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RESEARCH ARTICLE

Association between the XRCC1 Arg194Trp polymorphism and risk of cancer: evidence from 201 case–control studies

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Abstract The Arg194Trp polymorphism in the X-ray cross-complementing group 1 (XRCC1) had been implicated in cancer susceptibility. The previous published data on the association between XRCC1 Arg194Trp polymorphism and cancer risk remained controversial. Hence, we performed a meta-analysis to investigate the association between cancer susceptibility and XRCC1 Arg194Trp (59,227 cases and 81,587 controls from 201 studies) polymorphism in different inheritance models. We used odds ratios with 95 % confidence intervals to assess the strength of the association. Overall, significantly increased cancer risk was found (recessive model: (odds ration [OR]=1.18, 95 % confidence interval [CI]=1.09–1.27; homozygous model: OR=1.21, 95 % CI=1.10–1.33; additive model: OR=1.05, 95 % CI=1.01–1.09) when all eligible studies were pooled into the meta-analysis. In further stratified and sensitivity analyses, significantly increased glioma risk was found among Asians, significantly decreased lung cancer risk was found among Caucasians, and significant increased breast cancer risk was found among hospital-based studies. In summary, this meta-analysis suggests that Arg194Trp polymorphism may be associated with increased breast cancer risk, Arg194Trp polymorphism is associated with increased glioma risk among Asians, and Arg194Trp polymorphism is associated with decreased lung cancer risk among Caucasians. In addition, our work also points out the importance of new studies for Arg194Trp association in some cancer types, such as gastric, pancreatic, prostate, and nasopharyngeal cancers, where at least some of the covariates responsible for heterogeneity could be controlled, to obtain a more conclusive understanding about the function of the XRCC1 Arg194Trp polymorphism in cancer development (I^2>75 %).

Keywords XRCC1 · Arg194Trp · Polymorphism · Susceptibility · Meta-analysis · Cancer

Yan-Zhong Feng and Yi-Ling Liu contributed equally to this study.

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Introduction

DNA repair systems play critical roles in protecting against mutations and are essential for maintaining the integrity of the genome. Certain common genetic polymorphisms within the genes involved in DNA damage responses may contribute to the development of cancer and be associated with an increased risk of the disease. Because reduced DNA repair capacity may lead to genetic instability and carcinogenesis, genes involved in DNA repair have been proposed as candidate cancer susceptibility genes [1]. Until now, more than a hundred proteins implicated in DNA repair have been found in human cells. These proteins are implicated in four major DNA repair pathways, including nucleotide excision repair (NER), base

excision repair (BER), double-strand break repair (DSBR), and mismatch repair (MMR) [1,2].

The X-ray cross-complementing (*XRCC*) genes were initially discovered through their role in DNA damage response caused by ionizing radiation. They are important components of various DNA repair pathways contributing to DNA-damage processing and genetic stability [3]. The DNA repair enzymes *XRCC1* play a central role in the BER pathway [4,5]. *XRCC1* is located on chromosome no. 19q13.2–13.3, and its gene product is implicated in single-strand break repair and base excision repair mechanisms [6]. Although there are more than 300 validated single nucleotide polymorphisms (SNPs) in the XRCC1 gene reported in the dbSNP database (http://www.ncbi.nlm.nih.gov/SNP/), three of which are common [7] and lead to amino acid substitutions in XRCC1 at codon 194 (exon 6, base C to T, amino acid Arg to Trp, dbSNP no. rs1799782), codon 280 (exon 9, base G to A, amino acid Arg to His, dbSNP no. rs25489), and codon 399 (exon 10, base G to A, amino acid Arg to Gln, dbSNP no.rs25487), these non-conservative amino acid changes may alter XRCC1 function. This change in protein biochemistry leads to the supposition that variant alleles may diminish repair kinetics, thereby influencing susceptibility to adverse health effects, including cancer.

In the past decade, a number of molecular epidemiological studies have been done to evaluate the association between XRCC1 Arg194Trp polymorphism and different types of cancer risk in diverse populations [8–202]. The tumor types included breast cancer [8–34,170], lung cancer [35–51,53,54,163,178,189,190], head and neck cancer [68–77,79–83,117,119,122,123,125,128,137,146,157,165,172–174,191–194], esophageal cancer [101–106,141], and prostate cancer [96–100,126,166,175], and so on. However, the results were inconsistent or even contradictory. Partially because of the possible small effect of the polymorphism on cancer risk and the relatively small sample size in each of published studies. In addition, some recent meta-analyses analyzed such an association only for single cancer such as lung cancer, glioma, and leukemia, and so on [203–205]. Therefore, we performed a comprehensive meta-analysis by including the most recent and relevant articles to identify statistical evidence of the association between XRCC1 Arg194Trp polymorphism and risk of all cancers that have been investigated.

Materials and methods

Identification and eligibility of relevant studies

A comprehensive literature search was performed using the PubMed and ISI database for relevant articles published (the last search update was February 24, 2014) with the following key words "XRCC1," "polymorphism," "Variant," or "Mutation," and "Cancer" or "Carcinoma." MESH terms: XRCC1 [All Fields] and (("polymorphism, genetic" [MeSH Terms] OR ("polymorphism" [All Fields] AND "genetic" [All Fields]) or "genetic polymorphism" [All Fields] or "polymorphism" [All Fields]) or variant [All Fields] or ("mutation" [MeSH Terms] OR "mutation" [All Fields])) and (("neoplasms" [MeSH Terms] or "neoplasms" [All Fields] or "cancer" [All Fields]) or ("carcinoma" [MeSH Terms] or "carcinoma" [All Fields])). The search was not limited to language. Additional studies were identified by hand searching references in original articles and review articles. Authors were contacted directly regarding crucial data not reported in original articles. In addition, studies were identified by a manual search of the reference lists of reviews and retrieved studies. We included all the case–control studies and cohort studies that investigated the association between XRCC1 Arg194Trp polymorphism and cancer risk with genotyping data. All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. When the same sample was used in several publications, only the most complete information was included following careful examination.

Inclusion criteria

The included studies needed to have met the following criteria: (1) only the case–control studies or cohort studies were considered, (2) evaluated the XRCC1 Arg194Trp polymorphism and the risk of cancer, and (3) the genotype distribution of the polymorphisms in cases and controls were described in details and the results were expressed as odds ratio (OR) and corresponding 95 % confidence interval (95 % CI). Major reasons for exclusion of studies were as follows: (1) not for cancer research, (2) only case population, and (3) duplicate of previous publication (When the same sample was used in several publications, only the most complete information was included following careful examination).

Data extraction

Information was carefully extracted from all eligible studies independently by two investigators according to the inclusion criteria listed above. The following data were collected from each study: first author's name, year of publication, country of origin, ethnicity, source of controls, sample size, and numbers of cases and controls in the XRCC1 Arg194Trp genotypes whenever possible. Ethnicity was categorized as "Caucasian," "African," (including African Americans) and "Asian." We considered the samples of studies from India and Pakistan as of "Indian'" ethnicity, and samples from Middle Eastern countries as "Middle Eastern" ethnicity. When one study did not state which ethnic groups was included or if it was impossible to separate participants according to phenotype, the sample was termed as "mixed population." Meanwhile, studies investigating more than one kind of cancer were counted as

individual data set only in subgroup analyses by cancer type. We did not define any minimum number of patients to include in this meta-analysis. For articles that reported different ethnic groups and different countries or locations, we considered them different study samples for each category cited above.

Statistical analysis

Crude ORs together with their corresponding 95 % CIs were used to assess the strength of association between the XRCC1 Arg194Trp polymorphism and the risk of cancer. The pooled ORs were performed for co-dominant model (Trp/Trp versus Arg/Arg and Arg/Trp versus Arg/Arg), dominant model (Arg/Trp+Trp/Trp versus Arg/Arg), recessive model (Trp/Trp versus Arg/Arg+Arg/Trp), and additive model (Trp versus Arg), respectively. Between-study heterogeneity was assessed by calculating Q statistic (Heterogeneity was considered statistically significant if $P<0.10$) [206] and quantified using the I^2 value, a value that describes the percentage of variation across studies that are due to heterogeneity rather than chance, where $I^2=0$ % indicates no observed heterogeneity, with 25 % regarded as low, 50 % as moderate, and 75 % as high [207]. If results were not heterogeneous, the pooled ORs were calculated by the fixed-effect model (we used the Q statistic, which represents the magnitude of heterogeneity between-studies) [208]. Otherwise, a random-effect model was used (when the heterogeneity between-studies were significant) [209]. In addition to the comparison among all subjects, we also performed stratification analyses by cancer type (if one cancer type contained less than three individual studies, it was combined into the "other cancers" group), source of control, and ethnicity. Moreover, the extent to which the combined risk estimate might be affected by individual studies was assessed by consecutively omitting every study from the meta-analysis (leave-one-out sensitivity analysis). This approach would also capture the effect of the oldest or first positive study (first study effect). In addition, we also ranked studies according to sample size, and then repeated this meta-analysis. Sample size was classified according to a minimum of 200 participants and those with fewer than 200 participants. The cite criteria were previously described [210]. Last, sensitivity analysis was also performed, excluding studies whose allele frequencies in controls exhibited significant deviation from the Hardy–Weinberg equilibrium (HWE), given that the deviation may denote bias. Deviation of HWE may reflect methodological problems such as genotyping errors, population stratification, or selection bias. HWE was calculated by using the goodness-of-fit test, and deviation was considered when $P<0.05$. Begg's funnel plots [211] and Egger's linear regression test [212] were used to assess publication bias. A meta-regression analysis was carried out to identify the major sources of between-studies variation in the results, using the log of the ORs from each study as dependent variables and cancer type, ethnicity, and source of controls as the possible sources of heterogeneity. All of the calculations were performed using STATA version 10.0 (STATA Corporation, College Station, TX).

Results

Eligible studies and meta-analysis databases

Figure 1 graphically illustrates the trial flow chart. A total of 1,544 articles regarding XRCC1 polymorphisms with respect to cancer were identified. After screening the titles and abstracts, 689 articles were excluded because they were duplicated. In addition, 660 articles were excluded because they were review articles, case reports, and other polymorphisms of XRCC1. Last, of these published articles, six publications [52,63,78,162,170,201] were excluded because their populations overlapped with another six included studies [33,49,65,76,109,126]. As summarized in supplemental Table 1, 189 publications with 201 case–control studies were selected among the meta-analysis, including 59,227 cases and 81,587 controls. Among these studies, eghit studies were included in the dominant model only because they provided the genotypes of Arg/Trp+Trp/Trp versus Arg/Arg. In addition, there were 14 bladder cancer studies, 30 breast cancer studies, 4 cervical cancer studies, 18 colorectal cancer studies, 7 esophageal cancer studies, 10 gastric cancer studies, 11 glioma studies, 32 head and neck cancer studies, 18 leukemia studies, 25 lung cancer studies, 5 lymphoma studies, 3 pancreatic cancer studies, 9 prostate cancer studies, 6 skin cancer

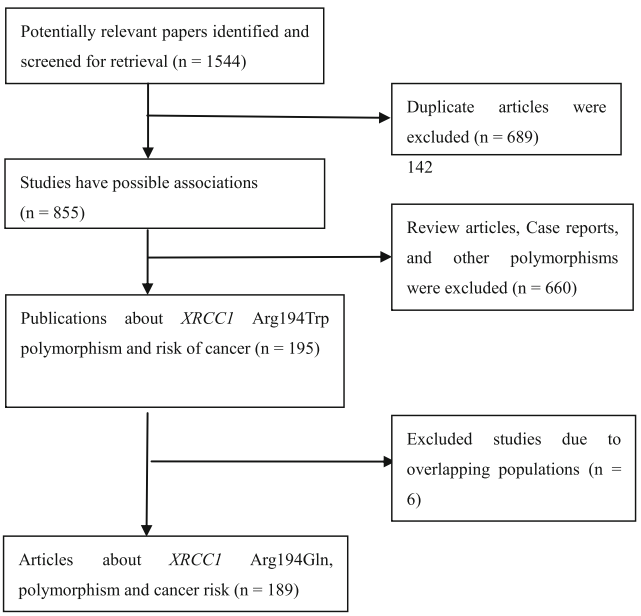

Fig. 1 Study flow chart explaining the selection of the 189 eligible case–control studies included in the meta-analysis

Table 1 Stratified analysis of XRCC1 Arg194Trp polymorphism on cancer risk

Variables	No. comparisons (SZ case/control)	Dominant model		Recessive model		Homozygous model		Heterozygous model		Additive model	
		OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)
Overall	201 (59,227/81,587)	1.04 (0.99–1.09)[a]	<0.001/55.5	1.18 (1.09–1.27)[a]	0.015/19.6	1.21 (1.10–1.33)[a]	<0.001/33.6	1.02 (0.97–1.06)[a]	<0.001/49.2	1.05 (1.01–1.09)[a]	<0.001/59.6
Cancer type											
Bladder cancer	14 (5,270/6,406)	0.98 (0.88–1.10)	0.334/10.9	1.31 (0.92–1.86)	0.199/26.6	1.42 (0.99–2.05)	0.232/22.9	0.97 (0.86–1.09)	0.402/4.4	1.01 (0.91–1.12)	0.162/28.1
Breast cancer	30 (13,914/14,793)	1.00 (0.92–1.10)[a]	0.007/43.2	1.04 (0.89–1.20)	0.725/0.0	1.06 (0.91–1.23)	0.622/0.0	0.99 (0.91–1.08)[a]	0.027/36.6	1.00 (0.91–1.08)[a]	0.003/47.1
Cervical cancer	4 (704/1,062)	1.14 (0.94–1.39)	0.421/0.0	1.29 (0.89–1.86)	0.182/41.3	1.33 (0.90–1.95)	0.170/43.6	1.12 (0.91–1.37)	0.244/29.2	1.14 (0.97–1.33)	0.213/35.3
Colorectal cancer	18 (5,267/8,713)	1.04 (0.95–1.13)	0.154/25.6	1.00 (0.83–1.20)	0.751/0.0	1.03 (0.85–1.24)	0.587/0.0	1.04 (0.95–1.14)	0.198/21.6	1.02 (0.95–1.10)	0.172/23.9
Esophageal cancer	7 (1,697/2,857)	0.99 (0.87–1.12)	0.676/0.0	*1.36* (*1.10–1.70*)	0.175/34.8	*1.32* (*1.05–1.66*)	0.271/21.7	0.93 (0.82–1.06)	0.616/0.0	1.05 (0.96–1.16)	0.504/0.0
Gastric cancer	10 (2,619/4,278)	[b]	<0.001/81.4	1.31 (0.93–1.83)[a]	0.090/41.6	1.32 (0.83–2.10)[a]	0.004/65.0	[b]	<0.001/77.9	[b]	<0.001/82.6
Glioma	11 (4,501/6,830)	[b]	<0.001/81.4	*1.77* (*1.41–2.22*)	0.805/0.0	*2.03* (*1.61–2.57*)	0.176/29.2	[b]	<0.001/80.3	[b]	<0.001/82.9
HNC	32 (6,018/9,865)	1.12 (0.97–1.30)[a]	<0.001/61.5	1.18 (0.84–1.65)[a]	0.049/33.7	1.26 (0.84–1.87)[a]	0.004/47.8	1.10 (0.95–1.26)*	0.001/50.8	1.10 (0.96–1.26)[a]	<0.001/64.5
Leukemia	18 (2,949/5,815)	1.16 (0.98–1.37)[a]	0.031/42.1	1.20 (0.82–1.76)[a]	0.042/40.7	1.16 (0.71–1.88)[a]	0.013/48.6	*1.18* (*1.04–1.33*)	0.121/29.7	1.16 (0.98–1.36)[a]	0.002/57.5
Lung cancer	25 (8,830/11,133)	0.93 (0.84–1.04)[a]	0.008/45.0	*1.16* (*1.01–1.35*)	0.182/20.9	1.19 (0.95–1.48)[a]	0.083/30.6	0.90 (0.82–1.01)[a]	0.070/31.2	0.97 (0.88–1.08)[a]	<0.001/56.7
Lymphoma	5 (1,383/1,919)	0.97 (0.68–1.37)[a]	0.024/64.3	1.14 (0.78–1.67)	0.102/48.3	1.05 (0.47–2.37)[a]	0.056/56.6	0.99 (0.73–1.35)[a]	0.073/53.3	0.94 (0.70–1.28)[a]	0.012/68.9
Pancreatic cancer	3 (749/1,277)	[b]	<0.001/88.2	1.14 (0.58–2.25)	0.780/0.0	1.21 (0.60–2.42)	0.668/0.0 %	[b]	<0.001/88.1	[b]	<0.001/87.7
Prostate cancer	9 (2,800/2,607)	1.00 (0.79–1.28)[a]	0.019/56.5	1.15 (0.82–1.62)	0.306/15.3	1.17 (0.83–1.66)	0.181/29.7	0.97 (0.76–1.25)[a]	0.023/55.0	1.02 (0.84–1.25)[a]	0.031/52.8
Skin cancer	6 (957/1,600)	0.96 (0.78–1.19)	0.204/30.9	0.73 (0.45–1.20)	0.874/0.0	0.74 (0.45–1.23)	0.831/0.0	0.99 (0.80–1.24)	0.116/43.3	0.93 (0.78–1.11)	0.470/0.0
Other cancer	9 (1,569/2,432)	0.93 (0.74–1.18)[a]	0.069/45.0	1.07 (0.84–1.38)	0.394/4.2	1.18 (0.90–1.55)	0.539/0.0	0.98 (0.83–1.14)	0.136/35.3	0.93 (0.77–1.13)[a]	0.035/51.8

All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by a), ORs were calculated using random-effects models

[a] Significant heterogeneity

[b] The results were excluded due to high heterogeneity, the italic values indicate that the results are statistically significant

studies, and 9 studies with the "other cancers." All of the cases were pathologically confirmed.

Quantitative synthesis

The evaluations of the association of XRCC1 Arg194Trp polymorphism with cancer risk are shown in Table 1. Overall, significantly increased cancer risk was observed (recessive model: OR=1.18, 95 % CI=1.09–1.27, P_h=0.015, I^2=19.6 %; homozygous model: OR=1.21, 95 % CI=1.10–1.33, P_h<0.001, I^2=33.6 %; additive model: OR=1.05, 95 % CI=1.01–1.09, P_h<0.001, I^2=59.6 %) when all the eligible studies were pooled the meta-analysis. Then, we performed subgroup analysis by cancer type. We found that individuals with the minor variant genotypes had a higher risk of esophageal cancer (recessive model: OR=1.36, 95 % CI=1.10–1.70, P_h=0.175, I^2=34.8 %; homozygous model: OR=1.32, 95 % CI=1.05–1.66, P_h=0.271, I^2=21.7 %), glioma (recessive model: OR=1.77, 95 % CI=1.41–2.22, P_h=0.805, I^2=0.0 %; homozygous model: OR=2.03, 95 % CI=1.61–2.57, P_h=0.176, I^2=29.2 %), leukemia (heterozygous model: OR=1.18, 95 % CI=1.04–1.33, P_h=0.121, I^2=29.7 %), and lung cancer (recessive model: OR=1.16, 95 % CI=1.01–1.35, P_h=0.182, I^2=20.9 %), as shown in Table 1. For the lung cancer studies, we also performed subgroup analysis by smoker habits, no significant association was found among smokers and non-smokers.

Ethnicity and cancer risk attributed to the XRCC1 Arg194Trp polymorphism

We further examined the association of the XRCC1 Arg194Trp polymorphism and cancer risk according to cancer type and ethnicity (Table 2) because there was significant heterogeneity between studies. For samples of Asians, we found that individuals with the minor variant genotypes had a higher risk of esophageal cancer (recessive model: OR=1.34, 95 % CI=1.07–1.68, P_h=0.122, I^2=41.5 %; homozygous model: OR=1.30, 95 % CI=1.03–1.65, P_h=0.185, I^2=35.4 %) and glioma (dominant model: OR=1.23, 95 % CI=1.09–1.39, P_h=0.237, I^2=26.4 %; recessive model: OR=1.80, 95 % CI=1.40–2.31, P_h=0.625, I^2=0.0 %; homozygous model: OR=1.87, 95 % CI=1.45–2.41, P_h=0.569, I^2=0.0 %; additive model: OR=1.29, 95 % CI=1.11–1.51, P_h=0.057, I^2=53.5 %). For samples of Caucasians, significantly increased cancer risk was observed among leukemia (dominant model: OR=1.28, 95 % CI=1.06–1.54, P_h=0.186, I^2=28.0 %; heterozygous model: OR=1.26, 95 % CI=1.04–1.53, P_h=0.496, I^2=0.0 %) and significantly decreased cancer risk was observed among lung cancer (dominant model: OR=0.84, 95 % CI=0.74–0.95, P_h=0.139, I^2=32.4 %; additive model: OR=0.83, 95 % CI=0.73–0.93, P_h=0.254, I^2=19.9 %) and lymphoma (additive model: OR=0.77, 95 % CI=0.59–0.99, P_h=0.400, I^2=0.0 %).

Source of controls and cancer risk attributed to the XRCC1 Arg194Trp polymorphism

We also examined the association of the XRCC1 Arg194Trp polymorphism and cancer risk according to cancer type and source of controls (Table 3). For the population-based studies, the XRCC1 Arg194Trp polymorphism was associated with risk of breast cancer (dominant model: OR=0.91, 95 % CI=0.84–0.99, P_h=0.117, I^2=30.7 %; heterozygous model: OR=0.91, 95 % CI=0.81–0.99, P_h=0.174, I^2=24.8 %), esophageal cancer (recessive model: OR=1.44, 95 % CI=0.81–0.99, P_h=0.174, I^2=24.8 %; homozygous model: OR=1.41, 95 % CI=1.11–1.78, P_h=0.386, I^2=1.2 %), gastric cancer (dominant model: OR=0.79, 95 % CI=0.63–0.98, P_h=0.727, I^2=0.0 %), and glioma (recessive model: OR=1.93, 95 % CI=1.07–3.46, P_h=0.525, I^2=0.0 %; homozygous model: OR=4.90, 95 % CI=2.46–9.76, P_h=0.641, I^2=0.0 %). For the hospital-based studies, significant association was observed among bladder cancer (recessive model: OR=1.78, 95 % CI=1.10–2.88, P_h=0.217, I^2=27.7 %; homozygous model: OR=1.81, 95 % CI=1.11–2.95, P_h=0.170, I^2=33.9 %), breast cancer (dominant model: OR=1.17, 95 % CI=1.05–1.30, P_h=0.266, I^2=17.6 %; heterozygous model: OR=1.16, 95 % CI=1.04–1.29, P_h=0.423, I^2=2.3 %; additive model: OR=1.14, 95 % CI=1.01–1.29, P_h=0.085, I^2=37.3 %), colorectal cancer (dominant model: OR=1.17, 95 % CI=1.03–1.33, P_h=0.238, I^2=21.6 %; heterozygous model: OR=1.17, 95 % CI=1.02–1.33, P_h=0.244, I^2=20.9 %; additive model: OR=1.14, 95 % CI=1.02–1.27, P_h=0.254, I^2=19.9 %), gastric cancer (recessive model: OR=1.48, 95 % CI=1.17–1.87, P_h=0.135, I^2=40.5 %), giloma (recessive model: OR=1.75, 95 % CI=1.37–2.23, P_h=0.682, I^2=0.0 %; homozygous model: OR=1.81, 95 % CI=1.41–2.32, P_h=0.611, I^2=0.0 %), and lung cancer (heterozygous model: OR=0.86, 95 % CI=0.75–1.00, P_h=0.025, I^2=47.4 %).

Anatomical site, histological type, and association of the XRCC1 Arg194Trp polymorphism with cancer risk

We next completed a subgroup analysis by cancer type and histological type or anatomical location (Table 4). Overall, there was no association between the XRCC1 Arg194Trp polymorphism and risk of lung adenocarcinoma, lung squamous cell carcinoma, and cardia gastric cancer. For head and neck cancer, significant increased oral cancer risk was observed among heterozygous model (OR=1.34, 95 % CI=1.07–1.68, P_h=0.183, I^2=35.7 %). For leukemia, significant increased acute myeloblastic leukemia (AML) risk was observed among

Table 2 Summary ORs (95 % CI) categorized by ethnicity for the XRCC1 Arg194Trp polymorphism under different genetic models and cancer type

Ethnicity	Cancer type	No. comparisons (SZ case/control)	Dominant model		Recessive model		Homozygote		Heterozygote		Additive model	
			OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)
Asian	Breast cancer	6 (2,860/3,211)	1.08 (0.98–1.20)	0.527/0.0	1.06 (0.89–1.26)	0.346/10.9	1.09 (0.92–1.31)	0.385/5.0	1.08 (0.97–1.20)	0.524/0.0	1.06 (0.98–1.15)	0.450/0.0
	Colorectal cancer	5 (1,852/3,391)	1.07 (0.87–1.31)[a]	0.024/64.3	0.98 (0.80–1.19)	0.870/0.0	1.01 (0.82–1.24)	0.463/0.0	1.08 (0.88–1.32)[a]	0.037/60.9	1.03 (0.90–1.19)[a]	0.063/55.1
	Esophageal cancer	5 (1,516/2,333)	0.99 (0.87–1.13)	0.802/0.0	*1.34* (*1.07–1.68*)	0.122/45.1	*1.30* (*1.03–1.65*)	0.185/35.4	0.94 (0.81–1.07)	0.799/0.0	1.05 (0.95–1.16)	0.457/0.0
	Gastric cancer	6 (1,833/1,978)	[b]	<0.001/87.1	1.33 (0.90–1.96)[a]	0.039/57.2	[b]	0.001/75.9	[2]	0.001/84.0	[b]	0.001/87.3
	Glioma	6 (2,207/2,418)	*1.23* (*1.09–1.39*)	0.237/26.4	*1.80* (*1.40–2.31*)	0.625/0.0	*1.87* (*1.45–2.41*)	0.569/0.0	1.12 (0.98–1.28)	0.557/0.0	*1.29* (*1.11–1.51*)[a]	0.057/53.5
	HNC	8 (1,388/1,744)	[b]	<0.001/80.8	1.04 (0.61–1.77)[a]	0.001/68.7	[b]	<0.001/77.1	1.17 (0.86–1.60)[a]	<0.001/73.7	[b]	<0.001/83.5
	Leukemia	5 (996/2,725)	0.99 (0.74–1.33)[a]	0.033/62.0	0.78 (0.41–1.49)[a]	0.088/54.2	0.76 (0.34–1.69)[a]	0.029/66.9	1.01 (0.75–1.35)[a]	0.063/58.9	0.92 (0.68–1.23)[a]	0.008/74.7
	Lung cancer	11 (3,672/3,921)	1.00 (0.87–1.15)[a]	0.058/43.9	1.16 (0.99–1.36)	0.191/26.6	1.19 (0.93–1.52)[a]	0.066/42.5	0.97 (0.89–1.07)	0.295/15.6	1.04 (0.92–1.17)	0.010/57.0
	Prostate cancer	3 (514/519)	[b]	<0.001/86.4	1.01 (0.67–1.52)	0.778/0.0	1.03 (0.67–1.57)	0.262/25.4	[b]	0.001/86.5	[b]	0.005/81.1
Caucasian	Bladder cancer	10 (4,597/5,672)	0.92 (0.81–1.04)	0.845/0.0	1.27 (0.68–2.34)	0.483/0.0	1.23 (0.66–2.28)	0.497/0.0	0.90 (0.79–1.03)	0.824/0.0	0.93 (0.82–1.05)	0.720/0.0
	Breast cancer	13 (5,984/6,084)	1.01 (0.91–1.12)	0.224/21.7	0.96 (0.67–1.36)	0.560/0.0	0.92 (0.62–1.35)	0.497/0.0	1.01 (0.91–1.12)	0.393/5.4	1.00 (0.91–1.11)	0.122/32.6
	Colorectal cancer	9 (1,793/3,596)	0.93 (0.77–1.12)	0.401/4.1	1.77 (0.86–3.63)	0.488/0.0	1.72 (0.84–3.52)	0.469/0.0	0.89 (0.74–1.08)	0.524/0.0	0.96 (0.81–1.15)	0.206/26.8
	Gastric cancer	3 (626/2,150)	0.83 (0.64–1.07)	0.654/0.0	1.24 (0.53–2.90)	0.261/20.8	1.19 (0.50–2.81)	0.269/18.3	0.82 (0.58–1.15)	0.536/0.0	0.90 (0.67–1.19)	0.183/43.6
	Glioma	4 (2,214/4,312)	0.87 (0.73–1.02)	0.538/0.0	1.34 (0.50–3.62)	0.447/0.0	1.32 (0.49–3.55)	0.441/0.0	0.86 (0.73–1.02)	0.414/0.0	0.88 (0.76–1.04)	0.324/11.4
	HNC	13 (2,210/3,941)	0.98 (0.83–1.16)	0.570/0.0	1.31 (0.65–2.64)	0.830/0.0	1.31 (0.65–2.65)	0.828/0.0	0.97 (0.82–1.15)	0.620/0.0	0.99 (0.84–1.16)	0.504/0.0
	Leukemia	10 (1,458/2,485)	*1.28* (*1.06–1.54*)	0.186/28.0	1.47 (0.89–2.44)	0.167/30.2	1.60 (0.70–3.65)[a]	0.094/39.5	*1.26* (*1.04–1.53*)	0.496/0.0	1.26 (0.98–1.61)[a]	0.042/48.5
	Lung cancer	11 (4,646/6,567)	*0.84* (*0.74–0.95*)	0.139/32.4	1.29 (0.57–2.92)[a]	0.097/40.5	1.26 (0.55–2.86)[a]	0.094/41.0	*0.83* (*0.73–0.93*)	0.254/19.9	0.88 (0.73–1.07)	0.025/51.2
	Lymphoma	3 (1,017/1,150)	0.78 (0.59–1.02)	0.187/40.4	0.55 (0.19–1.63)	0.292/16.8	0.53 (0.18–1.56)	0.340/7.4	0.80 (0.61–1.05)	0.143/48.5	*0.77* (*0.59–0.99*)	0.400/0.0
	Prostate cancer	3 (1,774/1,555)	0.86 (0.69–1.06)	0.826/0.0 %	0.99 (0.39–2.50)	0.656/0.0	0.97 (0.38–2.44)	0.659/0.0	0.85 (0.69–1.06)	0.825/0.0	0.87 (0.71–1.06)	0.745/0.0
African	Breast cancer	3 (982/917)	0.95 (0.73–1.25)	0.605/0.0	1.26 (0.34–4.62)	0.457/0.0	1.24 (0.34–4.56)	0.476/0.0	0.95 (0.72–1.25)	0.433/0.0	0.97 (0.75–1.25)	0.767/0.0
Indian	HNC	5 (1,103/1,182)	[b]	<0.001/81.6	1.13 (0.68–1.90)	0.149/47.4	1.57 (0.42–5.94)	0.064/63.6	[b]	0.004/77.7	[b]	0.001/83.0

All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by a), ORs were calculated using random-effects models

[a] Significant heterogeneity

[b] The results were excluded due to high heterogeneity, the italic values indicate that the results are statistically significant

Table 3 Summary ORs (95 % CI) and value of the heterogeneity of XRCC1 Arg194Trp polymorphism for studies according to source of controls and cancer type

Source of control	Cancer type	No. comparisons (SZ case/control)	Dominant model		Recessive model		Homozygous model		Heterozygous model		Additive model	
			OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)
PB	Breast cancer	16 (9,790/10,095)	*0.91 (0.84–0.99)*	0.117/30.7	0.99 (0.77–1.26)	0.820/0.0	0.95 (0.74–1.23)	0.806/0.0	*0.91 (0.81–0.99)*	0.174/24.8	0.91 (0.83–1.01)[a]	0.080/35.4
	Colorectal cancer	6 (2,016/4,987)	0.93 (0.82–1.05)	0.670/0.0	0.94 (0.74–1.19)	0.967/0.0	0.92 (0.72–1.17)	0.958/0.0	0.93 (0.81–1.06)	0.658/0.0	0.94 (0.85–1.04)	0.741/0.0
	Esophageal cancer	4 (1,401/2,346)	1.00 (0.87–1.14)	0.688/0.0	*1.44 (1.15–1.81)*	0.228/30.8	*1.41 (1.11–1.78)*	0.386/1.2	0.92 (0.80–1.07)	0.536/0.0	1.08 (0.97–1.19)	0.654/0.0
	Gastric cancer	4 (814/2,316)	*0.79 (0.63–0.98)*	0.727/0.0	0.86 (0.49–1.49)	0.249/28.2	0.78 (0.44–1.38)	0.211/35.8	0.78 (0.60–1.03)	0.755/0.0	0.83 (0.67–1.03)	0.285/20.3
	Glioma	3 (990/2,021)	[b]	<0.001/94.3	*1.93 (1.07–3.46)*	0.525/0.0	*4.90 (2.46–9.76)*	0.641/0.0	[b]	<0.001/97.2	[b]	<0.001/96.2
	HNC	5 (1,177/2,599)	0.98 (0.62–1.56)[a]	0.004/73.6	1.80 (0.83–3.92)	0.500/0.0	2.07 (0.96–4.46)	0.330/13.3	0.99 (0.65–1.51)[a]	0.015/67.8	0.97 (0.63–1.48)[a]	0.004/74.0
	Lung cancer	11 (2,610/4,446)	0.98 (0.87–1.11)	0.356/9.2	1.17 (0.93–1.49)	0.359/9.1	1.16 (0.91–1.48)	0.264/19.5	0.96 (0.85–1.09)	0.503/0.0	1.02 (0.92–1.12)	0.232/22.2
	Prostate cancer	4 (1,663/1,750)	0.88 (0.72–1.08)	0.791/0.0	1.14 (0.56–2.33)	0.149/43.7	1.12 (0.54–2.29)	0.152/43.3	0.87 (0.71–1.07)	0.976/0.0	0.90 (0.75–1.09)	0.343/10.0
HB	Bladder cancer	12 (4,934/5,062)	0.98 (0.87–1.09)	0.217/23.1	*1.78 (1.10–2.88)*	0.217/27.7	*1.81 (1.11–2.95)*	0.170/33.9	0.96 (0.85–1.09)	0.264/18.9	0.98 (0.85–1.14)[a]	0.090/38.9
	Breast cancer	13 (3,599/4,066)	*1.17 (1.05–1.30)*	0.266/17.6	1.07 (0.89–1.28)	0.356/9.1	1.13 (0.93–1.37)	0.283/16.4	*1.16 (1.04–1.29)*	0.423/2.3	*1.14 (1.01–1.29)*[a]	0.085/37.3
	Cervical cancer	4 (704/1,062)	1.14 (0.94–1.39)	0.421/0.0	1.29 (0.89–1.86)	0.182/41.3	1.33 (0.90–1.95)	0.170/43.6	1.12 (0.91–1.38)	0.244/29.2	1.14 (0.97–1.33)	0.213/35.3
	Colorectal cancer	11 (2,946/3,366)	*1.17 (1.03–1.33)*	0.238/21.6	1.13 (0.84–1.53)	0.435/0.2	1.27 (0.93–1.73)	0.396/4.9	*1.17 (1.02–1.33)*	0.244/20.9	*1.14 (1.02–1.27)*	0.254/19.9
	Esophageal cancer	3 (296/511)	0.93 (0.68–1.28)	0.303/16.2	0.67 (0.29–1.56)	0.382/0.0	0.64 (0.27–1.52)	0.391/0.0	0.96 (0.70–1.32)	0.329/0.0	0.92 (0.71–1.19)	0.291/19.1
	Gastric cancer	6 (1,805/1,962)	[b]	<0.001/84.0	*1.48 (1.17–1.87)*	0.135/40.5	1.60 (0.94–2.72)[a]	0.010/66.8	[b]	<0.001/80.7	[2]	<0.001/83.7
	Glioma	8 (3,511/4,809)	1.12 (0.94–1.33)[a]	0.012/61.0	*1.75 (1.37–2.23)*	0.682/0.0	*1.81 (1.41–2.32)*	0.611/0.0	1.03 (0.92–1.15)	0.156/34.1	1.16 (0.98–1.39)[a]	0.001/72.1
	HNC	27 (4,841/7,266)	1.14 (0.97–1.34)[a]	<0.001/60.2	1.13 (0.78–1.63)[a]	0.035/39.1	1.19 (0.78–1.82)[a]	0.004/51.0	1.11 (0.96–1.29)[a]	0.004/48.5	1.12 (0.97–1.30)[a]	<0.001/63.8
	Leukemia	16 (2,367/3,045)	1.15 (0.93–1.42)[a]	0.017/47.8	1.21 (0.76–1.95)[a]	0.041/42.6	1.11 (0.60–2.06)[a]	0.007/54.0	1.14 (0.93–1.39)[a]	0.087/35.2	1.17 (0.95–1.43)[a]	0.001/62.7
	Lung cancer	14 (6,220/6,687)	0.90 (0.77–1.05)[a]	0.003/59.0	1.16 (0.96–1.40)	0.120/32.8	1.17 (0.86–1.59)[a]	0.058/41.5	0.86 (0.75–1.00)[a]	0.025/47.4	0.95 (0.81–1.10)[a]	<0.001/68.9
	Lymphoma	3 (399/821)	1.07 (0.58–1.96)[a]	0.032/70.8	1.31 (0.87–1.97)	0.117/53.4	1.47 (0.62–3.47)[a]	0.076/61.3	1.10 (0.63–1.94)[a]	0.070/62.3	1.07 (0.68–1.67)[a]	0.029/71.9
	Pancreatic cancer	3 (749/1,277)	[b]	<0.001/88.2	1.14 (0.58–2.25)	0.780/0.0 %	1.21 (0.60–2.42)	0.668/0.0 %	[b]	<0.001/88.1	[b]	<0.001/87.7
	Prostate cancer	5 (1,137/857)	1.12 (0.73–1.71)[a]	0.004/74.3	1.16 (0.79–1.70)	0.389/3.2	1.19 (0.80–1.77)	0.189/34.8	[b]	0.003/75.4	1.13 (0.83–1.53)[a]	0.019/66.0
	Skin cancer	5 (742/737)	0.69 (0.70–1.13)	0.245/26.5	0.76 (0.46–1.27)	0.836/0.0	0.78 (0.46–1.30)	0.771/0.0	0.99 (0.80–1.24)	0.116/43.3	0.93 (0.78–1.11)	0.470/0.0

All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by a), ORs were calculated using random-effects models. The italic values indicate that the results are statistically significant

PB population-based studies, *HB* hospital-based studies

[a] Significant heterogeneity

[b] The results were excluded due to high heterogeneity

Table 4 Summary ORs (95 % CI) for the XRCC1 Arg194Trp polymorphism categorized by histological type or anatomical area in a specific tumor site

Cancer type	Histological type or anatomical area	No. comparisons (SZ case/control)	Dominant model		Recessive model		Homozygous model		Heterozygous model		Additive model	
			OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)
HNC	Nasopharyngeal cancer	3 (1,121/1,175)	[a]	<0.001/89.2	[a]	0.004/81.6	[a]	0.001/86.6	[a]	0.002/84.1	[a]	<0.001/91.1
	Oral cancer	5 (766/909)	1.36 (0.95–1.95)[b]	0.045/59.0	1.13 (0.69–1.87)	0.162/38.9	1.30 (0.78–2.19)	0.121/45.2	*1.34 (1.07–1.68)*	0.183/35.7	1.26 (0.89–1.78)[b]	0.011/69.5
	Thyroid cancer	7 (1,040/2,487)	1.01 (0.77–1.34)[b]	0.088/45.6	1.41 (0.62–3.23)[b]	0.041/56.8	1.42 (0.55–3.67)[b]	0.014/65.1	1.03 (0.85–1.26)	0.202/31.2	1.08 (0.81–1.42)[b]	0.019/63.1
	Thyroid cancer/ Asian	3 (499/674)	0.87 (0.52–1.44)[b]	0.026/72.7	0.88 (0.33–2.32)[b]	0.025/72.9	[a]	0.007/79.8	0.95 (0.74-1.21)	0.118/53.2	[a]	0.006/80.7
	Other sites[c]	13 (2,518/4,231)	1.06 (0.82–1.37)[b]	0.001/64.9	1.07 (0.69–1.65)	0.799/0.0	1.04 (0.67–1.61)	0.547/0.0	0.99 (0.78–1.27)[b]	0.014/53.8	1.01 (0.80–1.26)[b]	0.010/55.7
	Other site/Caucasian	9 (1,567/3,034)	0.98 (0.80–1.19)	0.266/19.9	0.89 (0.38–2.08)	0.924/0.0	0.90 (0.38–2.09)	0.918/0.0	0.98 (0.81–1.20)	0.315/14.2	0.97 (0.80–1.16)	0.255/21.2
Lung cancer	AC	5 (880/3,276)	0.97 (0.80–1.18)	0.634/0.0	1.43 (0.86–2.40)	0.587/0.0	1.41 (0.82–2.41)	0.682/0.0	1.38 (0.64–1.83)	0.542/0.0	1.01 (0.92–1.94)	0.632/0.0
	SC	3 (1,147/2,876)	0.86 (0.70–1.05)	0.850/0.0	1.38 (0.68–2.80)	0.558/0.0	1.35 (0.63–2.88)	0.554/0.0	1.22 (0.48–1.68)	0.614/0.0	0.98 (0.78–1.38)	0.527/0.0
Gastric cancer	Cardia	4 (692/2,420)	0.93 (0.77–1.13)	0.153/43.1	1.10 (0.80–1.52)	0.634/0.0	1.07 (0.76–1.49)	0.419/0.0	0.91 (0.74–1.12)	0.241/28.5	0.98 (0.84–1.13)	0.150/43.5
Leukemia	AML	4 (915/2,468)	*1.32 (1.11–1.56)*	0.120/48.6	1.50 (0.58–3.87)[b]	0.022/68.7	1.72 (0.61–4.81)[b]	0.014/71.8	*1.31 (1.10–1.57)*	0.380/2.4	1.33 (0.96–1.84)[b]	0.017/70.6
	CALL	8 (835/1,240)	1.16 (0.87–1.56)[b]	0.094/42.7	0.90 (0.52–1.56)	0.117/39.3	1.08 (0.40–2.95)[b]	0.071/46.4	1.11 (0.89–1.39)	0.353/9.9	1.16 (0.85–1.58)[b]	0.016/59.3
	CALL/ Caucasian	5 (582/668)	1.16 (0.88–1.54)	0.434/0.0	1.11 (0.50–2.45)	0.180/36.2	1.15 (0.52–2.54)	0.163/38.7	1.17 (0.88–1.57)	0.739/0.0	1.14 (0.89–1.47)	0.158/39.4

All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by b), ORs were calculated using random-effects models. The italic values indicate that the results are statistically significant

AC adenocarcinoma, *SC* squamous cell carcinoma

[a] The results were excluded due to high heterogeneity

[b] Significant heterogeneity

[c] Includes a diversity of head and neck cancer not separated by anatomical area in the studies analyzed

dominant model (OR=1.32, 95 % CI=1.11–1.56, P_h=0.120, I^2=48.6 %) and heterozygous model (OR=1.31, 95 % CI=1.10–1.57, P_h=0.380, I^2=2.4 %).

Heterogeneity analysis

There was significant heterogeneity among these studies for dominant model comparison (P_h<0.001), recessive model comparison (P_h=0.015), homozygous model comparison (P_h<0.001), heterozygous model comparison (P_h<0.001), and additive model comparison (P_h<0.001). Then, we assessed the source of heterogeneity by ethnicity, cancer type, source of controls, HWE, and sample size. Table 5 lists the results of meta-regression analysis. The results of meta-regression indicated that source of controls (dominant model: P=0.008; heterozygous model: P=0.012; additive model: P=0.012) and HWE (dominant model: P=0.002; homozygous model: P=0.022; heterozygous model: P=0.016; additive model: P=0.004) but not ethnicity (dominant model: P=0.857; recessive model: P=0.877; homozygous model: P=0.902; heterozygous model: P=0.994; additive model: P=0.955), cancer type (dominant model: P=0.637; recessive model: P=0.503; homozygous model: P=0.380; heterozygous model: P=0.658; additive model: P=0.458), and sample size (dominant model: P=0.082; recessive model: P=0.394; homozygous model: P=0.080; heterozygous model: P=0.182; additive model: P=0.058) contributed to substantial heterogeneity among the meta-analysis.

High between-studies heterogeneity was observed among gastric cancer (dominant model: I^2=81.4; heterozygous model: I^2=77.9; additive model: I^2=82.6), glioma (dominant model: I^2=81.4; heterozygous model: I^2=80.3; additive model: I^2=82.9), pancreatic cancer (dominant model: I^2=88.2; heterozygous model: I^2=88.1; additive model: I^2=87.7), Asians of gastric cancer (dominant model: I^2=87.1; homozygote model: I^2=75.9; heterozygous model: I^2=84.0; additive model: I^2=87.3), Asians of head and neck cancer (dominant model: I^2=80.8; homozygote model: I^2=77.1; additive model: I^2=83.5), Asians of prostate cancer (dominant model: I^2=86.4; heterozygous model: I^2=86.5; additive model: I^2=81.1), Indians of head and neck cancer (dominant model: I^2=81.6; heterozygous model: I^2=77.7; additive model: I^2=83.0), population-based studies of glioma (dominant model: I^2=94.3; heterozygous model: I^2=97.2; additive model: I^2=96.2), hospital-based studies of gastric cancer (dominant model: I^2=84.0; homozygote model: I^2=80.7; additive model: I^2=83.7), hospital-based studies of pancreatic cancer (dominant model: I^2=88.2; heterozygous model: I^2=88.1; additive model: I^2=87.7), hospital-based studies of prostate cancer (heterozygous model: I^2=75.4), nasopharyngeal cancer (dominant model: I^2=89.2; recessive model: I^2=81.6; homozygote model: I^2=86.6; heterozygous model: I^2=84.1; additive model: I^2=91.1), and Asians of thyroid cancer (homozygote

Table 5 meta-regression analysis of the main characteristics for XRCC1 Arg194Trp polymorphisms

Study characteristics	Dominant model			Recessive model			Homozygous model			Heterozygous model			Additive model		
	Coef.	95 % CI	*P*	Coef.	95 % CI	*P*	Coef.	95 % CI	*P*	Coef.	95 % CI	*P*	Coef.	95 % CI	*P*
Cancer type	–0.003	(–0.014; 0.009)	0.637	–0.007	(–0.028; 0.013)	0.637	–0.011	(–0.036; 0.014)	0.380	–0.002	(–0.013; 0.008)	0.658	–0.004	(–0.015; 0.007)	0.458
Ethnicity	0.004	(–0.041; 0.049)	0.857	–0.008	(–0.106; 0.090)	0.877	–0.007	(–0.120; 0.106)	0.902	0.0002	(–0.042; 0.043)	0.994	0.001	(–0.041; 0.043)	0.955
Source of controls	–0.125	(–0.217; –0.033)	0.008	–0.055	(–0.221; 0.112)	0.519	–0.088	(–0.287; 0.111)	0.387	–0.113	(–0.201; – 0.025)	0.012	–0.111	(–0.198; –0.024)	0.012
HWE	–0.314	(–0.518; –0.111)	0.002	–0.213	(–0.483; 0.056)	0.121	–0.375	(–0.695; –0.055)	0.022	–0.243	(–0.441; –0.046)	0.016	–0.252	(–0.425; –0.079)	0.004
Sample size	–0.194	(–0.412; 0.024)	0.082	–0.196	(–0.647; 0.255)	0.394	–0.453	(–0.961; 0.054)	0.080	–0.157	(–0.388; 0.074)	0.182	–0.193	(–0.392; 0.006)	0.058

model: I^2=79.8; additive model: I^2=80.7). Significant deviation from HWE was detected in the ten articles. When these studies were excluded, the high between-studies heterogeneity was deleted among glioma (dominant model: I^2=34.5; heterozygous model: I^2=23.7; additive model: I^2=53.8) and population-based studies of glioma (dominant model: I^2=0.0). When the small studies were excluded, the high between-studies heterogeneity was deleted among glioma (dominant model: I^2=54.7; heterozygous model: I^2=31.1; additive model: I^2=70.6) and population-based studies of glioma (dominant model: I^2=0.0).

Sensitivity analysis

Examining genotype frequencies in the controls, significant deviation from HWE was detected in the ten articles [106,118,145,156,161,169,180,182,185,200]. When these studies were excluded, the result was changed among population-based studies of glioma (recessive model: OR=3.34, 95 % CI=0.56–20.06; homozyhous model: OR=3.30, 95 % CI=0.55–19.80), as shown in Table 6. When the study of small sample was excluded, the results was changed among leukemia (heterozygous model: OR=1.14, 95 % CI=0.96–1.36), lung cancer (recessive model: OR=1.17, 95 % CI=0.97–1.41), Caucasians of lymphoma (additive model: OR=0.79, 95 % CI=0.61–1.03), population-based studies of glioma (recessive model: OR=3.34, 95 % CI=0.56–20.06; homozyhous model: OR=3.30, 95 % CI=0.55–19.80), hospital-based studies of bladder cancer (recessive model: OR=1.34, 95 % CI=0.69–2.58; homozygous model: OR=1.42, 95 % CI=0.74–2.75), and hospital-based studies of lung cancer (heterozygous model: OR=0.86, 95 % CI=0.74–1.01), as shown in Table 7. Last, when the study of Xing et al. [103] was excluded, the results were changed among esophageal cancer (recessive model: OR=1.18, 95 % CI=0.91–1.52; additive model: OR=1.15, 95 % CI=0.88–1.51), Asians of esophageal cancer (recessive model: OR=1.13, 95 % CI=0.86–1.48; additive model: OR=1.12, 95 % CI=0.84–1.48), and population-based studies of esophageal cancer (recessive model: OR=1.26, 95 % CI=0.96–1.65; additive model: OR=1.24, 95 % CI=0.93–1.64). When the study of Mitra et al. [27] was excluded, the results were changed among the population-based studies of breast cancer (dominant model: OR=0.93, 95 % CI=0.86–1.01; heterozygous model: OR=0.93, 95 % CI=0.86–1.01). When the study of Li et al. [206] was excluded, the results were changed among hospital-based studies of colorectal cancer (dominant model: OR=1.08, 95 % CI=0.93–1.25; heterozygous model: OR=1.08, 95 % CI=0.92–1.25; additive model: OR=1.07, 95 % CI=0.94–1.22). When the study of Shen et al. [113] was excluded, the results were changed among hospital-based studies of gastric cancer (recessive model: OR=1.27, 95 % CI=0.96–1.68). When the study of Ramachandran et al. [83] was excluded, the results were changed among oral cancer (heterozygous model: OR=1.21, 95 % CI=0.95–1.54).

Publication bias

Both Begg's funnel plot and Egger's test were performed to access the publication bias of this meta-analysis. Begg's funnel plots did not reveal any evidence of obvious asymmetry in any genetic model in the overall meta-analysis (Fig. 2). The Egger's test results also suggested no evidence of publication bias in the meta-analysis of Arg194Trp (dominant model: P=0.651; heterozygous model: P=0.697; recessive model: P=0.534; additive model: P=0.533; homozygous model: P=0.678), indicating that our results were statistically robust.

Discussion

Cancer is the result of a series of DNA alternations in single cell or clone of that cell, which lead to loss of normal function, aberrant or uncontrolled cell growth, and often metastases. BER is initiated by recognition and excision of damaged base by the specific DNA glycosylase. X-ray repair cross-complementing groups 1 protein is a scaffold protein directly associated with polymerase beta, DNA ligase III, and poly (ADP-ribose) polymerase in a complex to facilitate the BER and single-strand break repair (SSBR) processes [213–215]. A recent report provides data showing that the E2F1 transcription factor regulates XRCC1 and promotes DNA repair [216]. A XRCC1 deletion mutation in null homozygous mice is embryonic lethal [217]. XRCC1 has two BRCA1 carboxyl-terminal (BRCT) domains (BRCT1 and BRCT2), located centrally and at the C-terminal end, respectively. BRCT2 is responsible for binding and stabilizing DNA ligase III and is required for single-strand breaks and gaps repair (SSBR), specifically during the G0/G1 phases of the cell cycle [218]. The center of BRCT1 domain binds to and down-regulates the single-strand breaks and gaps recognition protein PARP1 and is required for efficient SSBR during both G1 and S/G2 phases of the cell cycle. Arg194Trp is located in a domain that separates but connects the XRCC1 NH2 terminal and BRCT. Arg194Trp mutation will change XRCC1's structure but may not influence the function of XRCC1. A number of studies have reported the association of XRCC1 Arg194Trp polymorphism with risk of cancer; however, the results remained controversial, although some original studies thought that Arg194Trp polymorphism was associated with risk of cancer, others had different opinions. In order to resolve this conflict, the meta-analysis of 201 eligible studies including 59,227 cases and 81,587 controls was performed to derive a more precise estimation of the association between

Table 6 Summary ORs (95 % CI) and value of the heterogeneity of XRCC1 Arg194Trp polymorphism under different genetic models according to studies with HWE on cancer risk

Variables	No. comparisons (SZ case/control)	Dominant model		Recessive model		Homozygous model		Heterozygous model		Additive model	
		OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)
Overall	190 (57,443/78,660)	1.02 (0.98–1.07)[a]	<0.001/52.3	*1.15 (1.06–1.25)*[a]	0.036/17.1	*1.16 (1.06–1.28)*[a]	<0.001/29.8	*1.00 (0.96–1.05)*[a]	<0.001/45.1	*1.03 (0.99–1.07)*[a]	<0.001/56.9
Cancer type											
Cervical cancer	3 (601/948)	1.09 (0.89–1.34)	0.679/0.0	1.99 (0.48–8.30)[a]	0.066/70.4	2.09 (0.47–9.27)[a]	0.060/71.8	1.06 (0.85–1.32)	0.672/0.0	1.11 (0.94–1.31)	0.202/38.5
Esophageal cancer	6 (1,572/2,428)	1.00 (0.88–1.14)	0.627/0.0	*1.34 (1.07–1.68)*	0.122/45.1	*1.30 (1.03–1.65)*	0.185/35.4	0.95 (0.83–1.09)	0.580/0.0	1.06 (0.96–1.17)	0.404/2.0
Gastric cancer	9 (2,533/3,849)	[b]	<0.001/83.3	1.26 (0.87–1.84)	0.062/47.9	1.28 (0.76–2.15)	0.002/69.3	[b]	<0.001/80.2	[b]	<0.001/84.6
Glioma	7 (3,553/5,624)	0.99 (0.86–1.11)	0.165/34.5	*1.46 (1.03–2.08)*	0.778/0.0	*1.49 (1.05–2.13)*	0.746/0.0	0.96 (0.86–1.08)	0.256/23.7	1.01 (0.87–1.18)[a]	0.055/53.8
Skin cancer	5 (760/1,507)	0.88 (0.69–1.11)	0.359/8.3	0.76 (0.40–1.46)	0.757/0.0	0.67 (0.34–1.31)	0.738/0.0	0.90 (0.71–1.14)	0.323/14.4	0.88 (0.72–1.08)	0.498/0.0
Ethnicity and cancer type											
Gastric cancer/ Caucasian	2 (540/1721)	0.77 (0.56–1.05)	0.707/0.0	0.48 (0.06–3.75)	–	0.46 (0.06–3.64)	–	0.74 (0.45–1.21)	–	0.71 (0.45–1.12)	–
Glioma/Asian	3 (1339/1312)	1.13 (0.96–1.32)	0.381/0.0	*1.48 (1.02–2.15)*	0.648/0.0	*1.52 (1.04–2.22)*	0.598/0.0	1.08 (0.92–1.27)	0.544/0.0	*1.14 (1.00–1.31)*	0.262/25.3
Source of control and cancer type											
Esophageal cancer/PB	3 (1,276/1,917)	1.02 (0.88–1.17)	0.651/0.0	*1.42 (1.12–1.80)*	0.130/50.9	*1.39 (1.09–1.78)*	0.230/32.0	0.94 (0.81–1.10)	0.459/0.0	1.09 (0.97–1.21)	0.535/0.0
Gastric cancer/PB	3 (728/1,887)	*0.74 (0.58–0.96)*	0.877/0.0	0.64 (0.33–1.25)	0.759/0.0	0.56 (0.28–1.12)	0.846/0.0	0.73 (0.53–1.02)	0.977/0.0	*0.74 (0.57–0.96)*	0.844/0.0
Glioma/HB	5 (2,643/3,703)	1.00 (0.83–1.21)[a]	0.075/52.8	1.42 (0.99–2.03)	0.802/0.0	*1.45 (1.01–2.08)*	0.750/0.0	0.98 (0.86–1.11)	0.191/34.6	1.02 (0.85–1.23)[a]	0.035/61.4
Glioma/PB	2 (910/1,921)	0.90 (0.68–1.20)	0.697/0.0	3.34 (0.56–20.06)	–	3.30 (0.55–19.80)	–	0.88 (0.66–1.18)	–	*0.94 (0.72–1.24)*	–
Cervical cancer/HB	3 (601/948)	1.09 (0.89–1.34)	0.679/0.0	1.99 (0.48–8.30)[a]	0.066/70.4	2.09 (0.47–9.27)[a]	0.060/71.8	1.06 (0.85–1.32)	0.672/0.0	1.11 (0.94–1.31)	0.202/38.5
Skin cancer/HB	4 (545/644)	0.77 (0.58–1.01)	0.810/0.0	0.82 (0.42–1.63)	0.683/0.0	0.72 (0.36–1.44)	0.611/0.0	0.77 (0.58–1.02)	0.930/0.0	0.81 (0.64–1.02)	0.744/0.0

All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by a), ORs were calculated using random-effects models. The italic values indicate that the results are statistically significant

PB population-based studies, *HB* hospital-based studies

[a] Significant heterogeneity

[b] The results were excluded due to high heterogeneity

Table 7 Summary ORs (95 % CI) and value of the heterogeneity of XRCC1 Arg194Trp polymorphism under different genetic models according to studies with a minimum of 200 participants on cancer risk

Variables	No. comparisons (SZ case/control)	Dominant model		Recessive model		Homozygous model		Heterozygous model		Additive model	
		OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)
Overall	177 (57,852/80,013)	1.03 (0.98–1.08)[a]	<0.001/55.2	*1.17* (*1.08–1.27*)[a]	0.010/21.8	*1.19* (*1.08–1.31*)[a]	<0.001/33.0	1.01 (0.97–1.06)[a]	<0.001/47.1	1.04 (0.99–1.08)[a]	<0.001/60.0
Cancer type											
Bladder cancer	11 (5,143/6,312)	1.00 (0.89–1.11)	0.291/16.0	1.28 (0.90–1.83)	0.159/32.4	1.40 (0.97–2.03)	0.175/30.5	0.98 (0.88–1.11)	0.394/5.0	1.02 (0.92–1.13)	0.107/37.8
Breast cancer	28 (13,818/14,687)	1.00 (0.91–1.10)[a]	0.004/46.3	1.03 (0.89–1.20)	0.717/0.0	1.05 (0.90–1.23)	0.607/0.0	1.00 (0.93–1.06)[a]	0.019/39.6	1.00 (0.95–1.06)[a]	0.002/50.4
Cervical cancer	3 (687/1,032)	1.15 (0.94–1.40)	0.262/25.4	1.29 (0.89–1.86)	0.182/41.3	1.33 (0.90–1.95)	0.170/43.6	1.12 (0.90–137)	0.244/29.2	1.14 (0.97–1.33)	0.213/35.3
Colorectal cancer	15 (5,072/8,517)	1.03 (0.95–1.13)	0.126/30.4	0.99 (0.82–1.19)	0.690/0.0	1.02 (0.84–1.23)	0.502/0.0	1.04 (0.95–1.14)	0.195/23.3	1.02 (0.95–1.10)	0.133/29.7
Esophageal cancer	6 (1,641/2,762)	0.98 (0.86–1.11)	0.836/0.0	*1.36* (*1.10–1.70*)	0.175/34.8	*1.32* (*1.05–1.66*)	0.271/21.7	0.92 (0.81–1.05)	0.817/0.0	1.05 (0.95–1.15)	0.575/0.0
Glioma	10 (4,421/6,730)	1.09 (0.93–1.27)[a]	0.019/54.7	*1.77* (*1.39–2.25*)	0.723/0.0	*1.83* (*1.43-2.34*)	0.666/0.0	1.01 (0.91–1.12)	0.170/31.1	1.14 (0.97–1.34)[a]	0.001/70.6
HNC	29 (5,772/9,612)	1.10 (0.94–1.29)[a]	<0.001/64.5	1.23 (0.86–1.76)[a]	0.040/36.4	1.31 (0.85–2.00)[a]	0.002/50.8	1.08 (0.93–1.25)[a]	<0.001/54.2	1.09 (0.94–1.26)[a]	<0.001/67.4
Leukemia	13 (2,663/5,426)	1.12 (0.93–1.37)[a]	0.013/52.9	1.13 (0.75–1.70)[a]	0.016/51.7	1.04 (0.61–1.76)[a]	0.005/57.9	1.14 (0.96–1.36)[a]	0.079/38.2	1.12 (0.94–1.34)[a]	0.001/63.7
Lung cancer	23 (8,692/11,004)	0.93 (0.83–1.04)[a]	0.005/48.7	1.17 (0.97–1.41)	0.220/18.1	1.17 (0.93–1.46)[a]	0.086/30.7	0.91 (0.82–1.01)[a]	0.060/33.6	0.97 (0.87–1.08)[a]	<0.001/59.9
Lymphoma	4 (1,350/1,867)	1.02 (0.75–1.38)[a]	0.055/60.6	0.94 (0.45–1.98)[a]	0.071/57.3	0.96 (0.40–2.29)[a]	0.033/65.8	1.02 (0.84–1.24)	0.180/38.6	0.99 (0.74–1.32)[a]	0.016/71.1
Skin cancer	5 (937/1,580)	0.97 (0.72–1.29)	0.135/43.0	0.71 (0.43–1.18)	0.931/0.0	0.72 (0.43–1.22)	0.871/0.0	1.01 (0.72–1.41)[a]	0.066/54.6	0.92 (0.77–1.10)	0.424/0.0
Ethnicity and cancer type											
Bladder cancer/Caucasian	8 (4,489/5,591)	0.92 (0.82–1.04)	0.732/0.0	1.17 (0.61–2.24)	0.420/0.0	1.16 (0.61–2.22)	0.410/0.9	0.91 (0.80–1.04)	0.739/0.0	0.93 (0.82–1.05)	0.523/0.0
Breast cancer/Caucasian	12 (5,941/6,053)	1.00 (0.90–1.12)	0.198/25.1	0.96 (0.67–1.36)	0.560/0.0	0.92 (0.62–1.35)	0.497/0.0	1.01 (0.90–1.12)	0.361/8.6	1.00 (0.91–1.10)	0.102/36.1
Colorectal cancer/ Caucasian	7 (1,645/3,448)	0.90 (0.74–1.09)	0.510/0.0	1.65 (0.77–3.53)	0.398/3.7	1.61 (0.75–3.43)	0.379/6.3	0.87 (0.71–1.06)	0.751/0.0	0.93 (0.78–1.12)	0.221/27.2
HNC/Asian	7 (1,295/1,646)	[b]	<0.001/83.5	1.12 (0.63–1.98)[a]	0.002/71.5	[b]	<0.001/79.7	[b]	<0.001/77.2	[b]	<0.001/85.8
HNC/Indian	4 (1,045/1,125)	[b]	<0.001/86.2	1.13 (0.68–1.90)	0.149/47.4	1.57 (0.42–5.94)[a]	0.064/63.6	[b]	<0.001/85.1	[b]	<0.001/88.6
HNC/Caucasian	12 (2,115/3,843)	0.95 (0.80–1.13)	0.705/0.0	1.27 (0.59–2.72)	0.759/0.0	1.26 (0.59–2.69)	0.761/0.0	0.94 (0.79–1.12)	0.741/0.0	0.96 (0.81–1.13)	0.637/0.0
Leukemia/Asian	4 (933/2,659)	0.95 (0.68–1.33)[a]	0.016/71.0	0.78 (0.41–1.49)[a]	0.088/54.2	0.76 (0.34–1.69)[a]	0.029/66.9	1.01 (0.75–1.35)[a]	0.063/58.9	0.92 (0.68–1.23)[a]	0.008/74.7
Leukemia/Caucasian	7 (1,263/2,300)	*1.26* (*1.04–1.54*)	0.160/35.1	1.16 (0.46–2.96)[a]	0.067/49.1	1.20 (0.43–3.35)[a]	0.032/56.6	*1.27* (*1.03–1.56*)	0.496/0.0	1.21 (0.91–1.60)[a]	0.030/56.9
Lung cancer/Asian	10 (3622/3871)	1.01 (0.88–1.16)	0.042/48.4	1.14 (0.98–1.34)	0.245/21.5	1.14 (0.96–1.34)[a]	0.067/43.7	0.98 (0.89–1.08)	0.319/13.5	1.04 (0.92–1.18)[a]	0.006/61.2
Lung cancer/Caucasian	10 (4558/6488)	*0.83* (*0.74–0.94*)	0.129/34.9	1.29 (0.57–2.92)[a]	0.097/40.5	1.26 (0.55–2.86)[a]	0.094/41.0	*0.82* (*0.72–0.93*)	0.247/21.3	0.87 (0.71–1.06)[a]	0.020/54.2
Lymphoma/Caucasian	2 (984/1098)	0.82 (0.62–1.08)	0.490/0.0	0.38 (0.11–1.31)	0.446/0.0	0.37 (0.11–1.29)	0.455/0.0	0.85 (0.65–1.13)	0.423/0.0	0.79 (0.61–1.03)	0.588/0.0
Source of control and cancer type											
Bladder cancer/HB	9 (4,807/4,968)	0.99 (0.88–1.11)	0.167/31.4	1.34 (0.69–2.58)[a]	0.071/48.4	1.42 (0.74–2.75)[a]	0.077/47.3	0.98 (0.86–1.11)	0.231/24.8	1.00 (0.85–1.17)[a]	0.048/50.7
Breast cancer/HB	11 (3,503/3,960)	*1.17* (*1.05–1.30*)	0.181/27.6	1.06 (0.88–1.27)	0.330/11.9	1.12 (0.92–1.36)	0.252/20.1	*1.16* (*1.04–1.30*)	0.349/10.0	*1.14* (*1.00–1.30*)[a]	0.044/46.5
Cervical cancer/HB	3 (687/1,032)	1.15 (0.94–1.40)	0.262/25.4	1.29 (0.89–1.86)	0.182/41.3	1.33 (0.90–1.95)	0.170/43.6	1.12 (0.90–137)	0.244/29.2	1.14 (0.97–1.33)	0.213/35.3
Colorectal cancer//PB	5 (1,969/4,939)	0.93 (0.82–1.05)	0.537/0.0	0.94 (0.74–1.19)	0.920/0.0	0.92 (0.72–1.17)	0.901/0.0	0.93 (0.82–1.06)	0.527/0.0	0.94 (0.85–1.04)	0.612/0.0
Colorectal cancer/HB	9 (2,798/3,218)	*1.17* (*1.03–1.32*)	0.223/24.8	1.11 (0.82–1.50)	0.409/3.0	1.24 (0.91–1.70)	0.349/10.3	*1.16* (*1.02–1.33*)	0.289/17.3	*1.13* (*1.01–1.26*)	0.214/25.8
Esophageal cancer/HB	2 (240/416)	0.87 (0.63–1.20)	0.882/0.0	0.67 (0.29–1.56)	0.382/0.0	0.64 (0.27–1.52)	0.391/0.0	0.89 (0.64–1.25)	0.921/0.0	0.87 (0.67–1.14)	0.684/0.0
Glioma/PB	2 (910/1,921)	0.90 (0.68–1.20)	0.697/0.0	3.34 (0.56–20.06)	–	3.30 (0.55–19.80)	–	0.88 (0.66–1.18)	–	0.94 (0.72–1.34)	–
HNC/HB	24 (4,595/7,013)	1.12 (0.95–1.33)[a]	<0.001/63.9	1.18 (0.79–1.76)[a]	0.026/42.7	1.24 (0.78–1.98)[a]	0.002/54.7	1.09 (0.93–1.28)[a]	0.002/52.7	1.11 (0.95–1.30)[a]	<0.001/67.3

Table 7 (continued)

Variables	No. comparisons (SZ case/control)	Dominant model		Recessive model		Homozygous model		Heterozygous model		Additive model	
		OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)	OR (95 % CI)	P_h/I^2 (%)
Leukemia/HB	11 (2,081/2,656)	1.10 (0.86–1.42)[a]	0.006/59.3	1.09 (0.64–1.85)[a]	0.012/55.7	0.93 (0.47–1.87)[a]	0.002/64.0	1.11 (0.89–1.40)[a]	0.053/44.8	1.12 (0.89–1.41)[a]	<0.001/69.7
Lung cancer/HB	12 (6,082/6,558)	0.89 (0.75–1.05)[a]	0.001/64.5	1.14 (0.94–1.37)	0.156/29.5	1.13 (0.83–1.55)[a]	0.060/42.3	0.86 (0.74–1.01)[a]	0.018/52.2	0.93 (0.79–1.09)[a]	<0.001/73.3
Lymphoma/HB	2 (366/769)	1.25 (0.96–1.62)	0.112/60.3	1.23 (0.55–2.73)[a]	0.055/72.8	[b]	0.028/79.2	1.22 (0.92–1.61)	0.294/9.3	[b]	0.045/75.1
Skin cancer/HB	4 (722/717)	0.88 (0.69–1.12)	0.163/41.5	0.73 (0.44–1.22)	0.951/0.0	0.74 (0.44–1.26)	0.826/0.0	0.93 (0.63–1.37)[a]	0.086/54.6	0.87 (0.72–1.07)	0.480/0.0

All summary ORs were calculated using fixed-effects models. In the case of significant heterogeneity (indicated by a), ORs were calculated using random-effects models. The italic values indicate that the results are statistically significant

[a] Significant heterogeneity

[b] The results were excluded due to high heterogeneity

XRCC1 Arg194Trp polymorphism and risk of different types of cancer.

Overall, significantly increased cancer risk was found when all eligible studies were pooled into the meta-analysis of Arg194Trp. In further stratified and sensitivity analyses, significantly increased glioma risk was found among Asians, significantly decreased lung cancer risk was found among Caucasians, and significant increased breast cancer risk was found among hospital-based studies. It also should be considered that the apparent inconsistency of these results may underlie differences in ethnicity, lifestyle, and disease prevalence as well as possible limitations due to the relatively small sample size. The current knowledge of carcinogenesis indicates a multi-factorial and multistep process that involves various genetic alterations and several biological pathways. Thus, it is unlikely that risk factors of cancer work in isolation from each other. And the same polymorphisms may play different roles in cancer susceptibility because cancer is a complicated multi-genetic disease, and different genetic backgrounds may contribute to the discrepancy. And even more importantly, the low penetrance genetic effects of single polymorphism may largely depend on interaction with other polymorphisms and/or a particular environmental exposure. We observed a wide variation of the Trp allele frequencies of control resources in Asians (0.296), Indians (0.200), Caucasians (0.077), and Africans (0.082), and this different allele frequency might account for the association between the XRCC1 Arg194Trp polymorphism and cancer susceptibility among different ethnicity.

Based on biochemical properties described for XRCC1 polymorphism, we would expect that the Trp allele would be associated with higher susceptibility for all types of cancer. However, our results showed that such association was observed just for breast cancer, glioma, and lung cancer, suggesting that other factors may be modulating the XRCC1 polymorphism functionality. However, the exact mechanism for association between different cancer types and XRCC1 Arg194Trp polymorphism was not clear, carcinogenetic mechanism may differ by different tumor sites and the XRCC1 genetic variants may exert varying effects in different cancers. Several previous meta-analyses assessed the association of XRCC1 Arg194Trp polymorphism with risk of gastric and lung cancer, and so on. Wang et al. [219] in 2009 found decreased lung cancer risk among subjects carrying *XRCC1* 194 Arg/Trp genotype (OR=0.88, 95 % CI=0.79–0.97). However, Dai et al. [203] in 2012 found that the risk for lung cancer was increased among the variant homozygote Trp/Trp of codon 194 polymorphism, compared with the wild-type Arg/Arg (OR: 1.19; 95 % CI=1.01–1.39). In the subgroup analyses by ethnicity, the OR for the variant homozygote Trp/Trp of codon 194 was 1.21(95 % CI=1.02–1.43) for Asian. Chen et al. [220] in 2012 suggested XRCC1 Arg194Trp homozygous mutant genotype (Trp/Trp) was found to be

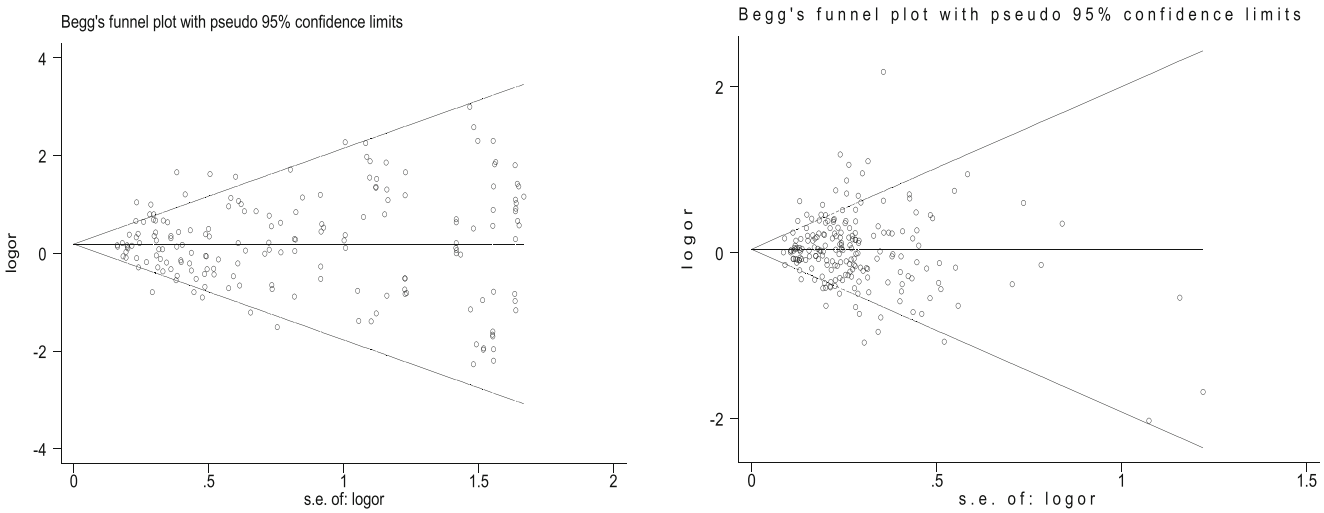

Fig. 2 Begg's funnel plot of for publication bias test between XRCC1 Arg194Trp polymorphism and cancer risk (homozygous model and dominant model)

associated with increased risk of gastric cancer. However, our meta-analysis indicates that Arg194Trp polymorphism is associated with decreased lung cancer in Caucasians and new study is important for Arg194Trp association in gastric cancer. Our meta-analysis should be more stringent and comprehensive. Firstly, more up to date studies were recruited to provide statistically significant results. Secondly, the association of Arg194Trp with risk of cancer had been explored in detail.

In the present meta-analysis, highly between-studies heterogeneity was observed in the hospital-based controls for some cancer types, such as gastric, prostate, and pancreatic cancers. The reason may be that the hospital-based studies have some biases because such controls may contain certain benign diseases which are prone to develop malignancy and may not be very representative of the general population. Thus, the use of a proper and representative cancer-free control subjects is very important in reducing biases in such genotype association studies. The results of meta-regression also indicated that source of controls contributed to substantial heterogeneity among the meta-analysis. And this indicates that it may be not appropriate to use an overall estimation of the relationship between XRCC1 Arg194Trp polymorphism and risk of cancer.

The current meta-analysis has some strength compared with individual studies and previous meta-analyses. First, differently from previous meta-analyses, we explored the impact of XRCC1 Arg194Trp on a great diversity of cancer sites, allowing for a general view of its influence on cancer susceptibility. Second, our meta-analysis explores and analyzes the sources of heterogeneity between studies about XRCC1 Arg194Trp in cancer. Third, more up to date studies were recruited to provide statistically significant results. As an example of these crucial features, differently from a recent pooled analysis of nine studies with a total of 1,709 colorectal cancer cases and 3,233 controls [221], we found 18 studies with 5,267 cases and 8,713 controls on colorectal cancer risk.

In summary, this meta-analysis suggests Arg194Trp polymorphism may be associated with increased breast cancer risk, Arg194Trp polymorphism is associated with increased glioma risk among Asians, and Arg194Trp polymorphism is associated with decreased lung cancer risk among Caucasians. In addition, our work also points out the importance of new studies for Arg194Trp association in some cancer types, such as gastric, pancreatic, prostate, and nasopharyngeal cancers, where at least some of the covariates responsible for heterogeneity could be controlled, to obtain a more conclusive understanding about the function of the XRCC1 Arg194Trp polymorphism in cancer development (I^2>75 %).

Conflicts of interest None

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