An updated quantitative evaluation of the association between leukaemia risk and XRCC3 Thr241Met polymorphism

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Abstract

Introduction: Several analyses have been conducted to assess the association between leukaemia risk and XRCC3 Thr241Met polymorphism. However, their results are conflicting. Hence, this comprehensive study was carried out to obtain a more accurate assessment of the association between leukaemia risk and XRCC3 Thr241Met (rs861539) polymorphism

Material and methods: We searched Ovid, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Google Scholar, PubMed database and Excerpta Medica Database (EMBASE) for potential eligible studies published as of July 2020. Pooled odds ratio (OR) and 95% confidence interval (CI) were used in evaluating the strength of the association between Thr241Met polymorphism of XRCC3 and leukaemia, and the *p*-value less than 0.05 ($p < 0.05$) was considered as the level of significance.

Results: A total of 17 studies consisting of 7241 controls and 4198 cases met our inclusion criteria. No significant association was observed between leukaemia risk and Thr241Met polymorphism of XRCC3 across the five genetic variants. In our ethnicity subgroup evaluation, we noted a significant association between leukaemia risk and Thr241Met polymorphism of XRCC3 among Caucasians under four genetic models. Furthermore, SNP (rs861539) of XRCC3 has a protective effect among Asians under four genetic models.

Conclusions: Thr241Met polymorphism of XRCC3 has a protective effect in the Asian population but has oncogenic potential in the Caucasian population.

Key words: XRCC3, Thr241Met, leukaemia, polymorphism, meta-analysis.

Introduction

Leukaemia is described as a group of progressive cancerous disorders of the haematopoietic system with an elevated or abnormal number of immature leukocytes or white blood cells (WBC) formed by the bone marrow. This

inhibits natural development of blood cells, causing anaemia thrombocytopenia, as well as other clinical disorders [1–4]. The prevalence and mortality rate of leukaemia in 2020 were estimated at 60,530 and 35,470 respectively; accounting for 3.4% of all new cancer cases and 3.8% of all cancer death worldwide [5]. The global incidence rate of leukaemia continues to rise due to its complex and vast characteristics contributing to its poor prognosis [6]. The four key forms of cytogenetic-based leukaemia are acute myeloid leukaemia, acute lymphocytic leukaemia, chronic lymphocytic leukaemia, and chronic myeloid leukaemia [7–10]. The occurrence of leukaemia has been linked with many risk factors, including genetic variations, chromosome 21q abnormalities, Fanconi anaemia, cytotoxic drug usage and ionising radiation exposure [11–13].

DNA repair mechanisms plays an essential role in sustaining the stability and integrity of genomes. It is generally established that abnormalities in repair mechanisms are linked to genomic instability, which can progressively stimulate the growth of certain cancers including leukaemia [14]. X-ray repair cross-complementing group 3 (XRCC3) is composed of some polymorphic genes which belongs to one of the key proteins in the DNA repair pathways, which is important for stability of the genome by stimulating the search for homology and spurring the single-stranded tails invasion into the homologous chromatid DNA double helix [15]. XRCC3 is positioned at chromosome 14 (human) band 14q32.33 (chromosome 14q32.33), is actively involved in the repair of DNA, and participates in homologous recombination (HR) of DNA double-strand breaks and cross-links [16, 17]. During the repair of the homologous recombination, the protein XRCC3 directly interacts with and stabilises the protein RAD51 [18–21]. A variety of genes which are engaged in repairing and preserving double-strand breaks have been found with genetic polymorphisms which involve genes that belong to the homologous recombination DNA double-strand breaks repair pathways [22].

The polymorphism in the XRCC3 gene at codon 241 leads to the substitution of amino acid threonine (Thr)-to-methionine (Met), which is an unconventional improvement [23]. The substitution of amino acid Thr241Met attributable to the exon 7 transition of 18607C/T in the XRCC3 gene was observed to function effectively, since it appears to be related to a number of elevated micronuclei in the peripheral blood lymphocytes of humans exposed to radiation [24, 25] and is also reported to be related with malignancies [26]. The operational importance of this shift in amino acids has not been clearly determined, even though some studies have noted significant relationships between cancers (such as oesophageal cancer, bladder cancer, breast cancer, colorectal) and this variant genotype [27–30]. This researched focused on ~18067C/T (rs861539), which is a single nucleotide polymorphism (SNP) in the X-ray repair cross-complementing group 3 gene [31]. The XRCC3 Thr241Met polymorphisms arises in three genetic variants: and homozygous (TT), heterozygous (CT), and wild-type (CC) genotypes.

Several analyses have been conducted to assess the relationship between leukaemia risk and XRCC3 Thr241Met polymorphism. However, their results are conflicting [31–33]. A study by Qin *et al.* appears not to be void of selection bias because only three databases (CNKI, EMBASE and PubMed) were used by the authors in their search for the relevant literature [31]. Furthermore, no flow chart showing the literature selection process was presented. Hence, this comprehensive study was carried out to obtain a more accurate assessment of the association between leukaemia risk and XRCC3 Thr241Met (rs861539) polymorphism.

Material and methods

Identification and eligibility of relevant studies

We searched Ovid, Chinese Biomedical Literature Database (CBM), China National Knowledge Infrastructure (CNKI), Google Scholar, PubMed database and Excerpta Medica Database (EMBASE) and grey literature for the potential eligible studies that had been published as of July 2020. The search utilized the following keywords: "leucocythemia" or "leukocythemia", "X-ray repair cross-complementing group 3" or "XRCC3", "leukaemia" and "variant or polymorphism". Additionally, we included other possible publications identified via manual search. This methodology is described in our previous studies [34, 35].

Inclusion and exclusion eligibility

The inclusion criteria of our studies were as follows: 1) cohort or case-control studies, 2) studies assessing the relationship between the risk of leukaemia and Thr241 polymorphism of XRCC3, 3) articles with the distribution of the control genotype in Hardy–Weinberg equilibrium, and 4) studies with adequate information for estimating odds ratios (ORs) and 95% confidence intervals (CIs). The exclusion criteria were as follows: 1) studies with incomplete data, 2) non-case-control studies, and 3) duplication of past publication.

Data extraction

Two reviewers independently extracted the data by following the standardised protocol and procedure for data extraction. Another investigator also participated in the extraction of data. Any disagreements and discrepancies were resolved through full discussion with the third reviewer. The extracted information comprised: the year of publication, the name of the first author, cases and controls genotype

distribution, ethnicity, country of origin, the control source, sample sizes, and methods for genotyping.

Quality score evaluation

The Newcastle-Ottawa Scale (NOS) for evaluating the quality of non-randomized studies was used in our meta-analyses. Two reviewers independently evaluated the quality of studies in accordance with the quality assessment scale. The cancer genetic factors and epidemiological factors were the basis for these scores. Any dispute between the reviewers was settled through dialogue. We used the aggregate score of quality items to determine the overall quality level in primary research. The range for the total score was from zero (low) to fifteen (high). A total score less than 5 was considered to be poor quality and was further excluded.

Statistical analysis

Pooled odds ratio (OR) and 95% confidence interval (CI) were used in evaluating the strength of the association between Thr241Met polymorphism of XRCC3 and leukaemia risk. The genotypes and alleles were compared using five different genetic models: allele contrast model (T vs C), dominant model (TT+TC vs CC), recessive model (TT vs TC+CC), over-dominant (TC vs TT+CC), as well as homozygote (TT vs CC) models. Hardy–Weinberg equilibrium was estimated in the various control groups for each study using the χ^2 test, and the p-value less than 0.05 ($p < 0.05$) was considered as the level of significance. The heterogeneity between the studies was evaluated by the index I^2. A high value of I^2 (> 50%) indicated heterogeneity. If heterogeneity was not present (I^2 <50%), a fixed-effect model was applied for analysis; otherwise, a random effect model was adopted. The outcomes of the overall odds ratio for all the included studies under the five genetic models were presented using forest plots. We conducted subgroup analyses based on ethnicities, control source and method of genotyping. Analysis of sensitivity was carried out to ascertain the impact of individual data sets on the combined estimates. Egger's test and Begg's funnel plot were used to assess bias in the publication. The Web tool MetaGenyo, Version 12.0. was used in all our analyses. MetaGenyo provides a detailed and complete workflow, which can be implemented without programming skills in an easier-to-use setting. In addition, MetaGenyo was designed to guide users via the key stages of a genetic association studies meta-analysis, covering subgroup analysis, heterogeneity test, Hardy-Weinberg analysis, analysis of publication bias, statistical relationship for the various genetic models, and robustness evaluation of the outcomes.

Results

Study characteristics

Figure 1 presents the flow charts of the selected articles. Via extensive search, 100 studies were identified. Upon elimination of duplicated articles, there were 65 articles available for title and abstract screening. Owing to inadequate information, we further omitted 40 studies which were not relevant to our study after title and abstract glancing and 8 full-text publications which were not case-control. Since Liu *et al.* and Seedhouse *et al.* reported the findings on various subpopulations, our meta-analysis viewed each population group as a separate sample. A total

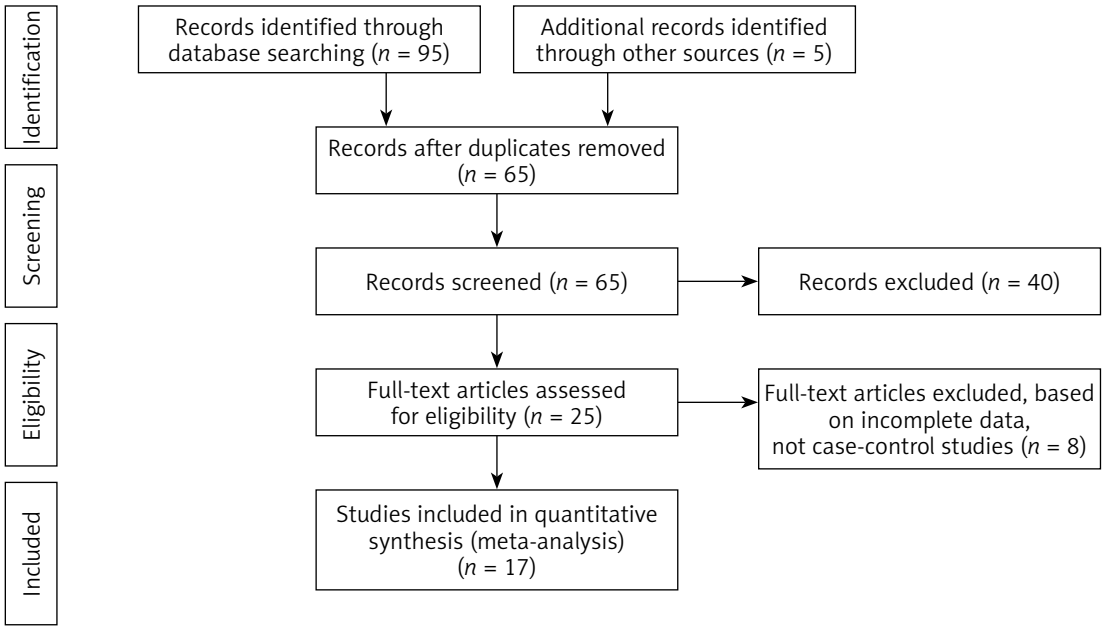

Figure 1. Selection of the final selected studies

of 17 studies consisting of 7241 controls and 4198 cases [36–52] met our inclusion requirements. Table I presents the characteristics of the eligible articles. Of the 17 eligible articles, twelve studies were carried out in Caucasians, four in Asians, one in persons of mixed descent and three in Africans. In addition, different studies investigated different types of leukaemia: four studies assessed acute lymphoblastic leukaemia (ALL), two investigated chronic lymphocytic leukaemia (CLL), thirteen investigated acute myeloid leukaemia and one assessed chronic myeloid leukaemia. When classified by the source of the controls, seventeen were population-based, and three were hospital-based. In all the included studies, the genotype distribution frequencies across the controls were consistent with Hardy-Weinberg equilibrium. We evaluated the link between Thr241Met polymorphism of XRCC3 and leukaemia risk susceptibility by evaluating the odds ratio (OR) and its 95% confidence interval (CI) among these five genetic variants: homozygote model (TT vs. CC), allele model (T vs. C), recessive model (TT vs. TC+CC), dominant model (TT+TC vs. CC), and over-dominant model (TC vs. TT+CC). No significant association was observed between leukaemia risk and Thr241Met polymorphism of XRCC3 across the five genetic variants (T vs. C: OR = 0.871, 95% CI: 0.606–1.251, p = 0.452; TT vs. TC+CC: OR = 0.881, 95% CI: 0.534–1.455, p = 0.622; TT+TC vs. CC: OR = 0.842, 95% CI: 0.629–1.127, p = 0.247; TC vs. TT+CC: OR = 1.247, 95% CI: 0.894–1.738, p = 0.194; TT vs. CC: OR = 0.778, 95% CI: 0.492–1.230, p = 0.282). Figures 2–4 represent overall pooled odds ratio in the three selected genetic models. The genotype data for Thr241Met polymorphism are presented in Table II.

Quantitative synthesis

In our ethnicity subgroup evaluation, we noted a significant protective effect of Thr241Met polymorphism of XRCC3 among Asians under four genetic models (T vs. C: OR = 0. 261, 95% CI: 0.131–0.520, p = 0.001; TT vs. TC+CC: OR = 0. 250, 95% CI: 0.112–0.558, p =0.001; TT+TC vs. CC: OR = 0. 081, 95% CI: 0.019–0.359, p = 0.001; TT vs. CC: OR = 0. 062, 95% CI: 0.013–0.288, p = 0.001) (Table III). Nevertheless, the oncogenic potential of Thr241Met polymorphism of XRCC3 among Asians was noted under one genetic model (TC vs. TT+CC: OR = 2.053, 95% CI: 0.843–

Table I. Included study characteristics

Author	Year	Country	Ethnicity	Cancer type	Source	Genotyping method
Fekry	2018	Egypt	African	ALL	PB	TaqMan
Pei	2018	China	Asian	ALL	PB	PCR-RFLP
Mutlu	2015	Turkey	Caucasian	CLL	PB	PCR-RFLP
Smolkova	2014	Germany	Caucasian	ALL	PB	TaqMan
Banescu	2014	Romania	Caucasian	CML	PB	PCR-RFLP
Banescu	2013	Romania	Caucasian	AML	PB	PCR-RFLP
Sorour	2013	Egypt	African	AML	HB	PCR-RFLP
Abramenko	2012	Ukraine	Caucasian	CLL	PB	PCR-RFLP
Yang	2011	China	Asian	AML	PB	PCR-RFLP
Liu	2011	China	Asian	AML	PB	PCR-RFLP
Liu	2011	China	Asian	AML	HB	PCR-RFLP
Hamdy	2011	Egypt	African	AML	HB	PCR-RFLP
Bhatla	2008	USA	Mixed	AML	PB	TaqMan
Guillem	2007	Spain	Caucasian	AML	PB	PCR-RFLP
Voso	2007	Italy	Caucasian	AML	PB	PCR-RFLP
Matullo	2006	Mixed	Caucasian	ALL	PB	TaqMan
Seedhouse	2004	UK	Caucasian	AML	PB	PCR-RFLP
Seedhouse	2004	UK	Caucasian	AML	PB	PCR-RFLP
Seedhouse	2002	UK	Caucasian	AML	PB	PCR-RFLP
Seedhouse	2002	UK	Caucasian	AML	PB	PCR-RFLP

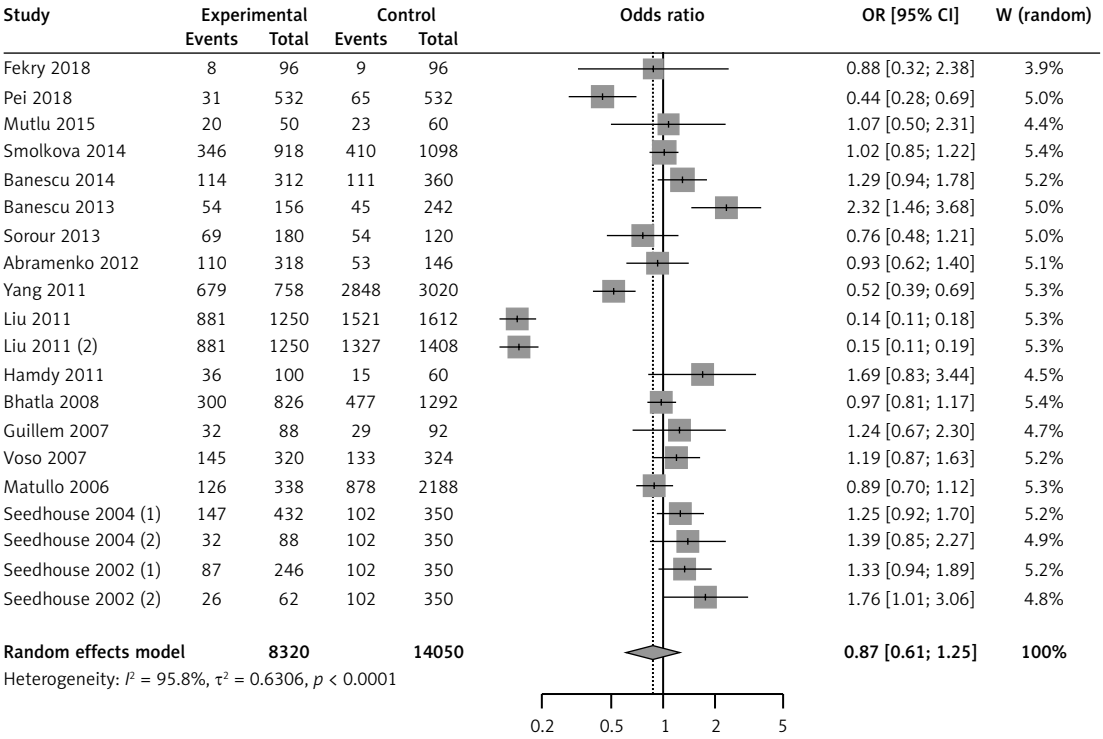

Figure 2. Overall pooled odds ratio for allele model

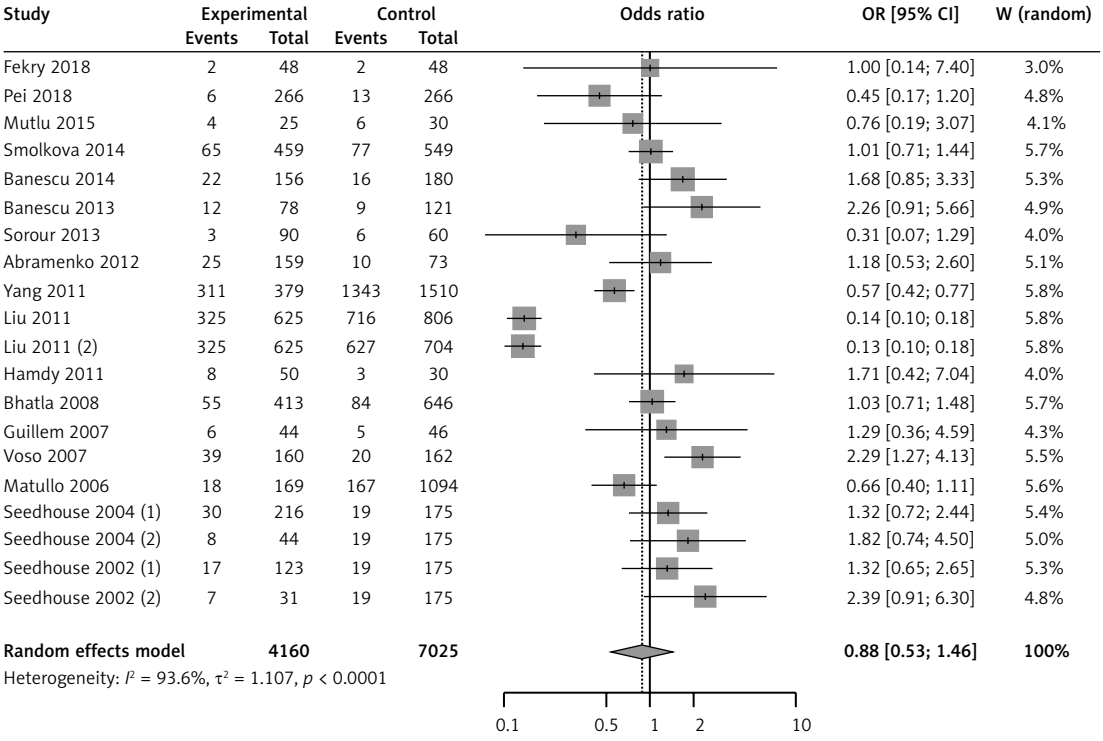

Figure 3. Overall pooled odds ratio for recessive model

4.997, p = 0.159). Regarding Caucasians, we observed oncogenic potential of Thr241Met polymorphism of XRCC3 under four genetic models (T vs. C: OR = 1. 206, 95% CI: 1.045–1.393, p = 0.010; TT vs. TC+CC: OR = 1. 255, 95% CI: 1.037–1.518, p = 0.020; TT+TC vs. CC: OR = 1. 159, 95% CI: 1.015–1.322, p = 0.029; TT vs. CC: OR = 1.298, 95% CI: 1.058–1.593, p = 0.001). No association was observed among Africans and persons of mixed ethnicity. No substantial association was found between XRCC3 Thr241Met polymorphism and risk of leukaemia when the source of control was taken into consideration. Our

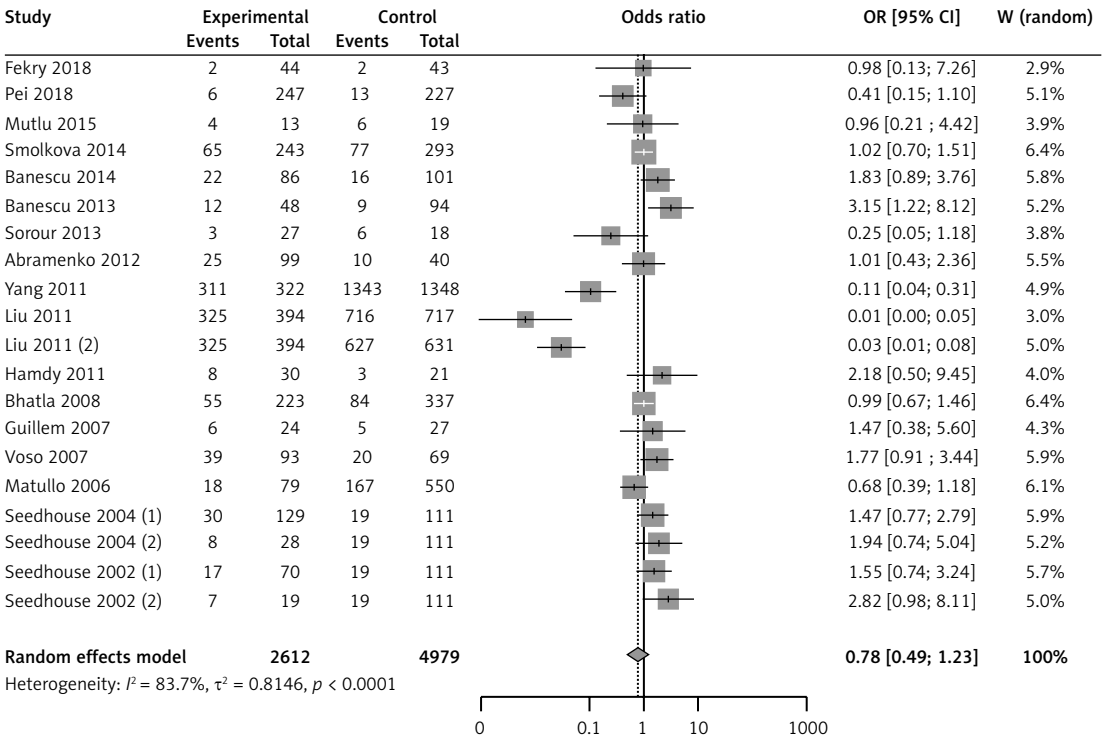

Figure 4. Overall pooled odds ratio for homozygous model

subgroup evaluation on the various types of leukaemia also showed no association between leukaemia risk (acute lymphoblastic leukaemia, acute myeloid leukaemia, chronic myeloid leukaemia and chronic lymphocytic leukaemia) and XRCC3 Thr241Met polymorphism under the various genetic models.

Publication bias and sensitivity analysis

Begg's funnel plot and Egger's test were used to determine the publication bias of the eligible articles used in our research. The symmetrical funnel plot for the different genetic models demonstrated that the results of our evaluation have not been influenced by selection bias (Figure 5). In addition, the results of the Egger test showed that there was no substantial bias among our eligible articles, because the *p*-values for all genetic models were larger than 0.05 (p = 0.257 for the homozygous model; p = 0.295 for the overdominant model; p = 0.151 for the dominant model; p = 0.974 for the recessive model; p = 0.365 for the allele model). Sensitivity was then analysed to evaluate the stability of our study findings (Figure 6). When a specific study was excluded, the statistical significance of the findings was not altered, confirming the validity and reliability of our study findings.

Discussion

Numerous molecular genomic research regarding the association of Thr241Met polymorphisms of XRCC3 with leukaemia risk have been conducted in various ethnic groups, but the findings are relatively ambiguous. The ambiguity among studies could be due to different sources of controls, research methodology and genetic ethnicities. In addition, it is understood that single studies with small sample size might not provide sufficient statistical power to evaluate minor risk factors. Hence, meta-analyses have the merit of pooling results from several relevant studies to achieve a more accurate estimation for possible genetic associations. We therefore performed this current meta-analysis comprising seventeen studies with the objective of presenting a precise and comprehensive conclusion.

Our study is the first comprehensive update analysis on the association between leukaemia risk and Thr241Met polymorphism of XRCC3. Seventeen individual case-control studies with 7061 controls and 4198 cases were included. Overall, no significant relationship was observed regarding increased leukaemia risk and Thr241Met polymorphism of XRCC3. No association was further noted despite the adjustment of primary studies' odds ratio and the assessment of potential confounding variables. The narrow confidence interval observed in the overall pooled odds ratio indicates the high power of the quantitative analysis; therefore the findings are convincing and conclusive. Yan et al. conducted a meta-analysis of 7 case-control studies on the association between leukaemia and Thr241Met polymorphism [33]. Their analysis of the pooled data of 1634 controls and 1070 cases showed an association among Asians but not Caucasians. However, our results contradict the findings of Yan *et al*. in that the outcomes of

Table II. Genotype data for selected studies

Study	Year	Cancer type	Case	Controls	TT_Case	TC_Case	CC_Case	TT_Controls	TC_Controls	TT_Controls	HW *p*-value	HW-adjusted *p*-value	Quality Score
Fekry	2018	ALL	48	48	2	4	42	2	5	41	0.007	0.037	11
Pei	2018	ALL	266	266	6	19	241	13	39	214	0.000	0.000	12
Mutlu	2015	CLL	25	30	4	12	9	6	11	13	0.219	0.415	13
Smolkova	2014	ALL	460	552	65	216	178	77	256	216	0.934	0.961	11
Banescu	2014	CML	156	180	22	70	64	16	79	85	0.697	0.821	11
Banescu	2013	AML	78	121	12	30	36	9	27	85	0.004	0.003	11
Sorour	2013	AML	90	60	3	63	24	6	42	12	0.001	0.013	11
Abramenko	2013	CLL	159	73	25	60	74	10	33	30	0.847	0.942	10
Yang	2011	AML	379	1510	311	57	11	1343	162	5	0.961	0.961	12
Liu	2011	AML	625	806	325	231	69	716	89	1	0.300	0.428	10
Liu	2011	AML	625	704	325	231	69	627	73	4	0.246	0.415	11
Hamdy	2011	AML	50	30	8	20	22	3	9	18	0.273	0.421	13
Bhatla	2008	AML	413	646	55	190	168	84	309	253	0.494	0.658	13
Guillem	2007	AML	44	46	6	20	18	5	19	22	0.769	0.905	12
Voso	2007	AML	160	162	39	67	54	20	93	49	0.018	0.071	12
Matullo	2006	ALL	169	1094	18	90	61	167	544	383	0.249	0.415	12
Seedhouse	2004	AML	216	175	30	87	99	19	64	92	0.130	0.289	13
Seedhouse	2004	AML	44	175	8	16	20	19	64	92	0.130	0.289	12
Seedhouse	2004	AML	123	175	17	53	53	19	64	92	0.130	0.289	11
Seedhouse	2004	AML	31	175	7	12	12	19	64	92	0.130	0.289	13

Table III. Subgroup analysis based on ethniCIty, source of control and type of cancer

Variables	No	T vs. C	P_{OR}	TT vs. TC+CC	P_{OR}	TT+TC vs. CC	P_{OR}	TC vs. TT+CC	P_{OR}	TT vs. CC	P_{OR}
Overall	20	0.871 (0.606–1.251)	0.452	0.881 (0.534–1.455)	0.622	0.842 (0.629–1.127)	0.247	1.247 (0.894–1.738)	0.194	0.778 (0.492–1.230)	0.282
Ethnicity:											
African	3	0.954 (0.663–1.374)	0.801	0.783 (0.319–1.920)	0.592	1.008 (0.592–1.717)	0.976	1.102 (0.649–1.871)	0.720	0.823 (0.321–2.108)	0.685
Asian	4	0.261 (0.131–0.520)	0.001	0.250 (0.112–0.558)	0.001	0.081 (0.019–0.359)	0.001	2.053 (0.843–4.997)	0.113	0.062 (0.013–0.288)	0.001
Caucasian	12	1.206 (1.045–1.393)	0.010	1.255 (1.037–1.518)	0.020	1.159 (1.015–1.322)	0.029	1.056 (0.880–1.266)	0.560	1.298 (1.058–1.593)	0.001
Mixed	1	0.975 (0.813–1.168)	0.780	1.028 (0.714–1.481)	0.883	0.939 (0.730–1.208)	0.623	0.929 (0.726–1.190)	0.561	0.986 (0.666–1.459)	0.944
Source of controls:											
HB	3	0.557 (0.125–2.485)	0.443	0.371(0.079–1.742)	0.209	0.398 (0.053–2.994)	0.371	2.078 (0.646–6.680)	0.220	0.244 (0.018–3.275)	0.287
PB	17	0.944 (0.675–1.319)	0.734	1.014(0.619–1.661)	0.955	0.954 (0.733–1.242)	0.725	1.141 (0.836–1.556)	0.406	0.979 (0.661–1.450)	0.915
Type of cancer:											
ALL	4	0.794 (0.572–1.101)	0.166	0.838 (0.634–1.106)	0.211	0.796 (0.540–1.174)	0.249	0.872 (0.600–1.269)	0.473	0.835 (0.620–1.125)	0.237
AML	13	0.865 (0.504–1.487)	0.601	0.879 (0.487–1.712)	0.703	0.750 (0.468–1.203)	0.233	1.465 (0.933–2.302)	0.097	0.673 (0.323–1.405)	0.292
CLL	2	0.958 (0.668–1.375)	0.816	1.057 (0.531–2.105)	0.874	0.895 (0.544–1.474)	0.663	0.866 (0.526–1.426)	0.572	1.001 (0.478–2.100)	0.997
CML	1	1.292 (0.937–1.781)	0.118	1.683 (0.850–3.332)	0.135	1.286 (0.834–1.983)	0.255	1.041 (0.676–1.602)	0.856	1.826 (0.888–3.756)	0.102

HB – hospital-based studies, Mixed – Caucasian, Asian, and blank, N – number of study, PB – population-based studies, AML – acute myeloid leukaemia, ALL – acute lymphoblastic leukaemia, CML – chronic myeloid leukaemia, CLL – chronic lymphocytic leukaemia.

our ethnicity-based subgroup analysis revealed that Thr241Met polymorphism of XRCC3 has a protective effect in the Asian population but has oncogenic potential in Caucasians. Nevertheless, oncogenic potential of Thr241Met polymorphism of XRCC3 among Asians was noted in the over-dominant genetic model. Our findings differ from those of Yan *et al.* in that individual studies with limited sample size could not have sufficient statistical strength to identify or provide a fluctuated estimate of a small risk factor. Hence, even though they observed no association in Caucasians, we object to this finding on the basis of the conclusive results obtained. Again, the oncogenic potential detected in our results among Asians under the over-dominant model necessitate extra studies due to the wide confidence intervals observed.

Heterogeneity plays a significant function in meta-analyses; hence it is essential to identify the cause of any possible heterogeneity in the end results. In our meta-analysis, we found substantial heterogeneity among the various studies; hence, we applied a subgroup model to investigate the source(s) of heterogeneity. Our ethnicity-based subgroup analysis showed that heterogeneity existed among the Asian population. This can be interpreted by the hypothesis that even though they possess an identical genetic background, different people have various habits and are prone to various risk factors, as well as different rates of risk factor exposure, which can induce heterogeneity. The stratification of the population is a disturbing problem and could contribute to snide and spurious proof on the relationship between disease and a marker, considering the differential influence of ethnicity and environmental disparities on genetic background. Our findings also confirm the findings of other studies where no association was observed between ovarian and gastric cancer risk and Thr241Met polymorphism of XRCC3 [53–55].

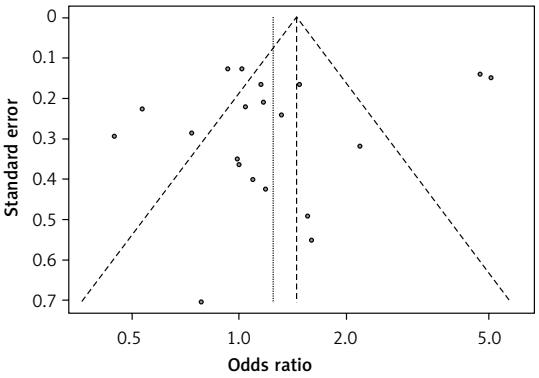

Figure 5. Funnel plot for all studies

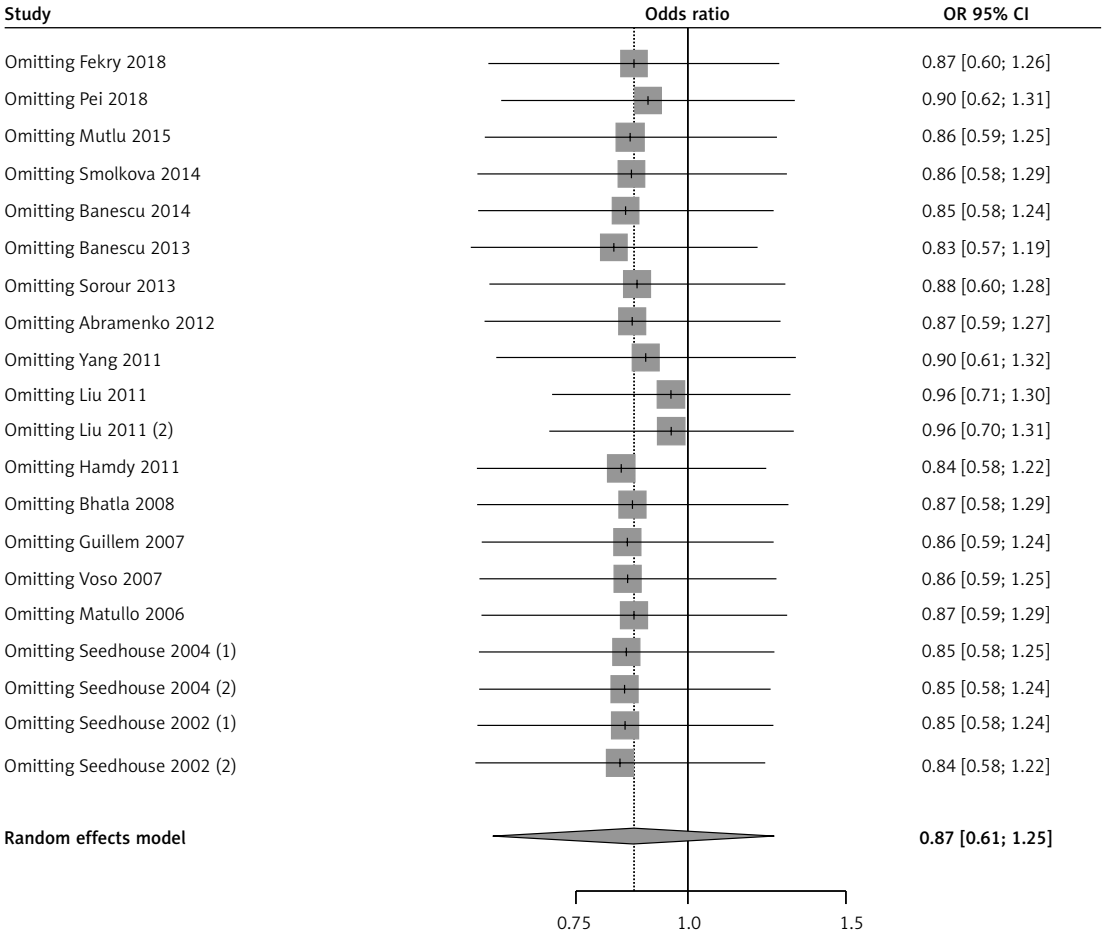

Figure 6. Sensitivity analysis for all studies

The DNA repair mechanism is integral to the maintenance of the stability of normal cell genomic functioning by reversing the damage to DNA. The damage of DNA at an elevated level accompanies the development and occurrence of different human diseases. XRCC3 is involved in the restoration phase of the DNA damage. Polymorphisms of XRCC3 can lead to cancer development by disrupting the repair of DNA capabilities of the protein encoded. Individuals with the genotype TT (Met/Met) could exhibit a DNA repair mechanism defect; therefore such individuals are more vulnerable to cancer, whereas individuals with one and/or two Thr alleles may have suitable mechanisms that protect against cancer.

Sensitivity analysis by repeatedly eliminating one test at a time revealed that the findings of the simplistic analysis were consistent, thus symbolizing the reliability of the study as per the findings of the sensitivity analysis. Another strength of our analysis was the consideration of adjusted odds ratio for monitoring the impact of confounding factors. Such a method confirmed our findings even further. In summary, we have conducted a high-quality quantitative analysis by following all meta-analysis steps (implementation of independent search, screening, selection, data extraction and quality score evaluation), including grey literature search and 6 databases (comprehensiveness).

Some limitations of our study exist. First, we included only Chinese and English published articles in our study, resulting in possible language bias. Secondly, subgroup analysis based on radiation exposure, gender and age was not conducted due to insufficient availability of primary studies' data. Again, in the subgroup analysis, only a handful of studies were included due to lack of information.

In conclusion, our updated quantitative evaluation of the association between leukaemia risk and XRCC3 Thr241Met polymorphism revealed no association in the overall population between Thr241Met single nucleotide polymorphism and leukaemia risk. However, we observed a protective effect in the Asian population and oncogenic potential in the Caucasian population.

Conflict of interest

The authors declare no conflict of interest.

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