DOI: 10.4149/BLL_2019_057

Bratisl Med J 2019; 120 (5)

349 – 355

REVIEW

The polymorphism of XRCC1 Arg399Gln (rs25487) and male infertility risk: a meta-analysis of 1,407 cases and 974 control studies

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ABSTRACT

X-ray repair cross-complementing group 1 (XRCC1) is a scaffold protein and a key element in DNA base excision repair process**.** Although, the role of XRCC1 polymorphisms in male infertility has been studied broadly, it is still a matter of debate. Hence, in order to shed light on the problem, we performed a meta-analysis to evaluate the overall effect of XRCC1 polymorphisms in male infertility risk.

Databases, Web of Science, PubMed, Scopus, and Google Scholar were searched until September 15, 2018. Afterwards, the genotypes' distribution, genotyping methods, and ethnicity groups were extracted, and overall analyses were conducted.

A total number of five researches on 1,407 subjects and 974 controls were found to meet our criteria in this meta-analysis. The XRCC1 Arg399Gln (rs25487) polymorphism was analyzed. This is the first meta-analysis to investigate the association of XRCC1 polymorphisms (codon 399) and male infertility risk. Our results indicated that the XRCC1 Arg399Gln polymorphism was not associated with male infertility risk in the total studied populations *(Tab. 2, Fig. 3, Ref. 26)*. Text in PDF *www.elis.sk.*

KEY WORDS: meta-analysis; male infertility; polymorphism; XRCC1 Arg399Gln.

Introduction

Infertility is defined as an inability to achieve clinical pregnancy after 12 or more months of consistent unprotected intercourse (1, 2). Infertility is categorized into primary and secondary types. Primary infertility is the occasion when no previous birth has occurred, or the woman is unable to become pregnant. Most infertilities are of primary type (67–71 %). Secondary infertility is involved when a couple have been fertile but they are no more, which includes about 29–33 % of cases (3). It is reported that 7 % of men at reproductive age are suffering from male infertility. Moreover, in about 50% of infertile men, the basic cause of their infertility is not defined (4). Nevertheless, in many of the cases, the male infertility is due to poor quality of sperm which is a complicated medical condition rooted in a variety of etiologies. Besides environmental factors, genetics is the main factor of male infertility. The genetic background is considered to be the corner stone in 15–30 % of male infertility cases (4). The impact of genetic factors on infertility has been reported in a variety of studies on specific genes in both, human and experimental models (5). As a result of high levels of reactive oxygen species (ROS) production in the course of spermatogenesis (6), medical complications such as varicocele (7), and effects of environmental elements and drugs, the genomic integrity of sperm is highly prone to be damaged (8). As a result, the DNA damage in somatic and germ cells may lead to azoospermia (9). It is also verified that the DNA damage is more common in patients with complete spermatogenesis failure, compared to patients with incomplete spermatogenesis failure (10). Furthermore, higher levels of sperm DNA damage and chromosomal fragility have been reported in infertile men in comparison with the healthy control group (11). Hence, sperm DNA integrity maintenance and DNA repair seem to be of paramount importance for male fertility. Two major types of DNA damage includes single-strand breaks (SSB) and double-strand breaks which are caused by a variety of factors such as reactive oxygen species, radiation exposure, chemical materials and alkylation (12). Oxidative stress can alter sperm DNA through different mechanisms, one of which

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is the oxidation of guanine bases that results in the production of 8-hydroxy-2′-deoxyguanosine (8-OHdG). The 8-OHdG is a mutagenic metabolite causing G:C→T:A transversion after replication (13). Localized DNA damage correction relies on the base excision repair (BER) pathway. BER is an important system that corrects damage caused by methylation or oxidation, or removes fragmented lesions of DNA and non-bulky adducts that can cause genetic instability or blockage of DNA replication (14). DNA repair enzymes check the chromosomes constantly for faulty nucleotides caused by methylation, or oxidative damage, and tend to correct them. (15) X-ray repair cross-complementing group 1 (XRCC1) is a scaffolding protein involved in several DNA repair systems and plays a central role in BER. The XRCC1 gene is located on chromosome 19q13.2 and holds 17 exons (16). Although numerous epidemiological studies have been conducted to investigate the association between *XRCC1* SNPs and risk of male infertility, the relation remains unclear. The genetic heterogeneity of studied participants, inadequate statistical power in individual studies, and so forth, can be the source of such uncertainty. Ergo, this meta-analysis is performed to thoroughly investigate the evidence for the association between XRCC1 Arg399Gln (rs25487) polymorphism and risk of male infertility.

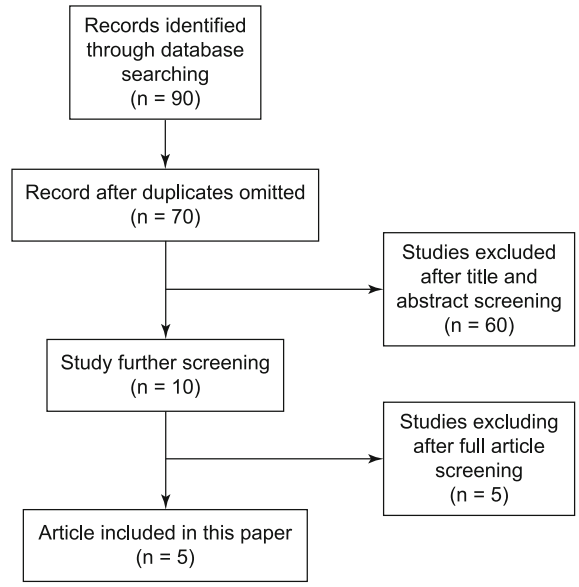


Fig. 1. Flow chart showing the detailed steps for literature selection.

Methods

Literature search

A search through the Web of Science, PubMed, Scopus, and Google Scholar databases was carried out in order to analyze all publications released up to September 15, 2018 and contributing to the knowledge on the association between XRCC1 Arg399Gln (rs25487) polymorphism and male infertility risk. The search strategy was "male infertility OR infertility" AND "XRCC1 OR XRCC1 Arg399Gln" AND "polymorphism OR mutation OR variant OR rs25487". Articles were included in the meta-analysis if they were in accordance with inclusion criteria as follows: 1) original case-control studies evaluating the association between XRCC1 polymorphism and male infertility; 2) articles that con-

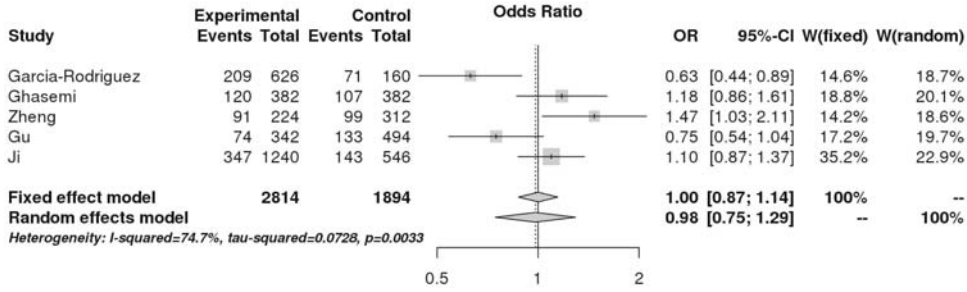
Tab. 1. Main characteristics of studies included in the meta-analysis.

Authors	Year	Country	Sample	Method	CaseAA/AG/GG	ControlAA/AG/GG	HW-p	HW-adj.p
Garcia-Rodriguez et al (19)	2018	Spain	Seminal samples	PCR-RFLP	40/129/144	13/45/22	0.2124	0.354
Ghasemi et al (18)	2017	Iran	Blood	PCR-RFLP	7/106/78	8/91/92	0.0122	0.061
Zheng et al (17)	2012	China	Blood	PCR-RFLP	12/67/33	15/69/72	0.7939	0.7939
Gu et al (20)	2007	China	Blood	PCR-RFLP	5/64/102	21/91/135	0.3167	0.3959
Ji et al (21)	2010	China	Blood	PCR-RFLP	54/339/327	23/97/153	0.1809	0.354

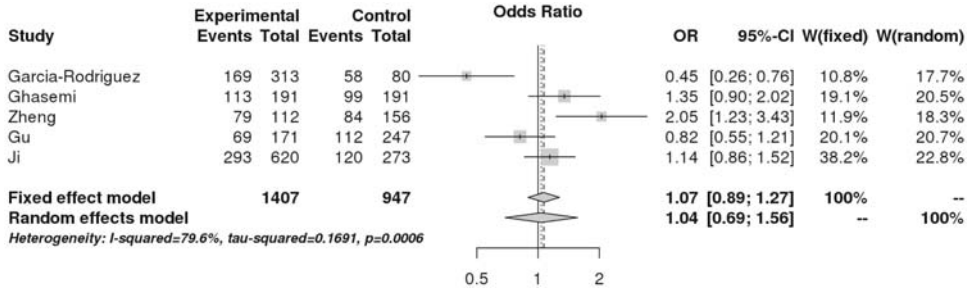
Tab. 2. Results of the meta-analysis for the association between the XRCC1 and male infertility.

Allelic and genotypic	No. of studies	Odds ratio		Model	Heterogeneity		p (Egger's test)
		OR[95%CI]	p		I^2	p	
A vs. G	6	1.0003[0.87;1.144]	0.996	Fixed effect	0.7473	0.0033	0.6835
A vs. G	6	0.9819[0.7456;1.293]	0.896	Random effect			
AA vs. AG+GG	6	0.8499[0.6144;1.1756]	0.3257	Fixed effect	0.1636	0.3104	0.3152
AA vs. AG+GG	6	0.8332[0.578;1.2002]	0.3270	Random effect			
AA+AG vs. GG	6	1.066[0.8938;1.2733]	0.4736	Fixed effect	0.7959	0.0006	0.766
AA+AG vs. GG	6	1.0373[1.6895;1.5606]	0.8603	Random effect			
AG vs. AA+GG	6	1.1231[0.9409;1.3405]	0.1986	Fixed effect	0.7033	0.0091	0.8448
AG vs. AA+GG	6	1.1105[0.7941;1.5528]	0.5402	Random effect			
AA vs. GG	6	0.8596[0.6105;1.2104]	0.3862	Fixed effect	0.5877	0.0458	0.5787
AA vs. GG	6	0.8069[0.458;1.4216]	0.4577	Random effect			
AA vs. AG	6	0.8324[0.5928;1.1688]	0.2895	Fixed effect	0	0.4456	0.1961
AA vs. AG	6	0.8324[0.5928;1.1688]	0.2895	Random effect			
AG vs. GG	6	1.1088[0.9219;1.3336]	0.2726	Fixed effect	0.7774	0.0012	0.7501
AG vs. GG	6	1.0782[0.7179;1.6193]	0.716	Random effect			

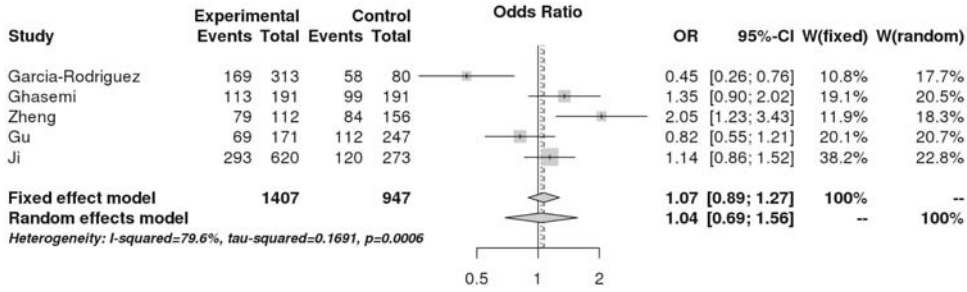
A vs. G



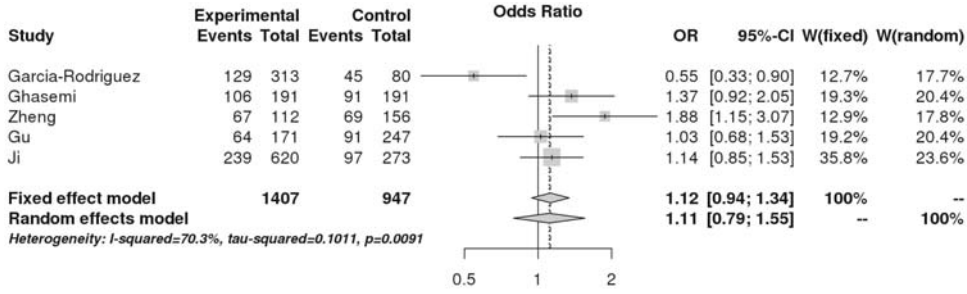
AA vs. AG+GG



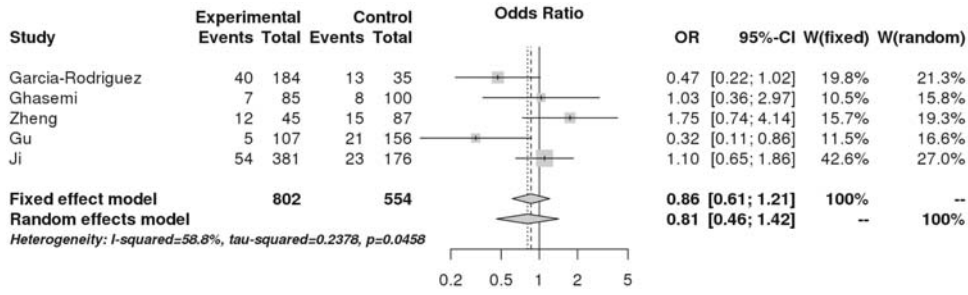
AA+AG vs. GG



AG vs. AA+GG



AA vs. GG



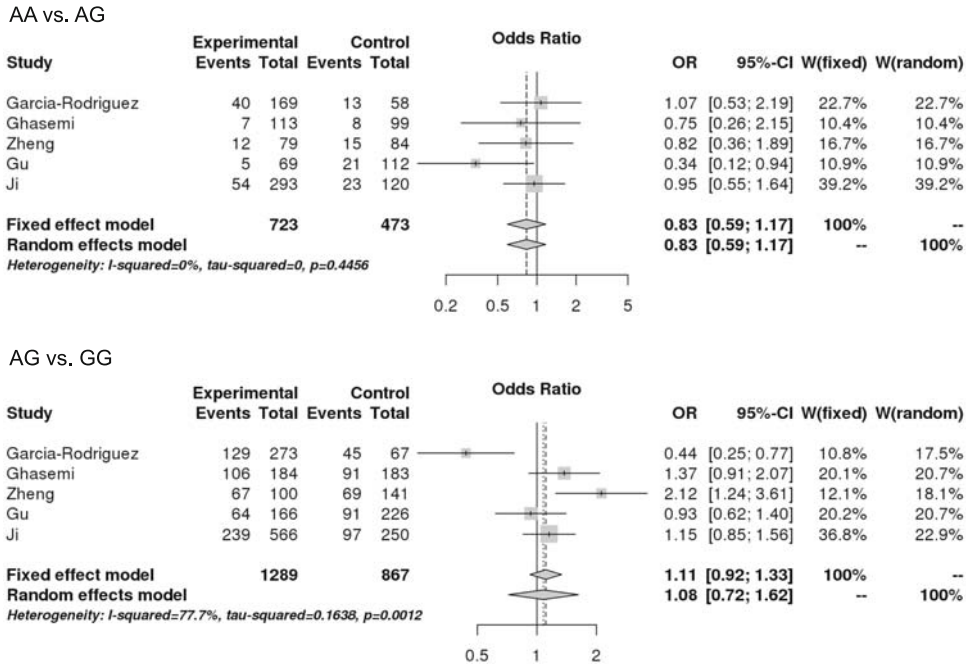


Fig. 2. Forest plots for the association between XRCC1 Arg399Gln SNP and male infertility risk.

tribute with necessary data of the genotype frequencies of the XRCC1 Arg399Gln rs25487 variant in both cases and controls. The exclusion criteria were as follows: 1) conference abstract, case reports, reviews, and duplication data; 2) insufficient genotype information. Also, the search investigated only the studies carried out on human subjects.

Data extraction

Upon the through appraisal of all articles meeting the inclusion and exclusion criteria, the relevant information was extracted. Afterwards, each study exploited variables as follows: first author's name, year of publication, country, genotyping method and sample type, sample size of the studied case and control groups, and results of the Hardy-Weinberg equilibrium test.

Statistical analysis

The significance of the relationships between XRCC1 Arg399Gln (rs25487) polymorphism and risk of male infertility risks were evaluated by means of OR and corresponding 95 % CI. The net ORs were used for allele comparison model, dominant model, recessive model and codominant model. Chi-square-based Q test was then performed in order to test the heterogeneity assumption. The value of $p < 0.10$ was considered to represent significant heterogeneity, and I^2 values of 25 %, 50 % and 75 % contributed to low, medium and high levels of heterogeneity, respectively. A fixed-effect model was used to assess the net OR, when the p value for heterogeneity was > 0.10 and $I^2 < 50$ %. Conversely, if $p \leq 0.10$ or $I^2 \geq 50$ %, we performed the random-effect model. The significance of the net OR was set on by the Z-test, and $p < 0.05$ was perceived as statistically significant. The statistical analysis was carried out by means of Reviewer Manager 5.3 and Stata 12.0. The potential publication bias was estimated using Egger's test and funnel plots. For the purpose of appraising the stability of the result, the sensitivity analysis was performed. The net ORs were calculated by excluding individual study, one at a time, to assess the significance of a single study.

Results

Upon primary search through scientific databases of PubMed, Scopus, Google Scholar and Web of Science, 90 results were retrieved. Of those chosen, 10 studies were excluded based on the screening criteria. Finally, after careful consideration, 5 case-control studies with a total of 1,407 cases and 974 controls were chosen and further investigated in this meta-analysis (17–21) (Fig. 1). These studies were published between years 2007 to 2018. All included studies were assessed performing the Hardy-Weinberg test (HWE) to evaluate all the included data, and the results confirmed that the XRCC1 Arg399Gln gene genotype frequencies of all five studies were in HWE in the controls. The elaborated characteristics of all included data are shown in Table 1.

XRCC1 polymorphism and male infertility risk

A total of 2,381 individuals in five studies were included, in which the influence of XRCC1 Arg399Gln (rs25487) polymorphism on the risk of male infertility were evaluated. The results of meta-analyses on the associations between XRCC1 Arg399Gln polymorphism and male infertility risk is summarized in Table 2.

As shown in Table 2, there is no significant relation between the XRCC1 genotype and male infertility. The forest plots are shown in Figure 2.

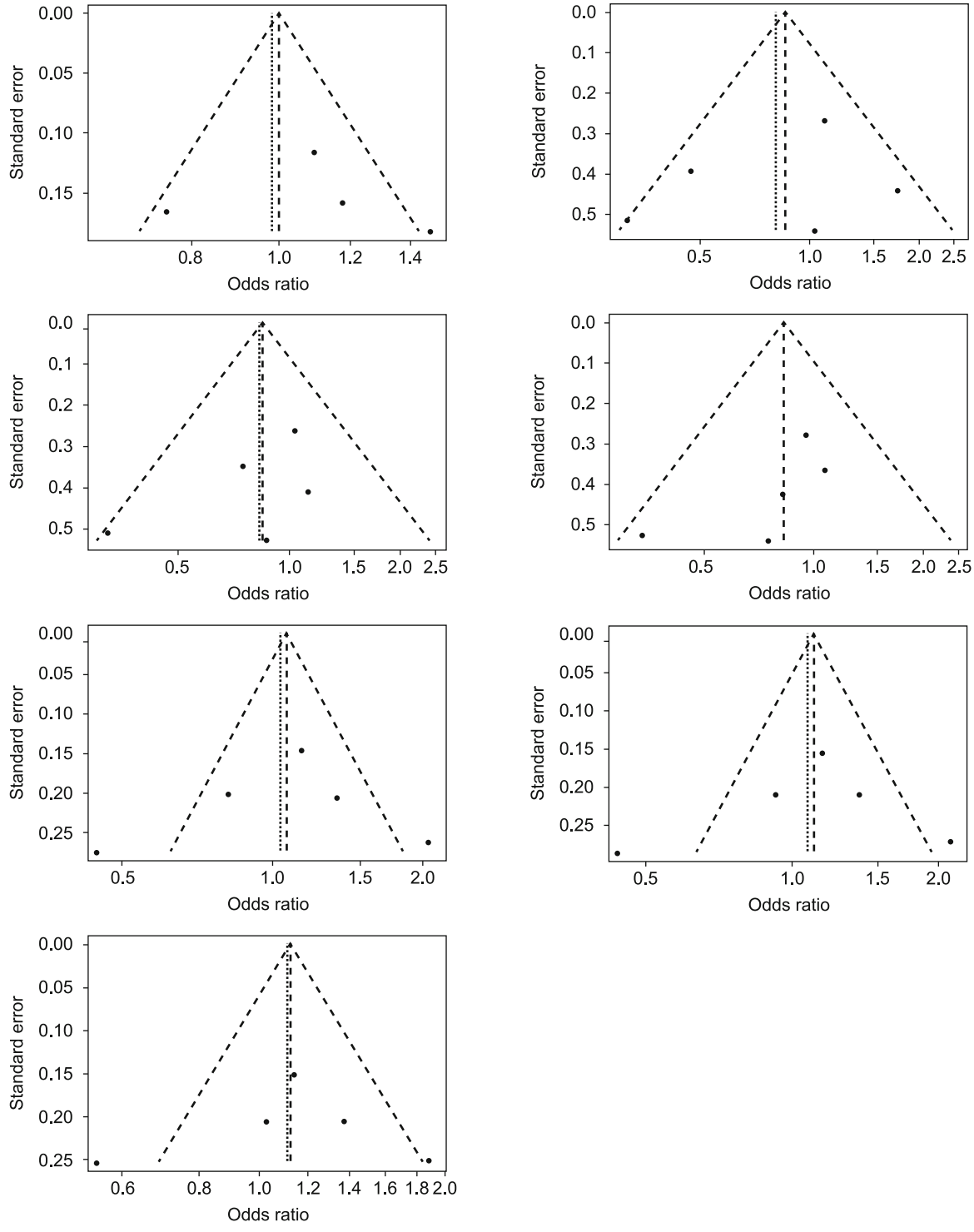


Fig. 3. Funnel plots of the association between cancer risk and rs25487 polymorphism in the overall study population.

Heterogeneity analysis

Overall comparisons approved the heterogeneity among studies (Tab. 2). To detect the risk of publication bias, a funnel plot was deployed as a visual aid (Fig. 3). Regarding the rs25487 variant, Egger's linear regression analysis showed no publication bias for this meta-analysis of the codominant, dominant, recessive, overdominant and allele model (all p values for bias < 0.05).

Discussion

Since 2007, several case-control studies have found a specific association between XRCC1 polymorphisms and increased risk of male infertility (20). In this meta-analysis, 5 relevant studies were screened. While two of them demonstrate a significant association between XRCC1 polymorphisms and male infertility (17, 19) , the other selected studies do not show any notable association (18, 20, 21). Hence, this meta-analysis was performed to evaluate the association of XRCC1 and male infertility in a comprehensive manner. We found out that Arg399Gln polymorphisms of the XRCC1 gene was not associated with male infertility risk in studied populations. No specific etiology is found in more than half of male infertility cases. In addition, a large proportion of male infertility is believed to be accompanied with idiopathic azoospermia. Idiopathic azoospermia is considered to result from changes in the DNA including microdeletions in Y chromosome, specific gene mutations and other chromosomal abnormalities (22). Nevertheless, there is no doubt that genetic polymorphisms might be also contributing to susceptibility to some forms of male infertility (23, 24). During spermatogenesis high amounts of reactive oxygen species are produced in the testes, which can cause several forms of DNA lesions (6) Moreover, agricultural and industrial chemicals as well as some drugs can damage the DNA in spermatogenic cells. Hence, interruptions in DNA repair mechanisms may be associated with the decrease in sperm count or production of abnormal sperms (25). Additionally, it was shown that polymorphism of DNA repair gene BRCA2 is in fact associated with idiopathic azoospermia (26). XRCC1, a necessary gene in the BER pathway, has a crucial part in single-strand breaks repair in meiotic recombination during spermatogenesis (15). Clearly, the publication bias is an important factor concerning the reliability of results, while the latter together with the study quality are crucial in conducting a meta-analytic study. We used Begg's funnel plots and Egger's test to analyze the publication bias in this study. Doing so, no significant publication bias was detected towards the reliability of our results. Same results were obtained using sensitivity analysis. Furthermore, we employed strict inclusion and exclusion criteria to diminish the selection bias. Although, this is an up-to-date meta-analysis, it suffers some limitations. Firstly, only selected databases were used to obtain data. Ergo, the publication might have been restricted. It is possible that some unpublished investigations with unidentified findings were missed. Secondly, as only Chinese, Iranian and Spanish populations were studied in our selected literature, the results might not be applicable to other ethnic populations. Hence, more studies especially those of different ethnicities might grant more solid evidence towards our questions. And thirdly, our analysis was based only on studies published in English.

Conclusions

At the time of conducting the present study, this was the first meta-analysis to investigate the association of XRCC1 polymorphisms (codon 399) and male infertility risk. Our results indicated that the XRCC1 Arg399Gln polymorphism was not associated with male infertility risk. More case-control investigations are needed to validate our finding.

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Received February 15, 2019.
Accepted March 9, 2019.