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MDM2 309 T/G polymorphism is associated with lung cancer risk among Asians

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ABSTRACT

Published data on the association between *MDM2* 309 T/G polymorphism and lung cancer risk are inconclusive. To derive a more precise estimation of the relationship, a meta-analysis was performed. A total of eight studies including 6063 cases and 6678 controls were involved in this meta-analysis. Overall, significantly elevated lung cancer risk was associated with GG variant genotype in recessive model when all the eligible studies were pooled into the meta-analysis (OR = 1.17; 95% CI = 1.02–1.34; $P_{heterogeneity}$ = 0.06). In the subgroup analysis by ethnicity, significantly increased risks were found among Asians for TG versus TT (OR = 1.20; 95% CI = 1.05–1.37; $P_{heterogeneity}$ = 0.30), GG versus TT (OR = 1.34; 95% CI = 1.01–1.79; $P_{heterogeneity}$ = 0.03) and dominant model (OR = 1.26; 95% CI = 1.11–1.43; $P_{heterogeneity}$ = 0.14). However, no significant associations were found in both Europeans and Africans for all genetic models. This meta-analysis suggests that the *MDM2* 309G allele is a low-penetrant risk factor for developing lung cancer in Asians.

1. Introduction

Lung cancer is currently the most frequently occurring cancer and one of the leading causes of cancer-related deaths in the world, which has become a major public health challenge.[1] The mechanism of lung carcinogenesis is still not fully understood. It has been suggested that low-penetrance susceptibility genes combining with environmental factors may be important in the development of cancer.[2] In recent years, several common low-penetrant genes have been identified as potential lung cancer susceptibility genes. An important one is *Murine double minute-2* (*MDM2*), a direct negative regulator of *p53*, which plays an important role in the *p53* pathway.[3] A functional single nucleotide polymorphism at the 309th nucleotide in the first intron (rs2279744), with a T to G change, has been proven to increase the affinity of the transcriptional activator Sp1 recently and lead to higher levels of *MDM2* RNA and protein and the subsequent attenuation of the p53 pathway.[4] Additionally, this SNP was found to be associated with accelerated tumour formation in both sporadic and

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Abbreviation: Murine double minute-2, MDM2; Odds ratio, OR; Confidence interval, CI

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hereditary cancers, and serves as a rate-limiting event in carcinogenesis.[4] A number of studies have reported the role of *MDM2* 309 T/G polymorphism in lung cancer risk,[5–11] but the results are inconclusive, partially because of the possible small effect of the polymorphism on lung cancer risk and the relatively small sample size in each of the published studies. Therefore, we performed a meta-analysis of the published studies to derive a more precise estimation of the association.

2. Material and methods

2.1. Publication search

Two electronic databases (PubMed and Embase) were searched (last search was updated on 10th September 2008, using the search terms: '*MDM2*', 'polymorphism' and 'lung'). All eligible studies were retrieved, and their bibliographies were checked for other relevant publications. Review articles and bibliographies of other relevant studies identified were hand-searched to find additional eligible studies. Only published studies with full text articles were included. When more than one of the same patient population was included in several publications, only the most recent or complete study was used in this meta-analysis.

2.2. Inclusion criteria

The inclusion criteria were (a) evaluation of the *MDM2* 309 T/G polymorphism and lung cancer risk, (b) case–control studies and (c) sufficient published data for estimating an odds ratio (OR) with 95% confidence interval (CI).

2.3. Data extraction

Information was carefully extracted from all eligible publications independently by two of the authors according to the inclusion criteria listed above. Disagreement was resolved by discussion between the two authors. If these two authors could not reach a consensus, another author was consulted to resolve the dispute and a final decision was made by the majority of the votes. The following data were collected from each study: first author's surname, publication date, ethnicity, characteristics of matching criteria in controls, genotyping methods, total number of cases and controls and numbers of cases and controls with the GG, GT and TT genotypes, respectively. Different ethnicity descents were categorised as European, Asian and African. When studies included subjects of more than one ethnicity, genotype data were extracted separately according to ethnicities for subgroup analyses. We did not define any minimum number of patients to include a study in our meta-analysis.

2.4. Statistical methods

ORs with 95% CI were used to assess the strength of association between the *MDM2* 309 T/G polymorphism and lung cancer risk. The pooled ORs were estimated for codominant model (TG versus TT; GG versus TT), dominant model (TG + GG versus TT) and recessive model (GG versus TG + TT), respectively. Heterogeneity assumption was checked by the chi-square-based Q-test.[12] A *P* value greater than 0.10 for the Q-test indicates a lack of heterogeneity among studies, so the pooled OR estimate of the each study was calculated by the fixed-effects model (the Mantel–Haenszel method).[13] Otherwise, the random-effects model (the DerSimonian and Laird method) was used.[14] To evaluate the ethnicity-specific effect, subgroup analyses were performed by ethnic group. One-way sensitivity analyses were performed to assess the stability of the results, namely, a single study in the meta-analysis was deleted each time to reflect the influence of the individual data-set to the pooled OR.[15] An estimate of potential publication bias was carried out by the funnel plot, in which the standard error of log (OR) of each study was plotted against its log (OR). An asymmetric plot suggests a possible publication bias. Funnel plot asymmetry was assessed by the method of Egger's linear regression test, a linear regression approach to measure the funnel plot asymmetry on the natural logarithm scale of the OR. The significance of the intercept was determined by the *t*-test suggested by Egger ($P < 0.05$ was considered representative of statistically significant publication bias).[16] All the statistical tests were performed with Review Manager version 4.2 (The Cochrane Collaboration, Oxford, England) and STATA version 9.2 (Stata Corporation, College Station, TX).

3. Results

3.1. Study characteristics

A total of eight publications met the inclusion criteria.[5–11,17] In Jun's study,[17] the subjects had been used in study of Park et al.,[10] so it was not included in the meta-analysis. In Pine's study,[8] the ORs were presented separately according to European descent and African descent, respectively, therefore, each group in the study was considered separately for pooling subgroup analyses. Hence, a total of eight groups including 6063 cases and 6678 controls were used in the pooled analyses. Table 1 lists the studies identified and their main characteristics. Of the eight groups, sample sizes ranged from 388 to 3147. There were four studies of Europeans, three studies of Asians and one study of Africans. Almost all the cases were histologically confirmed. Controls were mainly healthy populations and matched for sex and age.

3.2. Meta-analysis results

Table 2 lists the main results of this meta-analysis. Overall, significantly elevated lung cancer risk was associated with GG variant genotype in recessive model when all the eligible studies were pooled into the meta-analysis (OR = 1.17; 95% CI = 1.02–1.34; $P_{heterogeneity} = 0.06$). In the subgroup analysis by ethnicity, significantly increased risks were found among Asians for TG versus TT (OR = 1.20; 95% CI = 1.05–1.37; $P_{heterogeneity} = 0.30$), GG versus TT (OR = 1.34; 95% CI = 1.01–1.79; $P_{heterogeneity} = 0.03$) and dominant model (OR = 1.26; 95% CI = 1.11–1.43; $P_{heterogeneity} = 0.14$). However, no significant associations were found in both Europeans and Africans for all genetic models (Table 2).

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

Reference	Ethnicity	Matching criteria	Source of controls	Sample size (case/control)	Cases			Controls			MAF (controls)
					TT	TG	GG	TT	TG	GG	
Liu et al.[5]	European	–	Hospital	1787/1360	696	805	286	532	635	193	0.38
Li et al.[6]	European	Age, sex, smoke	Population	1026/1145	419	472	135	408	573	164	0.39
Lind et al.[7]	European	–	Population	341/412	130	156	55	161	207	44	0.36
Pine et al.[8]	European	Age and sex	Both	371/421	150	167	54	182	187	52	0.35
Hu et al.[9]	Asian	Age, sex, area	Population	717/1083	166	373	178	274	538	271	0.5
Park et al.[10]	Asian	Age and sex	Hospital	582/582	113	280	189	122	299	161	0.53
Zhang et al.[11]	Asian	Age and sex	Population	1106/1420	249	561	296	418	711	291	0.46
Pine et al.[8]	African	Age and sex	Both	133/255	111	20	2	203	47	5	0.11

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

	GG versus TT		TG versus TT		TG + GG versus TT		GG versus TG + TT	
	OR(95% CI)	$P_{heterogeneity}$	OR(95% CI)	$P_{heterogeneity}$	OR(95% CI)	$P_{heterogeneity}$	OR(95% CI)	$P_{heterogeneity}$
Total	1.20(0.98, 1.47)	0.004	1.01(0.89, 1.16)	0.02	1.05(0.91, 1.22)	0.002	1.17(1.02, 1.34)	0.06
European	1.11(0.85, 1.44)	0.05	0.92(0.83, 1.02)	0.29	0.95(0.86, 1.05)	0.11	1.11(0.97, 1.28)	0.12
Asian	1.34(1.01, 1.79)	0.03	1.20(1.05, 1.37)	0.30	1.26(1.11, 1.43)	0.14	1.21(0.97, 1.51)	0.05
African	0.73(0.14, 3.83)	–	0.78(0.44, 1.38)	–	0.77(0.45, 1.34)	–	0.76(0.15, 3.99)	–

$P_{heterogeneity}$: P value of Q-test for heterogeneity test; OR: odds ratio; CI: confidence interval.

3.3. *Sensitivity analyses*

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).

3.4. *Publication bias*

Begg's funnel plot and Egger's test were performed to access the publication bias of literatures. The shapes of the funnel plots did not reveal any evidence of obvious asymmetry (Figures not shown). Then, the Egger's test was used to provide statistical evidence of funnel plot symmetry. The results still did not suggest any evidence of publication bias ($P = 0.911$ for TG versus TT, $P = 0.876$ for GG versus TT, $P = 0.963$ for dominant model and $P = 0.925$ for recessive model, respectively).

4. Discussion

A recently published paper indicated that cancer prevention and management is moving in the right direction.[18] Due to the combination of earlier detection, better access to care and improved treatment, survival is increased and mortality is decreased. Still, cancer prevention efforts have much to attain, especially in the domain of smoking prevalence.[19,20] Lung cancer is still a very commonly diagnosed cancer, with a very poor survival, hence primary prevention by anti-smoking measures remains of utmost importance, but prevention and cessation of cigarette smoking in all smokers is a tough and long-term work.[21] Although cigarette smoking is considered as an important factor in causing lung cancer, only about 10–15% of smokers develop this disease, suggesting that genetic susceptibility might contribute to the variation in individual lung cancer risk. So potent markers for identifying high-risk populations of lung cancer are urgently needed, because prevention and cessation of cigarette smoking in high-risk populations is more feasible. Genetic susceptibility markers have been a research focus in scientific community and considered as an important guidance for early preventive care. Of the several most intensely studied markers, the *MDM2* polymorphism is an important one. Growing number of studies have suggested that 309G in the promoter region of the *MDM2* gene was emerging as a low-penetrance tumour susceptibility allele in the development of lung cancer. However, the results are inconclusive, we performed this meta-analysis to estimate the association specifically. At the same time, because the same polymorphism seemed to play different roles in cancer susceptibility among different ethnic populations and because the frequencies of single nucleotide polymorphisms might be different among different ethnic groups, subgroup analyses based on ethnicity were conducted.

Our results indicated that the *MDM2* 309G allele is a low-penetrant risk factor for developing lung cancer in Asians. However, no significant associations were found in both Europeans and Africans for all genetic models, suggesting a possible role of ethnic differences in genetic backgrounds and the environment they lived in.[22] The influence of the 309 G allele might be masked by the presence of other as-yet unidentified causal genes involved in lung cancer development. In addition, it is also likely that the observed ethnic differences may be due to chance because studies with small sample size may have insufficient statistical power to detect a slight effect or may have generated a fluctuated risk estimate.[23] Considering the limited studies and population numbers included in the meta-analysis, our results should be interpreted with caution.

Heterogeneity is a potential problem when interpreting the results of all meta-analyses.[24] Significant between-study

heterogeneity existed in overall comparisons. After subgroup analyses by ethnicity, the heterogeneity was effectively decreased or removed in Europeans and Asians. The reason might be that differences of genetic backgrounds and the environment existed among different ethnicities.

Some limitations of this meta-analysis should be acknowledged. Firstly, the controls were not uniformly defined. Although most of the controls were selected mainly from healthy populations, some had respiratory 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. Secondly, in the subgroup analyses, the number of Africans was relatively small, not having enough statistical power to explore the real association. Thirdly, our results were based on unadjusted estimates, while a more precise analysis should be conducted if individual data were available, which would allow for the adjustment by other covariates including age, ethnicity, smoking status, environmental factors and lifestyle.[25]

Despite these limitations, this meta-analysis suggests that the *MDM2* 309G allele is a low-penetrant risk factor for developing lung cancer in Asians. However, it is necessary to conduct large sample studies using standardised-unbiased genotyping methods, homogeneous lung cancer patients and well-matched controls. Moreover, gene–gene and gene–environment interactions should also be considered in the analysis. Such studies taking these factors into account may eventually lead to our better, comprehensive understanding of the association between the *MDM2* 309 T/G polymorphism and lung cancer risk.

Conflict of interest statement

None declared.

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