades. Initially 5-flurouracil was used as a chemotherapeutic agent for nearly half a century. Treatment regimens now include additional cytotoxic drugs such as irinotecan, oxaliplatin, and capecitabine, which in turn have opened more targeted treatment options [9, 10]. Combination chemotherapy regimens such as FOLFOX and FOLFIRI have shown improved clinical effectiveness [11]. Moreover, targeted drugs using monoclonal antibodies like bevacizumab, cetuximab, and panitumumab have shown better treatment outcomes [12, 13]. These targeted agents, when combined with chemotherapy, have shown improved survival rates and quality of life for metastatic CRC patients [14]. Platinum-based agents such as oxaliplatin via DNA damage mechanisms, mainly by the formation of intra-

*[1]Department of Bioscience & Biotechnology, Banasthali University, Rajasthan, India. [2]Department of Pharmacology, MVJ Medical College and Research Hospital, Bangalore-562114, Karnataka, India. [3]Department of Mutagenicity & Genetic Toxicology, Adgyl Life Sciences, Eurofins Advinus, Shameerpet - 500078, Telangana, India. [4]Department of Biotechnology, Dr.B.R.Ambedkar University, Srikakulam, India. [5]Department of Zoology, Guru Ghasidas Vishwavidyalaya, Bilaspur, Chhattisgarh-495009, India. *For Correspondence: lvksbhaskar@gmail.com*

and interstrand DNA crosslinks that inhibit replication and transcription [15]. Drug resistance to platinum-based drugs is a significant clinical challenge, frequently associated with enhanced DNA repair activity, mainly via the nucleotide excision repair and base excision repair pathways [16].

Among the DNA repair genes, *XRCC1* (X-ray repair cross-complementing group 1), present on chromosome 19q13.2, encodes for a 633 amino acid protein that works as a scaffold in base excision repair, single-strand breaks repair, and to lesser extend double-strand break repair [17, 18]. Its role is to coordinate and stabilize multi-protein complexes required for efficient assembly of DNA repair complexes. Several single nucleotide polymorphisms (SNPs) in the *XRCC1* gene such as rs1799782 (Arg194Trp), rs25489 (Arg280His) and rs25487 (Arg399Gln), have received a major focus of research due to their potential to influence DNA repair efficiency and their association with increased disease susceptibility. These mutations may change protein structure or function, potentially destabilizing the genome and increasing susceptibility to various cancers, including bladder cancer [19], glioma [20], and lung cancer [21].

In addition, *XRCC1* polymorphisms have also been associated with the risk of schizophrenia [22]. The gene's critical role in DNA repair was initially demonstrated through complementation studies in Chinese hamster ovary cells, where expression of *XRCC1* restored DNA strand break repair and reduced chromosomal abnormalities [23]. Previous studies have explained the correlation between *XRCC1* gene polymorphisms and CRC susceptibility across diverse ethnic groups, yielding mixed results. Further, no relevant correlation of *XRCC1* polymorphisms with CRC has been reported in some studies from Malaysian and Austrian populations [24, 25]. However, other research data reported an increased susceptibility to CRC associated with Arg194Trp and Arg399Gln polymorphisms in Kashmiri and Chinese cohorts [26, 27]. Findings from subsequent studies in other populations are largely inconclusive. These variations could be attributed to difference in sample size, ethnic origin, environmental exposure and study design. Therefore, to investigate the heterogeneity in existing literature regarding *XRCC1* gene polymorphism and CRC risk, we conducted a meta-analysis to determine their possible potential role as genetic risk factors.

Materials and Methods

A comprehensive literature search on research papers pertaining to *XRCC1* gene polymorphisms and CRC susceptibility was conducted using Web of Science, PubMed, and Embase databases. The MeSh terms and keywords used included "colorectal cancer" or "colorectal carcinoma" or "colorectal tumor" or "colorectal neoplasm", "*XRCC1*" or "rs1799782" or "Arg194Trp" or "rs25489" or "Arg280His" or "rs25487" or "Arg399Gln", and terms related to genetic variations such as "polymorphism" or "SNP" or "variant" or "variation" or "mutation" or "genotype". Studies were considered eligible if they met the following inclusion criteria: (1) case-control designs; (2) studies explaining the *XRCC1* polymorphism correlation with CRC risk; and (3) availability of genotype frequency data for both case and control groups. Exclusion criteria included (1) conference abstracts, letters to the editors, or reviews; (2) studies lacking genotype count data and (3) studies in other languages for data uniformity. The entire search strategy and inclusion of papers is followed with the guidelines set forth by the Meta-analysis of Observational Studies in Epidemiology (MOOSE) [28]. The checklist for MOOSE is available in Supplementary File 1. The last search was performed on March 30, 2025.

Two independent reviewers extracted data from all eligible studies, including the principal author, year of publication, country of study, ethnic origin of the population and genotype distribution in both cases and controls. The methodological quality of included studies was assessed using the Newcastle-Ottawa Scale (NOS) [29]. Hardy-Weinberg equilibrium (HWE) was checked for control group in each study to confirm genetic consistency.

The association between CRC risk and the three *XRCC1* polymorphisms, rs1799782 (Arg194Trp), rs25489 (Arg280His) and rs25487 (Arg399Gln) was measured in terms of pooled odds ratio (ORs) with respective 95% confidence intervals (CIs), computed under the dominant genetic model. Between study heterogeneity across studies was assessed by Cochrane's Q test and the I^2 statistics (Higgins and Thompson). Based on the degree of heterogeneity, either a fixed-effect model or random-effects model was used for conducting the pooled analysis. For assessing the robustness of the meta-analysis results, prime end point sensitivity analyses were conducted by excluding each study sequentially ("Leave-one-out" approach). Publication bias was estimated by visual inspection of Begg's funnel plots and tested further using Egger's regression test. All statistical analyses were performed with the help of MetaGenyo web tool [30].

Results

The study selection process for this meta-analysis is illustrated in Figure 1. A total of 52 eligible case controls studies were included based on predefined criteria (Figure 1). For this meta-analysis, 23 papers with 6821 CRC cases and 10394 controls investigated the *XRCC1* Arg194Trp polymorphism [24-27, 31-49], 8 papers with 3750 CRC cases and 4582 controls examined the *XRCC1* Arg280His polymorphism [24, 32-34, 39, 40, 42, 47], and 42 papers with 11327 CRC cases and 16343 controls analysed the *XRCC1* Arg399Gln polymorphism [24, 25, 31-70], met the inclusion criteria (Table 1). The association of CRC with all three *XRCC1* polymorphic variants was evaluated under a dominant model (Table 1).

Pooled analysis of data identified a statistically significant relationship between *XRCC1* Arg399Gln polymorphism and increased risk of CRC (OR = 1.10, 95% CI = 1.01–1.20, p = 0.038, random-effects model) (Figure 2C). However, no significant association was seen between Arg194Trp (OR = 1.12, p = 0.125) and Arg280His (OR = 1.03, p = 0.681) variants and CRC

Table 1. Overall Meta-Analysis and Subgroup Analysis by Ethnicity for *XRCC1* Arg194Trp, Arg280His and Arg399Gln Polymorphisms

Ethnicity	Number of studies	Test of association		Model	Test of heterogeneity		Egger's test p-value
		OR (95% CI)	p-value		I^2%	p-value	
2A: *XRCC1* rs1799782 Arg194Trp; Dominant model (TT+TC vs. CC)							
Overall	23	1.12 (0.97-1.28)	0.125	REM	61	<0.001	0.623
African	2	5.88 (1.19-29.05)	0.029	REM	77	0.04	NA
Asian	9	1.14 (0.97-1.34)	0.109	REM	61	0.008	0.388
Caucasian	9	0.97 (0.80-1.18)	0.772	FEM	0	0.44	0.34
Mixed	3	1.10 (0.92-1.30)	0.291	FEM	10	0.329	0.084
XRCC1 rs25489 Arg280His; Dominant model (AA+AG vs. GG)							
Overall	8	1.03 (0.90-1.17)	0.681	FEM	0	0.499	0.163
Asian	4	1.06 (0.88-1.27)	0.518	FEM	12	0.331	0.519
Caucasian	2	1.23 (0.83-1.83)	0.304	FEM	14	0.28	NA
Mixed	2	0.93 (0.75-1.16)	0.516	FEM	0	0.83	NA
XRCC1 rs25487 Arg399Gln; Dominant model (AA+AG vs. GG)							
Overall	42	1.10 (1.01-1.20)	0.038	REM	61	<0.001	0.311
African	3	1.73 (0.70-4.31)	0.235	REM	66	0.055	0.91
Asian	17	1.10 (0.97-1.25)	0.14	REM	56	<0.001	0.606
Caucasian	15	1.02 (0.88-1.19)	0.803	REM	38	0.068	0.945
Mixed	7	1.17 (0.93-1.46)	0.176	REM	79	<0.001	0.094

CI, confidence interval; OR, odds ratio; NA, not applicable.; FEM, fixed effects model; REM, random effects model

risk (Figure 2B). Subgroup analyses based on ethnic background showed no significant association between any of these three *XRCC1* variants and the risk of CRC among ethnic groups (Table 1).

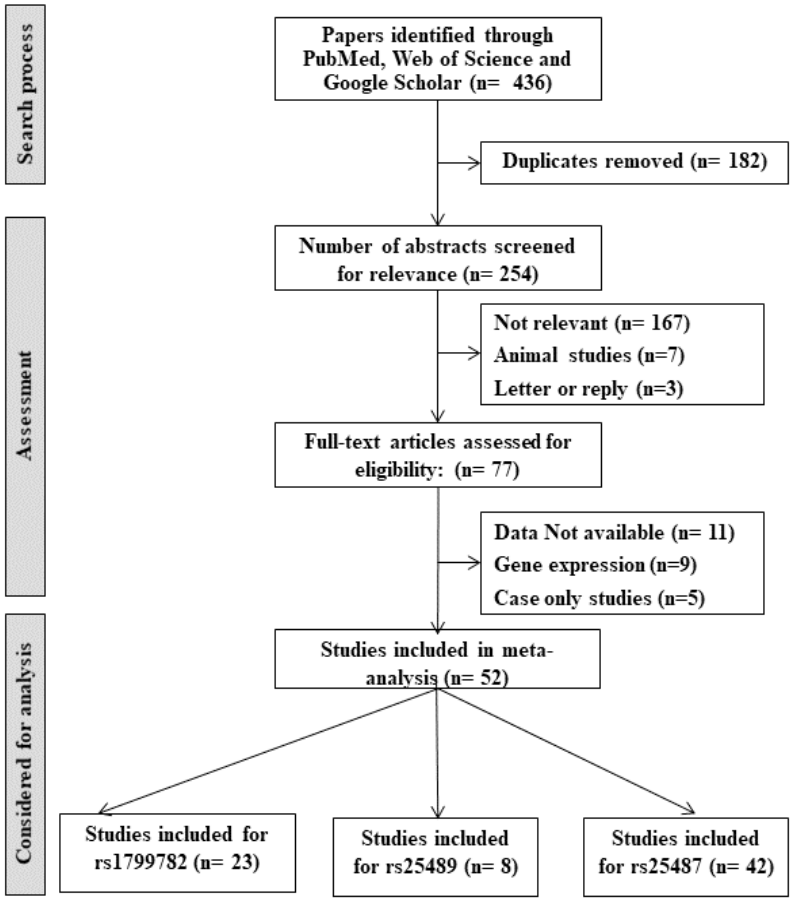

Figure 1. The MOOSE Flow Diagram Showing Study Selection Process

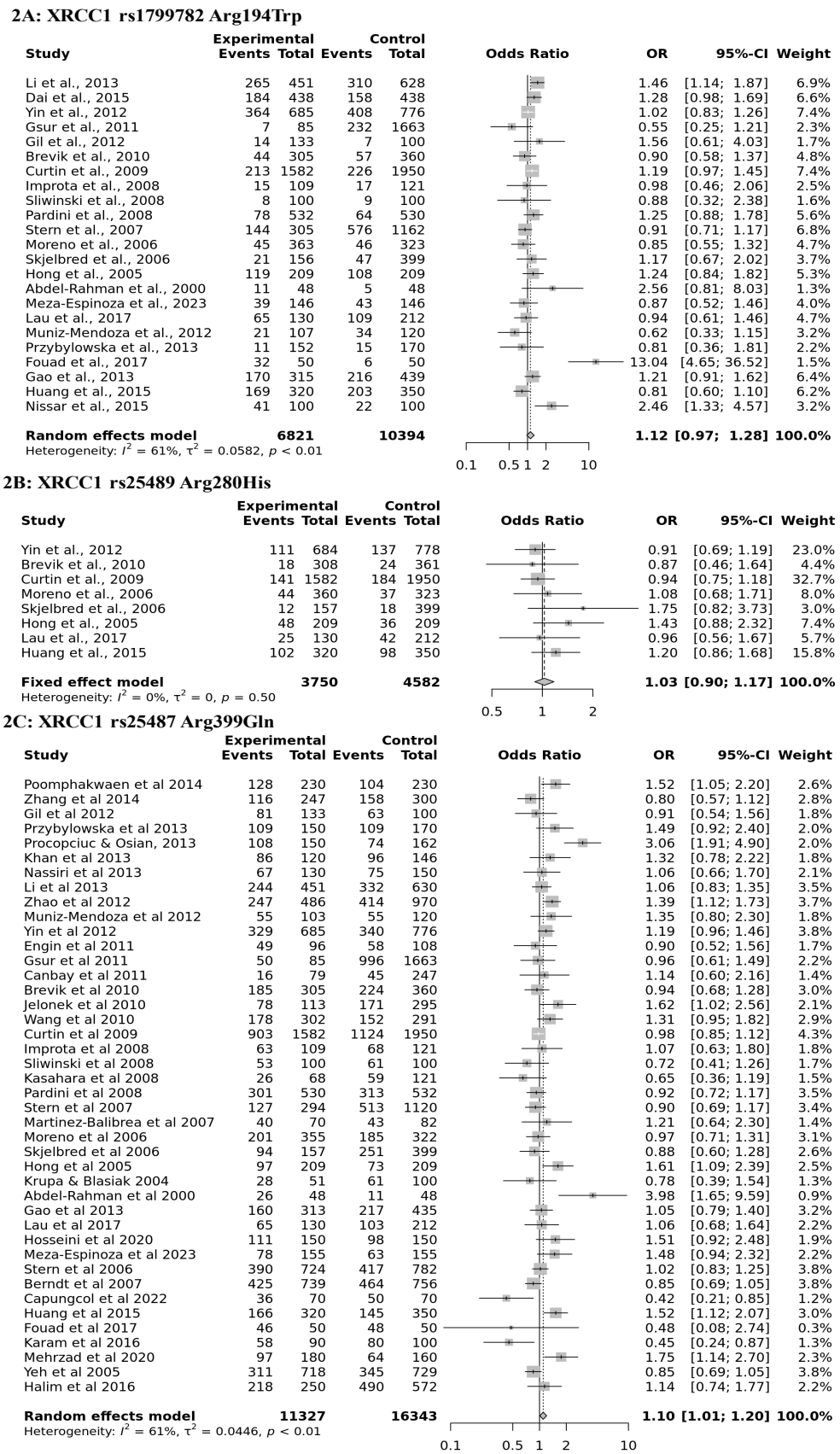

Figure 2. Forest Plot Depicting the Association between CRC and *XRCC1* Gene Polymorphisms. CRC, colorectal cancer; Experimental, colorectal cancer cases; Events, mutant genotypes; OR, odds ratio; CI, confidence interval.

Heterogeneity testing revealed no variability among studies that assessed *XRCC1* Arg280His polymorphism (I^2 = 0%, P = 0.499). Significant moderate heterogeneity was found for the other two polymorphisms, Arg194Trp and Arg399Gln (Arg194Trp: I^2 = 61%, P < 0.001; Arg399Gln: I^2 = 61%, P < 0.001). Sensitivity analysis conducted on

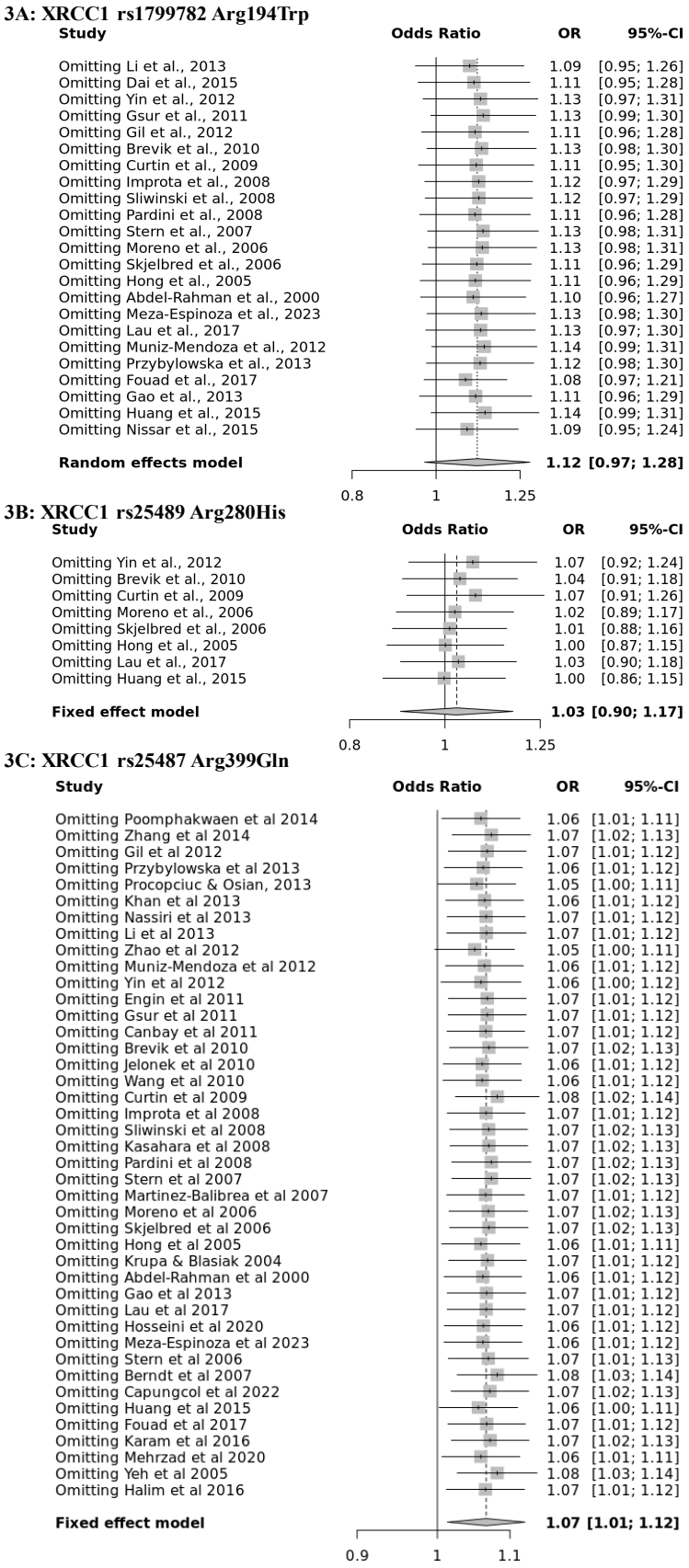

Figure 3. Sensitivity Analysis Evaluating the Robustness of the Association between CRC and *XRCC1* Gene Polymorphisms

pooled data using "leave-one-out" approach, established negligible impact on the pooled ORs for all three *XRCC1* polymorphisms. This indicates that the results of the current meta-analysis are reliable and consistent (Figure 3). Assessment of possible publication bias by Begg's funnel plots and Egger regression tests demonstrated symmetrical

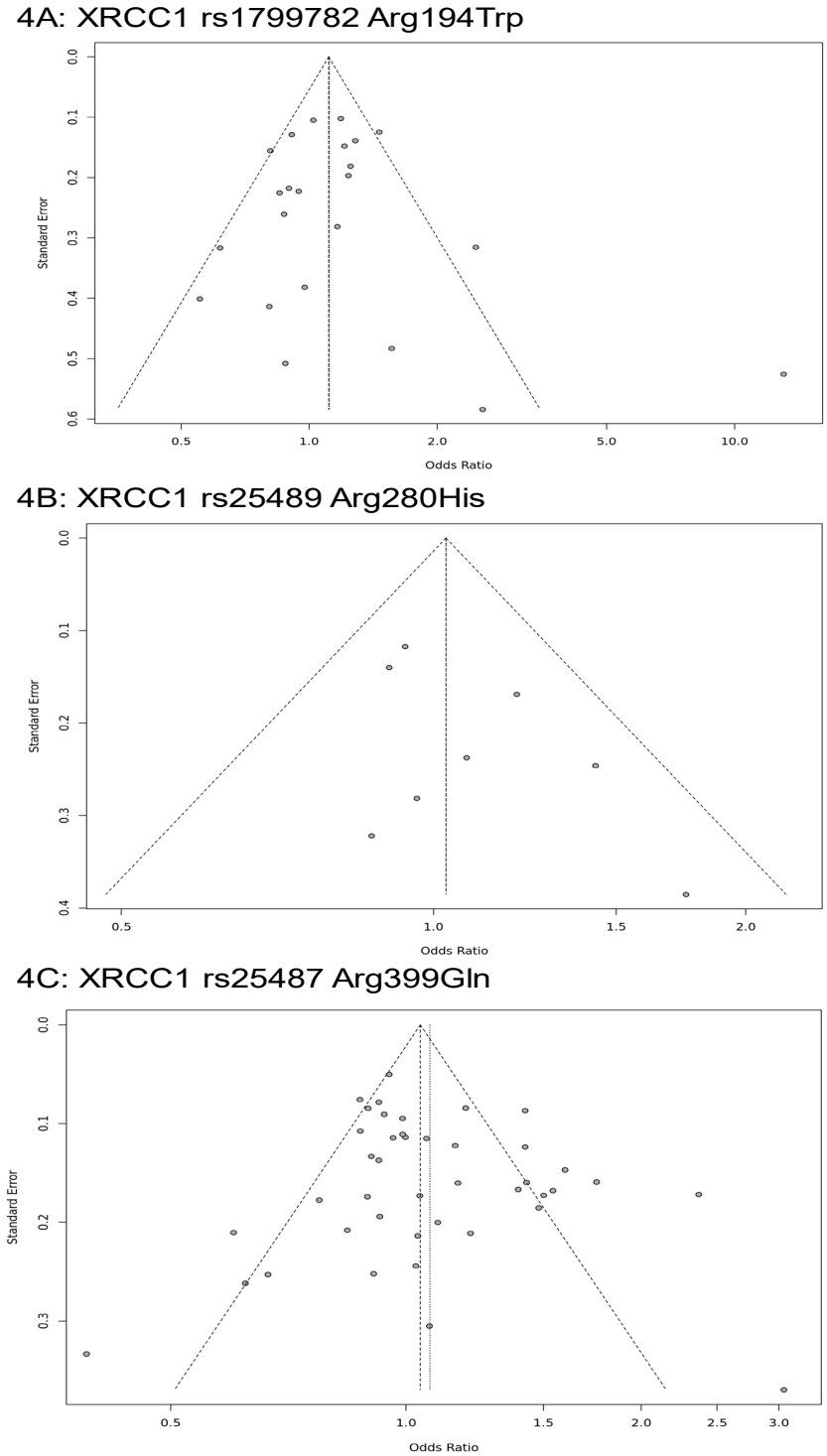

Figure 4. Funnel Plot Analysis for Detecting Publication Bias in the Meta-Analysis of *XRCC1* Gene Polymorphisms Associated with CRC

funnel plots for all three *XRCC1* polymorphisms. The p-values of Egger's test were 0.623 for Arg194Trp, 0.163 for Arg280His, and 0.211 for Arg399Gln, indicating the lack of significant publication bias (Figure 4).

Discussion

The *XRCC1* gene polymorphisms selected in this meta-analysis are non-synonymous (Arg194Trp, Arg280His, and Arg399Gln) which are established to affect DNA repair processes such as base-excision repair (BER) pathway in different ways. All of these polymorphism change protein structure in functionality critical domains of *XRCC1* and may influence it's activity in DNA damage responses. The Arg194Trp and Arg280His mutations are respectively located in N-terminal and BRCT (BRCA1 C Terminus) domains, leading to slight to moderate stability loss. While the Arg399Gln variant is located in the BRCT I domain which is an area essential for protein-protein interaction, and has been linked to a greater loss of *XRCC1* function and severely disturbs DNA repair capacity [71].

Therefore, the Arg194Trp and Arg280His variants are seen to have slight decrease in DNA repair function and slightly increase cancer risk, while the Arg399Gln variant significantly impairs DNA repair function and significantly increases risk of cancer.

Colorectal cancer is a complex disease with polygenic etiology and is influenced by gene-gene and gene-environment interactions [72]. Besides host genetic factors determinants, the development and prognosis of colorectal cancer is influenced by other factors such as chronic inflammation, environmental factors, diet, lifestyle, and gut microbiota. Environmental factors such as smoking, poor diet, chronic inflammation and pollution tend to results in oxidative stress and inflammation, inducing DNA damage and tumorigenesis and colorectal cancer progression [73]. The genes and environmental factor interactions are turning out to be evident for CRC risk. For instance, a case-control study from Thailand demonstrated that individuals having certain *XRCC1* polymorphisms had increased risk of CRC when combined with familial cancer history and high frequency of pork consumption [56]. Further, individuals carrying 399Gln allele who were habitual heavy smokers or drinkers are also found to have higher CRC risk [47]. Gene-gene interactions have also been known to influence the progression of HCC. Aflatoxin B1 (AFB1) exposure to rats under a vitamin A deficient diet has been shown to increase colon cancer incidence by 29% due to increased AFB1-DNA adduct levels [74]. This study demonstrates dietary influence on formation of DNA adducts and repairs proficiency. Furthermore, individuals with the 399Gln allele were more susceptible to developing detectable AFB1-DNA adducts [75].

The current study evaluated the combined data from 52 qualified case-control studies and evaluated the correlation between CRC and *XRCC1* gene polymorphisms. Based on the meta-analysis, a significant correlation were seen between Arg399Gln variant and increased the risk of CRC. From the data it is seen that the other two polymorphisms (Arg194Trp and Arg280His) did not demonstrate a statistically significant correlation with the CRC risk. Subgroup analyses using ethnicity data, did not demonstrate a statistically significant correlation between the three variants (Arg194Trp, Arg280His, and Arg399Gln) and CRC risk. Although the overall results for Arg280His did not demonstrate heterogeneity, the Arg194Trp and Arg399Gin variants had significant heterogeneity. Sensitivity analyses revealed that the meta-analysis is robust, and absence of publication bias was observed for all three SNPs.

Several meta-analyses have examined the association between *XRCC1* gene polymorphsism and CRC risk, but the results have been inconclusive. Two independent meta-analyses reported a protective effect of the 399Q allele in both recessive and homozygous models [76, 77]. However, Bin Wang et al. analyzed 14 studies on three *XRCC1* variants (Arg399Gln, Arg280His, Arg194Trp) and found no significant association with CRC risk in the overall population and Asian and Caucasian subgroups [78]. A statistically significant increase in CRC risk for the Arg399Gln and Arg194Trp variants in Asian and Chinese populations, respectively, was documented in two separate meta-analyses [79, 80]. In contrast to this, *XRCC1* R399Q showed no significant association with CRC in any genetic model in the Chinese Han population [81]. Larger meta-analyses have revealed ethnicity specific associations in Asian and Caucasian populations [82, 83]. On the other hand, a global meta-analysis of 61 variants in 26 DNA repair genes (BER, NER, and DRR pathways), including *XRCC1*, found several low-impact genetic variations on CRC risk, indicating the *XRCC1*'s role in CRC susceptibility. The results of the present meta-analysis are consistent with earlier studies, which reported association between *XRCC1* polymorphisms in CRC risk [82, 83]. The inconsistencies in previous meta-analyses is mainly due to variations in the distribution of allele frequencies between ethnic groups, variability in sample size, and possible gene-environment interactions that were not equally controlled across studies. A study assessing CRC risk using a meta-analysis of 910 variants in 150 candidate genes found no significant association with *XRCC1* gene polymorphisms. Despite its biological importance, *XRCC1* was not included in the list of strong or moderate evidence groups due to a lack of consistent evidence [84].

This study has some limitations that need to be pointed out. First, the control groups of the independent studies might have included some undiagnosed CRC cases, leading to a potential selection bias. Second, we were unable to further assess the effects of other confounders such as age, gender, smoking, and alcohol consumption on CRC etiology. To conclude, the present meta-analysis revealed that *XRCC1* Arg399Gln polymorphism is strongly associated with the susceptibility of CRC. As previous meta-analyses produced inconsistent results for the other two polymorphisms, along with disagreements in the literature, highlight the complexity of genetic factors in cancer risk. Large-scale studies involving environmental, lifestyle, and genetic data along with ethnically diverse cohorts and uniform control selection methods are needed in future studies to understand the role of *XRCC1* variants in CRC etiology and to investigate their potential use as biomarkers for cancer risk stratification.

Author Contribution Statement

Conceptualization: Alam A, Sujatha P. LVKS B., Resources: Alam A, Sujatha P. LVKS B., Supervision: Alam A, Sujatha P. LVKS B., Data Collection: Praveen K. Writing-original draft: Praveen K., Writing-manuscript & editing: Praveen K, Mavillapalli RC and Ghanta MK. Approval of final manuscript: all authors.

Acknowledgements

The authors extend their sincere appreciation to their respective host institutions for continuous support in the completion of this meta-analysis.

Ethical Declaration

This meta-analysis is a review article that does not have any ethical declaration file.

Financial Support

The authors did not receive any financial assistance for the research, writing, and/or publication of this article.

Data Availability Statement

The data used in the manuscript is already provided as part of the submitted article.

Conflict of interest

All authors declare that they have no conflict of interest.

References

1. Xi Y, Xu P. Global colorectal cancer burden in 2020 and projections to 2040. Transl Oncol. 2021;14(10):101174. https://doi.org/10.1016/j.tranon.2021.101174.
2. Morgan E, Arnold M, Gini A, Lorenzoni V, Cabasag CJ, Laversanne M, et al. Global burden of colorectal cancer in 2020 and 2040: Incidence and mortality estimates from globocan. Gut. 2023;72(2):338-44. https://doi.org/10.1136/gutjnl-2022-327736.
3. Cao Q, Tian Y, Deng Z, Yang F, Chen E. Epigenetic alteration in colorectal cancer: Potential diagnostic and prognostic implications. Int J Mol Sci. 2024;25(6). https://doi.org/10.3390/ijms25063358.
4. Baidoun F, Elshiwy K, Elkeraie Y, Merjaneh Z, Khoudari G, Sarmini MT, et al. Colorectal cancer epidemiology: Recent trends and impact on outcomes. Curr Drug Targets. 2021;22(9):998-1009. https://doi.org/10.2174/1389450121999201117115717.
5. Rawla P, Sunkara T, Barsouk A. Epidemiology of colorectal cancer: Incidence, mortality, survival, and risk factors. Prz Gastroenterol. 2019;14(2):89-103. https://doi.org/10.5114/pg.2018.81072.
6. Stoffel EM, Murphy CC. Epidemiology and mechanisms of the increasing incidence of colon and rectal cancers in young adults. Gastroenterology. 2020;158(2):341-53. https://doi.org/10.1053/j.gastro.2019.07.055.
7. Shaukat A, Levin TR. Current and future colorectal cancer screening strategies. Nat Rev Gastroenterol Hepatol. 2022;19(8):521-31. https://doi.org/10.1038/s41575-022-00612-y.
8. Zhang J, Zhu H, Liu W, Miao J, Mao Y, Li Q. Prognostic and predictive molecular biomarkers in colorectal cancer. Front Oncol. 2025;15:1532924. https://doi.org/10.3389/fonc.2025.1532924.
9. Ramalakshmi S, Kavimani S, Srineevas S, Vetriselvi V, Lvks B, Pharmacy K, et al. Molecular markers for capecitabine therapy: A review. Int J Pharm Sci Res. 2016;7(11):4315-26. https://doi.org/10.13040/IJPSR.0975-8232.7(11).4315-26.
10. Ramalakshmi S, Kavimani S, Srineevas S, Vettriselvi V, Bhaskar S. A pharmacogenetic study of capecitabineoxaliplatin therapy in colorectal cancer patients among South Indian population. Eur J Pharm Med Res. 2016;3(9):520-28.
11. Lee JJ, Chu E. An update on treatment advances for the first-line therapy of metastatic colorectal cancer. Cancer J. 2007;13(5):276-81. https://doi.org/10.1097/PPO.0b013e3181570062.
12. Köhne CH, Lenz HJ. Chemotherapy with targeted agents for the treatment of metastatic colorectal cancer. Oncologist. 2009;14(5):478-88. https://doi.org/10.1634/theoncologist.2008-0202.
13. Cats A. New developments in systemic chemotherapy in advanced colorectal cancer. Scand J Gastroenterol Suppl. 2003(239):78-86. https://doi.org/10.1080/00855920310002744.
14. Gustavsson B, Carlsson G, Machover D, Petrelli N, Roth A, Schmoll HJ, et al. A review of the evolution of systemic chemotherapy in the management of colorectal cancer. Clin Colorectal Cancer. 2015;14(1):1-10. https://doi.org/10.1016/j.clcc.2014.11.002.
15. Seetharam R, Sood A, Goel S. Oxaliplatin: Pre-clinical perspectives on the mechanisms of action, response and resistance. Ecancermedicalscience. 2009;3:153. https://doi.org/10.3332/ecancer.2009.153.
16. Altaha R, Liang X, Yu JJ, Reed E. Excision repair cross complementing-group 1: Gene expression and platinum resistance. Int J Mol Med. 2004;14(6):959-70.
17. Lévy N, Martz A, Bresson A, Spenlehauer C, de Murcia G, Ménissier-de Murcia J. Xrcc1 is phosphorylated by DNA-dependent protein kinase in response to DNA damage. Nucleic Acids Res. 2006;34(1):32-41. https://doi.org/10.1093/nar/gkj409.
18. Audebert M, Salles B, Calsou P. Involvement of poly(adp-ribose) polymerase-1 and xrcc1/DNA ligase iii in an alternative route for DNA double-strand breaks rejoining. J Biol Chem. 2004;279(53):55117-26. https://doi.org/10.1074/jbc.M404524200.
19. Stern MC, Umbach DM, van Gils CH, Lunn RM, Taylor JA. DNA repair gene xrcc1 polymorphisms, smoking, and bladder cancer risk. Cancer Epidemiol Biomarkers Prev. 2001;10(2):125-31.
20. Hu XB, Feng Z, Fan YC, Xiong ZY, Huang QW. Polymorphisms in DNA repair gene xrcc1 and increased genetic susceptibility to glioma. Asian Pac J Cancer Prev. 2011;12(11):2981-4.
21. Park JY, Lee SY, Jeon HS, Bae NC, Chae SC, Joo S, et al. Polymorphism of the DNA repair gene xrcc1 and risk of primary lung cancer. Cancer Epidemiol Biomarkers Prev. 2002;11(1):23-7.
22. Saadat M, Pakyari N, Farrashbandi H. Genetic polymorphism in the DNA repair gene xrcc1 and susceptibility to schizophrenia. Psychiatry Res. 2008;157:241-5. https://doi.org/10.1016/j.psychres.2007.07.014.
23. Thompson LH, Brookman KW, Jones NJ, Allen SA, Carrano AV. Molecular cloning of the human xrcc1 gene, which corrects defective DNA strand break repair and sister chromatid exchange. Mol Cell Biol. 1990;10(12):6160-71. https://doi.org/10.1128/mcb.10.12.6160-6171.1990.
24. Lau TP, Lian LH, Cheah PL, Looi LM, Roslani AC, Goh KL, et al. Lack of correlation between x-ray repair cross-complementing group 1 gene polymorphisms and the susceptibility to colorectal cancer in a malaysian cohort. Eur J Cancer Prev. 2017;26(6):506-10. https://doi.org/10.1097/cej.0000000000000336.
25. Gsur A, Bernhart K, Baierl A, Feik E, Weber G, Hofer P, et al. No association of xrcc1 polymorphisms arg194trp and arg399gln with colorectal cancer risk. Cancer epidemiology. 2011;35:e38-41. https://doi.org/10.1016/j.canep.2011.03.005.
26. Nissar S, Sameer AS, Rasool R, Chowdri NA, Rashid F. Polymorphism of the DNA repair gene xrcc1 (arg194trp) and its role in colorectal cancer in kashmiri population: A case control study. Asian Pac J Cancer Prev. 2015;16(15):6385-90. https://doi.org/10.7314/apjcp.2015.16.15.6385.
27. Dai Q, Luo H, Li XP, Huang J, Zhou TJ, Yang ZH. Xrcc1 and ercc1 polymorphisms are related to susceptibility and survival of colorectal cancer in the chinese population. Mutagenesis. 2015;30(3):441-9. https://doi.org/10.1093/mutage/geu088.

28. Stroup DF, Berlin JA, Morton SC, Olkin I, Williamson GD, Rennie D, et al. Meta-analysis of observational studies in epidemiology: A proposal for reporting. Meta-analysis of observational studies in epidemiology (moose) group. Jama. 2000;283(15):2008-12. https://doi.org/10.1001/jama.283.15.2008.
29. Stang A. Critical evaluation of the newcastle-ottawa scale for the assessment of the quality of nonrandomized studies in meta-analyses. Eur J Epidemiol. 2010;25(9):603-5. https://doi.org/10.1007/s10654-010-9491-z.
30. Martorell-Marugan J, Toro-Dominguez D, Alarcon-Riquelme ME, Carmona-Saez P. Metagenyo: A web tool for meta-analysis of genetic association studies. BMC Bioinformatics. 2017;18(1):563. https://doi.org/10.1186/s12859-017-1990-4.
31. Abdel-Rahman SZ, Soliman AS, Bondy ML, Omar S, El-Badawy SA, Khaled HM, et al. Inheritance of the 194trp and the 399gln variant alleles of the DNA repair gene xrcc1 are associated with increased risk of early-onset colorectal carcinoma in egypt. Cancer Lett. 2000;159(1):79-86. https://doi.org/10.1016/s0304-3835(00)00537-1.
32. Hong YC, Lee KH, Kim WC, Choi SK, Woo ZH, Shin SK, et al. Polymorphisms of xrcc1 gene, alcohol consumption and colorectal cancer. Int J Cancer. 2005;116(3):428-32. https://doi.org/10.1002/ijc.21019.
33. Moreno V, Gemignani F, Landi S, Gioia-Patricola L, Chabrier A, Blanco I, et al. Polymorphisms in genes of nucleotide and base excision repair: Risk and prognosis of colorectal cancer. Clin Cancer Res. 2006;12(7 Pt 1):2101-8. https://doi.org/10.1158/1078-0432.Ccr-05-1363.
34. Skjelbred CF, Saebø M, Wallin H, Nexø BA, Hagen PC, Lothe IM, et al. Polymorphisms of the xrcc1, xrcc3 and xpd genes and risk of colorectal adenoma and carcinoma, in a norwegian cohort: A case control study. BMC Cancer. 2006;6:67. https://doi.org/10.1186/1471-2407-6-67.
35. Stern MC, Conti DV, Siegmund KD, Corral R, Yuan JM, Koh WP, et al. DNA repair single-nucleotide polymorphisms in colorectal cancer and their role as modifiers of the effect of cigarette smoking and alcohol in the singapore chinese health study. Cancer Epidemiol Biomarkers Prev. 2007;16(11):2363-72. https://doi.org/10.1158/1055-9965.Epi-07-0268.
36. Improta G, Sgambato A, Bianchino G, Zupa A, Grieco V, La Torre G, et al. Polymorphisms of the DNA repair genes xrcc1 and xrcc3 and risk of lung and colorectal cancer: A case-control study in a southern italian population. Anticancer Res. 2008;28(5b):2941-6.
37. Sliwinski T, Krupa R, Wisniewska-Jarosinska M, Lech J, Morawiec Z, Chojnacki J, et al. No association between the arg194trp and arg399gln polymorphisms of the xrcc1 gene and colorectal cancer risk and progression in a polish population. Exp Oncol. 2008;30(3):253-4.
38. Pardini B, Naccarati A, Novotny J, Smerhovsky Z, Vodickova L, Polakova V, et al. DNA repair genetic polymorphisms and risk of colorectal cancer in the czech republic. Mutat Res. 2008;638(1-2):146-53. https://doi.org/10.1016/j.mrfmmm.2007.09.008.
39. Curtin K, Samowitz WS, Wolff RK, Ulrich CM, Caan BJ, Potter JD, et al. Assessing tumor mutations to gain insight into base excision repair sequence polymorphisms and smoking in colon cancer. Cancer Epidemiol Biomarkers Prev. 2009;18(12):3384-8. https://doi.org/10.1158/1055-9965.Epi-09-0955.
40. Brevik A, Joshi AD, Corral R, Onland-Moret NC, Siegmund KD, Le Marchand L, et al. Polymorphisms in base excision repair genes as colorectal cancer risk factors and modifiers of the effect of diets high in red meat. Cancer Epidemiol Biomarkers Prev. 2010;19(12):3167-73. https://doi.org/10.1158/1055-9965.Epi-10-0606.
41. Muñiz-Mendoza R, Ayala-Madrigal ML, Partida-Pérez M, Peregrina-Sandoval J, Leal-Ugarte E, Macías-Gómez N, et al. Mlh1 and xrcc1 polymorphisms in mexican patients with colorectal cancer. Genet Mol Res. 2012;11(3):2315-20. https://doi.org/10.4238/2012.June.27.6.
42. Yin G, Morita M, Ohnaka K, Toyomura K, Hamajima N, Mizoue T, et al. Genetic polymorphisms of xrcc1, alcohol consumption, and the risk of colorectal cancer in japan. J Epidemiol. 2012;22(1):64-71. https://doi.org/10.2188/jea.je20110059.
43. Gil J, Ramsey D, Stembalska A, Karpinski P, Pesz KA, Laczmanska I, et al. The c/a polymorphism in intron 11 of the xpc gene plays a crucial role in the modulation of an individual's susceptibility to sporadic colorectal cancer. Mol Biol Rep. 2012;39(1):527-34. https://doi.org/10.1007/s11033-011-0767-5.
44. Li Y, Li S, Wu Z, Hu F, Zhu L, Zhao X, et al. Polymorphisms in genes of ape1, parp1, and xrcc1: Risk and prognosis of colorectal cancer in a northeast chinese population. Med Oncol. 2013;30(2):505. https://doi.org/10.1007/s12032-013-0505-z.
45. Przybylowska K, Kabzinski J, Sygut A, Dziki L, Dziki A, Majsterek I. An association selected polymorphisms of xrcc1, ogg1 and mutyh gene and the level of efficiency oxidative DNA damage repair with a risk of colorectal cancer. Mutat Res. 2013;745-746:6-15. https://doi.org/10.1016/j.mrfmmm.2013.04.002.
46. Gao CM, Ding JH, Li SP, Liu YT, Cao HX, Wu JZ, et al. Polymorphisms in xrcc1 gene, alcohol drinking, and risk of colorectal cancer: A case-control study in jiangsu province of china. Asian Pac J Cancer Prev. 2014;14(11):6613-8. https://doi.org/10.7314/apjcp.2013.14.11.6613.
47. Huang Y, Li X, He J, Chen L, Huang H, Liang M, et al. Genetic polymorphisms in xrcc1 genes and colorectal cancer susceptibility. World J Surg Oncol. 2015;13:244. https://doi.org/10.1186/s12957-015-0650-2.
48. Fouad H, Sabry D, Morsi H, Shehab H, Abuzaid NF. Xrcc1 gene polymorphisms and mir-21 expression in patients with colorectal carcinoma. Eurasian J Med. 2017;49(2):132-6. https://doi.org/10.5152/eurasianjmed.2017.17021.
49. Meza-Espinoza JP, Peralta-Leal V, Durán-González J, Macías-Gómez N, Bocanegra-Alonso A, Leal-Ugarte E. Xrcc1 r194w and r399q polymorphisms and colorectal cancer risk in a northeastern mexican population. Genet Res (Camb). 2023;2023:5565646. https://doi.org/10.1155/2023/5565646.
50. Poomphakwaen K, Promthet S, Suwanrungruang K, Chopjitt P, Songserm N, Wiangnon S. Xrcc1 gene polymorphism, diet and risk of colorectal cancer in thailand. Asian Pac J Cancer Prev. 2014;15(17):7479-86. https://doi.org/10.7314/apjcp.2014.15.17.7479.
51. Zhang SH, Wang LA, Li Z, Peng Y, Cun YP, Dai N, et al. Ape1 polymorphisms are associated with colorectal cancer susceptibility in chinese hans. World J Gastroenterol. 2014;20(26):8700-8. https://doi.org/10.3748/wjg.v20.i26.8700.
52. Procopciuc LM, Osian G. Lys751gln xpd and arg399gln xrcc1 in romanians. Association with sporadic colorectal cancer risk and different stages of carcinomas. Chirurgia (Bucur). 2013;108(5):711-8.
53. Khan NP, Pandith AA, Yousuf A, Khan NS, Khan MS, Bhat IA, et al. The xrcc1 arg399gln gene polymorphism and risk of colorectal cancer: A study in kashmir. Asian Pac J Cancer Prev. 2013;14(11):6779-82. https://doi.org/10.7314/apjcp.2013.14.11.6779.
54. Nassiri M, Kooshyar MM, Roudbar Z, Mahdavi M,

Doosti M. Genes and snps associated with non-hereditary and hereditary colorectal cancer. Asian Pac J Cancer Prev. 2013;14(10):5609-14. https://doi.org/10.7314/apjcp.2013.14.10.5609.
55. Zhao Y, Deng X, Wang Z, Wang Q, Liu Y. Genetic polymorphisms of DNA repair genes xrcc1 and xrcc3 and risk of colorectal cancer in chinese population. Asian Pac J Cancer Prev. 2012;13(2):665-9. https://doi.org/10.7314/apjcp.2012.13.2.665.
56. Engin AB, Karahalil B, Karakaya AE, Engin A. Association between xrcc1 arg399gln and p53 arg72pro polymorphisms and the risk of gastric and colorectal cancer in turkish population. Arh Hig Rada Toksikol. 2011;62(3):207-14. https://doi.org/10.2478/10004-1254-62-2011-2098.
57. Canbay E, Cakmakoglu B, Zeybek U, Sozen S, Cacina C, Gulluoglu M, et al. Association of ape1 and hogg1 polymorphisms with colorectal cancer risk in a turkish population. Curr Med Res Opin. 2011;27(7):1295-302. https://doi.org/10.1185/03007995.2011.573544.
58. Jelonek K, Gdowicz-Klosok A, Pietrowska M, Borkowska M, Korfanty J, Rzeszowska-Wolny J, et al. Association between single-nucleotide polymorphisms of selected genes involved in the response to DNA damage and risk of colon, head and neck, and breast cancers in a polish population. J Appl Genet. 2010;51(3):343-52. https://doi.org/10.1007/bf03208865.
59. Wang J, Zhao Y, Jiang J, Gajalakshmi V, Kuriki K, Nakamura S, et al. Polymorphisms in DNA repair genes xrcc1, xrcc3 and xpd, and colorectal cancer risk: A case-control study in an indian population. J Cancer Res Clin Oncol. 2010;136(10):1517-25. https://doi.org/10.1007/s00432-010-0809-8.
60. Kasahara M, Osawa K, Yoshida K, Miyaishi A, Osawa Y, Inoue N, et al. Association of mutyh gln324his and apex1 asp148glu with colorectal cancer and smoking in a japanese population. J Exp Clin Cancer Res. 2008;27(1):49. https://doi.org/10.1186/1756-9966-27-49.
61. Martinez-Balibrea E, Manzano JL, Martinez-Cardus A, Moran T, Cirauqui B, Catot S, et al. Combined analysis of genetic polymorphisms in thymidylate synthase, uridine diphosphate glucoronosyltransferase and x-ray cross complementing factor 1 genes as a prognostic factor in advanced colorectal cancer patients treated with 5-fluorouracil plus oxaliplatin or irinotecan. Oncol Rep. 2007;17(3):637-45.
62. Krupa R, Blasiak J. An association of polymorphism of DNA repair genes xrcc1 and xrcc3 with colorectal cancer. J Exp Clin Cancer Res. 2004;23(2):285-94.
63. Hosseini SM, Mohammadiasl J, Talaiezadeh A, Alidadi R, Bijanzadeh M. Influence of two DNA repair pathway polymorphisms in colorectal cancer risk in southwest iran. Asian Pac J Cancer Prev. 2020;21(7):1919-24. https://doi.org/10.31557/apjcp.2020.21.7.1919.
64. Stern MC, Siegmund KD, Conti DV, Corral R, Haile RW. Xrcc1, xrcc3, and xpd polymorphisms as modifiers of the effect of smoking and alcohol on colorectal adenoma risk. Cancer Epidemiol Biomarkers Prev. 2006;15(12):2384-90. https://doi.org/10.1158/1055-9965.Epi-06-0381.
65. Berndt SI, Huang WY, Fallin MD, Helzlsouer KJ, Platz EA, Weissfeld JL, et al. Genetic variation in base excision repair genes and the prevalence of advanced colorectal adenoma. Cancer Res. 2007;67(3):1395-404. https://doi.org/10.1158/0008-5472.Can-06-1390.
66. Capungcol M, Bathan G, Fellizar A, Bangaoil R, Sy Ortin T, Ramos MC, et al. Association of xrcc1 arg399gln and rad51 135 g>c polymorphisms and epidemiologic risk factors with colorectal cancer among selected filipinos. Acta medica Philippina. 2021;56. https://doi.org/10.47895/amp.vi0.2788.
67. Karam RA, Al Jiffry BO, Al Saeed M, Abd El Rahman TM, Hatem M, Amer MG. DNA repair genes polymorphisms and risk of colorectal cancer in saudi patients. Arab J Gastroenterol. 2016;17(3):117-20. https://doi.org/10.1016/j.ajg.2016.08.005.
68. Mehrzad J, Dayyani M, Erfanian-Khorasani M. The independent and combined effects of selected risk factors and arg399gln xrcc1 polymorphism in the risk of colorectal cancer among an iranian population. Med J Islam Repub Iran. 2020;34:75. https://doi.org/10.34171/mjiri.34.75.
69. Yeh CC, Sung FC, Tang R, Chang-Chieh CR, Hsieh LL. Polymorphisms of the xrcc1, xrcc3, & xpd genes, and colorectal cancer risk: A case-control study in taiwan. BMC Cancer. 2005;5:12. https://doi.org/10.1186/1471-2407-5-12.
70. Halim NH, Chong ET, Goh LP, Chuah JA, See EU, Chua KH, et al. Variant alleles in xrcc1 arg194trp and arg399gln polymorphisms increase risk of gastrointestinal cancer in sabah, north borneo. Asian Pac J Cancer Prev. 2016;17(4):1925-31. https://doi.org/10.7314/apjcp.2016.17.4.1925.
71. London RE. The structural basis of xrcc1-mediated DNA repair. DNA Repair (Amst). 2015;30:90-103. https://doi.org/10.1016/j.dnarep.2015.02.005.
72. Rashid G, Bhat G, Rather T, Akhtar K, Parveiz I, Maqbool I, et al. Gene-environment interactions and colorectal cancer risk: A case-control study on xenobiotic metabolizing enzyme polymorphisms in the jammu& kashmir, india population. Adv Biomarker Sci Technol. 2024;6. https://doi.org/10.1016/j.abst.2024.10.001.
73. Caliri AW, Tommasi S, Besaratinia A. Relationships among smoking, oxidative stress, inflammation, macromolecular damage, and cancer. Mutat Res Rev Mutat Res. 2021;787:108365. https://doi.org/10.1016/j.mrrev.2021.108365.
74. Suphakarn VS, Newberne PM, Goldman M. Vitamin a and aflatoxin: Effect on liver and colon cancer. Nutr Cancer. 1983;5(1):41-50. https://doi.org/10.1080/01635588309513777.
75. Lunn RM, Langlois RG, Hsieh LL, Thompson CL, Bell DA. Xrcc1 polymorphisms: Effects on aflatoxin b1-DNA adducts and glycophorin a variant frequency. Cancer Res. 1999;59(11):2557-61.
76. Jiang Z, Li C, Xu Y, Cai S. A meta-analysis on xrcc1 and xrcc3 polymorphisms and colorectal cancer risk. Int J Colorectal Dis. 2010;25(2):169-80. https://doi.org/10.1007/s00384-009-0817-9.
77. Wu W, Wu Y, Wang M, Zhang D. Meta-analysis of the association between the xrcc1 gene r399q polymorphism and colorectal cancer: An update. Int J Colorectal Dis. 2013;28(10):1453-4. https://doi.org/10.1007/s00384-012-1627-z.
78. Wang B, Wang D, Huang G, Zhang C, Xu DH, Zhou W. Xrcc1 polymorphisms and risk of colorectal cancer: A meta-analysis. Int J Colorectal Dis. 2010;25(3):313-21. https://doi.org/10.1007/s00384-009-0866-0.
79. Tian Z, Li YL, Liu JG. Xrcc1 arg399gln polymorphism contributes to increased risk of colorectal cancer in chinese population. Mol Biol Rep. 2013;40(7):4147-51. https://doi.org/10.1007/s11033-012-2463-5.
80. Wang L, Qian J, Ying C, Zhuang Y, Shang X, Xu F. X-ray cross-complementing groups 1 rs1799782 c>t polymorphisms and colorectal cancer susceptibility: A meta-analysis based on chinese han population. J Cancer Res Ther. 2016;12(Supplement):C264-c7. https://doi.org/10.4103/0973-1482.200753.
81. Qin CJ, Xu KW, Chen ZH, Zhai ET, He YL, Song XM.

Xrcc1 r399q polymorphism and colorectal cancer risk in the chinese han population: A meta-analysis. Tumour Biol. 2015;36(2):461-6. https://doi.org/10.1007/s13277-015-3054-6.
82. Forat-Yazdi M, Gholi-Nataj M, Neamatzadeh H, Nourbakhsh P, Shaker-Ardakani H. Association of xrcc1 arg399gln polymorphism with colorectal cancer risk: A huge meta analysis of 35 studies. Asian Pac J Cancer Prev. 2015;16(8):3285-91. https://doi.org/10.7314/apjcp.2015.16.8.3285.
83. Zeng FR, Ling Y, Yang J, Tian XC, Yang X, Luo RC. X-ray repair cross-complementing group 1 arg399gln gene polymorphism and susceptibility to colorectal cancer:A meta-analysis. Tumour Biol. 2013;34(1):555-63. https://doi.org/10.1007/s13277-012-0581-2.
84. Ma X, Zhang B, Zheng W. Genetic variants associated with colorectal cancer risk: Comprehensive research synopsis, meta-analysis, and epidemiological evidence. Gut. 2014;63(2):326-36. https://doi.org/10.1136/gutjnl-2012-304121.