

# Association of polymorphism *TP53* Arg72Pro with radon-induced lung cancer in the Kazakh population

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Lung cancer is a problem of great concern and one of the commonest cancer diseases worldwide and in the Republic of Kazakhstan in particular. Radon exposure is classified as the second most important cause of lung cancer. According to the experts, the contribution of natural sources to the average annual radiation dose of the Kazakh population currently stands at 80 %, including 50 % from radon. However, the effect of radon on human health in the Republic of Kazakhstan is almost unknown. The tumor suppressor gene *TP53* is a key mediator of the DNA damage response cascade following cell exposure to ionizing radiation. The common polymorphism *TP53* Arg72Pro (rs1042522) is a risk factor for lung cancer in the Asian population, but until now no genetic association studies have been done in the Kazakh population. No information on the synergistic carcinogenic effect of radon exposure and polymorphism *TP53* Arg72Pro (rs1042522) is available either. This paper presents the results of the study of association between alteration in the *TP53* gene and radon-induced lung cancer risk in the Kazakh population. Genetic association was assessed in a case-control study including 44 radon-exposed patients with lung cancer, 41 patients with lung cancer without radon exposure and 42 age/sex-matched healthy controls. We found that polymorphism *TP53* Arg72Pro (rs1042522) was associated with lung cancer risk in the Kazakh population (OR = 6.95, 95 % CI = 2.41–20.05). Individuals with the Arg72Pro genotype also showed a significantly higher risk of radon-induced lung cancer (OR = 8.6, 95 % CI = 2.6–28.59).

Key words: polymorphism *TP53* Arg72Pro (rs1042522); radon; lung cancer; Kazakh population.

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## Ассоциация полиморфизма *TP53* Arg72Pro с риском развития радон-индуцированного рака легкого в казахской популяции

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Самый распространенный тип рака в структуре онкологических заболеваний – рак легкого, который представляет собой серьезную проблему не только в Республике Казахстан, но и по всему миру. Воздействие радона классифицируется как вторая причина развития онкологии легкого. По оценкам экспертов, естественный радиационный фон составляет 80 % от среднегодовой дозы облучения населения Казахстана, из которых 50 % приходится на радон. Однако следует отметить, что влияние радона на здоровье населения Республики Казахстан остается невыясненным. Ген-супрессор опухолей *TP53* является ключевым медиатором в каскаде реакций активируемых при повреждениях ДНК в результате воздействия на клетку ионизирующего излучения. Известно, что полиморфизм *TP53* Arg72Pro (rs1042522) часто встречается в азиатской популяции и считается фактором риска развития рака легкого, но до настоящего времени не была изучена его ассоциация с патогенезом этого заболевания в казахской популяции. Нет информации относительно синергетического канцерогенного эффекта воздействия радона и полиморфизма *TP53* Arg72Pro (rs1042522). В этой статье представлены результаты поиска связи полиморфного варианта гена *TP53* с риском развития рака легкого, вызванного радоном, в казахской популяции. Генетическая ассоциация была оценена по методу «случай-контроль». В исследование были включены 44 пациента (подвергшиеся воздействию радона) с диагнозом рак легкого, 41 пациент с диагнозом рак легкого из регионов с допустимыми показателями содержания радона и 42 здоровых человека соответствующего возраста и пола. Мы обнаружили корреляцию между полиморфизмом гена *TP53* Arg72Pro (rs1042522)

и риском развития рака легкого в казахской популяции (OR = 6.95, 95 % CI = 2.41–20.05). Необходимо отметить, что лица с генотипом Arg72Pro также показали более высокую вероятность развития радон-индуцированного рака легкого (OR = 8.6, 95 % CI 2.6–28.59).

Ключевые слова: полиморфизм *TP53* Arg72Pro (rs1042522), радон; рак легкого; казахская популяция.

## Introduction

Radon is considered to be the second most frequent cause of lung cancer only to tobacco smoking (WHO Handbook on Indoor Radon..., 2009). According to the experts, the contribution of natural sources to the mean annual radiation dose for the Kazakh population currently stands at 80 %, including 50 % from radon (Stegnar et al., 2013; Bersimbaev, Bulgakova, 2015). However, the effect of radon on human health in Kazakhstan is not studied sufficiently.

Lung cancer is the leading cause of cancer death in Kazakhstan and the commonest form of cancer (Bersimbaev, Bulgakova, 2017). The incidence rates of lung cancer in various regions of Kazakhstan vary quite widely. The morbidity of lung cancer in regions with high radon concentrations (North Kazakhstan, Akmola region) is higher than that observed in areas with generally low radon levels (Bersimbaev, Bulgakova, 2017).

Radon emits radiation in the form of alpha particles, which interact with DNA either directly or indirectly through the generation of free radicals, producing double-strand breaks, large chromosomal aberrations, and point mutations (Robertson et al., 2013).

The key role in maintaining the genome stability is played by *TP53*, including the response to damage caused by radiation (Yngveson et al., 1999). *TP53* mutations were spotted in the development of tumors of many locations, including lung cancer (Deben et al., 2016). A number of *TP53* mutations are associated with tobacco smoking-induced lung cancers, and similar mutation hotspots have been identified that are not associated with other types of cancer, e. g., codon 157 (Vähäkangas et al., 2001). These mutation spectra are also different between smokers and non-smokers (Hainaut, Pfeifer, 2001).

Specific “hotspot” mutations in cancer-relevant genes have been described in radon-induced lung cancer. Most papers on *TP53* mutations in radon-associated lung cancer are dedicated to occupational studies on uranium miners (Vähäkangas et al., 1992).

Taylor et al. (1994) were the first to detect a *TP53* mutational spectrum different from those seen in lung cancers caused by tobacco smoke, and they reported a radon-related *TP53* hotspot in codon 249, exon 7. Few studies analyzed *TP53* punctual mutations in lung tumors from residential radon-exposed individuals, and their results were not univocally supportive of the mentioned hotspot in codon 249 (Lo et al., 1995; Yngveson et al., 1999). Radon-induced lung tumor mutations in the *TP53* gene were also found in codons 248 and 245 (Holstein et al., 1997). A recent study shows that alterations in several genes, including *TP53*, are implicated in lung cancer resulting from exposure to radon indoors (Choi et al., 2017).

The published data on the association between polymorphism *TP53* Arg72Pro (rs1042522) and lung cancer risk in Asians remain controversial (Wang et al., 2013). Zhao et al. (2018) have shown that the Pro72Pro genotype is associated with a higher risk of cancer due to poorer ability to induce apoptosis.

However, no studies of the sort have been conducted in the Kazakh population. We have not found case-control studies providing evidence for polymorphism *TP53* Arg72Pro (rs1042522) and radon exposure interaction in the risk of lung cancer. So, in the present study we aim to study the association between *TP53* gene allelism and radon-induced lung cancer in the Kazakh population.

## Materials and methods

**Study design and population.** A case-control study was conducted in 2015–2017. Eighty-five lung cancer patients (cases) and forty-two healthy individuals (controls) from the Akmola region of Kazakhstan were recruited for the study. The Akmola region is characterized for having high indoor radon concentrations due to uranium deposits and uranium mining enterprises located in this area (Bersimbaev, Bulgakova, 2015). All participants of the study had lived in this region for at least five years.

The cases had morphopathologically confirmed lung cancer. Subsequent to the results of the radon measurements, lung cancer patients were divided into two groups: 44 radon-induced lung cancer patients (RLC) and 41 lung cancer patients without high level of radon exposure (LC). The criterion for the RLC group participants was indoor radon level exceeding 80 Bq/m<sup>3</sup> in the homes. All participants should have lived for at least five years in their current residence. We chose 80 Bq/m<sup>3</sup> as a threshold level in our study because WHO Handbook on Indoor Radon indicated that the threshold level of radon having a biological effect was no more than 100 Bq/m<sup>3</sup> (WHO Handbook on Indoor Radon..., 2009).

Controls (C) were recruited from individuals attending hospital for reasons other than cancer. They were matched with the cases of lung cancer (LC) with respect to age, gender, and tobacco consumption. The indoor radon level in the residence of participants from control group should be less than 80 Bq/m<sup>3</sup>. Characteristics of subjects are presented in Table 1.

**Exposure assessment.** Radon detectors were placed in the participants' homes. The devices were Canary 222 Digital Electronic Radon Gas Monitor (LR-03) radiometers (Corentium AS, Oslo, Norway). A radiometer was installed away from doors, windows, or electrical devices and within 60–180 cm off the floor in rooms previously unventilated for at least 24 h according to the manufacturer's instructions. In each room, radon in the air was measured for seven days and the average value was used for further calculations.

The annual effective dose (H) was calculated according to the formula (Quarto et al., 2015):

$$H(\text{mSv/y}) = C \times F \times O \times T \times D,$$

where C stands for the average radon concentration Bq/m<sup>3</sup>; F is the equilibrium factor for indoor, set at 0.4; O is the occupancy factor, taken to be 0.8; T is time in hours in a year (8760 h/y); and D is the dose conversion factor;  $1.4 \times 10^{-8}$  Sv per Bq/m<sup>3</sup>·h.

**Table 1.** Characteristics of the subject participating in the study

Parameter		Radon lung cancer (RLC) (n = 44)	Lung cancer (LC) (n = 41)	p	C (n = 42)	p
Gender	Male	34 (77 %)	34 (83 %)	> 0.05 <sup>b</sup>	33 (79 %)	> 0.05 <sup>a</sup>
	Female	10 (23 %)	7 (17 %)		9 (21 %)	
Age, years	≤ 60	14 (32 %)	15 (37 %)	> 0.05 <sup>a</sup>	22 (52 %)	> 0.05 <sup>a</sup>
	> 60	25 (57 %)	25 (61 %)		20 (48 %)	
	Unknown	5 (11 %)	1 (2 %)		–	
Tobacco consumption	Non-smokers	22 (50 %)	10 (24 %)	< 0.05 <sup>c</sup>	16 (38 %)	> 0.05 <sup>a</sup>
	Smokers	22 (50 %)	31 (76 %)		26 (62 %)	

Notes: <sup>a</sup> – *t* test for both cases (RLC and LC) and control (C) groups; <sup>b</sup> – *t* test for RLC and LC groups; <sup>c</sup> –  $\chi^2$  test for RLC and LC groups. Columns: RLC – lung cancer patients exposed to radon; LC – lung cancer patients without exposure to radon; C – control group. All information regarding participants was rendered anonymous after data and blood sample collection. Informed consent was obtained from each study participant before interview and blood collection. The present study was approved by the Ethical Committee of the Semey State Medical University (Semey, Kazakhstan; approval No. 2).

**Table 2.** The PCR amplification and restriction protocols

Alteration in the <i>TP53</i> gene	Primers for PCR (5'→3')	PCR conditions	Amplicon length, bp	Restriction enzyme	Restricted product length and corresponding genotype
<i>TP53</i> Arg72Pro (rs 1042522)	FTTGGCGTCCAAGCAATGGATGA; rTCTGGGAAGGGACAGAAGATGAC	Pre-denaturation: 94 °C, 5 min; 40 cycles of 94 °C for 30 s, 60 °C for 30 s, 72 °C for 30 s; postextension: 72 °C, 7 min	199	BstUI (cat no. R0518S; NEB, USA)	Arg72Arg – 199 bp; Arg72Pro – 199 bp, 113 bp, 87 bp; Pro72Pro – 113bp, 87 bp

**Collection of blood samples, DNA extraction and genotyping.** Blood samples were collected from all participants by the vein puncture method, and DNA was extracted from blood by the conventional phenol-chloroform method (Sambrook et al., 1989). The genotyping of polymorphism *TP53* Arg72Pro (rs1042522) was performed by PCR-RFLP as previously described by M.K. Chowdhury et al. (2015). The PCR details and relevant information are provided in Table 2.

**Assay of cotinine in plasma.** The smoking status of the participants was verified using blood plasma cotinine as a marker. The cotinine level was determined using an ELISA kit (Cotinine ELISA kit; cat no. KA0930; Abnova, Taipei, Taiwan) as described in (Bulgakova et al., 2018).

**Statistical analysis.** Student's unpaired *t* test was performed to calculate statistically significant difference in gender, age, and tobacco consumption between the LC and control groups. Student's *t* test was also used to compare the distribution of variables between RLC and LC cohorts. The Chi-square test was used to compare the distributions of tobacco consumption between the RLC and LC groups. All statistical analyses were performed using GraphPad Prism 6 software (GraphPad Software, Inc., La Jolla, CA, USA). "Case-control Study Estimating Calculator" from Gene Expert Company (State Research Institute of Genetics and Selection of Industrial Microorganisms of the National Research Center "Kurchatov Institute", Russian Federation, [http://gen-exp.ru/calculator\\_or.php](http://gen-exp.ru/calculator_or.php)) was used in calculating OR, 95 % CI, and *p* values for association between the case-control status and polymorphism *TP53* Arg72Pro (rs1042522). A *p* value of ≤ 0.05 was considered significant. To assess whether the genetic polymorphism modified the effect of residential radon exposure on lung cancer, logistic regression was performed. We also assessed the possibility of a synergism between radon exposure and tobacco

consumption using the method proposed by D. Hosmer and S. Lemeshow (1992). Analyses were conducted with MedCalc software (Version 18.6, MedCalc Software, Belgium).

## Results

**Characterization of the sample studied.** Initially, the case-control study involved a larger number of participants. The exclusion criteria from our study were occupation of dwelling for less than five years, absence of histological confirmation of lung cancer, and belonging to other ethnic groups (Russians, Ukrainians, Germans, etc.) Participants younger than 30 years were also excluded from the study. Patients diagnosed with lung cancer were included in the study regardless of the histological type of cancer. When selecting the control group of healthy individuals, every attempt was made to match them with the cancer patients according to the basic population characteristics. There were no significant differences in the distribution of age, gender, and smoking status between the cases (LC) and controls (C), but there was a small difference between smokers in the RLC and LC groups (see Table 1).

**Effective annual radon exposure dose and decay product inhalation.** The average equivalent equilibrium radon volume activity (EEVA) in the RLC group was 307.6 Bq/m<sup>3</sup> according to the measurements of radon at the homes of monitored subjects. The range of EEVA was from 105 to 716 Bq/m<sup>3</sup>.

To evaluate the effect of radon exposure on the lung tissue, we used the effective annual dose, which is the tissue-weighted sum of the equivalent doses. The mean effective annual dose for lung cancer patients living in areas with high radon levels (RLC) was 7.5 mSv/y. The minimum and maximum effective annual doses in the RLC group were 4.12 and 20.76 mSv/y.

The same data in the lung cancer patients living in the area with a low level of radon (LC) were 40.6 Bq/m<sup>3</sup> (from 8 to

**Table 3.** Association between polymorphism *TP53* Arg72Pro (rs1042522) and development of lung cancer

Genotype	LC (n = 41)	C (n = 42)	OR	95 % CI	p
Arg72Arg	11 (27 %)	30 (72 %)	0.15	0.06–0.38	0.0001
Arg72Pro	22 (54 %)	6 (14 %)	6.95	2.41–20.05	
Pro72Pro	8 (19 %)	6 (14 %)	1.45	0.46–4.64	

**Table 4.** Association between polymorphism *TP53* Arg72Pro (rs1042522) and the risk of radon-induced lung cancer

Genotype	Lung cancer (LC) (n = 41)	Radon lung cancer (RLC) (n = 44)	OR	95 % CI	p
Arg72Arg	11 (27 %)	1 (2 %)	0.06	0.01–0.52	0.0004
Arg72Pro	22 (54 %)	40 (91 %)	8.64	2.61–28.59	
Pro72Pro	8 (19 %)	3 (7 %)	0.30	0.07–1.23	

78 Bq/m<sup>3</sup>) and 2.0 mSv/y (from 0.31 to 3.06 mSv/y), respectively.

EVA levels in the control group fell within the range from 2 to 80 Bq/m<sup>3</sup> with the average value 22.5 Bq/m<sup>3</sup>. The mean effective annual dose for the control group was 0.88 mSv/y. The minimum and maximum effective annual doses in the control group were 0.08 and 3.14 mSv/y, respectively.

**Association of polymorphism *TP53* Arg72Pro (rs1042522) with lung cancer in the Kazakh population.** We investigated polymorphism *TP53* Arg72Pro (rs1042522) and lung cancer risk in the Kazakh population regardless of radon exposure. For this purpose, we analyzed the distribution of polymorphism *TP53* Arg72Pro (rs1042522) genotypes Arg72Arg, Arg72Pro and Pro72Pro in LC and control groups. The genotype frequencies in the control and LC groups are shown in Table 3.

Statistical analysis of association between a genetic polymorphism and development of lung cancer was conducted by evaluating the data with regard to the general and additive models. Unfortunately, we could not use the recessive and dominant models in view of the small number of participants. According to the general model (see Table 3), there is a significant risk of lung cancer associated with the Arg72Pro (OR = 6.95, 95 % CI = 2.41–20.05) and Pro72Pro genotypes (OR = 1.45, 95 % CI = 0.46–4.64), for all genotypes  $\chi^2 = 18.22$ ,  $p = 0.0001$ . The additive model confirmed this finding ( $\chi^2 = 9.22$ ,  $p = 0.002$ ). When we analyze separately non-smokers and smokers, we can observe a higher risk of lung cancer for the Arg72Pro genotype (OR = 4.33 95 % CI = 1.17–15.99) in smokers, but the results are not statistically significant ( $p = 0.06$ ). Cotinine levels < 10 ng/ml were considered the criterion of the absence of current smoking.

**Effects of residential radon exposure and polymorphism *TP53* Arg72Pro (rs1042522) on lung cancer risk.** To estimate OR for radon-induced lung cancer, we analyzed the distribution of polymorphism *TP53* Arg72Pro (rs1042522) genotypes Arg72Arg, Arg72Pro and Pro72Pro in both lung cancer groups (LC and RLC). The logistic regression employed the effective annual dose, which was modeled with one indicator variable for  $\geq 4.12$  mSv/y and one indicator variable for missing with < 3.14 mSv/y as the common reference exposure. As shown in Table 4, the risk of radon-induced lung cancer is higher in participants with the Arg72Pro genotype.

The odds ratio is 8.64 (95 % CI = 2.61–28.59;  $p = 0.0004$ ). No additive interaction was observed for Arg72Pro, radon exposure, and tobacco consumption ( $\chi^2 = 10.33$ ,  $p = 0.066$ ). Cotinine levels < 10 ng/ml were considered the criterion for the absence of current smoking.

### Discussion

It was shown that polymorphism *TP53* Arg72Pro (rs1042522) plays an important role in the development of different types of cancer (Francisco et al., 2011), including lung cancer (Neumann et al., 2018). Katkooori et al. (2017) demonstrated the high survival of cells that express P72<sup>wt</sup>. This effect can be explained by the fact that the Pro72Pro variant has a weaker *TP53* transcriptional activity compared to Arg72Arg (Thomas et al., 1999; Zhao et al., 2018). As many of the *TP53* target genes are involved in apoptosis regulation, the Pro72Pro genotype can dysregulate programmed cell death and activate the tumor-promoting phenotype.

On the other hand, the protein product of the Arg72Arg genotype is more effective in inducing apoptosis, although Arg72Arg is associated with faster degradation than Pro72Pro (Storey et al., 1998). Neumann et al. (2018) have shown an adverse prognostic value for the presence of heterozygous genotype Arg72Pro in tumor samples from lung cancer patients. In a meta-analysis of 51 studies, polymorphism *TP53* Arg72Pro (rs1042522) was significantly associated with lung cancer risk in any genetic model (Ye et al., 2014). According to S. Wang et al. (2013), the Arg72Pro genotype positively correlated with lung cancer risk in Asians. Only few studies attempted to determine the impact of polymorphism *TP53* Arg72Pro (rs1042522) on cancer risk in the Kazakh population.

The results of this study indicate a significant risk of lung cancer for Arg72Pro (OR = 6.95, 95 % CI = 2.41–20.05) and Pro72Pro genotypes (OR = 1.45, 95 % CI = 0.46–4.64), for all genotypes  $\chi^2 = 18.22$ ,  $p = 0.0001$  in the Kazakh population.

The product of the *TP53* gene is involved in the response to damage caused by radiation (Yngveson et al., 1999).

Radon is a decay product of uranium. It emits  $\alpha$  radiation, which is carcinogenic for humans. The effects of  $\alpha$  radiation include different types of DNA damage leading to mutations, chromosomal aberrations, and cell transformation. Some studies infer that the radon-induced mutation spectra in lung cancer may differ from the mutations in patients with lung cancer

induced by tobacco smoking (Taylor et al., 1994; Hollstein et al., 1997). Yngveson et al. (1999) have shown that residential exposure to radon seems to contribute to a higher mutation prevalence of the *TP53* gene in lung tumors, especially among nonsmokers.

There are only few studies on radon exposure and gene polymorphisms (Bonner et al., 2006; Ruano-Ravina et al., 2014; Leng et al., 2016). Two of them provided evidence for an interaction between members of the glutathione S-transferase family *GSTT1* (Ruano-Ravina et al., 2014) and *GSTM1* (Bonner et al., 2006; Ruano-Ravina et al., 2014) and radon in lung cancer risk. The association between *IL-6* promoter SNPs and squamous cell carcinoma was studied in uranium miners (Leng et al., 2016).

Choi et al. (2018) identified that *CHD4* rs74790047, *TSC2* rs2121870, and *AR* rs66766408 are found to be common exonic mutations in both lung cancer patients and normal individuals exposed to radon indoors.

Our study shows that the effect of radon on lung cancer risk depends on polymorphism *TP53* Arg72Pro (rs1042522). Thus, radon-inducible lung cancer risk increases in participants with the Arg72Pro genotype as compared to two other genotypes, Arg72Arg and Pro72Pro.

A possible explanation for these findings is that radon causes a genetic damage (Jostes, 1996). Druzhinin et al. (2015) reported that the frequencies of chromosomal aberrations in peripheral blood lymphocytes were significantly elevated in long-term resident children in a boarding school under conditions of high exposure to radon. The polymorphism *TP53* Arg72Pro (rs1042522) can affect the induction of cell apoptosis (Pereira et al., 2011) and the repair of damaged DNA (Hu et al., 2005). It is possible that the Arg72Pro genotype does not promote efficient DNA repair or apoptosis in comparison with Arg72Arg and these events lead to malignant transformation of cells. So, Y. Hu et al. (2005) have shown that the Pro72Pro genotype is associated with higher frequency of *TP53* mutations in non-small-cell lung cancer.

There are some limitations in our study. The number of participants was insufficient for comprehensive study of the effect of the *TP53* gene polymorphism-radon interaction. Therefore, we could not analyze the influence of the Pro72Pro genotype on the risk of radon-induced lung cancer. Further studies are warranted to address the relationships among residential radon exposure, *TP53* gene polymorphisms, and lung cancer risk.

## Conclusion

To sum up, the exposure to residential radon interacts with the Arg72Pro genotype to increase the risk of lung cancer in the Kazakh population. Our study supports the hypothesis that polymorphism *TP53* Arg72Pro (rs1042522) can modulate the pathogenic effect of radon in lung tissue.

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