Polymorphisms in DNA Repair Gene *XRCC1* and Skin Cancer Risk: A Meta-analysis

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Abstract. *Published data on the association between polymorphisms of the X-ray repair cross-complementing group 1 (XRCC1) gene and skin cancer risk are inconsistent. Hence, we conducted a meta-analysis of three frequently occurring XRCC1 polymorphisms and risk of skin cancer to obtain the most reliable estimate of the association. Odds ratios (ORs) with 95% confidence intervals (CIs) were extracted from a total of 10 eligible studies describing 4,801 cases and 4,960 controls for the Arg399Gln (G>A) polymorphism, 1,026 cases and 1,089 controls for the Arg194Trp (C>T) polymorphism, and 1,392 cases and 1,476 controls for the Arg280His (G>A) polymorphism. The distributions of genotypes in the controls were consistent with Hardy-Weinberg equilibrium. The Arg399Gln and Arg194Trp polymorphisms were not correlated with skin cancer risk when all studies were pooled into the meta-analysis under three genetic models. No significant association was observed in stratified analyses of Arg399Gln and Arg194Trp polymorphisms by tumor type, race, or control source. In contrast, the Arg280His polymorphism was associated with an approximate 3.5-fold increase in skin cancer risk in homozygote codominant and recessive models.*

DNA repair is essential for maintaining genomic stability and the prevention of cancer. However, polymorphisms in DNA repair genes may result in individual differences in DNA repair activity and mutation rates (1), and these differences could be used to predict susceptibility to certain types of cancer, including skin cancer (2). X-Ray repair cross-complementing group 1 (XRCC1) is a protein involved in repairing DNA damaged by ionizing radiation, alkylating agents, and oxidative stress. As an important component of base excision repair (BER) (3), XRCC1 interacts with a DNA repair protein complex consisting of poly (ADP-ribose) polymerase (PARP), DNA ligase III, and DNA polymerase β (4-6). Several single nucleotide polymorphisms (SNPs) in the *XRCC1* gene, located at chromosome 19q13.2, have been reported for amino acid differences between arginine and glutamine at codon 399 (Arg399Gln, G to A base change), arginine and tryptophan at codon 194 (Arg194Trp, C to T base change), and arginine and histidine at codon 280 (Arg280His, G to A base change). If any of these *XRCC1* polymorphisms contribute to impaired DNA repair, it would be expected to heighten the risk of developing skin cancer.

Previous reviews and meta-analyses have discussed the association between *XRCC1* polymorphisms and the risk of developing cancer (7-10), but not skin cancer specifically. In these studies, the *XRCC1* 399Gln/Gln variant was associated with increased risk of tobacco-related cancer in light smokers but with lower risk among heavy smokers (10); the 194Trp allele showed a protective effect in various tumor types (8-10); and 280His was a risk factor in a number of cancer types (9). Although several epidemiological studies have explored the relationship between *XRCC1* polymorphisms and the development of melanoma, basal cell carcinoma, and squamous cell carcinoma, these studies have reached inconsistent conclusions on whether any *XRCC1* genetic variant could serve as a biomarker for skin cancer, with some studies showing an association (11-15) and others failing to show any clear association (16-23). A quantitative overview of these epidemiological data would help to resolve these discrepant findings. Although the pathobiology of different skin cancer types might be dissimilar, all three types of skin cancer share common genetic risk factors (24), which makes analysis of polymorphisms of *XRCC1* feasible. In this study, we performed a meta-analysis focusing on the association

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Key Words: X-ray repair cross-complementing group 1, XRCC1, polymorphism, DNA repair, skin cancer, meta-analysis.

Table I. *Study characteristics by XRCC1 polymorphism.*

Characteristic	Arg399Gln (G>A)			Arg194Trp (C>T)			Arg280His (G>A)		
	No. of studies	Cases	Controls	No. of studies	Cases	Controls	No. of studies	Cases	Controls
Total	10	4801	4960	3	1026	1089	2	1392	1476
Tumor type									
Melanoma	4	2498	3126	1	215	863	1	1182	1270
BCC	7	1687	2649	3	431	1089	1	114	206
SCC	3	616	1451	2	380	1069	1	96	206
Race									
Caucasian	8	3848	3940	1	20	20	1	1182	1270
Mixed*	2	953	1020	2	1006	1069	1	210	206
Control Source									
Population	6	3398	3522	2	816	883	1	1182	1270
Hospital	4	1403	1438	1	210	206	1	210	206

*Includes study populations in which the race was mixed or Asian. BCC, basal cell carcinoma; SCC, squamous cell carcinoma.

between XRCC1 polymorphisms and skin cancer risk, in addition to stratifying the analysis by tumor type, race, and source of the control population.

Materials and methods

Study selection. Published studies (last search, March 6th, 2011) were identified by a computerized search of PubMed, ISI Web of Knowledge, ScienceDirect, Cochrane, and EBSCO databases. Search terms were combinations of the following: skin cancer, melanoma, non-melanoma, squamous cell carcinoma, and basal cell carcinoma; polymorphism, genotype, and variant; and XRCC1 and X-ray repair cross-complementing group 1. Identified studies were screened manually to find additional eligible studies.

Selection criteria. A study was included in this meta-analysis if it satisfied all of the following inclusion criteria: (i) case-control study design, (ii) analysis of the association between XRCC1 polymorphisms and skin cancer risk, (iii) reported sufficient details of relevant genotype frequencies for statistical analysis, (iv) written in the English language; if the same subjects were used in a series of publications, only the latest or complete study was included. Duplicate publications were excluded.

Data collection. The following information was extracted from selected studies: last name of first author, year of publication, country where the study was conducted, tumor type, race, source of control subjects, and number of subjects with the genotype in both cases and controls.

Effect size and statistical analysis. Hardy-Weinberg equilibrium for control subjects of each study was checked by the goodness-of-fit test. Odds ratios (ORs) and 95% confidence intervals (CIs) were used to assess the strength of association between XRCC1 polymorphisms and skin cancer risk. Three genetic models (codominant model, dominant model, and recessive model) were used for calculating pooled ORs. For Arg399Gln and Arg280His polymorphisms, pooled ORs were calculated for the codominant model (homozygote comparison, AA *vs.* GG; heterozygote comparison, AG *vs.* GG), dominant model (AA+AG *vs.* GG), and recessive model (AA *vs.* AG+GG). For Arg194Trp, pooled ORs were calculated for the codominant model (homozygote comparison, TT *vs.* CC; heterozygote comparison, TC *vs.* CC), dominant model (TT+TC *vs.* CC), and recessive model (TT *vs.* TC+CC). Statistical heterogeneity among studies was checked based on the Q statistic. (25) If the *p*-value was greater than 0.1 for the test of heterogeneity, pooled ORs were calculated with a fixed effects model using the Mantel-Haenszel method (26); otherwise, pooled ORs were calculated with a random effects model using DerSimonian and Laird method (27). Weighting was used for pooling individual studies based on model selected. Publication bias was evaluated by rank correlation test (28) and linear regression test. (29) Stratified analyses were performed by tumor type, race, and control source. Power of statistics and sample size needed to observe the suggested association for each polymorphism, if it was present, was calculated by OpenEpi program (Version 2.3.1, www.OpenEpi.com). All the other statistical analyses were performed using R (30).

Results

Study characteristics and genotype distribution. Ten case–control studies were included in this meta-analysis (Table I) (11-14, 16-18, 20, 22, 23). The genotype distribution for controls was consistent with Hardy-Weinberg equilibrium (Table II). Four studies were excluded because of insufficient genotype information (Figure 1) (15, 21, 31, 32). Another study (19) was excluded because the study population overlapped with that in the study by Han *et al.* (11), the latter of which provided more tumor type information. Four reviews or meta-analyses were also excluded (7-10).

XRCC1 polymorphisms and skin cancer risk. Pooled ORs were calculated using three genetic models to estimate the association between *XRCC1* polymorphisms and skin cancer risk (Figure 2 and Table III). No statistically significant

Table II. *Genotype distribution of selected studies by XRCC1 polymorphism.*

Gene variant	Study	Race	Cases			Controls			HWE
Arg399Gln (G>A)			AA	AG	GG	AA	AG	GG	
	Nelson *et al*., 2002 (14)	C	84	340	321	71	185	175	0.066
	Yin *et al*., 2002 (22)	C	9	25	29	9	46	42	0.475
	Yin *et al*., 2003 (18)	C	2	15	3	3	10	7	0.852
	Han *et al*., 2004 (11)	M	97	335	312	119	351	345	0.056
	Festa *et al*., 2005 (16)	C	21	82	94	61	240	247	0.814
	Li *et al*., 2006 (13)	C	77	269	256	74	280	249	0.729
	Thirumaran *et al*., 2006 (23)	C	68	244	217	66	252	215	0.552
	Kang *et al*., 2007 (12)	A	15	107	87	12	85	108	0.373
	Povey *et al*., 2007 (20)	C	77	232	198	66	201	170	0.603
	Figl *et al*., 2010 (17)	C	147	539	499	168	590	513	0.936
Arg194Trp (C>T)			TT	TC	CC	TT	TC	CC	
	Yin *et al*., 2003 (18)	C	0	3	17	1	3	16	0.160
	Han *et al*., 2004 (11)	M	3	108	685	6	93	764	0.095
	Kang *et al*., 2007 (12)	A	14	85	111	18	98	90	0.229
Arg280His (G>A)			AA	AG	GG	AA	AG	GG	
	Kang *et al*., 2007 (12)	A	3	44	163	2	35	169	0.900
	Figl *et al*., 2010 (17)	C	17	117	1048	4	129	1137	0.867

HWE, *P*-value for Hardy–Weinberg equilibrium test; C, Caucasian; M, mixed; A, Asian.

association between the Arg399Gln or Arg194Trp polymorphisms and skin cancer risk was evident under any of the genetic models. For the Arg280His polymorphism, a 3.5-fold increase in skin cancer susceptibility was observed under the codominant model in comparisons of homozygotes (AA *vs*. GG) and under the recessive model (AA *vs*. AG+GG); however, only 20 cases of the AA genotype and 6 controls were included in these analyses. No increased skin cancer risk was observed under the codominant model for heterozygote comparisons (AG *vs*. GG) or the dominant model (AA+AG *vs*. GG). Because the meta-analysis of the Arg280His polymorphism was based on only two eligible studies, we analyzed each study separately to test if the association detected originated from a specific study. Indeed, after omitting the study of Figl *et al*. (17), the association between the Arg280His polymorphism and skin cancer risk was not present under any of the genetic models, including the homozygote codominant model (AA *vs*. GG, OR=1.56, 95% CI=0.26-9.43) and recessive model (AA *vs*. AG+GG, OR=1.48, 95% CI=0.24-8.94). Pooled ORs for the Arg399Gln and Arg194Trp polymorphisms were not affected by stratified analysis according to tumor type, race, or control source (Table IV). For Arg280His, stratified analysis was not performed because only one study would have been included in each subdivision of each subgroup. Statistical heterogeneity ($p<0.1$ for the test of heterogeneity) was evident in two genetic model analyses of Arg194Trp and in several stratified analyses, although in general, the differences between individual studies were small; however, the results for individual studies appeared to vary slightly for the Arg194Trp polymorphism in squamous cell carcinoma in analyses using the heterozygous codominant and dominant genetic models (Table IV).

Publication bias. Rank correlation test and linear regression test did not demonstrate statistically significant publication bias in the main analyses of Arg399Gln and Arg194Trp (data not shown). Because only two studies were included in the analysis of the Arg280His genotype, tests for publication bias could not be performed; however, considering that removal of either of the studies altered the conclusion, it is possible that bias related to subject selection of individual studies and small sample size were responsible for the association observed for this genotype.

Discussion

Our meta-analysis of polymorphisms in the *XRCC1* gene shows that the Arg399Gln and Arg194Trp polymorphisms might have no influence on skin cancer risk regardless of tumor type, race, or control source. Based on the current data, although the Arg280His polymorphism was associated with

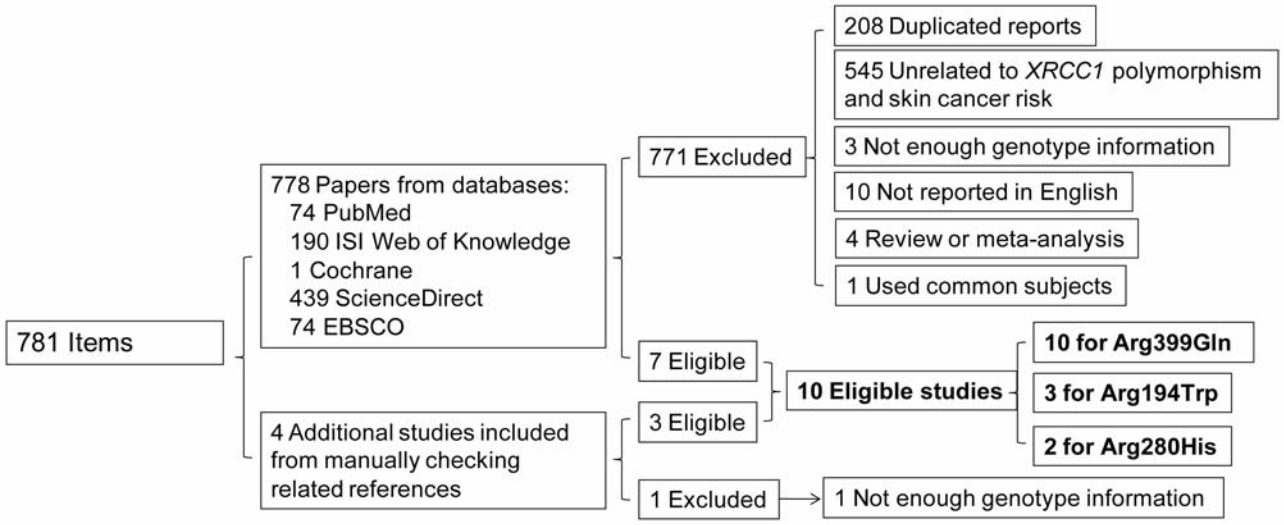

Figure 1. *Flow chart showing literature selection process.*

Table III. *Pooled ORs with 95% CIs under different genetic models.*

Gene variant	Homozygous codominant	Heterozygous codominant	Dominant	Recessive
Arg399Gln (G>A)	AA *vs.* GG	AG *vs.* GG	AA+AG *vs.* GG	AA *vs.* AG+GG
OR	0.92	0.99	0.98	0.93
(95% CI)	(0.81-1.05)	(0.91-1.08)	(0.90-1.06)	(0.82-1.05)
P_h	0.64	0.42	0.44	0.58
Arg194Trp (C>T)	TT *vs.* CC	TC *vs.* CC	TT+TC *vs.* CC	TT *vs.* TC+CC
OR	0.59	0.97	0.92	0.67
(95% CI)	(0.31-1.13)	(0.58-1.62)	(0.56-1.53)	(0.36-1.26)
P_h	0.92	0.06	0.05	0.83
Arg280His (G>A)	AA *vs.* GG	AG *vs.* GG	AA+AG *vs.* GG	AA *vs.* AG+GG
OR	3.58	1.05	1.14	3.54
(95% CI)	(1.43-8.94)	(0.83-1.32)	(0.91-1.43)	(1.42-8.82)
P_h	0.31	0.32	0.50	0.29

OR, Odds ratio; CI, confidence interval; P_h, *P* value for heterogeneity test.

susceptibility to skin cancer under some genetic models, the strength of this association is reduced by the limited number of studies (n=2) included in the meta-analysis of this genetic variant. Therefore, the question of whether the Arg280His polymorphism is associated with skin cancer risk requires further study. Furthermore, previous studies of *XRCC1* polymorphisms and cancer risk have reached divergent conclusions, suggesting that these polymorphisms may have different roles depending on cancer type. A recent review found that the Arg399Gln and Arg280His variants appeared to reduce DNA repair, while the Arg194Trp polymorphism appeared to increase it (7). The effects of these polymorphisms on cancer risk also varies, appearing to have protective effects, carcinogenic effects, or no effect depending on the cancer type (7). Considering the complex roles that *XRCC1* polymorphisms appear to play in different malignancies, our meta-analysis is only applicable to skin cancer risk.

The 10 case-control studies included in our analysis were limited in many respects and reached different conclusions about the association between *XRCC1* polymorphisms and

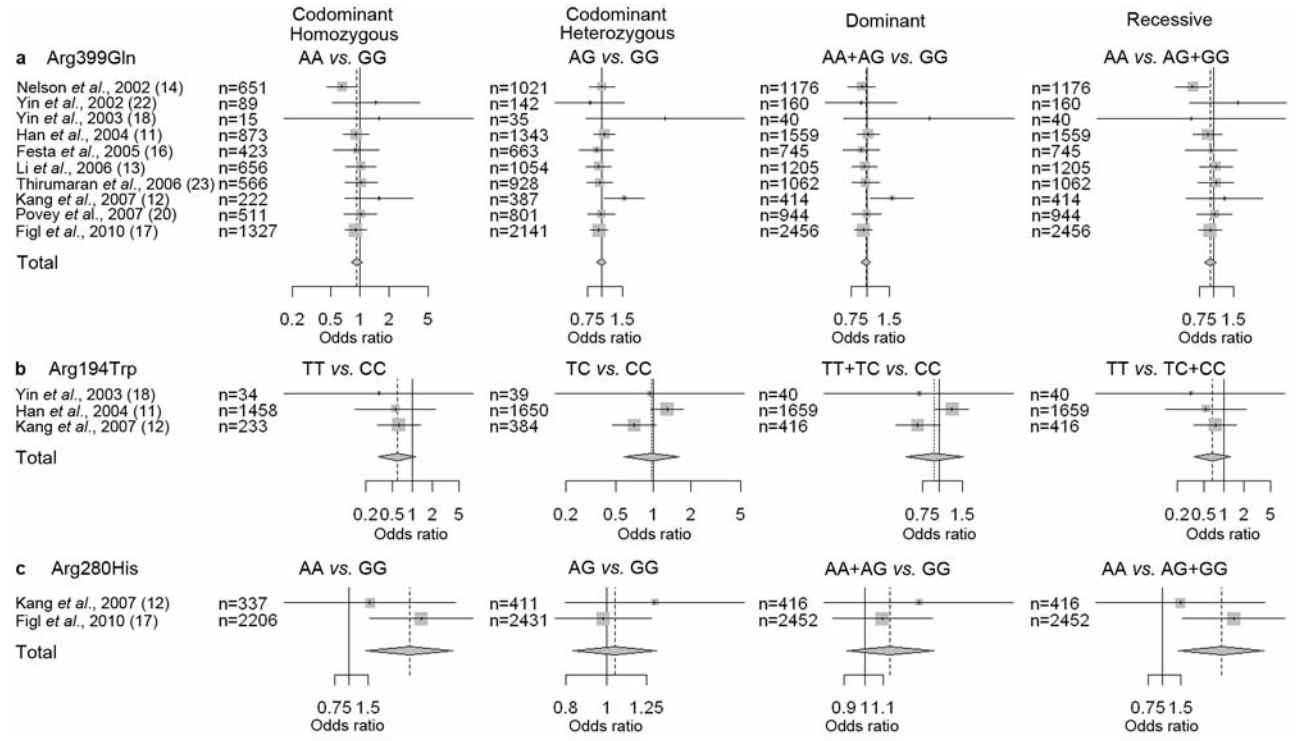

Figure 2. *Meta-analysis of XRCC1 polymorphisms and skin cancer susceptibility. The Arg399Gln (a), Arg194Trp (b), and Arg280His (c) polymorphisms were analyzed under codominant, dominant, and recessive genetic models. Odds ratios (ORs) and 95% confidence intervals (CIs) for individual studies and pooled results are shown. Pooled ORs were calculated using a fixed effects model or random effects model as indicated by the study protocol described in the Methods. Vertical dashed lines represent pooled ORs calculated from fixed effects model; vertical dotted lines represent pooled ORs calculated from random effects model.*

cancer risk. For the Arg399Gln polymorphism, our conclusions are consistent with five of the included studies (16-18, 20, 22, 23), whereas three other studies reported an association between this polymorphism and skin cancer risk (12, 14). In addition, two studies (11, 13) did not show an independent effect of the variant on skin cancer risk, and the findings of these studies were highly dependent on gene–gene or gene–environment interactions, which we were not able to test in our analysis because of lack of such data in other studies. One of the studies (14) claimed that 399Gln/Gln lowered the risk of skin cancer, but only 84 cases and 71 controls were included in this genotype, and gene–environment effects were also present. Although some studies found an association between the Arg194Trp variant and skin cancer risk (11, 12), which contradicted our results, gene–family history interaction (11) and limited subject numbers (12) compromise the conclusions of those reports. In both studies reporting data on the Arg280His polymorphism, no association was observed, consistent with our findings in two genetic models (see below for detail discussion about the apparent association detected in another two genetic models).

There are several limitations associated with our study. Firstly, except in two models of Arg194Trp, most ORs of each polymorphism are close to 1, in these contexts, the power of the statistical analysis (data not shown) is not great enough to detect possible positive associations; the sample size needed to observe the suggested association for each polymorphism (Table V) is much larger than the currently available data. From these power and sample size calculations, it seems unlikely that such a large the case–control study will ever be performed. Secondly, although there were a large number of participants with the Arg194Trp and Arg280His polymorphisms, only four studies were included in our meta-analysis, resulting in possible bias related to selection of individual study participants and inadequate numbers of cases and controls for some genotypes of these polymorphisms. Since the *XRCC1* Arg280His and G to A is a rare polymorphism, only 20 cases and 6 controls were analyzed with the AA genotype. In the homozygous codominant (AA *vs*. GG) and recessive (AA *vs*. AG+GG) genetic models under which the Arg280His variant was associated with skin cancer, AA alone was used to compare with other genotypes. This small subject number may limit

Table IV. *Pooled ORs with 95% CIs for stratified analysis under different genetic models.*

	Homozygous codominant		Heterozygous codominant		Dominant		Recessive	
Arg399Gln (G>A)	AA *vs.* GG		AG *vs.* GG		AA+AG *vs.* GG		AA *vs.* AG+GG	
	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Tumor type								
Melanoma	0.97 (0.82-1.15)	0.87	0.98 (0.88-1.11)	0.41	0.98 (0.88-1.09)	0.47	0.97 (0.83-1.14)	0.95
BCC	0.90 (0.73-1.10)	0.77	1.11 (0.88-1.40)	0.03	1.07 (0.87-1.31)	0.06	0.88 (0.72-1.07)	0.56
SCC	0.86 (0.48-1.54)	0.05	0.93 (0.76-1.14)	0.78	0.89 (0.73-1.08)	0.54	0.89 (0.50-1.58)	0.04
Race								
Caucasian	0.91 (0.79-1.05)	0.62	0.95 (0.87-1.05)	0.85	0.94 (0.86-1.03)	0.91	0.93 (0.81-1.06)	0.44
Mixed*	0.97 (0.72-1.29)	0.22	1.24 (0.85-1.80)	0.09	1.22 (0.80-1.85)	0.05	0.91 (0.70-1.20)	0.41
Control source								
Population	0.87 (0.75-1.01)	0.63	0.98 (0.89-1.09)	0.62	0.96 (0.87-1.05)	0.68	0.87 (0.76-1.01)	0.53
Hospital	1.08 (0.84-1.38)	0.73	1.01 (0.87-1.18)	0.13	1.03 (0.89-1.19)	0.15	1.09 (0.86-1.40)	0.84
Arg194Trp (C>T)	TT *vs.* CC		TC *vs.* CC		TT+TC *vs.* CC		TT *vs.* TC+CC	
	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Tumor type								
Melanoma	0.32 (0.02-5.65)	-	1.33 (0.86-2.07)	-	1.25 (0.81-1.94)	-	0.31 (0.02-5.45)	-
BCC	0.91 (0.44-1.86)	0.64	0.98 (0.72-1.33)	0.80	0.98 (0.72-1.32)	0.68	0.95 (0.47-1.91)	0.66
SCC	0.40 (0.15-1.06)	0.71	0.92 (0.34-2.48)	<0.01	0.88 (0.34-2.29)	<0.01	0.50 (0.19-1.29)	0.56
Race								
Caucasian	0.31 (0.01-8.27)	-	0.94 (0.17-5.36)	-	0.71 (0.14-3.66)	-	0.32 (0.01-8.26)	-
Mixed*	0.61 (0.32-1.19)	0.88	0.97 (0.53-1.76)	0.02	0.94 (0.53-1.68)	0.02	0.69 (0.37-1.32)	0.69
Control source								
Population	0.51 (0.14-1.82)	0.75	1.28 (0.96-1.72)	0.72	1.23 (0.92-1.63)	0.50	0.49 (0.14-1.77)	0.77
Hospital	0.63 (0.30-1.34)	-	0.70 (0.47-1.05)	-	0.69 (0.47-1.02)	-	0.75 (0.36-1.54)	-

Includes study populations in which the race was mixed or Asian. BCC, Basal cell carcinoma; CI, confidence interval; OR, odds ratio; P_h, *P*-value for heterogeneity test; SCC, squamous cell carcinoma.

Table V. *Sample size needed to observe suggested association for each polymorphism.*

Gene variant	Homozygous codominant	Heterozygous codominant	Dominant	Recessive
Arg399Gln (G>A)	AA *vs.* GG	AG *vs.* GG	AA+AG *vs.* GG	AA *vs.* AG+GG
	46194	1246608	1278218	74296
Arg194Trp (C>T)	TT *vs.* CC	TC *vs.* CC	TT+TC *vs.* CC	TT *vs.* TC+CC
	15284	35098	126244	17114
Arg280His (G>A)	AA *vs.* GG	AG *vs.* GG	AA+AG *vs.* GG	AA *vs.* AG+GG
	3040	130948	15248	3178

Above data were calculated based on the study design that cases and controls are in 1:1 ratio.

the reliability of the conclusion drawn in this variant analysis. In a previously published meta-analysis of XRCC1 and cancer risk with a larger sample for Arg280His polymorphisms, only the risk of combined variant genotypes AA+AG *vs.* its wild-type homozygote GG (*e.g.*, dominant model) was tested because of the rare variant allele frequencies of this polymorphism (9). However, in the dominant model analysis of our study, we did not address the association between genotype and skin cancer risk. Furthermore, the positive associations detected in Arg280His are based on only two studies, one on melanoma (17) and one on basal cell carcinoma and squamous cell carcinoma; (12) one is based on a Caucasian population (17) and the other on a Korean population (12); one used population-based controls (17) and the other used hospital-based controls (12). In addition the statistically significant associations derived only

from the study on melanoma (17). Given the low number of cases for the genotype assumed to be associated with risk, the authors in the original study (17) refrained from making any firm conclusions. Thirdly, four studies were excluded from the analysis because they failed to provide sufficient genotype frequencies needed for statistical analysis (15, 21, 31, 32). Among these studies, that by Winsey *et al*. (21) reported no association between disease and Arg399Gln and Arg194Trp polymorphisms, consistent with our conclusion. Two other studies (31, 32) are meeting abstracts and the related research with full text publication and complete genotype information were included in our analysis (14). The other study (15) is also a meeting abstract reporting that the Arg194Trp variant increases the risk of basal cell carcinoma at sun-exposed sites in a Japanese population. However, this study included a limited number of cases with different skin cancer types (n=120) and controls (n=53) compared to the larger number of cases (n=1,026) and controls (n=1,089) in our meta-analysis. Thus, it seems unlikely that the inclusion of this missing data would change our conclusion about the Arg194Trp polymorphism. Fourthly, stratified analysis was limited by the fact that many studies failed to define patient characteristics, such as family history, age, or gender, making it problematic to control for these factors. Finally, there might be haplotypic effects because these three polymorphisms are physically close to each other. However, the information provided by the original literature is too limited to perform this analysis.

Despite these limitations, our meta-analysis suggests that Arg280His polymorphism of the *XRCC1* gene could be a risk factor for skin cancer, while the Arg399Gln and Arg194Trp polymorphisms are unlikely to be associated with skin cancer risk.

Conflict of Interest

The Authors state no conflict of interest.

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