

Original Article

Association of the XRCC1 Arg280His polymorphism with leukemia risk: a meta-analysis

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Abstract: We performed a meta-analysis by summarizing all relevant studies to evaluate the association of the Arg280His polymorphism in repair cross-complementing group 1 (XRCC1) with the risk of leukemia. Studies published in PubMed and Embase databases were found by searching for the key words 'XRCC1', 'polymorphism' and 'leukemia'. A total of seven studies involving 1601 patients with leukemia and 2085 controls were enrolled into this meta-analysis. Overall, the results showed no significant association between the XRCC1 gene Arg280His polymorphism and leukemia risk when all studies were pooled into the meta-analysis (Arg/Arg vs His/His: OR = 0.80, 95% CI = 0.44-1.46; Arg/His vs His/His: OR = 0.97, 95% CI = 0.52-1.80; the dominant model: OR = 0.87, 95% CI = 0.48-1.58; the recessive model: OR = 0.92, 95% CI = 0.76-1.10). Similarly, in the subgroup analysis regarding ethnicity and cancer type, no association was observed. Meta-analysis results suggest the XRCC1 gene Arg280His polymorphism is not associated with leukemia susceptibility. Well-designed studies with more subjects will be required for further validation of these results.

Keywords: Leukemia, XRCC1, Arg280His polymorphism, susceptibility

Introduction

Leukemia is the most common childhood cancer and the fifteenth most common cancer among in adults [1]. The disease can be subdivided into four major groups according to which cells are affected. The four major groups of leukemia are acute myeloid leukemia (AML), chronic myeloid leukemia (CML), acute lymphocytic leukemia (ALL), and chronic lymphocytic leukemia (CLL) [2]. The mechanisms for leukemia genesis are not completely understood. Previous studies have found that environmental exposures associated with the pathogenesis of leukemia, include radiation exposure, cigarette smoking, and exposure to chemical carcinogens [3, 4]. In addition, previous candidate gene and genome-wide association studies have indicated that genetic factors may contribute to leukemia pathogenesis [5, 6].

The DNA repair system plays a key role in the maintenance of genetic integrity, thereby countering the negative effects of environmental stresses that can cause errors in DNA replication [7]. The DNA repair pathways of base exci-

sion repair (BER), nucleotide excision repair (NER), mismatch repair (MMR), and double strand break repair (DSBR) play essential roles in maintaining genome integrity [8]. The X-ray repair cross-complementing group 1 gene (XRCC1) is a component of the BER pathway and allows efficient repair of DNA single-strand breaks that can result from exposure to ionizing radiation or alkylating agents [7]. In humans, the XRCC1 gene is located at chromosomal locus 19q13.2 and encodes a 633 amino acid protein after the removal of 17 exons [9]. Recently, a polymorphism in the XRCC1 gene has been identified as Arg280His (rs 25489, a G/A substitution at nucleotide 27466 within exon 9) [10]. Previous meta-analyses suggested the Arg280His polymorphism can be associated with an increased risk of bladder cancer and thyroid carcinoma [10, 11].

In the past decade, studies suggested that XRCC1 gene Arg280His polymorphism was associated with susceptibility to leukemia. However, the conclusions of these studies are inconsistent. To help clarify the role of this polymorphism with leukemia risk, we conducted this meta-analysis.

Arg280His polymorphism and leukemia

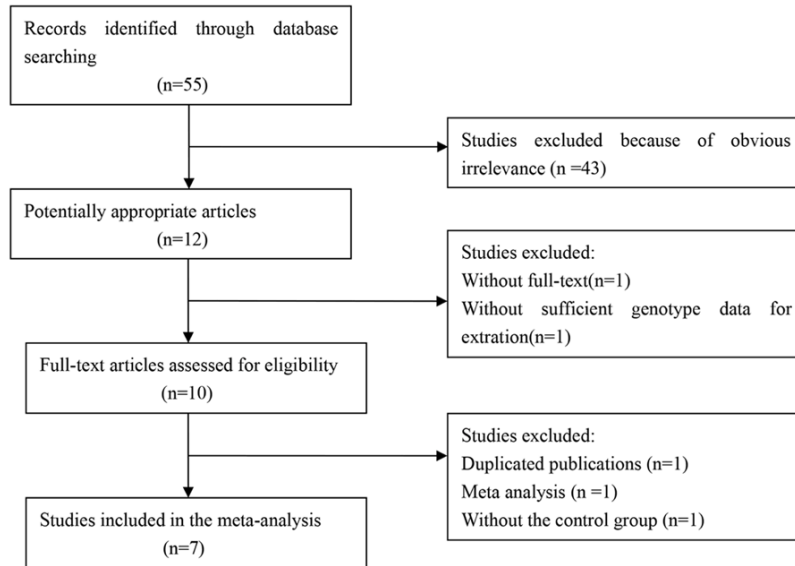


Figure 1. The flow chart of study selection.

Materials and methods

Publication search

We searched the PubMed and Embase databases using a combination of terms as follows: ('x-ray repair cross-complementing group 1', 'XRCC1' and 'leukemia') and ('Arg280His' and 'rs 25489') and ('polymorphism', 'SNP', 'allele' and 'variant'). When necessary, we contacted the authors of the original studies for additional data. The publication search was conducted without limitations on publication date.

Inclusion criteria

The study was included in our analysis if it met the following criteria: 1) case-control studies that included both diseased individuals and healthy individuals; 2) studies on the correlation of XRCC1 gene Arg280His polymorphism and susceptibility to leukemia and 3) studies with sufficient data to be allowed of extraction. We did not include reviews, case reports, letters, or editorial articles, studies that were based on incomplete information, or studies lacking usable data or duplicate data.

Data extraction

Data extracted from the selected papers included: first author's last name, publication year, country where the study was performed, race of the subjects, number of patients and

controls, and the polymorphisms present.

Statistical analysis

The strength of the relationship between the XRCC1 gene Arg280His polymorphism and leukemia was measured as the odds ratio (OR) with a 95% confidence interval (95% CI). We examined the relationship of the XRCC1 gene Arg280His polymorphism and leukemia risk by comparing the homozygous His/His genotype (wild type), the variant heterozygous Arg/His, and the homozygous Arg/Arg genotype. The dominant

effect model (Arg/Arg+Arg/His vs. His/His) and recessive effect model (Arg/Arg vs. Arg/His+His/His) were used to obtain pooled results [12]. We calculated the I^2 statistic as an indicator of heterogeneity (0-25% indicates no heterogeneity; 25-50% indicates moderate heterogeneity; 50-75% indicates a large degree of heterogeneity; and 75-100% indicates extreme heterogeneity) [13]. We used the χ^2 test to evaluate whether the genotypic frequencies of the control samples were in Hardy-Weinberg equilibrium (HWE). Stratified analyses were performed after separation of the data by subject race and the type of tumor. We excluded studies in which allelic frequencies in controls exhibited significant deviation from HWE to perform sensitivity analysis [14]. We used the Begg's funnel plot to examine publication bias, and a p -value of < 0.05 was considered statistically significant [15]. All data analyses were performed using the STATA version 12.0 statistical package (StataCorp LP, College Station, Texas, USA).

Results

Characteristics of eligible studies

The search strategy identified 55 relevant studies, seven of these were case-control studies that met our inclusion criteria and were included in this meta-analysis [16-22]. The flow chart of study selection is shown in **Figure 1**. Together,

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Table 1. Characteristics of the included studies for meta-analysis

Study included	Year	Area	Race	Tumor type	Cases/Controls	Genotypes for cases			Genotypes for controls		
						Arg/Arg	Arg/His	His/His	Arg/Arg	Arg/His	His/His
Joseph [16]	2005	India	Asian	ALL	117/117	76	38	3	85	30	2
Ganster [17]	2005	Austria	Mestizo	CLL	443/443	396	47	0	388	53	2
Pakakasama [18]	2007	Thailand	Asian	ALL	108/317	94	14	0	272	42	3
Meza-Espinoza [19]	2009	Mexico	Mestizo	ALL	120/120	87	31	2	88	31	1
Shi [20]	2011	China	Asian	AML	307/558	236	66	5	445	109	4
Annamaneni [21]	2012	India	Asian	CML	350/350	346	4	0	338	11	1
Banescu [22]	2014	Romania	Caucasian	CML	156/180	82	64	10	112	58	10

AML, acute myeloid leukemia; ALL, acute lymphocytic leukemia; CML, chronic myeloid leukaemia; CLL, chronic lymphocytic leukemia.

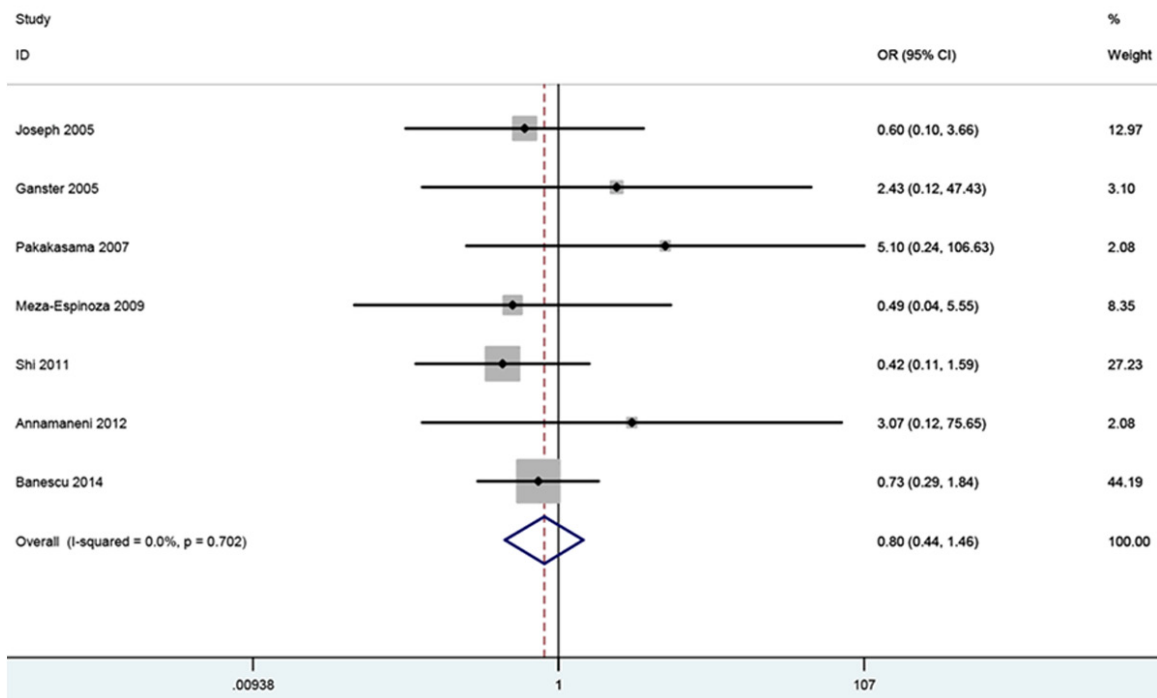


Figure 2. Forest plot of leukemia associated with the XRCC1 gene Arg280His polymorphism (Arg/Arg vs His/His).

these seven selected studies included 1601 cases and 2085 healthy controls. One study participants were of Caucasian descent [22], four studies were of subjects of Asian descent [16, 18, 20, 21], and two studies had subjects of mixed descent [17, 19]. The HWE test was used to assess the genotype distribution of the controls, and the frequencies were in agreement with HWE, with the exception of Annamaneni et al [21]. Our meta-analysis included one chronic lymphocytic leukemia (CLL) study [17], one acute myeloid leukemia (AML) study

[20], three acute lymphocytic leukemia studies [16, 18, 19], and two chronic myeloid leukaemia studies [21, 22]. The main findings from the articles are presented in **Table 1**.

Meta-analysis results

The evaluation of association between Arg-280His polymorphism in the XRCC1 gene and the risk of leukemia are presented in **Figure 2** and **Table 2**. Meta-analysis results revealed no significant relationship between the XRCC1

Arg280His polymorphism and leukemia

Table 2. Summary of different comparative results

Variables	N	Cases/ controls	Arg/Arg vs His/His			Arg/His vs His/His			Dominant model			Recessive mode		
			OR (95% CI)	P	I ²	OR (95% CI)	P	I ²	OR (95% CI)	P	I ²	OR (95% CI)	P	I ²
Total	7	1601/2085	0.80 (0.44-1.46)	0.70	0.0%	0.97 (0.52-1.80)	0.85	0.0%	0.87 (0.48-1.58)	0.72	0.0%	0.92 (0.76-1.10)	0.16	35.8%
Ethnicity														
Asian	4	882/1342	0.82 (0.33-2.00)	0.38	3.5%	0.84 (0.33-2.13)	0.61	0.0%	0.84 (0.34-2.07)	0.40	0.0%	0.97 (0.77-1.22)	0.08	56.5%
Caucasian	1	156/180	0.73 (0.29-1.84)	/	/	1.10 (0.43-2.84)	/	/	0.86 (0.35-2.12)	/	/	0.67 (0.44-1.04)	/	/
Mestizo	2	563/563	1.02 (0.19-5.45)	0.41	0.0%	1.01 (1.08-5.59)	0.43	0.0%	1.02 (0.19-5.43)	0.42	0.0%	1.02 (0.67-1.57)	0.74	0.0%
Tumor type														
ALL	3	345/345	0.96 (0.29-3.15)	0.42	0.0%	1.09 (0.32-3.71)	0.53	0.0%	1.00 (0.30-3.29)	0.45	0.0%	0.98 (0.74-1.30)	0.31	13.6%
CML	2	506/530	0.84 (0.35-2.00)	0.40	0.0%	1.11 (0.45-2.76)	0.97	0.0%	0.96 (0.41-2.27)	0.46	0.0%	1.31 (0.30-5.74)	0.02	83.2%
The others	2	750/1001	0.63 (0.20-1.95)	0.29	11.7%	0.69 (0.21-2.19)	0.34	0.0%	0.64 (0.21-1.98)	0.30	8.3%	0.90 (0.67-1.21)	0.46	0.0%
HWE														
Yes	6	1251/1735	0.75 (0.41-1.39)	0.70	0.0%	0.96 (0.51-1.80)	0.75	0.0%	0.82 (0.45-1.51)	0.70	0.0%	0.88 (0.73-1.06)	0.43	0.0%
No	1	350/350	3.07 (0.12-75.65)	/	/	1.17 (0.04-34.52)	/	/	3.01 (0.12-74.11)	/	/	3.07 (0.98-9.62)	/	/

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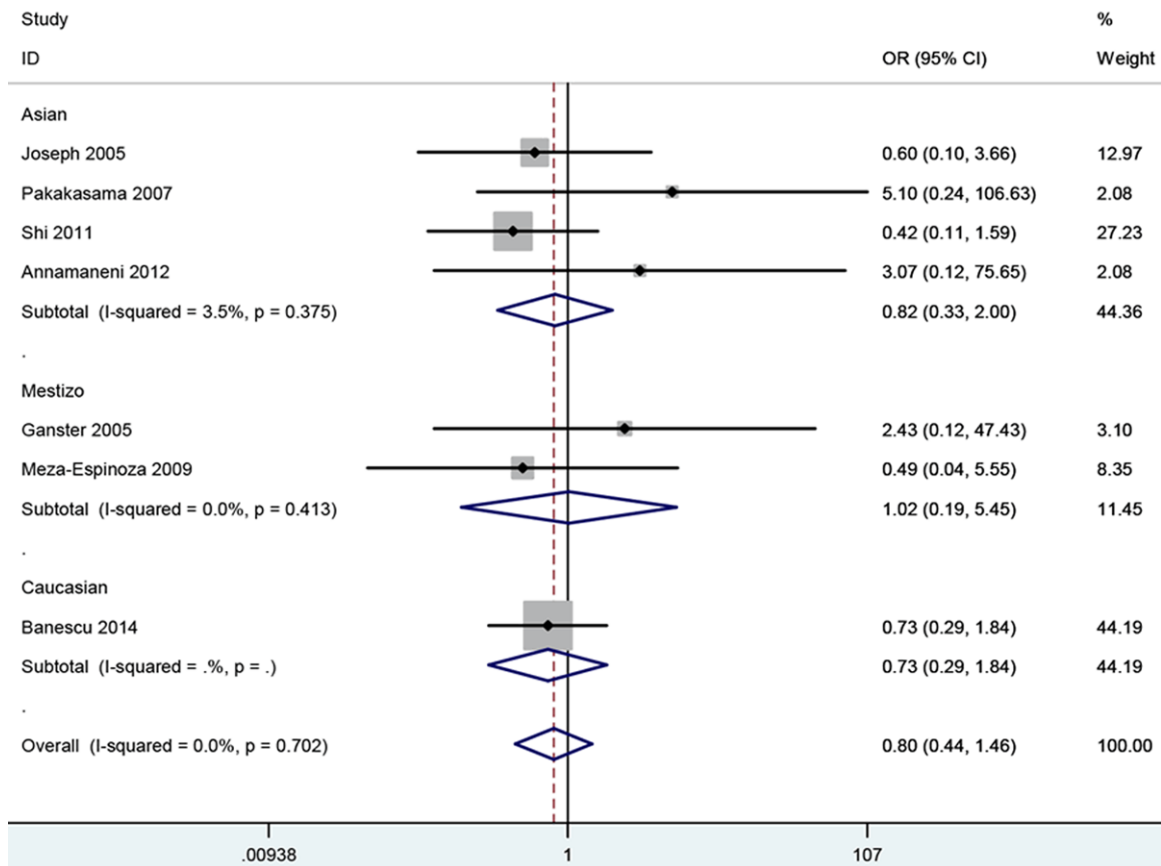


Figure 3. Forest plot of leukemia associated with the XRCC1 gene Arg280His polymorphism in the stratified analyses by race (Arg/Arg vs His/His).

gene Arg280His polymorphism and leukemia risk (Arg/Arg vs His/His: OR = 0.80, 95% CI = 0.44-1.46; Arg/His vs His/His: OR = 0.97, 95% CI = 0.52-1.80; the dominant model: OR = 0.87, 95% CI = 0.48-1.58; the recessive model: OR = 0.92, 95% CI = 0.76-1.10). We removed the one non-HWE study [21], and the result was not altered, indicating our meta-analysis was statistically significant.

To evaluate the impact of ethnicity and cancer type as potential confounding factors, we performed subgroup analyses (Figures 3 and 4). In stratified analysis by race, the included studies were classified as Asians, Caucasians, and Mestizo populations, and no significant correlation was found between the Arg280His polymorphism in the XRCC1 gene and incidence of leukemia. When patients were stratified according to cancer type, again, no significant association was found for AML, ALL, CML, or CLL (Table 2).

Publication bias

Publication bias of the literature was assessed by Begg's funnel plot. The results indicated that there was no evidence of publication bias visually from the funnel plot, implying that the publication bias was low in the present meta-analysis (Figure 5).

Discussion

Genetic polymorphisms in DNA repair genes can modify DNA repair capacity and, therefore, could be related to the risk of cancer [23]. Human XRCC1 is an important component of the BER pathway that repairs base damage and DNA single-strand breaks that can result from exposure to ionizing radiation or other environmental stresses [24]. Polymorphisms in the XRCC1 gene have been reported to be associated with altered risk of several types of cancer [25, 26]. Recently, an important polymorphism named Arg280His was identified in the XRCC1

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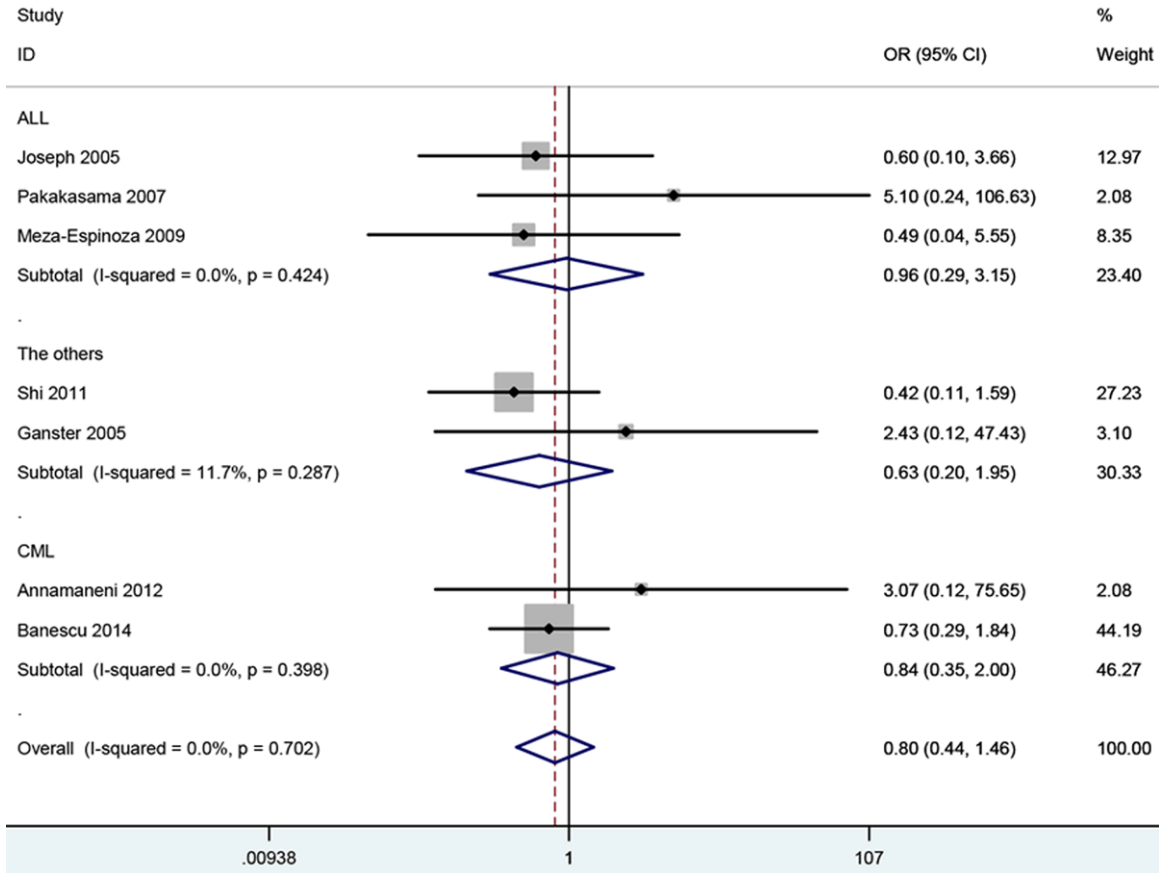


Figure 4. Forest plot of leukemia associated with the XRCC1 gene Arg280His polymorphism in the stratified analyses by cancer type (Arg/Arg vs His/His).

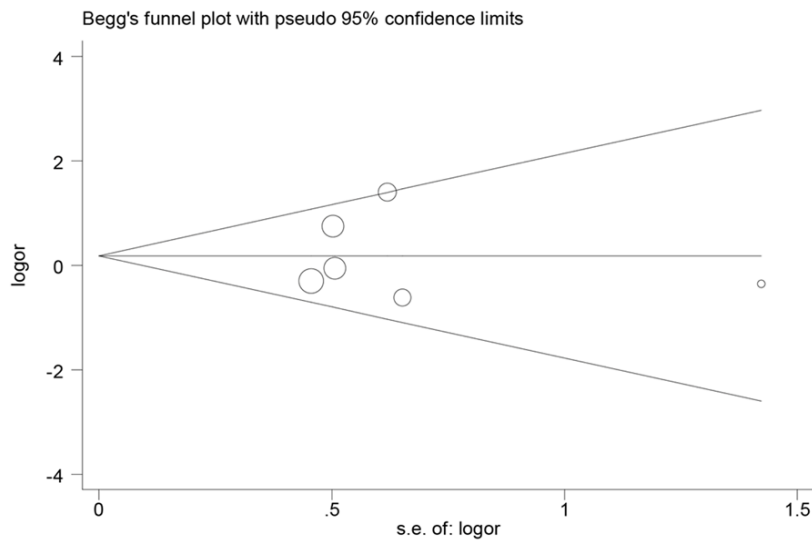


Figure 5. Begg's funnel plot for publication bias test.

gene. Consequently, several case-control studies have evaluated the relationship of this poly-

morphism to the development of leukemia. However, the results have been inconclusive. The inconclusive result of these studies could be due to the fact that they were single studies and compared a relatively small number of samples. Thus, in the current study, we have extensively reviewed the literature and performed a meta-analysis to evaluate the association between the Arg-280His polymorphism and leukemia risk.

We analyzed data from 1601 cases and 2085 controls in seven case-control studies and found no statistical relationship between this

polymorphism and the susceptibility to leukemia. This suggests that individuals who carry the variant allele of the Arg280His polymorphism may not have an increased risk of leukemia. In the stratified analysis regarding ethnicity and cancer types, no significant result was obtained. Thus, the effect of the polymorphism may not vary dependent for subjects of different ethnicities or cancer types. Previous meta-analyses suggested that the Arg280His polymorphism was associated with an increased propensity to develop bladder cancer and thyroid carcinoma [10, 11]. There are several factors that may contribute to different roles of the same polymorphism regarding susceptibility to different cancer types. Therefore, discrepancies between studies could possibly be due to a different role of Arg280His polymorphism in different cell types or tissues. Another explanation may be that cancer is a complicated multi-genetic disease and the different findings may be based on gene-gene and gene-environment interactions [27]. Considering the limited numbers of studies, further large and well-designed studies are needed to investigate this matter in great detail.

There are several limitations in this meta-analysis. First, our results relied on studies of small sample size with small numbers of samples with the polymorphism. These factors, may allow a small study bias. Second, only studies published in English were included in our meta-analysis. Finally, the potential influence of Arg280His polymorphism may be affected by gene-gene and gene-environment interrelationship.

In summary, our meta-analysis finds no association of the XRCC1 gene Arg280His polymorphism with altered risk of leukemia. Well-designed studies with more subjects will be required for further validation of these results.

Disclosure of conflict of interest

None.

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