XRCC1 Polymorphisms and Cancer Risk: A Meta-analysis of 38 Case-Control Studies

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Abstract

Several potential functional polymorphisms ($Arg^{194}Trp$, $Arg^{280}His$, $Arg^{399}Gln$) in the DNA base excision repair gene X-ray repair cross-complementing group 1 (*XRCC1*) have been implicated in cancer risk. Our meta-analysis on total of 11,957 cancer cases and 14,174 control subjects from 38 published case-control studies showed that the odds ratio (OR) for the variant genotypes (Trp/Trp + Arg/Trp) of the $Arg^{194}Trp$ polymorphism, compared with the wild-type homozygote (Arg/Arg), was 0.89 [95% confidence interval (95% CI), 0.81-0.98] for all tumor types without between-study heterogeneity. Similarly, the overall risk for the combined variant genotypes (His/His + Arg/His) of the $Arg^{280}His$, compared with the wild homozygote (Arg/Arg), was 1.19 (95% CI, 1.00-1.42). However, there was no main effect in either recessive or dominant modeling for the $Arg^{399}Gln$, and the variant Gln/Gln homozygote was not associated with overall cancer risk (OR, 1.01; 95% CI, 0.90-1.14). The analyses suggest that *XRCC1* $Arg^{194}Trp$, $Arg^{280}His$ polymorphisms may be biomarkers of cancer susceptibility and a single larger study with thousands of subjects and tissue-specific biochemical and biological characterization is warranted to further evaluate potential gene-to-gene and gene-to-environment interactions on *XRCC1* polymorphisms and cancer risk. (Cancer Epidemiol Biomarkers Prev 2005;14(7):1810–8)

Introduction

Human cancer can be initiated by DNA damage caused by UV, ionizing radiation, and environmental chemical agents. To safeguard the integrity of genome, humans have developed a set of complex DNA repair systems. Among the five main DNA maintenance mechanisms operating in mammals, base excision repair is the primary guardian against damage that results from cellular metabolism, including reactive oxygen species, methylation, deamination, and hydroxylation. Therefore, base excision repair is a universal event in the cells and is relevant for preventing mutagenesis.

X-ray repair cross complementing group 1 (*XRCC1*), one of the >20 genes that participate in base excision repair pathway, encodes a scaffolding protein that functions in the repair of single-strand breaks, the most common lesions in cellular DNA (1). Both biological and biochemical evidence indicates a direct role for XRCC1 in base excision repair because it interacts with a complex of DNA repair proteins, including poly(ADP-ribose) polymerase, DNA ligase 3, and DNA polymerase-β (1-3). There are a total of eight nonsynonymous coding single nucleotide polymorphisms in *XRCC1*, three of which are common (variant allele frequency > 0.05) and lead to amino acid substitutions in XRCC1 at codon 194 (exon 6, base C to T, amino acid Arg to Trp), codon 280 (exon 9, base G to A, amino acid Arg to His), and codon 399 (exon 10, base G to A, amino acid Arg to Gln) (http://egp.gs.washington.edu). Because the $Arg^{399}Gln$ polymorphism is located in the region of the BRCT-I interaction domain of XRCC1 within a poly(ADP-ribose) polymerase binding region, this polymorphism has been extensively investigated both in its function and in its association with cancer risk. The presence of the variant Gln^{399} allele has been shown to be associated with measurable reduced DNA repair capacity as assessed by the persistence of DNA adducts (4-6), elevated levels of sister chromatid exchanges (5, 7), increased RBC glycophorin A (4), *p53* mutations (8), and prolonged cell cycle delay (9). However, Taylor et al. (10) reported that whereas BRCT-I is critical for XRCC1-dependent SSBR for maintenance of genetic integrity, the $Arg^{399}Gln$ polymorphism in BRCT-I does not have a significant impact on this function and negative findings were also obtained from other individual studies (11-13). A large number of molecular epidemiologic studies have been conducted to evaluate the role of the $Arg^{399}Gln$ polymorphism on cancer risk; however, the results remain conflicting rather than conclusive (6, 14-49).

Both the *XRCC1* $Arg^{194}Trp$ and $Arg^{280}His$ variants occur in the newly identified proliferating cell nuclear antigen binding region (50), which consists of polar Pro-, Ser-, and Arg/Lys-rich regions. The transition from a positively charged Arg to a hydrophobic Trp within the conserved region may alter XRCC1 function. Recently, Wang et al. (51) reported that individuals with the variant Trp^{194} allele had fewer bleomycinor benzo(*a*)pyrene diol epoxide–induced chromosomal breaks than those with wild-type genotype; however, others did not find a significant association of $Arg^{194}Trp$ with altered levels of DNA adducts (4) and G_2 cell cycle delay (9). Molecular epidemiologic studies on the association between this polymorphism and cancer risk also presented contradicting results (14-17, 19-23, 26-29, 31-34, 39-43, 49). To date, there are relatively few studies conducted to examine the association between $Arg^{280}His$ variant and cancer risk (19, 20, 22, 31, 33, 35, 40, 52) and only one study evaluated the association of $Arg^{280}His$ and altered DNA adducts (4). Because a single study may have been underpowered to detect the effect of low-penetrance genes and particularly their dose-response relationships, a quantitative synthesis to accumulate data from different studies may provide evidence on the association of genetic polymorphisms with cancer risk. In this meta-analysis, we aimed to obtain summary risk estimates for the above-mentioned three nonsynonymous coding single nucleotide polymorphisms of *XRCC1* associated with cancer risk, as well as to quantify the potential between-study heterogeneity.

Received 10/28/04; revised 3/4/05; accepted 4/18/05.

Grant support: National Key Basic Research Program grants 2002CB512900 and National Natural Science Foundation grant 30371240.

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Materials and Methods

Identification and Eligibility of Relevant Studies. We have attempted to include all the case-control association studies of cancer with genotyping data for at least one of the three polymorphisms, $Arg^{399}Gln$, $Arg^{194}Trp$, and $Arg^{280}His$. Eligible studies were identified by searching the electronic literature MEDLINE for relevant reports (last search update July 15, 2004, using the search terms ''*XRCC1* and cancer''). Additional studies were identified by a hand search of references of original studies or review articles on this topic and by personal contact with the authors if necessary.

A total of 43 published studies examined the relationship between *XRCC1* polymorphisms and cancer risk, three of which were excluded because they did not have an appropriate case-control design (53) or they did not present detailed genotyping information for the three polymorphisms (54, 55). Another three studies were excluded because they investigated the same or a subset population of reported articles (56-58). Hence, the data for this analysis were available from 38 case-control studies, including 11,542 cancer cases and 13,694 controls for $Arg^{399}Gln$ (from 37 studies), 4,933 cancer cases and 6,775 controls for $Arg^{194}Trp$ (from 22 studies), and 1,688 cancer cases and 2,129 controls for $Arg^{280}His$ (from 8 studies).

Data Extraction. Two investigators independently extracted data and reached a consensus on all of the items. The following information was sought from each article: author, journal and year of publication, country of origin, selection and characteristics of cancer cases and controls, demographics, ethnicity, and genotyping information. For studies including subjects of different ethnicities, data were extracted separately and categorized as European, African, and Asian. However, if the authors did not clearly state the ethnic information or we could not separate them according to genotypes, the term ''mixed ethnicity'' was used (Table 1).

Meta-analysis. The risks (odds ratios, ORs) of cancer associated with the *XRCC1* polymorphisms were estimated for each study. For the $Arg^{399}Gln$, we first estimated the risk of the variant genotype Gln/Gln, compared with the wild-type Arg/Arg homozygotes, and then evaluated the risks of Gln/Gln versus (Arg/Gln + Arg/Arg) and (Gln/Gln + Arg/Gln) versus Arg/Arg, which assumed recessive and dominant

Table 1. Number of cases and controls, allele frequencies, and quality score of the studies included in the meta-analysis

First author year (reference)	Country	Cancer	Racial descent	Genotyped subjects, codon 399 (codon 194) [codon 280]	Allele frequency among controls, codon 399 (codon 194) [codon 280]
Hao 2004 (52)	China	Esophageal cancer	Asian	[415/480]	[0.104]
Forsti 2004 (49)	Finland	Breast cancer	Mixed ethnicity	223/298 (223/298)	0.320 (0.027)
Figueiredo 2004 (48)	Canada	Breast cancer	Mixed ethnicity	402/402	0.372
Sanyal 2004 (47)	Sweden	Bladder cancer	European	311/246	0.317
Harms 2004 (46)	American	Lung cancer	European	110/119	0.298
Matsuo 2004 (45)	Japan	Malignant lymphomas	Asian	369/500	0.243
Shu 2003 (44)	China	Breast cancer	Asian	1,088/1,182	0.273
Han 2003 (43)	American	Breast cancer	Mixed ethnicity	986/1,337 (998/1,369)	0.362 (0.066)
Shen 2003 (42)	Italy	Bladder cancer	European	201/214	0.341
Smith 2003 (41)	American	Breast cancer	European	251/267 (246/266)	0.339 (0.047)
Moullan 2003 (40)	France	Breast cancer	Mixed ethnicity	254/312 (254/312) [254/312]	0.359 (0.069) [0.046]
Varzim 2003 (39)	Portugal	Larynx cancer	European	88/178 (88/178)	0.326 (0.051)
Cho 2003 (38)	China	Nasopharyngeal cancer	Asian	334/282	0.268
Yu 2003 (37)	China	Hepatocellular cancer	Asian	577/389	0.256
Zhou 2003 (36)	American	Lung cancer	European	1,091/1,240	0.335
Misra 2003 (35)	Finland	Lung cancer	Mixed ethnicity	315/313 [309/302]	0.300 [0.070]
Smith 2003 (34)	American	Breast cancer	European	162/300 (162/301)	0.353 (0.063)
Van Gils 2002 (33)	American	Prostate cancer	Mixed ethnicity	76/182 (76/182) [76/182]	0.363 (0.088) [0.049]
Seedhouse 2002 (32)	England	Myeloblastic leukemia	European	167/178 (126/87)	0.478 (0.063)
Lee 2002 (31)	Korea	Gastric cancer	Asian	190/172 (190/172) [190/172]	0.253 (0.331) [0.102]
Duell 2002 (30)	American	Pancreatic adenocarcinoma	European	250/832	0.319
			Asian	17/51	0.265
			African	26/36	0.153
Chen 2002 (29)	China	Lung cancer	Asian	103/99 (103/102)	0.273 (0.245)
Xing 2002 (28)	China	Esophageal cancer	Asian	433/524 (433/524)	0.281 (0.288)
Kim 2002 (27)	Korea	Breast cancer	Asian	205/205 (205/205)	0.315 (0.341)
Olshan 2002 (26)	American	Head and neck cancer	European	98/161 (98/161)	0.360 (0.081)
Park 2002 (25)	Korea	Lung cancer	Asian	192/135	0.222
Nelson 2002 (24)	England	Nonmelanoma skin cancer	European	745/431	0.379
David-Beabes 2001 (23)	American	Lung cancer	European	180/461 (180/461)	0.361 (0.059)
			African	154/243 (154/243)	0.181 (0.082)
Lee 2001 (22)	China	Esophageal cancer	Asian	105/264 (105/264) [105/264]	0.295 (0.299) [0.102]
Matullo 2001 (6)	Italy	Bladder cancer	Mixed ethnicity	124/84	0.387
Duell 2001 (21)	American	Breast cancer	European	386/381 (233/221)	0.362 (0.075)
			African	253/266 (155/160)	0.135 (0.063)
Stern 2001 (20)	American	Bladder cancer	European	214/197 (213/197) [214/195]	0.365 (0.086) [0.044]
			African	19/13 (19/13) [19/13]	0.154 (0.115) [0.000]
Ratnasinghe 2001 (19)	China	Lung cancer	Asian	107/208 (108/210) [106/209]	0.245 (0.348) [0.077]
Divine 2001 (18)	American	Lung adenocarcinoma	European	129/71	0.296
			Hispanic American	43/72	0.347
Winsey 2000 (17)	England	Malignant melanoma	European	125/211 (125/211)	0.365 (0.085)
Abdel-Rahman 2000 (16)	Egypt	Colorectal cancer	African	48/48 (48/48)	0.135 (0.052)
Shen 2000 (15)	China	Gastric adenocarcinoma	Asian	188/166 (188/166)	0.256 (0.346)
Sturgis 1999 (14)	American	Head and neck cancer	Mixed ethnicity	203/424 (203/424)	0.341 (0.072)

NOTE: Mixed ethnicity: Forsti 2004, unknown; Figueiredo 2004, mostly European; Han 2003, mostly European; Moullan 2003, unknown; Misra 2003, unknown; van Gils 2002, European and African American; Matullo 2001, unknown; Sturgis 1999, Non-Hispanic White, Mexican-American, and African American.

effects, respectively, of the variant Gln^{399} allele. For the $Arg^{194}Trp$ and $Arg^{280}His$ polymorphisms, we evaluated only the risk of combined variant genotypes (Trp/Trp + Arg/Trp for $Arg^{194}Trp$ and His/His + Arg/His for $Arg^{280}His$) versus their wild-type homozygote Arg/Arg, because of the rare variant allele frequencies of these two polymorphisms.

In addition to comparisons for total subjects, studies were categorized into different subgroup analyses according to the ethnicity and tumor type (if the tumor type contains less than three individual studies, it was categorized into the ''other cancer'' group). For each subgroup, we estimated the between-study heterogeneity across the eligible comparisons using the χ^2-based Q test (59) and the heterogeneity was considered significant for $P < 0.05$. Values from single studies were combined using models of both fixed effects (Mantel-Haenszel) and random effects (DerSimonian and Laird; ref. 60). Random effects incorporate an estimate of the between-study variance and tend to provide wider confidence intervals when the results of the constituent studies differ among themselves. In the absence of between-study heterogeneity, the two methods provide identical results. We also did cumulative meta-analysis to evaluate whether the summary OR for the allele contrasts changed over time as more data accumulated (61). Inverted funnel plots and the Egger's test were used to provide diagnosis of publication bias (linear regression analysis; ref. 62).

All analyses were done in Statistical Analysis System software (v.8.0; SAS Institute, Cary, NC) and Review Manage (v.4.2; Oxford, England). All the P values were two-sided.

Results

Meta-analyses Databases. We established a database according to the extracted information from each article. Table 1 lists the cancer type of the study, ethnicity of the population, and the number of cases and controls for each *XRCC1* polymorphisms. There are total 37 case-control studies concerning $Arg^{399}Gln$ polymorphism, 22 for $Arg^{194}Trp$, and 8 for $Arg^{280}His$. All studies indicated that the distribution of genotypes in the controls was consistent with Hardy-Weinberg equilibrium [goodness of fit χ^2 test, degree of freedom (df) = 1], except for three studies for $Arg^{399}Gln$ (21, 27, 44), one study for $Arg^{194}Trp$ (32), and one study for $Arg^{280}His$ (20). However, only 27% of the studies for $Arg^{399}Gln$, 14% for $Arg^{194}Trp$, and none for $Arg^{280}His$ had a statistical power >80% based on the assumption that the cancer risk (OR) associated with the variant genotypes was >1.5. According to quality control on genotyping, three studies obtained DNA from surgically resected ''normal'' tissues adjacent to the tumor instead of peripheral blood (18, 28, 52). A classic PCR-RFLP assay was done in 81% of the studies, 41% randomly repeated a portion of samples while genotyping, and 22% used other genotyping assay to validate the data. Only 19% of the studies described use of blindness of the case-control status of DNA samples while genotyping.

Quantitative Synthesis

XRCC1 $Arg^{399}Gln$. The eligible studies included 11,542 cancer patients and 13,694 control subjects. There were significant differences in terms of the variant Gln^{399} allele frequency between the three major ethnicities [European, 34.7%; 95% confidence interval (95% CI), 33.8-35.6; Asian, 26.5%; 95% CI, 25.6-27.4; African, 15.5%; 95% CI, 13.5-17.7; $P < 0.0001$; Fig. 1]. Figure 2 shows the cancer risks (ORs) associated with the *XRCC1* Gln/Gln genotype compared with the Arg/Arg genotype. Overall, individuals carrying the *XRCC1* Gln/Gln genotype did not have elevated cancer risk compared with the individuals with the Arg/Arg genotype (OR, 1.01; 95% CI, 0.90-1.14; $P = 0.02$ for heterogeneity), and this negative associations were also observed in subgroups stratified by cancer type and ethnicity (Fig. 2). Similarly, no association with cancer risk was found, neither in the recessive (Gln/Gln versus Arg/Gln + Arg/Arg: OR, 1.03; 95% CI, 0.92-1.15, $P = 0.02$ for heterogeneity) nor in the dominant model of the Gln^{399} allele (Gln/Gln + Arg/Gln versus Arg/Arg: OR, 1.00; 95% CI, 0.95-1.05; Table 2). In the stratified analyses, however, significantly increased risks were found in the Asian subjects (OR, 1.18; 95% CI, 1.00-1.39) in the recessive model and among the African subjects (OR, 1.45; 95% CI, 1.13-1.88) in the dominant model (Table 2).

XRCC1 $Arg^{194}Trp$. The eligible studies included 4,933 cancer patients and 6,775 controls for this locus. Because of the low frequency of the variant allele in some ethnic subgroups, we only did the analysis with the dominant model of the Trp^{194} allele. Overall, the Trp^{194} allele was 31.2% (95% CI, 29.6-32.8) among Asian controls, which was significantly higher than that in Caucasians (6.6%; 95% CI, 5.9-7.4) and in African population (7.3%; 95% CI, 5.7-9.2; $P < 0.0001$; Fig. 1). Overall, a significantly decreased risk was associated with the variant genotypes (Trp/Trp + Arg/Trp), compared with the wild homozygote Arg/Arg genotype (OR, 0.89; 95% CI, 0.81-0.98; Fig. 3). In stratified analyses, however, no significant associations were found in populations with either different ethnicity or different tumor types (Table 2).

XRCC1 $Arg^{280}His$. Because only eight studies have investigated the $Arg^{280}His$ polymorphism and cancer risk to date, we did not perform stratification analysis. The eight studies included 1,688 cancer patients and 2,129 control subjects. Similar to the $Arg^{194}Trp$, we did the analysis only with the dominant model of the His^{280} allele because of its low frequency. Overall, individuals with the variant genotypes (His/His + Arg/His) had a borderline significantly increased cancer risk, compared with individuals with the Arg/Arg genotype (OR, 1.19; 95% CI, 1.00-1.42) without between-study heterogeneity (Fig. 4).

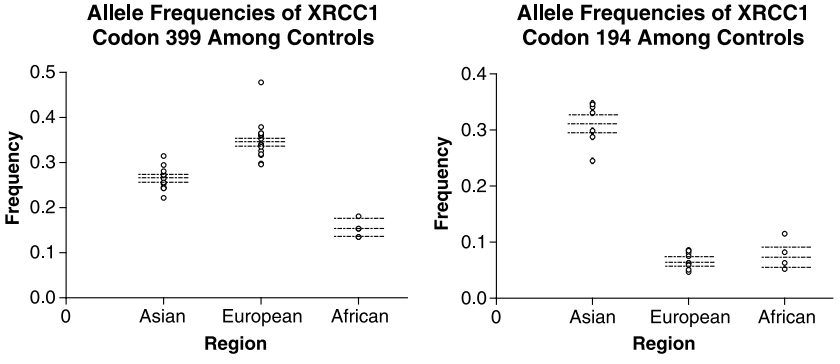

Figure 1. Allele frequencies and their 95% CIs of the *XRCC1* codon 399 and 194 polymorphisms among control subjects by different ethnicity. Each data point represents a separate study for the indicated association.

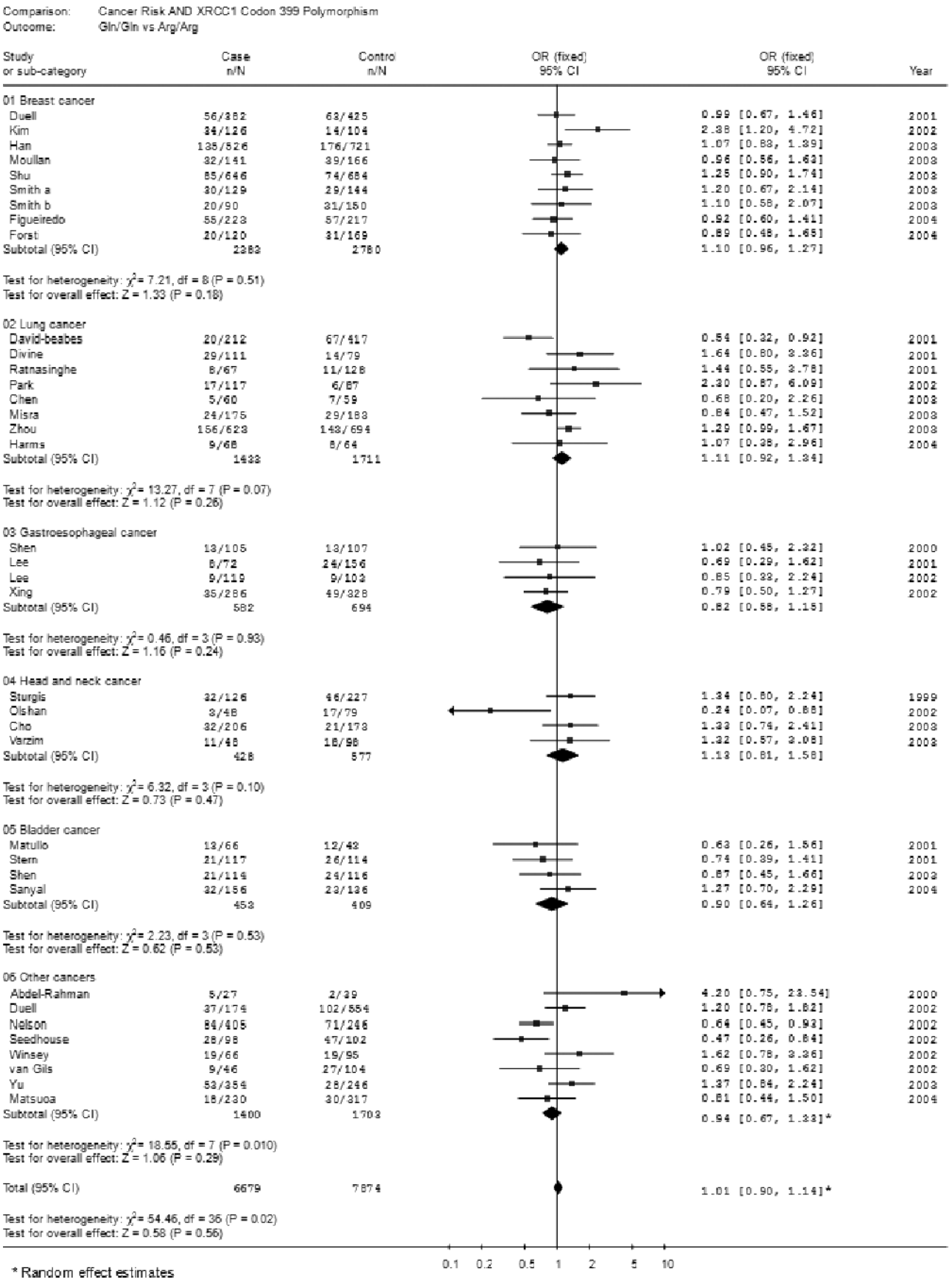

Figure 2. ORs (log scale) of cancer associated with *XRCC1* codon 399 for the Gln/Gln genotype compared with the Arg/Arg genotype. For each study, the estimate of OR and its 95% CI is plotted with a box and a horizontal line. ♦, pooled OR and its 95% CI.

Table 2. Summary ORs for various contrasts of the *XRCC1* codon 399 and codon 194 polymorphisms and cancer risk

Ethnicity/contrast	OR (%95 CI) Gln/Gln vs Arg/Arg	Comparisons	*XRCC1* codon 399				*XRCC1* codon 194	
			OR (%95 CI) Gln/Gln vs Arg/Gln + Arg/Arg	Comparisons	OR (%95 CI) Gln/Gln + Arg/Gln vs Arg/Arg	Comparisons	OR (%95 CI) Trp/Trp + Arg/Trp vs Arg/Arg	Comparisons
Asian	1.16 (0.98-1.38)	13	1.18 (1.00-1.40)	13	1.00 (0.92-1.09)	13	0.91 (0.78-1.05)	7
European	0.96 (0.78-1.19)*	16	0.98 (0.80-1.19)*	16	0.99 (0.91-1.07)	16	0.96 (0.78-1.18)	9
African	1.43 (0.68-2.99)	5	1.24 (0.59-2.60)	5	1.45 (1.13-1.88)	5	0.68 (0.44-1.04)	4
Mixed ethnicity	0.98 (0.83-1.15)	9	1.00 (0.86-1.17)	9	0.96 (0.87-1.07)	9	0.85 (0.70-1.03)	5
Total	1.02 (0.90-1.14)*	43	1.03 (0.92-1.15)*	43	1.00 (0.95-1.05)	43	0.89 (0.81-0.98)	25
Breast cancer	1.10 (0.96-1.27)	9	1.09 (0.96-1.25)	9	1.03 (0.95-1.12)	9	0.95 (0.81-1.11)	8
Lung cancer	1.11 (0.92-1.34)	8	1.14 (0.95-1.37)	8	0.98 (0.88-1.10)	8	0.87 (0.67-1.14)	3
Gastroesophageal cancer	0.82 (0.58-1.15)	4	0.86 (0.61-1.20)	4	0.88 (0.74-1.05)	4	0.86 (0.72-1.03)	4
Head and neck cancer	1.13 (0.81-1.58)	4	1.20 (0.87-1.65)	4	0.95 (0.78-1.16)	4	0.85 (0.59-1.23)	3
Bladder cancer	0.90 (0.64-1.26)	4	0.87 (0.64-1.20)	4	1.03 (0.84-1.25)	4	—	—
Other carcinoma†	0.94 (0.67-1.33)*	8	0.95 (0.70-1.29)*	8	1.00 (0.82-1.22)*	8	0.80 (0.58-1.10)	5
Total	1.01 (0.90-1.14)*	37	1.03 (0.92-1.15)*	37	1.00 (0.95-1.05)	37	0.89 (0.81-0.98)	22

*Random effect estimate.

† Including cancers of colorectal, malignant melanoma, pancreatic adenocarcinoma, nonmelanoma skin, myeloblastic leukemia, hepatocellular, malignant lymphomas, and prostate for $Arg^{399}Gln$ polymorphism; and cancers of colorectal, malignant melanoma, bladder, myeloblastic leukemia, and prostate for $Arg^{194}Trp$ polymorphism.

Test of Heterogeneity. There was substantial heterogeneity among the 37 studies that included the $Arg^{399}Gln$ polymorphism ($\chi^2 = 54.46$, $df = 36$, $P = 0.02$) but not among the 22 studies that included the $Arg^{194}Trp$ polymorphism ($\chi^2 = 25.50$, $df = 21$, $P = 0.23$) and other 8 studies that included the $Arg^{280}His$ polymorphism ($\chi^2 = 10.12$, $df = 7$, $P = 0.18$). Therefore, we evaluated the source of heterogeneity for the Gln/Gln genotype (Gln/Gln versus Arg/Arg) by study sample size, ethnicity, and tumor type. When we dichotomized the 37 studies by the sample size cutoff value of 400 lung cancer cases, the difference of study sample size did not significantly contribute to the observed heterogeneity ($\chi^2 = 0.19$, $df = 1$, $P = 0.66$), nor did ethnicity ($\chi^2 = 3.41$, $df = 3$, $P = 0.33$) and tumor type ($\chi^2 = 5.79$, $df = 5$, $P = 0.33$).

Bias Diagnostics

XRCC1 $Arg^{399}Gln$. The magnitude of the summary ORs had been fluctuating at around 1 in the past years (in random effect model, summary OR for Gln/Gln versus Arg/Arg: 1.03 at the end of 2001, 0.98 at the end of 2002, 1.04 at the end of 2003, and 1.03 till now). In the funnel plot analysis of publication bias (contrast of homozygous genotype plotted against the precision), the shape of the funnel plot seems asymmetrical, suggesting that the larger estimate of the association belongs to the smaller study, whereas the larger study shows little effect (Fig. 5). Furthermore, an Egger's test was used to provide statistical evidence for funnel plot symmetry (62). In the linear regression analysis, the intercept value provides a measure of asymmetry—the larger its deviation from zero, the more pronounced the asymmetry. We observed the intercept values of 1.57, which significantly deviated from zero ($t = 3.85$, $P < 0.001$).

XRCC1 $Arg^{194}Trp$. The magnitude of the summary ORs had been undergoing a trend toward a more and more stable effect as postulated (summary ORs for Trp/Trp + Arg/Trp versus Arg/Arg: 0.75 at the end of 2001, 0.86 at the end of 2002, 0.88 at the end of 2003, and 0.89 till now). The change of the summary OR was in dispersion in the last 2 years. Although the funnel plot analyses and Egger's test suggest that publication bias may influence the results (intercept values 1.31, $P = 0.004$), indeed it reinforces the postulated effect because the smaller studies suggest a risk effect on cancer with the variant genotypes (Fig. 5).

XRCC1 $Arg^{280}His$. In cumulative meta-analysis and recursive cumulative meta-analysis, the summary ORs changed considerably in the year 2004 with a sharp reduction of the postulated effect (summary ORs for His/His + Arg/His versus Arg/Arg: 1.36 at the end of 2001, 1.38 at the end of 2002, 1.40 at the end of 2003, and 1.19 till now). This change mainly resulted from the study of esophageal cancer by Hao et al. (52), which is the only study that presented a protective effect of the variant genotypes. Furthermore, the funnel plot and Egger's test revealed that publication bias might have influenced the estimates (intercept values 2.15, $P = 0.002$).

Discussion

This meta-analysis, including a total of 11,957 cancer cases and 14,174 controls from 38 case-control studies, examined the association of three well-characterized polymorphisms of the DNA repair gene *XRCC1* ($Arg^{194}Trp$, $Arg^{280}His$, and $Arg^{399}Gln$) with cancer risk. There was no overall effect either in recessive or dominant modeling for the $Arg^{399}Gln$ polymorphism, and compared with the wild Arg/Arg genotype, variant Gln/Gln homozygote was not associated with overall cancer risk. For the $Arg^{194}Trp$, the variant genotypes (Trp/Trp + Arg/Trp), compared with the wild-type homozygote (Arg/Arg), were associated with a significantly decreased cancer risk (OR, 0.89; 95% CI, 0.81-0.98) for all tumor types without between-study heterogeneity. Similarly, we observed a fixed overall 19% increased risk of cancer for the variant genotypes (His/His + Arg/His) of the $Arg^{280}His$ polymorphism, compared with the wild homozygote (OR, 1.19; 95% CI, 1.00-1.42). However, considering the relatively small sample size and marginal statistical evidence for $Arg^{280}His$, our result in relation to this polymorphism should always be treated as preliminary. Nevertheless, our analysis shows that even if a common variant in the functional region of a definitively meaningful gene had an effect on human disease, such as cancer, it may play only a small role in the disease causation, which is consistent with the characteristics of low-penetrance genes (63).

Given the multiplicity of possible comparisons and the unavoidable flexibility of choosing and defining the correlates, associations may have been detected by chance alone. Several criteria have been proposed for assessing associations

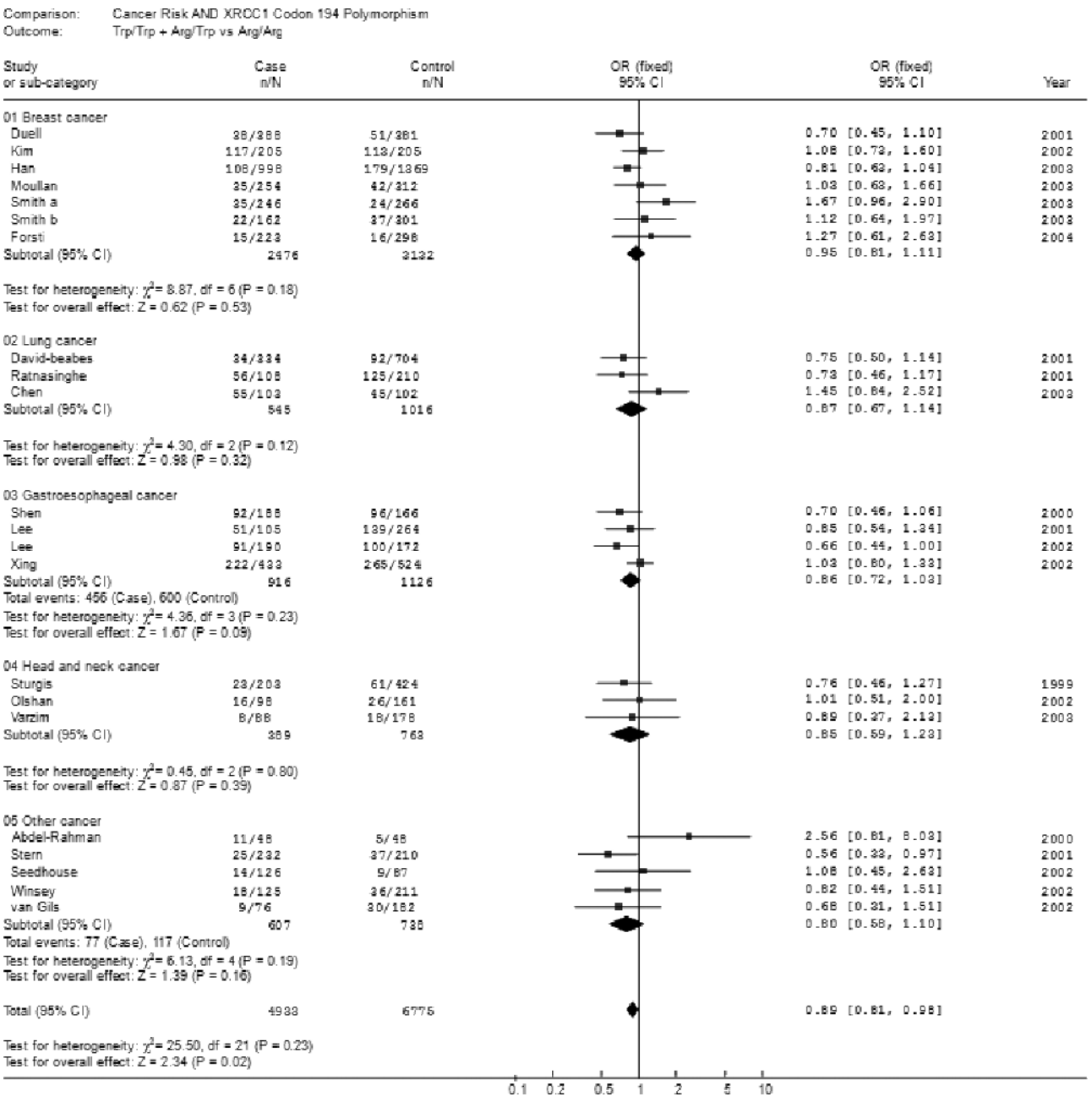

Figure 3. ORs (log scale) of cancer associated with *XRCC1* codon 194 for the Trp/Trp and Arg/Trp genotypes compared with the Arg/Arg genotype. For each study, the estimate of OR and its 95% CI is plotted with a box and a horizontal line. ♦, pooled OR and its 95% CI.

between genetic polymorphisms and disease (64); the claim was that studies ''ideally should have large sample sizes, small *P* values, report associations that make biological sense, and alleles that affect the gene product in a physiologically meaningful way.'' The sample size and scientific hypotheses of the study are obviously important to know the proportion of false-positive findings of meta-analysis that are attributable to constituent studies with poor study design, nondifferential misclassification errors, and selection bias from publication (65). Although considerable effort and resources have been put into testing possible associations between DNA repair gene *XRCC1* polymorphisms and cancer risk, there are still serious limitations inherited from the published studies. First, selection bias could have played a role because the genotype distributions of at least one polymorphism among control subjects disobeyed the law of Hardy-Weinberg equilibrium in five studies (20, 21, 27, 32, 44). Second, demographic parameters are not well matched and are statistically adjusted in a few studies (26, 32, 36, 39, 44, 49). Third, misclassifications on disease status and genotypes may also influence the results because cases in several studies were not confirmed by pathology or other gold standard methods, and the quality control of genotyping was also not well-documented in some studies. Finally, the Egger's test revealed that there are considerable unpublished negative studies not included in this meta-analysis although they are likely to be small in terms of sample size. However, because the Trp^{194} allele was associated with a decreased cancer risk and the unpublished studies on this polymorphism are likely to show a protective effect, the association between the $Arg^{194}Trp$ variant and cancer risk may be slightly underestimated. To further evaluate the results derived from Egger's test, we searched the abstracts from annual meetings of AACR between 2000 and 2004 and found 24 eligible case-control studies. Among

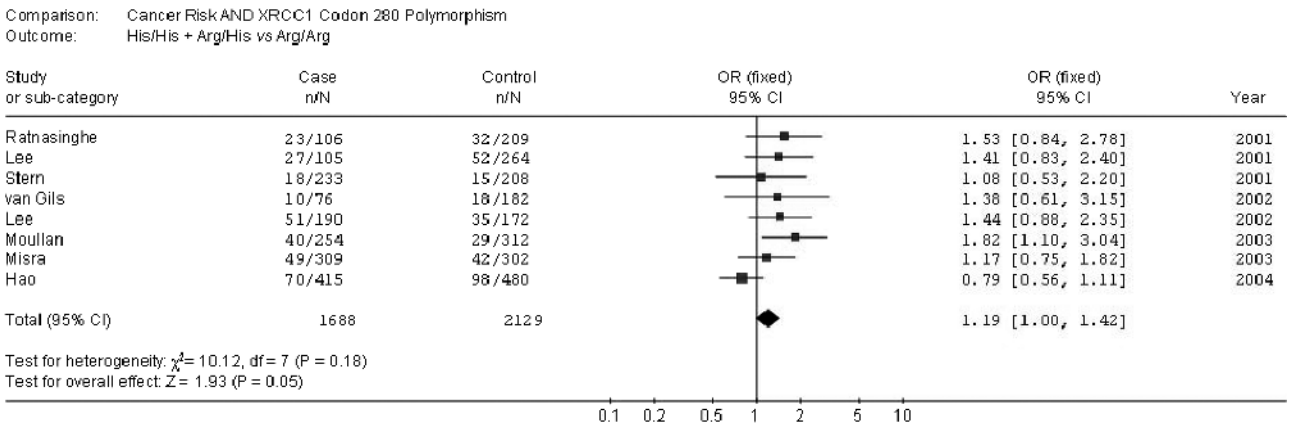

Figure 4. ORs (log scale) of cancer associated with XRCC1 codon 280 for the His/His and Arg/His genotypes compared with the Arg/Arg genotype. For each study, the estimate of OR and its 95% CI is plotted with a box and a horizontal line. ♦, pooled OR and its 95% CI.

the 24 abstracts, 11 were fully or partially published and had been included in the current meta-analysis and only 2 unpublished studies were with a sample size of >300 cases. One study conducted in Finland with 483 breast cancer patients and 482 controls reported that no association between the Arg^{399}Gln polymorphism and breast cancer risk (66). The other multicentric study in central and eastern Europe consisted of a large sample size (2,073 cases and 1,953 controls) showed that Arg^{280}His, Arg^{399}Gln did not confer an effect on lung cancer, whereas Arg^{194}Trp showed a protective effect among current smokers (OR, 0.76; 95% CI, 0.42-0.99; ref. 67). These two meeting abstracts with relatively large sample size also support the current meta-analysis that *XRCC1* Arg^{194}Trp rather than Arg^{280}His and Arg^{399}Gln may play a role in individual susceptibility to cancers.

Several studies suggested a possible interaction between *XRCC1* Arg^{399}Gln and family history on breast cancer risk (48), indicating that family history, particularly in first-degree relatives, broadly represents shared genes and environmental factors, and that the weak effect of a single polymorphism on the individual's phenotype may not be measurable except in the context of these risk factors. In addition, cigarette smoking (36), alcohol consumption (35), and antioxidant vitamins intake (43) are associated with the production of free radical intermediates, including hydroxyethyl free radicals and reactive oxygen species, which are corrected in part by the involvement of *XRCC1*. Therefore, gene-to-environment interactions have been of great interest to evaluate the exact roles of genetic polymorphisms. However, lacking of the original data of the meta-analysis limited our further evaluation of potential gene-to-gene and gene-to-environment interactions.

The heterogeneity test revealed that there was no significant between-study heterogeneity in terms of the *XRCC1* Arg^{194}Trp polymorphism for all tumor types. In addition, different tumor types also did not significantly contribute to the overall heterogeneity in relation to the Arg^{399}Gln polymorphism, indicating that our current combined analyses were unbiased, regardless of tumor types. Because we did not find any significant heterogeneity in the distribution of the Arg^{399}Gln genotypes by ethnicity and the study sample size, it is possible that other unmeasured characteristics in different study populations and/or inherited limitations of the recruited studies may partially contribute to the observed overall heterogeneity. Although heterogeneity among different ethnic groups was not statistically significant in our combined analysis, other population stratification factors may have played a role in the heterogeneity when the sample size of a combined analysis become sufficient large (68) and, therefore, we suggest a careful matching on ethnicity for future larger genetic association studies.

In conclusion, our current study support that *XRCC1* Arg^{194}Trp polymorphism may contribute to individual susceptibility of cancers. To further evaluate gene-to-gene and gene-to-environment interactions on *XRCC1* polymorphisms and cancer risk, a single larger study with thousands of subjects and tissue-specific biochemical and biological characterizations are required.

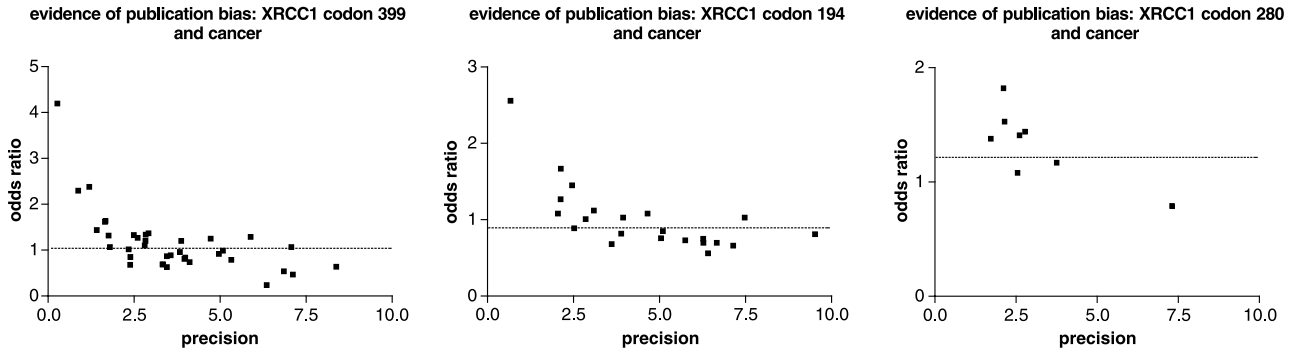

Figure 5. Funnel plot analysis to detect publication bias. Each point represents a separate study for the indicated association. For each study, the OR is plotted on a logarithmic scale against the precision (the reciprocal of the SE). If bias is absent, small studies will have ORs that are widely scattered but still centered around the OR estimates provided by large, more precise studies.

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Cancer Epidemiol Biomarkers Prev 2005;14:1810-1818.