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The cell cycle regulatory gene polymorphisms *TP53* (*rs1042522*) and *MDM2* (*rs2279744*) in lung cancer: a meta-analysis

O. Bulgakova ✉, A. Kussainova, R. Bersimbaev

L.N. Gumilyov Eurasian National University, Institute of Cell Biology and Biotechnology, Nur-Sultan, Kazakhstan
✉ e-mail: ya.summer13@yandex.kz

Abstract. Lung cancer is one of the most common types of cancer in the world. Although the mechanism of lung cancer is still unknown, a large number of studies have found a link between gene polymorphisms and the risk of lung cancer. The tumor suppressor p53 plays a crucial role in maintaining genomic stability and tumor prevention. MDM2 is a critical regulator of the p53 protein. Despite the importance of p53 pathway in cancer, data on the contribution of SNPs of *TP53* (*rs1042522*) and *MDM2* (*rs2279744*) to the development of lung cancer are very contradictory. A meta-analysis that collects quantitative data from individual studies and combines their results has the advantage of improving accuracy, providing reliable estimates, and resolving those issues in which studies on individual associations are not effective enough. The aim of this study was to determine whether the *TP53* (*rs1042522*) and *MDM2* (*rs2279744*) polymorphisms confer susceptibility to lung cancer. A meta-analysis was conducted on the associations between the *TP53* (*rs1042522*) and *MDM2* (*rs2279744*) polymorphisms and lung cancer. A total of 51 comparison studies including 25,366 patients and 25,239 controls were considered in this meta-analysis. The meta-analysis showed no association between lung cancer and *MDM2* (*rs2279744*) under any model. A noteworthy association of *TP53* (*rs1042522*) with susceptibility to lung cancer in overall pooled subjects was observed under three different models (allele contrast, homozygote contrast (additive) and dominant). Stratification by ethnicity indicated an association between the *TP53* (*rs1042522*) and lung cancer in Asians and Caucasians. This meta-analysis demonstrates that the *TP53* (*rs1042522*), but not *MDM2* (*rs2279744*) polymorphism may confer susceptibility to lung cancer.
Key words: *TP53* (*rs1042522*) and *MDM2* (*rs2279744*) gene polymorphism; lung cancer; meta-analysis.

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Полиморфизмы генов *TP53* (*rs1042522*) и *MDM2* (*rs2279744*) в раке легкого: метаанализ

О. Булгакова ✉, А. Кусаинова, Р. Берсимбаев

Евразийский национальный университет им. Л.Н. Гумилева, Институт клеточной биологии и биотехнологии, Нур-Султан, Казахстан
✉ e-mail: ya.summer13@yandex.kz

Аннотация. Рак легкого – один из наиболее распространенных видов рака в мире. Хотя механизм возникновения заболевания по-прежнему остается в значительной степени неизвестным, благодаря многочисленным исследованиям была выявлена связь между полиморфизмами генов и риском развития рака легкого. Решающую роль в поддержании стабильности генома и профилактике опухолей играет онкосупрессор p53. Ключевым регулятором белка p53 является MDM2. Несмотря на важность p53 сигнального пути в канцерогенезе, данные о вкладе SNP *TP53* (*rs1042522*) и *MDM2* (*rs2279744*) в развитие рака легкого очень противоречивы. Метаанализ, собирающий количественные данные из отдельных исследований и объединяющий их результаты, имеет преимущество, которое заключается в повышении точности, предоставлении надежных оценок и решении тех вопросов, когда исследование отдельных ассоциаций недостаточно эффективно. Целью нашей работы было изучение роли полиморфизмов *TP53* (*rs1042522*) и *MDM2* (*rs2279744*) в формировании предрасположенности к раку легкого. Проведен метаанализ ассоциации полиморфизмов *TP53* (*rs1042522*) и *MDM2* (*rs2279744*) и рака легкого. В общей сложности рассмотрено 51 исследование типа «случай–контроль», включающее 25 366 пациентов с раком легкого и 25 239 здоровых индивидуумов. Результаты метаанализа показали отсутствие связи между раком легкого и *MDM2* (*rs2279744*) во всех моделях. Примечательно, что ассоциация *TP53* (*rs1042522*) с предрасположенностью к раку легкого наблюдалась в трех разных моделях (мультипликативная, аддитивная и доминантная). Стратификация по этническому признаку также указывает на связь между *TP53* (*rs1042522*) и риском развития рака легкого как в азиатской, так и в европейской популяции. Проведенный метаанализ позволяет сделать вывод, что полиморфизм *TP53* (*rs1042522*), но не *MDM2* (*rs2279744*), может обусловливать предрасположенность к раку легкого.
Ключевые слова: полиморфизм генов *TP53* (*rs1042522*) и *MDM2* (*rs2279744*); рак легкого; метаанализ.

Introduction

Lung cancer remains one of the most common forms of cancer in the world. Every year World Health Organization (WHO) includes lung cancer in the lists of the leading cause of death worldwide. Thus, there were 2.1 million cases of lung cancer and 1.8 million deaths in 2018 (https://www.who.int/ru/news-room/fact-sheets/detail/the-top-10-causes-of-death). Cancer incidence rate varies in different regions of our planet, so the highest incidence of lung cancer is observed in Eastern Europe and Central and East Asia (Bray et al., 2018).

A large number of researches have been conducted to study the molecular base of lung cancer. One of the risk factors for the development of pulmonary neoplasms is genes polymorphisms. The main cause of carcinogenesis is disorders in the regulation of cell cycle control. The tumor suppressor gene *TP53* plays an important role in regulating the cell cycle. p53 protein is known as the "guardian of the genome". p53 regulates many genes expression in response to cellular stress induced by various adverse environmental factors (Haronikova et al., 2019). This protein plays a key role in processes such as DNA repair, cell cycle arrest, apoptosis and senescence (Nicolai et al., 2015). *MDM2* is a key regulator of p53 protein activity and degradation. Polymorphic variants of the *TP53* and *MDM2* genes have been found in various types of cancer, including lung cancer. Analysis of the literature data showed that polymorphisms of the *TP53 Arg72Pro* (*rs1042522*) and *MDM2 SNP309* (*rs2279744*) genes cause an increased predisposition to tumor development. The *TP53 (rs1042522*) gene polymorphism is localized on chromosome 17 position 7676154 Genotype frequency in the Caucasian population GG: 0.074, CC: 0.503, CG: 0.423. In the East Asian population, GG: 0.173, CC: 0.345, CG: 0.482 (http://www.ensembl.org/).

Meta-analyses have shown that the *TP53 Arg72Pro* polymorphic allele is associated with the development of stomach cancer (Xiang et al., 2012), bladder (Xu et al., 2012), colorectal cancer (Tian et al., 2017) and acute lymphocytic leukemia (Tian et al., 2016). However, no association was found between *TP53 Arg72Pro* and the risk of acute myeloid leukemia (Tian et al., 2016), oral squamous cell carcinoma (Sun et al., 2018), and esophagus cancer (Jiang et al., 2011).

The polymorphic allele of the *MDM2* gene *rs2279744* is located at 68808800 position on chromosome 12 Genotype frequency in the Caucasian population TT: 0.404, GG: 0.113, GT: 0.483. In the East Asian population TT: 0.200, GG: 0.276, GT: 0.524 (http://www.ensembl.org/).The *MDM2 SNP309* polymorphism was also found to increase the risk of colorectal cancer (Qin et al., 2013), breast cancer (Cheng et al., 2012) and liver cancer (Tang et al., 2014). But there was no association with prostate, urinary tract (Ding et al., 2016) and stomach (Ma et al., 2013).

Many population studies have been conducted on the influence of the mutant alleles *TP53 Arg72Pro* (*rs1042522*) and *MDM2 SNP309* (*rs2279744*) on the predisposition to the development of pulmonary neoplasia. It was shown that the polymorphism of the *TP53 Arg72Pro* gene is associated with a high risk of small cell lung cancer among Spaniards (Fernández-Rubio et al., 2008). Similar data were found for non-small cell lung cancer in Norwegians (Lind et al., 2007) and Poles (Szymanowska et al., 2006), squamous cell lung cancer in German residents (Popanda et al., 2007), and lung adenocarcinoma in the Chinese population (Zhang X. et al., 2006; Ren et al., 2013).

Data on the contribution of *MDM2 SNP309* to the development of lung cancer are very contradictory. Most studies have shown an association of the *MDM2* (*rs2279744*) mutant allele with a high risk of lung tissue carcinogenesis (Enokida et al., 2014; Wang X. et al., 2015; Li, 2017). However, Pine et al. (2006) did not find that *MDM2 SNP309* is associated with lung neoplasia in the European population.

The data on the association of polymorphisms of the *TP53* genes *Arg72Pro* (*rs1042522*) and *MDM2 SNP309* (*rs2279744*) with the development of tumors as a whole are very contradictory. Therefore, it would be interesting to perform a meta-analysis on the association of *TP53 Arg72Pro* (*rs1042522*) and *MDM2 SNP309* (*rs2279744*) with a risk of developing lung cancer in Asian and European populations.

Materials and methods

Search strategy. Search for relevant studies was conducted using online databases, such as Scopus, PubMed and Web of Science. The search strategy was performed using a combination of the following keywords: "*TP53*", "Murine double minute 2" or "*MDM2*", "polymorphism", "SNP", "*rs1042522*", "*rs2279744*", "*Arg72Pro*", "*codon 72 Arg*", "c.215C > G", "SNP309", "c.291 T > G" "lung cancer", "non-small cell lung cancer", "association".

Inclusion and exclusion criteria. The eligible inclusion criteria for the meta-analysis were (i) case-control study, (ii) identification of different histological types of lung cancer which was confirmed histologically or pathologically, (iii) having an available genotype for estimating an odds ratio (OR) with 95 % confidence interval (95 % CI), (iv) genotype frequencies in controls were consistent with those expected from Hardy–Weinberg equilibrium ($p > 0.05$).

The studies were excluded when (i) they were not case-control studies, (ii) with duplicated data from previous articles, (iii) they were not original articles, e. g. review, (iv) inadequate genotype data were available.

Data extraction and quality assessment. Two researchers (O.B. and A.K.) evaluated the eligibility of all retrieved studies and extracted the pertinent data from the specified publications in standardized tables. The extracted data included: (i) the first author name, (ii) publication year, (iii) ethnicity, (iv) lung cancer patients and healthy controls sample size for each studied polymorphism. Disagreement was resolved by consulting with a third investigator (R.B.). The study quality was assessed in accordance with the Newcastle–Ottawa Scale (NOS) (Wells et al., 2009).

Statistical analysis. Hardy–Weinberg equilibrium (HWE) in control population was assessed utilizing the "Calculation of Chi-square test for deviation from Hardy–Weinberg equilibrium" online software (http://www.husdyr.kvl.dk/htm/kc/popgen/genetik/applets/kitest.htm). The statistical analysis was performed using Comprehensive Meta Analysis version 2.2.064 (Biosta, Englewood, NJ, USA). Estimates were summarized as ORs with 95 % CIs for each study. The heterogeneity was evaluated by using the I^2 index. An I^2 value of > 50 % was considered to indicate high heterogeneity (Lee, 2015). The random effects model for analysis was used in case

Table 1. Characteristics of the studies of *TP53* (*rs1042522*) polymorphism included in the meta-analysis

First author, year	Lung cancer			Control			Ethnicity	*p* (HWE) Control
	GG	GC	CC	GG	GC	CC		
Kawajiri, 1993	148	127	53	144	165	38	Asian	0.65
Murata, 1996	80	89	22	53	76	23		0.59
Wang Y., 1999	68	74	52	47	75	30		0.56
Pierce, 2000	41	51	19	82	65	23		0.67
Hiraki, 2003	68	99	24	90	106	43		0.60
Sakiyama, 2004	398	460	144	302	310	73		0.67
Zhang X., 2006	321	506	279	425	731	264		0.56
Jung, 2008	108	130	42	120	136	37		0.64
Sreeja, 2009	70	84	57	98	76	37		0.65
Sobti, 2009	37	73	41	42	73	36		0.54
Chua, 2010	28	69	26	42	88	31		0.53
Kiyohara, 2010	206	194	62	162	175	42		0.66
Piao, 2011	1458	1821	657	734	776	190		0.66
Liu D., 2013	144	137	79	126	115	119		0.51
Li Y., 2013	118	146	99	161	196	89		0.58
Mostaid, 2014	27	40	39	62	35	19		0.69
Saikia, 2014	95	125	52	225	260	59		0.65
Zhang F., 2014	124	311	205	133	330	222		0.44
Chowdhury, 2015	19	19	12	11	18	21		0.40
Bulgakova, 2019	12	62	11	30	6	6		0.78
Birgander, 1995	148	127	53	144	165	38	Caucasian	0.65
To-Figueras, 1996	52	32	6	92	47	8		0.79
Pierce, 2000	84	46	8	87	76	10		0.72
Fan, 2000	212	204	66	237	212	61		0.67
Liu G., 2001	604	465	99	728	441	87		0.76
Papadakis, 2002	27	27	0	24	64	11		0.56
Miller, 2002	367	299	101	496	339	92		0.72
Wu, 2002	299	177	40	352	156	32		0.80
Su, 2003	28	31	4	9	9	3		0.64
Szymanowska, 2006	110	120	10	311	225	40		0.74
Popanda, 2007	209	156	40	244	131	29		0.75
Nadji, 2007	55	64	10	41	29	19		0.62
Mechanic, 2007	166	125	16	193	122	20		0.76
Giuliani, 2007	32	26	5	30	15	5		0.75
Fernández-Rubio, 2008	308	249	32	338	209	35		0.76
Buyru, 2008	32	25	8	24	49	14		0.56
Souto-García, 2012	341	267	43	318	198	32		0.76

high heterogeneity (Lee, 2015). Otherwise, the fixed-effects model was used. Publication bias was measured via "Begg's funnel plot" and "Egger's linear regression" method (Egger et al., 1997). A two-tailed p-value < 0.05 implied a statistically significant publication bias.

Results

Studies included in the meta-analysis

A total of 531 potential articles were identified from the databases search. After 236 duplicate records were removed, a total of 295 potential articles were reviewed. Amongst these articles, 216 were excluded after titles and abstracts review. Afterwards, we excluded 28 studies for no case-control design. Finally, 51 studies with a total of 25,239 controls and 25,366 cases that met the inclusion criteria were included in this meta-analysis (Suppl. Fig. 1)[1].

Characteristics of studies included in this meta-analysis

A total of 37 articles that examined *TP53* (*rs1042522*) association with lung cancer risk were determined. Two of these articles included data of two different sets (*TP53* (*rs1042522*) and *MDM2* (*rs2279744*)) (Zhang X. et al., 2006; Chua et al., 2010) and these sets were examined autonomously. Thus, the identified 37 articles encompassed case-controls studies involving 16,229 lung cancer patients and 14,897 controls (Table 1). Among 37 articles, 20 studies were established in Asian populations and 17 in Caucasian populations. The

[1] Supplementary Figures 1– 5 are available in the online version of the paper: http://www.bionet.nsc.ru/vogis/download/pict-2020-24/appx13.pdf

Table 2. Characteristics of the studies of *MDM2* (*rs2279744*) polymorphism included in the meta-analysis

First author, year	Lung cancer			Control			Ethnicity	*p* (HWE) Control
	GG	GC	CC	GG	GC	CC		
Hu, 2006	166	373	178	274	538	271	Asian	0.5
Zhang X., 2006	249	561	296	418	711	291		0.54
Jun, 2007	113	280	189	122	299	161		0.47
Chua, 2010	29	65	29	51	83	25		0.58
Kohno, 2011	68	183	126	79	151	95		0.48
Enokida, 2014	153	379	230	152	335	213		0.46
Li, 2017	58	96	32	44	101	51		0.48
Li G., 2006	419	472	135	408	573	164	Caucasian	0.60
Lind, 2006	130	156	55	161	207	44		0.64
Pine, 2006	150	167	54	182	187	52		0.65
Liu G., 2008	702	802	283	530	631	199		0.62
Mittelstrass, 2008	270	293	70	547	598	149		0.65
Zhuo, 2012	419	472	135	408	573	164		0.61
Javid, 2015	20	56	24	40	50	10		0.65

genotype frequencies in controls of all studies were consistent with those expected from HWE ($p > 0.05$).

Another 14 articles identified *MDM2* (*rs2279744*) association with increased lung cancer risk were retrieved (Table 2). These 14 articles encompassed case-controls studies involving 9,137 lung cancer patients and 10,342 controls. Among 14 articles, 7 studies were established in Asian populations and 7 in Caucasian populations. The genotype frequencies in controls of all studies were consistent with those expected from HWE ($p > 0.05$).

All estimated published articles were executed under accredited genotyping methods.

Meta-analysis of the relationship between the *TP53* (*rs1042522*) polymorphism and lung cancer risk

Meta-analysis of *TP53* (*rs1042522*) polymorphism was associated with lung cancer (G versus C: OR = 0.82, 95 % CI 0.71–0.94, $p = 0.005$; GG versus CC: OR = 0.86, 95 % CI 0.74–0.99, $p = 0.039$; GG+GC versus CC: OR = 0.86, 95 % CI 0.76–0.98, $p = 0.02$; GG versus GC+CC: OR = 1.12, 95 % CI 0.89–1.42, $p = 0.336$). And the association was statistically significant under allele model (G versus C), homozygote model (GG versus CC) (Suppl. Fig. 2) and dominant model (GG+GC vs. CC) (Suppl. Fig. 3) ($p < 0.05$). A summary of meta-analysis findings concerning associations between the *TP53* (*rs1042522*) polymorphism and lung cancer risk is shown in Table 3.

Further subgroup analysis was conducted on the association between *TP53* (*rs1042522*) polymorphism and the risk of lung cancer (see Table 3). After stratifying by ethnicity, this meta-analysis indicated an obvious association of *TP53* (*rs1042522*) and lung cancer risk among Caucasians (G versus C: OR = = 0.83, 95 % CI 0.73–0.95, $p = 0.005$; GG versus CC: OR = 0.83, 95 % CI 0.73–0.95, $p = 0.005$; GG+GC versus CC: OR = 0.88, 95 % CI 0.77–1.00, $p = 0.045$) and among Asians (G versus C: OR = 0.76, 95 % CI 0.63–0.92, $p = 0.005$; GG versus CC: OR = 0.84, 95 % CI 0.67–1.06, $p = 0.136$; GG+GC versus CC: OR = 0.81, 95 % CI 0.69–0.96, $p = 0.012$).

Meta-analysis of the relationship between the *MDM2* (*rs2279744*) polymorphism and lung cancer risk

In this meta-analysis was shown no association *MDM2* (*rs2279744*) polymorphism with lung cancer (G versus T: OR = 0.86, 95 % CI 0.71–1.03, $p = 0.1$; GG versus TT: OR = 0.86, 95 % CI 0.71–1.03, $p = 0.1$; GG+GT versus TT: OR = 0.90, 95 % CI 0.79–1.02, $p = 0.5$; GG versus GT+TT: OR = 1.10, 95 % CI 0.94–1.22, $p = 0.276$). A summary of meta-analysis findings concerning associations between the *MDM2* (*rs2279744*) polymorphism and lung cancer risk is shown in Table 4. Subgroup analysis detected no association *MDM2* (*rs2279744*) polymorphism with lung cancer.

Heterogeneity and publication bias

Between-study heterogeneities were found in all subjects for both polymorphisms *TP53* (*rs1042522*) and *MDM2* (*rs2279744*) (see Table 3, 4). Because of this the meta-analysis was designed using "a random effect model" to establish pooled OR and corresponding 95 % CI for all models. We performed the meta-regression to explore the potential source of between-study. A big problem for meta-analysis is the disproportionate number of positive studies that leads to a bias in the publication. The funnel plot indicated some evidence of publication bias for Caucasians, but not for Asians in analysis of *TP53* (*rs1042522*) and *MDM2* (*rs2279744*) gene polymorphisms (Suppl. Fig. 4, 5). The publication bias was observed from Egger's test ($p \leq 0.05$) also for Caucasian population (see Table 3, 4).

Discussion

The tumor suppressor gene *TP53* (previously named *p53*), is key regulator of a cell cycle network, apoptosis and DNA repair pathway. *TP53* is one of the most carcinogenesis-associated genes. There were several studies assessing the effects of *TP53* polymorphisms on the risk of lung cancer, but the results are very contradictory. For example, no associations of the *TP53* (*rs1042522*) polymorphism with lung cancer were found in Jung et al.'s (2008) article. But, increased risk

Table 3. Meta-analysis of the association between *TP53* (*rs1042522*) polymorphism and lung cancer risk

Polymorphism	Test of association			Test of heterogeneity		
	OR	95 % CI	*p*	Model	I^2	*p*
G versus C						
Overall	0.82	0.71–0.94	0.005	Random effects model	64	0.02
Asian	0.76	0.63–0.92	0.005	Random effects model	73	0.5
Caucasian	0.83	0.73–0.95	0.005	Fix effects model	26	0.001
GG versus CC						
Overall	0.859	0.744–0.993	0.039	Random effects model	66	0.001
Asian	0.84	0.67–1.06	0.136	Random effects model	82	0.001
Caucasian	0.83	0.73–0.95	0.005	Fix effects model	34	0.06
Dominant model (GG+GC vs. CC)						
Overall	0.86	0.76–0.98	0.02	Random effects model	62	0.01
Asian	0.81	0.69–0.96	0.012	Random effects model	71	0.29
Caucasian	0.88	0.77–1.00	0.045	Fix effects model	39	0.002
Recessive model (GG vs. GC+CC)						
Overall	1.08	0.89–1.42	0.336	Random effects model	86	0.624
Asian	1.12	0.89–1.42	0.336	Random effects model	91	0.749
Caucasian	1.12	0.98–1.27	0.086	Random effects model	61	0.01

Table 4. Meta-analysis of the association between *MDM2* (*rs2279744*) polymorphism and lung cancer risk

Polymorphism	Test of association			Test of heterogeneity		
	OR	95 % CI	*p*	Model	I^2	*p*
G versus T						
Overall	0.86	0.71–1.03	0.10	Random effects model	75	0.38
Asian	0.81	0.63–1.10	0.122	Fix effects model	73	0.49
Caucasian	0.82	0.63–1.10	0.122	Random effects model	26	0.49
GG versus TT						
Overall	0.86	0.71–1.03	0.10	Random effects model	75	0.001
Asian	0.82	0.63–1.06	0.122	Random effects model	73	0.001
Caucasian	0.90	0.71–1.06	0.435	Random effects model	72	0.04
Dominant model (GG+GT vs. TT)						
Overall	0.90	0.79–1.02	0.50	Random effects model	60	0.09
Asian	0.89	0.74–1.10	0.212	Random effects model	66	0.58
Caucasian	0.91	0.76–1.10	0.303	Random effects model	56	0.05
Recessive model (GG vs. GT+TT)						
Overall	1.10	0.94–1.22	0.276	Random effects model	74	0.14
Asian	1.18	0.99–1.40	0.059	Random effects model	57	0.43
Caucasian	0.98	0.84–1.14	0.812	Random effects model	69	0.05

to develop lung cancer was observed in association with the *Pro/Pro* genotype variant in Chowdhury et al.'s (2015) research. Mostaid et al. (2014) found that *TP53 Arg72Pro* and *Pro72Pro* genotype significantly associated with increased relative risk of lung cancer. Our previous study also demonstrated the association of genotype *Arg72Pro* of *TP53* gene with lung cancer risk (Bulgakova et al., 2019). Papadakis et al. (2002) demonstrated that subjects with *Arg72Arg* genotype of *rs1042522* had significantly increased lung cancer risk. We comprehensively searched the up-to-date electronic databases to reveal the associations between *TP53* genetic polymorphisms (*rs1042522*) and risk of lung cancer. The genome-wide association study (GWAS) is very popular method to detect a variation in SNPs with variation in common diseases. In 2017, data from a study of new loci of susceptibility to lung cancer were published. The study identified *RNASET2*, *SECISBP2L*, *NRG1*, *CHRNA2*, *OFBC1* and *RTEL1* as candidate genes associated with lung cancer (McKay et al., 2017). The polymorphisms of *TP53* (*rs1042522*) and *MDM2* (*rs2279744*) weren't detected in this GWAS (McKay et al., 2017).

A total of 37 case-control comparisons for *TP53* (*rs1042522*) (16,229 lung cancer patients and 14,897 healthy controls) were

investigated in this meta-analysis. A noteworthy association of *TP53* (*rs1042522*) with susceptibility to lung cancer in overall pooled subjects was observed under three different models: the allele contrast, homozygote contrast (additive) and dominant model. Also, stratification analysis explained a strong evidence of this variant with risk of lung cancer among Asians and Caucasian under allelic, homozygote (only for Caucasian) and dominant models. Moreover, the *Arg72Arg* genotype was associated with the obvious protective effect (OR = 0.82, 95 % CI 0.71–0.94, $p = 0.005$).

Compared to *TP53*, whose role has been widely discussed in lung cancer developing, its main negative modifier – *MDM2*, has not been sufficiently studied. The data on the association of polymorphism of *MDM2* (*rs2279744* or *309T > G*) with the risk of developing lung cancer as well as in the case of *TP53* (*rs1042522*) are contradictory. Thus, Enokida et al. (2014) did not found any association between polymorphism of *MDM2* (*rs2279744*) and lung cancer risk. Chua et al. (2010) demonstrated that the *MDM2 (rs2279744*) TT rather than the GG genotype is associated with increased risk of lung cancer in Asian. But, the *MDM2* TT genotype was associated with a decreased risk of developing NSCLC compared with that of the *MDM2* GG genotypes in Li G. et al.'s (2006) research. A total of 14 case-control comparisons for *MDM2* (*rs2279744*) (9,137 lung cancer patients and 10,342 healthy controls) were investigated in this meta-analysis. There were no significant associations between *MDM2* (*rs2279744*) polymorphisms and lung cancer with regard to G allele vs. T allele: OR = 0.86, 95 % CI 0.71–1.03, $p = 0.1$; homozygote model: OR = 0.86, 95 % CI 0.71–1.03, $p = 0.1$; dominant model: OR = 0.90, 95 % CI 0.79–1.02, $p = 0.5$ and recessive model: OR = 1.10, 95 % CI 0.94–1.22, $p = 0.276$. The stratification analysis also did not demonstrate the association of this polymorphism with risk of lung cancer among Asians and Caucasian under all models. Thus, *MDM2* (*rs2279744*) polymorphism does not affect the risk of developing lung cancer.

This meta-analysis has some limitations. First, heterogeneity level was high. But we tried to eliminate this effect using a random effects model rather than a fixed effects model. Publication bias could also have biased the results, as studies that produced negative results may not have been published. Despite our use of Egger's regression test, we cannot eliminate the possibility of bias. Second, the relative importance of the *MDM2* (*rs2279744*) polymorphism during the development of lung cancer may vary between ethnic groups, but we were only able to perform ethnic-specific meta-analysis in Asians and Europeans. Thus, our results are applicable to only these ethnic groups. Therefore, additional studies with other ethnic populations are warranted to assess the association between *MDM2* (*rs2279744*) polymorphism and the risk of lung cancer.

But, the present meta-analysis has also several strengths. We used a strong comprehensive search strategy, and had a well-defined inclusion and exclusion criteria. Reviewers performed the study selection and extracted data independently. Moreover, we assessed the quality of the included studies by predefined criteria and the score of included studies was high. Finally, all genotype data extracted from the studies were reported in the study. The advantage of this study over other meta-analyzes is a more complete review of literature and the inclusion of recent data.

Conclusion

In summary, this meta-analysis study indicated evidence of association for *TP53* (*rs1042522*), but not *MDM2* (*rs2279744*) variants with lung cancer based on 51 case-control published studies. Additionally, stratified analysis based on ethnicity observed an obvious association of *TP53* (*rs1042522*) both among Asian and European subjects under allelic, homozygote and dominant models. However, polymorphism *MDM2* (*rs2279744*) may not impart susceptibility to lung cancer in either Asians or Europeans.

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ORCID ID

O. Bulgakova orcid.org/0000-0003-3272-0638
A. Kussainova orcid.org/0000-0002-1313-9779
R. Bersimbaev orcid.org/0000-0002-9671-1178

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