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ERCC2 Lys751Gln polymorphism is associated with lung cancer among Caucasians

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ABSTRACT

To derive a more precise estimation of the relationship between the excision repair cross-complementing rodent repair deficiency, group 2 (*ERCC2*) Lys751Gln polymorphism and lung cancer risk, a meta-analysis was performed. A total of 23 studies including 8137 cases and 9824 controls were involved in this meta-analysis. Overall, significantly elevated lung cancer risk was associated with *ERCC2* Gln allele when all studies were pooled into the meta-analysis (Lys/Gln versus Lys/Lys: odds ratio (OR) = 1.10, 95% confidence interval (CI) = 1.03–1.19; Gln/Gln versus Lys/Lys: OR = 1.20, 95% CI = 1.06–1.35; dominant model: OR = 1.13, 95% CI = 1.05–1.20; and recessive model: OR = 1.15, 95% CI = 1.03–1.29). In the subgroup analysis by ethnicity, significantly increased risk was only found for Caucasians (Gln/Gln versus Lys/Lys: OR = 1.25, 95% CI = 1.08–1.45; dominant model: OR = 1.10, 95% CI = 1.00–1.22; and recessive model: OR = 1.22, 95% CI = 1.06–1.40). When stratified by study design, statistically significantly elevated risks were found in hospital-based studies (Lys/Gln versus Lys/Lys: OR = 1.12, 95% CI = 1.03–1.22; Gln/Gln versus Lys/Lys: OR = 1.24, 95% CI = 1.06–1.44; dominant model: OR = 1.15, 95% CI = 1.06–1.24; and recessive model: OR = 1.19, 95% CI = 1.03–1.37) and population-based studies (Gln/Gln versus Lys/Lys: OR = 1.57, 95% CI = 1.12–2.20 and recessive model: OR = 1.50, 95% CI = 1.08–2.07). In the subgroup analysis whether or not the studies were matched on smoking, significantly increased risk was found not in those matched studies but in the unmatched studies (Lys/Gln versus Lys/Lys: OR = 1.11, 95% CI = 1.03–1.19; Gln/Gln versus Lys/Lys: OR = 1.22, 95% CI = 1.07–1.40; dominant model: OR = 1.13, 95% CI = 1.05–1.22; and recessive model: OR = 1.18, 95% CI = 1.04–1.33). In conclusion, this meta-analysis suggests that the *ERCC2* Lys751Gln polymorphism may contribute to lung cancer susceptibility among Caucasians.

1. Introduction

In Europe, lung cancer is the most commonly diagnosed cancer, with nearly 400,000 new cases each year.[1] There were an estimated 391,000 cases of lung cancer in Europe in the year 2008; 291,000 in men and 100,000 in women. The number of lung cancer deaths in Europe is only slightly less—about 342,000 in the year 2008 (255,000 in men and 87,000 in women).[2] Although tobacco smoking is the major cause of lung cancer, not all smokers develop lung cancer, which suggests that other causes such as genetic polymorphisms might contribute to lung cancer susceptibility.[3,4] Recently, as one of the common low-penetrant genes, excision repair cross-complementing rodent repair deficiency, group 2 (*ERCC2*) gene, also called xeroderma pigmentosum group D (*XPD*) gene, has been identified as a potential lung cancer susceptibility

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gene, which is located on chromosome 19q13.3 and comprises 23 exons and spans about 54,000 base pairs.[5] The *ERCC2* gene codes for an evolutionarily conserved helicase, a subunit of the core transcription factor IIH (TFIIH) which is involved in nucleotide excision repair of DNA by opening DNA around the damage.[6] Point mutations in *ERCC2* prevent the protein from interacting with p44, another subunit of TFIIH[7] and decrease helicase activity, resulting in a defect in nucleotide excision repair (NER).[8] One of the common *ERCC2* polymorphisms in the coding regions is A35931C (Lys751Gln) in exon 23. Though a series of studies have evaluated the potential role of *ERCC2* Lys751Gln polymorphism in lung cancer development, results were generally inconsistent and inconclusive, probably due to the possible small effect of the polymorphism on lung cancer risk or the relatively small sample size in each of published studies. Therefore, we conducted this meta-analysis to summarise the results of the effect of the *ERCC2* Lys751Gln polymorphism on lung cancer.

2. Methods

2.1. Search strategy

The databases, PubMed, Medline, Embase and Web of Science, were searched (updated to 15th February 2010) using the terms: '*ERCC2*', 'excision repair cross-complementing rodent repair deficiency, group 2', '*XPD*', 'xeroderma pigmentosum group D', 'polymorphism' and 'lung cancer'. All the searched studies were retrieved, and their references were checked as well for other relevant publications. Review articles were also searched to find additional eligible studies. Only those published in English language with full text articles were included. For overlapping studies, only the first published one was selected; for republished studies, only the one with the largest sample numbers was included.

2.2. Eligible studies and data extraction

Selection criteria were: (a) retrospective or prospective cohort case-control lung cancer studies of *ERCC2* Lys751Gln polymorphism with complete genotypes distribution data; (b) the diagnosis of lung cancer patients was confirmed pathologically and controls were confirmed to be free from lung cancer; (c) written in English; and (d) fulfilling Hardy–Weinberg equilibrium (HWE) in the control group ($P > 0.05$ was eligible).

The following variables were extracted from each study if available: first author's surname, publication year, country of origin, study design, genotype distributions, minor allele frequency of cases and controls and HWE of controls, respectively. Taking account of that DNA repair genes might modulate the risk of smoking-related lung cancer, the information on whether or not the studies were matched on smoking and smoking parameter chosen was also collected.

Different ethnicity descents were categorised as Caucasian, Asian, Latino-American, African-American or mixed. Study design was stratified into hospital-based studies, population-based studies and nested case-control studies. Minimum number of patients of a study to be included in the meta-analysis was not defined. Data were extracted independently by two investigators and consensuses were reached on all items. If they could not come to an agreement, a third investigator (Chang, J.H.) adjudicated the disagreements.

2.3. Statistics

Based on the genotype frequencies in cases and controls, crude odds ratios (ORs) as well as their 95% confidence intervals (CIs) were calculated to assess the strength of association between the *ERCC2* Lys751Gln polymorphism and lung cancer risk. The pooled ORs were performed with co-dominant model (Lys/Gln versus Lys/Lys, Gln/Gln versus Lys/Lys), dominant model (Lys/Gln + Gln/Gln versus Lys/Lys) and recessive model (Gln/Gln versus Lys/Lys + Lys/Gln), respectively. Subgroup analyses were performed by ethnicity, study design and whether or not the studies were matched on smoking if relevant data were available.

The fixed-effects model (Mantel–Haenszel method), or the random effects (DerSimonian Laird) model, was appropriately used to calculate the pooled OR. Between-study heterogeneity and between-study inconsistency were assessed by using Cochran Q statistic and by estimating I^2, respectively.[9] In case significant heterogeneity was detected, the random effects model was chosen. Meta-analysis was performed using the 'metan' STATA command.

Evidence of publication bias was determined using Egger's[10] formal statistical test and by visual inspection of the funnel plot. For the interpretation of Egger's test, statistical significance was defined as $P < 0.10$. The Egger's test was performed using the 'metabias' STATA command.

Moreover, sensitivity analysis was performed excluding studies whose allele frequencies in controls exhibited significant deviation from the HWE, given that the deviation may denote bias. For the assessment of the deviation from HWE, the appropriate goodness-of-fit chi-square test was performed.[11,12] For the interpretation of the goodness-of-fit chi-square test, statistical significance was defined as $P < 0.05$. Analyses were conducted using STATA 10.0 (STATA Corp., College Station, TX, USA).

3. Results

3.1. Study characteristics

A total of 24 publications met the inclusion criteria.[13–34] The studies of Vogel and colleagues,[35] Raaschou-Nielsen and colleagues[36] and Sorensen and colleagues[37] did not meet the criteria because they were case-cohort studies, which meant that the comparison groups were random samples of the cohorts and included a few lung cancer cases. The study by Zhou and colleagues[13] was excluded because the subjects had been included by study by Zhou and colleagues.[14] While in other two publications,[15,16] the ORs were presented separately according to the different subgroups of ethnicity. Therefore, each group in one publication was considered separately for subgroup analysis. Hence, a total of 23 studies including 8137 cases and 9824 controls were used in the meta-analysis.[14–34] The studies were characterised and listed in Table 1, including first author, year of publication, country of origin, study design, genotype distributions, minor allele frequency of cases and controls, HWE of controls and matching criteria

Table 1 – Main characteristics of all studies included in the meta-analysis.

Author	Year	Country	Ethnicity	Source	Cases			MAF of cases (%)	Controls			MAF of controls (%)	HWE of controls	Matching criteria of smoking
ERCC2 Lys751Gln					*Gln/Gln*	*Lys/Gln*	*Lys/Lys*		*Gln/Gln*	*Lys/Gln*	*Lys/Lys*			
Spitz	2001	USA	Caucasian	HB	47	153	141	36	39	162	159	33	Y	History
David-Beabes (a)	2001	USA	Caucasian	PB	34	77	67	41	58	198	197	35	Y	None
David-Beabes (b)	2001	USA	African-American	PB	11	63	79	28	13	91	130	25	Y	None
Chen	2002	China	Asian	HB	11	47	51	32	20	48	41	40	Y	History
Zhou	2002	USA	Caucasian	HB	166	498	428	38	166	575	499	37	Y	None
Park	2002	Korea	Asian	HB	1	29	220	6	0	18	145	6	Y	None
Xing	2002	China	Asian	HB	5	57	289	10	3	49	331	7	Y	None
Hou	2002	Sweden	Caucasian	HB	32	82	71	39	28	65	69	37	Y	History
Misra	2003	Finland	Caucasian	Nest	53	145	112	40	46	153	103	41	Y	None
Liang	2003	China	Asian	HB	14	153	839	9	6	166	848	9	Y	None
Harms	2004	USA	Caucasian	HB	6	55	49	30	7	51	61	27	Y	None
Popanda	2004	German	Caucasian	HB	79	214	170	40	64	207	188	36	Y	None
Shen	2005	China	Asian	PB	0	11	107	5	2	20	86	11	Y	None
Matullo	2006	Europe	Mixed	Nest	21	58	37	43	193	504	397	41	Y	History[a]
Huang	2006	USA	Mixed	Nest	95	348	300	36	112	332	315	37	Y	None
Yin	2006	China	Asian	HB	0	18	129	6	0	7	138	2	Y	None
Hu	2006	China	Asian	HB	7	141	827	8	5	127	865	7	Y	None
De Ruyck	2007	Belgium	Caucasian	HB	15	53	42	38	11	53	45	34	Y	None
Lopez-Cima	2007	Spain	Caucasian	HB	57	237	222	34	50	240	243	32	Y	None
Chang (a)	2008	USA	Latino-American	PB	14	36	63	28	14	103	182	22	Y	None
Chang (b)	2008	USA	African-American	PB	12	100	143	24	14	98	168	23	Y	None
Sreeja	2008	India	Indian	HB	13	89	109	27	11	61	139	20	Y	None
Yin	2009	China	Asian	HB	4	61	220	12	3	40	242	8	Y	None

PB: population-based study; HB: hospital-based study; and Nest: nested case-control study.

MAF: minor allele frequency; HWE: Hardy–Weinberg equilibrium; Y: yes; and N: no.History: never smoking, former smoking and current smoking.

a Only never smoking and former smoking.

Table 2 – Main results of pooled ORs in the meta-analysis.

ERCC2 Lys751Gln	Lys/Gln versus Lys/Lys		Gln/Gln versus Lys/Lys		Dominant model		Recessive model	
	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h	OR (95% CI)	P_h
Total	1.10 (1.03–1.19)	0.20	1.20 (1.06–1.35)	0.42	1.13 (1.05–1.20)	0.14	1.15 (1.03–1.29)	0.40
Ethnicity								
Caucasian	1.06 (0.96–1.18)	0.93	1.25 (1.08–1.45)	0.94	1.10 (1.00–1.22)	0.92	1.22 (1.06–1.40)	0.96
Asian	1.12 (0.87–1.42)	0.02	1.09 (0.69–1.71)	0.15	1.11 (0.86–1.43)	0.01	1.08 (0.69–1.68)	0.20
African-American	1.10 (0.96–1.26)	0.86	1.17 (0.65–2.10)	0.59	1.17 (0.90–1.53)	0.99	1.10 (0.62–1.95)	0.56
Study design								
HB	1.12 (1.03–1.22)	0.15	1.24 (1.06–1.44)	0.76	1.15 (1.06–1.24)	0.15	1.19 (1.03–1.37)	0.82
PB	1.07 (0.88–1.30)	0.24	1.57 (1.12–2.20)	0.22	1.13 (0.94–1.36)	0.11	1.50 (1.08–2.07)	0.19
Nest	1.10 (0.89–1.37)	0.20	0.98 (0.77–1.24)	0.66	1.04 (0.89–1.22)	0.57	0.95 (0.76–1.18)	0.49
Matching of smoking								
Yes	1.09 (0.89–1.34)	0.61	1.08 (0.81–1.44)	0.15	1.09 (0.89–1.32)	0.35	1.02 (0.78–1.34)	0.23
No	1.11 (1.03–1.19)	0.12	1.22 (1.07–1.40)	0.54	1.13 (1.05–1.22)	0.11	1.18 (1.04–1.33)	0.47

P_h: *P* value of Q-test for heterogeneity test; HB: hospital-based study; PB: population-based study; and Nest: nested case-control study.

of smoking. Of the 23 studies, sample sizes ranged from 218 to 2332. There were nine studies of Caucasians, eight studies of Asians, two studies of African-Americans, one study of Latino-Americans, one study of Indians and two studies of mixed populations. In these studies, 15 were hospital-based, five were population-based and three were nested case-control studies. Almost all of the cases were pathologically confirmed. Controls were mainly healthy populations and matched for age. Among these studies, only four studies were matched on smoking and the smoking parameters chosen were all smoking history which was categorised as never smoking, former smoking and current smoking.

3.2. *Main results*

Table 2 listed the main results of this meta-analysis. Overall, significantly elevated lung cancer risk was associated with *ERCC2* Gln allele when all studies were pooled into the meta-analysis (Lys/Gln versus Lys/Lys: OR = 1.10, 95% CI = 1.03–1.19; Gln/Gln versus Lys/Lys: OR = 1.20, 95% CI = 1.06–1.35; dominant model: OR = 1.13, 95% CI = 1.05–1.20; and recessive model: OR = 1.15, 95% CI = 1.03–1.29). In the subgroup analysis by ethnicity, significantly increased risk was only found for Caucasians (Gln/Gln versus Lys/Lys: OR = 1.25, 95% CI = 1.08–1.45; dominant model: OR = 1.10, 95% CI = 1.00–1.22; and recessive model: OR = 1.22, 95% CI = 1.06–1.40) (Fig. S1). When stratified by study design, statistically significantly elevated risks were found in hospital-based studies (Lys/Gln versus Lys/Lys: OR = 1.12, 95% CI = 1.03–1.22; Gln/Gln versus Lys/Lys: OR = 1.24, 95% CI = 1.06–1.44; dominant model: OR = 1.15, 95% CI = 1.06–1.24; and recessive model: OR = 1.19, 95% CI = 1.03–1.37) and population-based studies (Gln/Gln versus Lys/Lys: OR = 1.57, 95% CI = 1.12–2.20 and recessive model: OR = 1.50, 95% CI = 1.08–2.07). In the subgroup analysis whether or not the studies were matched on smoking, significantly increased risk was found not in those matched studies but in the unmatched studies (Lys/Gln versus Lys/Lys: OR = 1.11, 95% CI = 1.03–1.19; Gln/Gln versus Lys/Lys: OR = 1.22, 95% CI = 1.07–1.40; dominant model: OR = 1.13, 95% CI = 1.05–1.22; and recessive model: OR = 1.18, 95% CI = 1.04–1.33).

3.3. *Sensitivity analysis and publication bias*

A single study involved in the meta-analysis was deleted each time to reflect the influence of the individual data-set to the pooled ORs, and the corresponding pooled ORs were not materially altered (data not shown), indicating that our results were statistically robust. Begg's funnel plot and Egger's test were performed to evaluate the publication bias of the literatures. The shape of the funnel plot did not reveal any evidence of obvious asymmetry (figures not shown) and the Egger's test suggested the absence of publication bias ($P = 0.28$ for Lys/Gln versus Lys/Lys; $P = 0.47$ for Gln/Gln versus Lys/Lys; $P = 0.33$ with dominant model; and $P = 0.52$ with recessive model).

4. Discussion

In the present meta-analysis that involved 8137 cases and 9824 controls, the association between the *ERCC2* Lys751Gln polymorphism and lung cancer risk was explored. The results from our meta-analysis indicate that the *ERCC2* Gln allele is a low-penetrant risk factor for developing lung cancer. *ERCC2* is an important DNA repair gene, playing critical role in NER pathway which is the most important system to repair a wide variety of structurally DNA lesions, including bulky adducts, cross-links,[38] oxidative DNA damage, thymidine dimmers[39] and alkylating damage.[40] Although the exact mechanisms how *ERCC2* Lys751Gln polymorphism affects cancer risk at the molecular level remain to be unravelled, the published studies on the structure and biological functions of the *ERCC2* gene as well as their genetic variants help us understand the potential roles of this polymorphism. The *ERCC2* protein takes part in the unwinding of DNA and forms a complex with the basal transcription factor TFIIH during transcription-coupled repair.[41] Mutations in *ERCC2* cause a severe but variable depression of NER.[42] Hou and colleagues reported that the common variant allele (codon 751) of *ERCC2* gene might be associated with reduced repair of aromatic DNA adducts.[30] Several studies have also shown that the Lys751Gln polymorphism is associated with phenotypes of repair of BPDE- and UV-induced DNA damage.[17,43] These studies showed the

functional role of *ERCC2* Lys751Gln polymorphism and suggested that functional and common sequence variations of DNA repair genes may be potential cancer susceptibility actors in the general population exposed to environmental carcinogens such as polycyclic aromatic hydrocarbons (PAHs).[44,45]

In the subgroup analysis based on ethnicities, significant association was found in Caucasians but not in Asians or African-Americans under three genetic models (Gln/Gln versus Lys/Lys, dominant model and recessive model), suggesting a possible role of ethnic differences in genetic backgrounds and the environment they live in.[46] The influence of the Gln allele might be masked by the presence of other as-yet unidentified causal genes involved in lung cancer development in Asians and African-Americans. On the other hand, the linkage patterns between Lys751Gln and Asp312Asn of *ERCC2* gene are different in Caucasians, Asians and African-Americans, which could also contribute to the observed differences. Moreover, it is likely that the observed ethnic differences may be due to chance because small sample size and relatively lower allele frequency of Lys751Gln among Asians and African-Americans may lead to insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate.[47] Considering all these factors, our results of this meta-analysis should be interpreted with caution.

In the subgroup analysis whether or not the studies were matched on smoking, significantly increased risk was not detected in the matched studies, which might be due to the relatively few studies and small sample size. For Caucasian population, there were only two studies matched on smoking between cases and controls, thus, it is necessary to conduct large sample studies with well-matched controls to avoid the bias and ensure sufficient statistical power to verify the possible slight effect of the polymorphism on lung cancer risk in Caucasian population.

Several limitations of this meta-analysis should be summarised and addressed. Firstly, the sample size was still relatively small for some stratified analyses. Secondly, in our analysis, the controls were not uniformly defined. Although most of the controls were selected mainly from healthy populations, some had benign disease. Therefore, non-differential misclassification bias was possible because these studies may have included the control groups who have different risks of developing lung cancer. Finally, our results were based on unadjusted estimates, while a more precise analysis should be conducted if all individual raw data were available, which would allow for the adjustment by other co-variants including age, gender, smoking status, drinking status, obesity, environmental factors and other lifestyle.

In spite of these limitations, our meta-analysis had several strengths. First, sufficient number of cases and controls were pooled from different studies, which significantly increased the statistical power of the analysis. Second, no publication biases were detected, indicating that the whole pooled results may be unbiased.

In conclusion, this meta-analysis suggests that *ERCC2* Lys751Gln polymorphism may contribute to lung cancer susceptibility among Caucasians. Further investigations of the combined effects of polymorphisms between DNA repair genes and drug-metabolising genes should be considered. More consortia and international collaborative studies, which may be a way to maximise study efficacy and overcome the limitations of individual studies, are needed to help further illuminate the landscape of *ERCC2* Lys751Gln polymorphism and lung cancer risk.

Conflict of interest statement

None declared.

Appendix A. Supplementary material

Supplementary data associated with this article can be found, in the online version, at doi:10.1016/j.ejca.2010.05.008.

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