LETTER to the EDITOR

Association of COX-2 8473T>C Gene Polymorphism with Lung Cancer Risk

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Dear Editor

Recently, we read with great interest the article by Liu et al, which was published in your journal (Liu et al., 2010). The aim of the study was to evaluate the impact of the COX-2 gene 8473T>C polymorphism on lung cancer risk. The results indicated that the COX-2 gene was a factor for suffering from lung cancer, especially of small cell type among Asians. After carefully reading the article, we noted several issues which should be considered.

First, the authors appeared to have missed one paper published by Lim et al. (2010). The detailed search process was not well-documented.

Second, evidence suggested that deviation from Hardy-Weinberg equilibrium (HWE) might reflect the presence of genotyping errors, population stratification, and selection bias in the controls (Boccia et al., 2010). Though, the authors stated that genotype frequencies of all studies in the controls were consistent with HWE, we found a significant deviation from HWE in one study(Liu et al., 2010).

Third, we examined the characterization of studies included in the meta-analysis carefully. One study which published by Liu et al. (2010) was wrongly considered to be 716 lung cancer patients and 358 controls, and the actual numbers were the other way around. Therefore, we thought that the genotype frequencies of Liu's study in the meta-analysis might be wrong. It is better to present the genotype frequencies of cases and controls to be more readable in a separate table.

Fourth, in the article, though the genotype contrasts (CC genotype vs. TT genotype, CC/CT genotypes vs. TT genotype) were included, the allele (C allele vs. T allele) contrast was not included. It is needed.

Fifth, Park's study (2006) provided available information for smoking status. The authors did not consider this when performing the subgroup analyses.

Lastly, based on these issues listed above, we tried to improve this meta-analysis. The distributions of genotype in each study were present in Table 1. We also assessed HWE in controls of each study. We re-calculated the main results of the meta-analysis which are shown in Table 2.

Table 1. Distribution of Genotype in Each Studies

Study	Cases		Controls		P value of HWE
	TT/TC/CC	Subtotal	TT/TC/CC	Subtotal	
Hu et al., 2005	234/83/5	322	209/107/7	323	0.285
Park et al., 2006	352/205/25	582	330/220/32	582	0.838
Vogel et al., 2008	182/183/38	403	310/341/93	744	0.999
Campa et al., 2005	855/886/224	1965	805/904/228	1937	0.565
Liu et al., 2010	239/119/0	358	468/248/0	716	0.000
Lim et al., 2010	182/100/15	297	462/228/28	718	0.999

Table 2. Main Results of the Meta-analysis

Contrast groups	CC vs. TT			CC/CT vs. TT			C vs. T		
(No. studies)	OR (95% CI)	P value	I^2	OR (95% CI)	P value	I^2	OR (95% CI)	P value	I^2
Total (6)	0.88 (0.74-1.04)	0.127	0.0%	0.81 (0.65-1.01)	0.065	80.4%	0.87 (0.76-1.01)	0.069	70.0%
HWE (5)	0.88 (0.74-1.04)	0.127	0.0%	0.79 (0.61-1.03)	0.077	84.0%	0.86 (0.72-1.02)	0.084	75.7%
Ethnicity									
Asian (4)	0.90 (0.60-1.33)	0.588	17.9%	0.90 (0.75-1.09)	0.275	45.1%	0.92 (0.78-1.09)	0.324	48.5%
HWE(3)	0.90 (0.60-1.33)	0.588	17.9%	0.89 (0.68-1.15)	0.367	62.8%	0.91 (0.72-1.15)	0.411	65.2%
Caucasian (2)	0.87 (0.72-1.05)	0.152	29.5%	0.67 (0.35-1.28)	0.227	94.7%	0.79 (0.55-1.15)	0.227	90.6%
Histological types									
AC (3)	0.70 (0.43, 1.15)	0.163	0.0%	0.81 (0.48, 1.36)	0.421	79.9%	0.80 (0.57-1.12)	0.195	67.3%
SCC (3)	0.62 (0.37, 1.05)	0.075	0.0%	0.93 (0.76, 1.15)	0.521	0.0%	0.90 (0.76-1.07)	0.222	0.0%
Small cell (3)	0.77 (0.43-1.37)	0.371	0.0%	0.60 (0.44-0.81)	0.001	58.4%	0.71 (0.55-0.91)	0.008	59.0%
Others (3)	0.88 (0.48, 1.62)	0.689	0.0%	0.84 (0.61, 1.15)	0.280	0.0%	0.89 (0.69-1.14)	0.349	0.0%
Smoking status									
Smoking (4)	NA			0.75 (0.58-0.97)	0.028	66.2%	NA		
No-smoking (4)	NA			0.91 (0.59-1.40)	0.654	56.4%	NA		

AC, adenocarcinomas; SCC, squamous cell carcinomas; NA, not available

A total of six studies including 3927 lung cancer cases and 5020 controls evaluated the association of COX-2 8473T>C gene polymorphism with lung cancer risk. The pooled results showed that no associations were found in a worldwide population. After an ethnicity-based sub-analysis, no significant associations with lung cancer risk were found among Asian and Caucasians population. After stratification by histological type, we found a significant association for small cell lung cancer (CC/CT vs.TT: OR=0.60, 95% CI= 0.44-0.81, P=0.001; C vs. T: OR=0.71, 95% CI= 0.55-0.91, P=0.008). However, other types did not reach statistical significance. In the subgroup analysis by smoking status, we found a significant association in smoking group (CC/CT vs. TT: OR=0.75,95% CI= 0.58-0.97, P=0.028).

In conclusion, we found that the 8473T>C polymorphism of COX-2 gene might be a risk factor for small cell lung cancer, and smokers would be a higher risk for lung cancer than non-smokers. Since the number of studies is relatively small, more well-designed studies are required to assess the associations.

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The authors declare that they have no competing interests.

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