Chapter 7

Residential Radon Exposure and Lung Cancer Risk in Kazakhstan

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Additional information is available at the end of the chapter

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Abstract

Many published data have demonstrated the potential of radon exposure to induce biological damage. All these studies suggest that exposure to radon and its progeny can represent a significant public health risk. Radon exposure is considered as the second cause of lung cancer and it is the first in never smokers. Many countries have depicted residential radon exposure maps in order to characterize those areas with the highest indoor radon concentrations. There are areas in Kazakhstan with a number of factors leading to natural radioactivity. The genotoxic effects of radon on population of Kazakhstan are poorly understood. These studies conducted in compliance with all requirements of genotoxic studies will provide an extensive and reliable data for a detailed radon zoning of Kazakhstan. Our review attempts to integrate data about the association between residential radon levels and morbidity of population in Kazakhstan. In addition, we tried to cover all points of the cytogenetic and molecular changes induced by radon exposure.

Keywords: radon, uranium, lung cancer, p53, miRNA

1. Introduction

The radioactive contamination is a significant factor affecting the environment and human health. Radon and its decay products are the major contributors to human exposure from natural radiation sources. WHO has identified the chronic residential exposure to radon and its decay products as the second cause of lung cancer after tobacco consumption and the most common cause of lung cancer in non-smokers. Radon is a chemically inert radioactive gas, occurring naturally as an indirect decay product of uranium. Uranium has been actively mined and milled in the Republic of Kazakhstan [1]. Uranium ore mining and processing

were initiated in Kazakhstan shortly after Second World War, and lasted for almost half a century. It has been estimated that during the Soviet period, about 30–40% of the uranium was extracted from the Asian region [2, 3].

Accordingly, the population of Kazakhstan might be exposed to a variety of hazardous materials including radon. Almost the whole eastern and northern part of Kazakhstan is potentially radon-affected area. The analysis of the cancer rate on the territory of Kazakhstan showed that there is a significant relationship between the areas with high level of morbidity and radon-affected areas. It is worth emphasizing that lung cancer is ahead of other cancer diseases in some areas of Kazakhstan that are radon-affected territories.

Lung cancer in the structure of oncology occupies the second rank position, and its share at the moment was 11.4%. This is the most widely distributed form of cancer leading since 1985 in Republic. The highest morbidity of lung cancer is observed in the North Kazakhstan, Pavlodar, Akmola, and East Kazakhstan regions. Almost the whole of Kazakhstan to the east of the Kustanai-Shymkent line (North Kazakhstan, Pavlodar, Akmola, East Kazakhstan, Kustanai and Karaganda regions) is potentially radon-affected areas. Thus, it becomes evident that one of the measures to reduce the incidence of lung cancer is to identify areas with high level of radon and reduce the impact of radon on the population.

When radon is inhaled, α-particles could affect lung tissue and may cause lung cancer via DNA and oxidative damages [4]. However the molecular effect of radon on lung cancer is not understood.

In addition to the mutations that arise in oncogenes or tumor-suppressor genes that are necessary for tumor transformation, epigenetic changes can play a key role in the pathogenesis of cancer. At the epigenetic level, specific alterations including alterations in DNA methylation, histone modifications leading to generation of γ-H2AX species (indicative of double-strand DNA breaks) and miRNAs expression patterns have been associated with radon exposure. Nevertheless, the mechanistic details underlying the molecular pathways by which genetic and epigenetic mechanisms are associated with lung cancer remain unclear. This review attempts to integrate data about the association between residential radon levels and morbidity of population in Kazakhstan living in these regions. In addition, we tried to cover all the points of the cytogenetic and molecular changes induced by radon exposure.

2. Uranium pollution in Kazakhstan

Uranium (U) is a radioactive chemical element of group III of the periodic system with atomic number 92 that belongs to the family of actinides. Uranium is readily soluble in water, easily reacts with the basic elements of organic compounds. In nature, uranium is found as uranium-238, uranium-235, and a very small amount of uranium-234.

The Republic of Kazakhstan is rich for uranium deposits and second in the world for mining resource, which contributes to the pollution of the environment with uranium tailings. Total deposits are estimated to be 2 million tons, representing 25% of uranium deposits in the world. The mining and milling of uranium ore have caused contamination of the environment through a number of activities, especially the open-pit mining process, transportation to and from milling sites, the milling and processing of ore, and open-air storage of radioactive and non-radioactive mining wastes. The main concern in Kazakhstan is that approximately 85% of the urban population lives in territories where environmental pollution is known to exceeded permissible standards [5, 6] together with vastly unknown contamination problems.

The largest region enriched with the uranium deposits is located within the North Kazakhstan containing approximately 16.4% of the uranium resources of Republic [7]. Besides, there are also large storage facilities for the radioactive waste in the North and West Kazakhstan. The total area exposed to radioactive waste from the uranium industry enterprises is estimated to approximately 100,000 hectares with a total activity of 250,000 Curie. In mining, the uranium and its decay products buried deep in the earth are brought to the surface, and the rock containing them is crushed into fine sand. After the uranium is chemically removed, the sand is stored in huge reservoirs [8]. Conservation and liquidation of uranium deposits in northern Kazakhstan was completed in 2008 in accordance with the State program "Preservation of non-uranium mining enterprises and liquidation of the consequences of uranium deposits for 2001–2010" [9].

The decay chain of uranium is commonly called the "uranium series" or "radium series" and includes protactinium, radium, thorium, and radon.

The high levels of radon are observed in the North and East areas of Kazakhstan because of the natural radiation sources and the long-term and large-scale mining of uranium.

3. Characteristic of radon and its decay product

Radon (Rn) is a radioactive colorless and odorless inert gas. In nature, radon occurs in two forms: radon-222 (^{222}Rn), formed by the decay products of uranium-238; and radon-220 is the product of the decay of thorium-232. However, most of the radioactivity in the atmosphere at sea level is attributable to ^{222}Rn. For that reason, the term "radon" identifies mainly the ^{222}Rn.

The main sources of indoor radon are soil, building materials, water sources, natural gas, and outdoor air. There is a large variation of indoor air concentrations of this gas, mainly depending on the geology of the area and on factors affecting the differential pressure between inside and outside of the buildings, such as ventilation rates, heating systems, and meteorological conditions. The rocks with high radioactivity and tectonic faults with the high emanation can lead to a significant increase of radon concentration indoor and its contribution becomes dominant in the collective dose of the population.

4. Indoor radon data in Kazakhstan

According to the experts, the contribution of natural sources in the average annual radiation dose of the Kazakhstan population currently stands at 80%, including 50% from radon. The level of average annual radiation dose due to radon for the population of Kazakhstan is considered to be 1.5 times higher than the world average [10].

As showed in Summary Report "Legacy of uranium mining activities in central Asia—contamination, impact and risks", the highest dose contribution to humans was derived from indoor radon concentrations in houses and dwellings in the vicinity of the Kurday site. The values of indoor and outdoor radon concentrations in Kurday are considerably higher than global average corresponding values. The indoor radon concentrations (70–330 Bq/m^3) were found to be higher than the outdoor radon concentrations (30–90 Bq/m^3) [11].

In some settlements in 70% of the buildings, radon concentration exceeds the maximum permissible concentration (200 Bq/m^3). There are official data showing that the concentration of radon in the soil in some areas of Kazakhstan reaches 300,000 Bq/m^3, and the concentration of indoor reaches 6000–12,000 Bq/m^3, which exceeds the maximum permissible concentration by 60 times [12]. The radon-affected areas in Kazakhstan are shown in **Figure 1**.

Stegnar et al. [2] measured indoor ^{222}Rn concentrations in 27 selected houses and public buildings in Ust-Kamenogorsk city in East Kazakhstan area. According to their data, the values of radon ranged from 22 to 2100 Bq/m^3, the average concentration of radon was 230 Bq/m^3. The corresponding annual effective doses ranged from 0.5 to 20 mSv, the average dose being

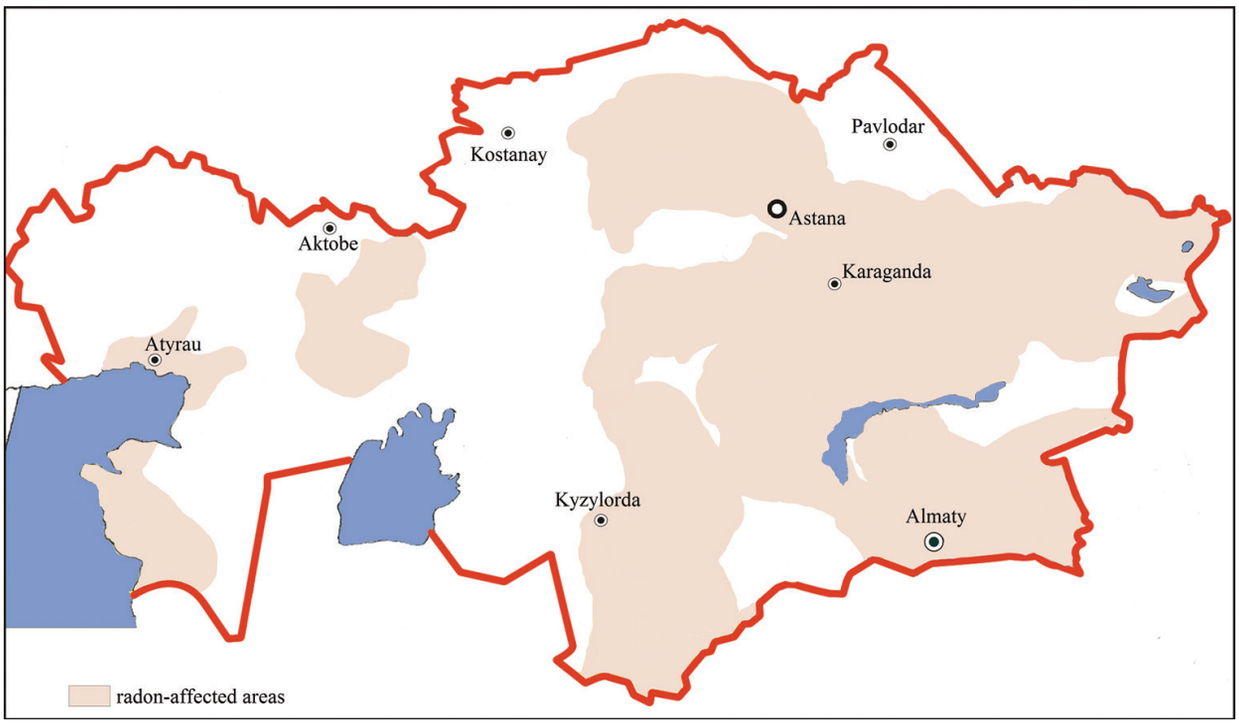

Figure 1. Radon-affected areas of Kazakhstan.

5 mSv per year. The studies conducted in Altai (East Kazakhstan) revealed radon levels from 200 to 8000 Bq/m^3 in 15 of the 18 settlements [13].

The territory of North Kazakhstan is characterized by the areas with the high levels of radiation, arising both from natural radiation sources, as well as by long-term and the large-scale activities of uranium mines and uranium-processing companies [11].

The Akmola region (North Kazakhstan) is one of the largest world's uranium ore provinces. It contains more than 30 uranium deposits [12]. During 50 years, open and underground mining of uranium ore was conducted in the North Kazakhstan that led to the accumulation of the significant amount of radioactive waste with the high risk of radioactive contamination to the environment and toxic effects on the human health. All these factors contribute to the formation of elevated concentrations of radon in this region. The measurement of the radon activity in indoor air was carried out in 2010 in the territory of three districts of Akmola region. As a result of this work, 47 settlements regions were revealed, including the Astana and Kokshetau cities, 35 settlements (76.1%) which were characterized by excess of standard values (200 Bq/m^3) radon activity [12].

In 2010, 814 measurements of radon in indoor air of the residential and public buildings were carried out in Astana in order to implement the preventive health surveillance. Exceeding levels of radon has been established in eight newly built homes (207–1150 Bq/m^3). It also revealed that excess radon activity in the Balkashino village school (1022 Bq/m^3) and in the preschool of the village "Shantobe" (789 Bq/m^3). It revealed maximum values of ^{222}Rn activity in the settlements: Vasilkivka—866 Bq/m^3, Granite—611 Bq/m^3, and Ondiris—419 Bq/m^3. In the village of Aksu, there were 42 surveyed areas of which 22 cases were detected exceeding the permissible radon activity. Activity of radon in homes ranged from 8 to 858 Bq/m^3, in schools—153–2162 Bq/m^3, and in the basement—130–5870 Bq/m^3. In Saumalkol village, the value of radon activity was in the range from 590 to 3977 Bq/m^3. In some kinder gardens of Aryk-Balyk village, radon concentrations range from 510 to 4500 Bq/m^3, that is in 22.5 higher than the allowable level of 200 Bq/m^3. The most famous case of a high level of radon in mines and in a residential area in Kazakhstan is mine "Akchatau". The major sources of ^{222}Rn concentration, in the opinion of Soroka and Molchanov, in dwellings in Akchatau village was condition radon flux from the surface of the granite massive (especially in a zone of geological rupture) and radioactivity of local construction materials (granite and adobe) including sand from mill plant tailings. The high level was of radon in 44% of the residential buildings in Akchatau village with a peak concentration at 37,650 Bq/m^3 [14]. It was under a comprehensive survey of radon in mines and homes, as well as the health of miners and residents. As a result, it has been found that the incidences of respiratory diseases, nervous system, and cardiovascular system exceed the average for the region is 2.9 times. It is most likely indicative of radon exposure on the health of the village.

A large group of the population is exposed to radon in the workplace. It is interesting that the workers employed in the mining and processing of non-ferrous metals most affected by radon, but not the workers of uranium mines. This is due to the fact that, there are high concentrations of naturally radioactive dust in the air. In some cases, exposure doses for lungs of underground miners exceeded 5 Sv y^{-1}, while the allowable level is 0.015 Sv y^{-1} [15].

In Almaty city, during the period from 1990 to 1993, preliminary measurements of level of radon in public buildings and kindergartens were carried out. Several places with level of radon between 380 and 532 Bq/m^3 were identified [16]. In some other areas of the North Kazakhstan region (Akkol, Yenbekshilder, and Sandyktau villages), 112 settlements were examined. More than 60% of the settlements were identified with exceeding activity of radon in indoor air and the drinking water sources in 32% of villages.

5. Radon concentrations in drinking water in Kazakhstan

The source of drinking water in most parts of Kazakhstan is groundwater and in many settlements there are no alternative sources of drinking water. However, often underground water is saturated with uranium, radium, radon, the concentrations of which exceed the permissible level. Therefore, a survey of water sources and water quality control are extremely relevant for preventing radiation risk of the population.

The active study of the concentrations of the natural radioactive elements in natural waters in Kazakhstan began in the late 1940s of last century due to an increase in geological prospecting for radioactive materials. From 1960 to 1992, the entire territory of Kazakhstan was covered by the hydrogeological surveys for water supply of the settlements. To carry out these activities in large volumes, the strictly regulated selections of water samples were conducted for determination of uranium, radium, and radon. The amount of available information in the archives and reports of specialized organizations includes information on approximately 30,000 water sources [5]. It has been shown that in the drinking water of some settlements, specific activity for ^{238}U reached 96 Bq/l, activity for ^{226}Ra 45 Bq/kg, and activity for ^{222}Rn 5100 Bq/kg [17].

In Kazakhstan, there are numerous sources of radon waters, which are determined by the presence of highly radioactive rocks enriched in uranium. Basically, water sources with a high content of radon (more than 100 Bq/l) are located in the submontane and mountain regions in the south, south-east, and north of Kazakhstan. These are uranium provinces Kendyktas-Chuili-Betbakdalin (Zhambyl, Almaty regions), North Kazakhstan (Akmola region) and the North-Pribalkhash rare-metal area (Karaganda region). In these regions, especially in villages near the mines, radiological services have identified the most numerous cases of high radon level in the air of residential and industrial premises.

The radiological evaluations of drinking water were carried out according the norms established by "Sanitary requirements for radiation safety" representing the main technical document regulating norms of ionizing radiation in Kazakhstan. According to this document, the contents of the natural and artificial radionuclides in drinking water, creating an effective dose less than 0.1 mSv/year does not require measurements to reduce the radioactivity of drinking water. Over the last years in Akmola region (North Kazakhstan), 1271 drinking water samples were investigated, from which 550 samples did not meet the standards for total alpha activity (43%). On average, the radiation dose of the population received drinking water is 0.21 mSv/year in this region [12]. Thus, studies on groundwater sources in North Kazakhstan

have shown the presence of radon in drinking water sources from 8 to 300 Bq/l. A total of 32 surveyed drinking sources in 15 cases (47%) had high levels of radon in drinking water [12].

The studies of groundwater in Ust-Kamenogorsk (East Kazakhstan), conducted in 2005, showed the average level of radon (^{222}Rn) 60 Bq/l [12]. The concentration of radon in drinking groundwater may be associated with the presence of water in its long-lived daughter product ^{210}Pb, which is one of the most radiotoxic beta-active natural radionuclides.

6. Health effect of uranium on the population in Kazakhstan

The analysis of medical statistics of North Kazakhstan showed that the level of overall mortality and cancer among adults and children is one of the highest in the region [18], although it has not revealed a direct relationship between these indicators and the radiation factor as a result of uranium mining and processing enterprises.

The production of uranium involves a large contingent of workers whose work takes place in the specific conditions exposing to radiation and chemical factors present in the ore mined. Klodzinskiy et al. [19] have shown a deterioration of health of uranium miners in North Kazakhstan. The results of epidemiological and medical studies found the high frequency of respiratory diseases (61%) in the cohort of uranium miners in North Kazakhstan. According to Ref. [20], the most common somatic diseases among uranium workers of Stepnogorsk city were hypertension, chronic obstructive pulmonary disease, and chronic gastritis. Moreover dysfunction of all parts of the immune system was observed in the studied groups of uranium workers [21]. Comprehensive clinical assessment of health status of children and adults living near Stepnogorsk uranium-processing enterprises showed a high risk of developing chronic diseases in internal organs due to long-term toxic effects of radiation. The study of reproductive health of women living in areas adjacent to the uranium mines showed a low percentage of healthy women (13%) [22]. Among children in Stepnogorsk city, the urinary tract infections and chronic bronchitis amounted to a high percentage of the total somatic pathology [23].

In our previous study [24, 25], uranium mine workers in the Stepnogorsk mining-milling complex in North Kazakhstan were investigated for the expression of chromosome aberrations and for genetic factors that can modify the exposure-related expression of chromosome damage. The study has demonstrated an increased frequency of chromosomal aberrations in uranium miners compared to the matched control subjects, which were not exposed to uranium compounds or to any other known chemical or physical mutagens. The study of chromosomal aberrations in the workers of uranium mining showed a high frequency of acentric chromosomes, dicentric and centric ring chromosomes in dose/ dependent manner.

The uranium workers were classified into three groups according to their duration of exposure: group I: 1–10 years, II: 11–20 years, and III: 21–25 years. The received data show that all three groups of workers had higher frequencies of chromosomal aberrations than the control group. In the first group of workers, the frequency of dicentrics was higher (1.95 ± 0.15) than

that of the matched control group (0.50 ± 0.09) ($0.05 < p < 0.01$). In the second group of uranium workers, the frequency of dicentrics and the total chromosomal aberrations were significantly higher (2.33 ± 0.17) than the control group (0.55 ± 0.08). In the third group of workers, the frequency of chromosomal aberrations was also significantly higher (2.68 ± 0.26) than the control group (0.36 ± 0.10). The frequency of chromosomal aberrations observed in exposed group III was also higher compared to the first and second exposed groups ($0.05 < p < 0.01$).

Furthermore, a significant increase in the frequency of chromosomal aberrations in the workers who were heavy smokers was observed compared with those who were moderate smokers or non-smokers. Uranium-exposed workers who had inherited the null GSTM1 and/or GSTT1 genotypes had a significant increase in the frequency of chromosome aberrations compared with those who had intact GSTM1 and GSTT1 genes for different group of workers [26]. We have shown that the uranium mining conditions in North Kazakhstan can cause a long-term health risk among the workers. In uranium miners, the various forms of malignant tumors of the lung, liver, and stomach were observed [27].

Lung cancer is the leading cause of cancer death and the second most common cancer among population in the Kazakhstan (11.4%). The incidence of lung cancer in men is higher than in women and accounts for 20% of the total number of cancer diseases. Over past 30 years in East Kazakhstan, there was a sharp increase in cancer rates. This growth is particularly noticeable in the Ust-Kamenogorsk city. The increase in total cancer morbidity indicator is mainly due to an increase in the incidence of lung cancer, breast cancer, and skin cancer [28].

As mentioned above, the villages where there is a high radon activity, marked by the territory of Kazakhstan, are characterized by the highest levels of radon in East and North Kazakhstan (67% of settlements in excess). Interestingly, in the Eastern and Northern part of the country, there is an increase (up to 1.5 times or more) in cancer rates, which makes it possible to assume a correlation between radon levels and cancer incidence [29].

Influence of environmental factors including radon on cancer development among population of North and East Kazakhstan regions were investigated by group of researchers from North Kazakhstan State University. They found a positive association between residential radon concentration in these two regions of Kazakhstan and different cancer diseases, predominating lung cancer [29].

7. Health effect of radon

Alpha radiation in chronic exposure can cumulate the biological effect. In comparison with the damaging effects of beta and gamma radiation, alpha particles cause 23–43 times more severe radiation damage. The long-term after effect of the radon is its high blastomogenic activity.

The role of radon and its radioactive decay products as human carcinogens has been established by the International Agency for Research on Cancer in 1988 and is supported by experimental evidences obtained in laboratory animals [30] and epidemiologic studies in

humans [31]. In 1990, Schoenberg et al. [32] published a report on the strong association between indoor radon exposure and lung cancer risk. In 2002, Wang et al. [33] has shown that high levels of residential radon increase the risk of lung cancer. Some studies demonstrated that lung cancer risk increases with increasing indoor radon concentration. As reported by Darby et al. [34], cumulative risk of lung cancer when reaching the age of 75 years is estimated to never smokers at 0.4, 0.5, and 0.7% for the radon concentrations of 0, 100, and 400 Bq/m^3, respectively. While cumulative risk of lung cancer at the age of 75 years for smokers reaching 10, 12, and 16% for radon concentrations of 0, 100, and 400 Bq/m^3, respectively. Baysson et al. [35] found that the risk of lung cancer increases from 4 to 28% with increasing radon levels per 100 Bq/m^3. Moreover, the risk of cancer increases in smokers group from 2 to 80% with an increasing radon levels per 100 Bq/m^3.

Specifically, radon emerged as a prominent non-tobacco carcinogen strongly associated with lung cancer. Although the initial evidence supporting the association of radon and lung cancer came from studies involving mine workers, in recent years research has focused on indoor Radon exposure and its risk to the general population. In 2009, the WHO identified chronic residential exposure to radon and its decay products as the second cause of lung cancer after tobacco consumption and as the main risk-factor in never smokers [36]. Torres-Durán et al. [37] studied 192 lung cancer cases and 329 controls in Galicia, Spain. The study subjects were male or female never smokers aged over 30 years. According to their study, adenocarcinoma was the most common histologic type of lung cancer.

In the literature, there are different data on the histological types of lung cancer induced by radon. Some studies have reported that radon increases the risk of small cell lung cancer. Barros-Dios and colleagues [38] found that less frequent histologic types (including large cell carcinomas), followed by small cell lung cancer, had the highest risk associated with radon exposure. According to the study of Taeger et al. [39], a small cell lung cancer and squamous carcinoma is associated with the radon exposure, but adenocarcinoma is associated less. Some studies have found a positive correlation between the incidence of adenocarcinoma in the group of non-smoking women and the increasing concentration of radon in the living room [40]. Wilcox et al. [41] failed to show a statistically showed that radon exposure had a strong effect on small cell lung cancer in cases of both genders, but the causative relation of indoor radon and squamous cell carcinoma was only demonstrated in male cases. Some studies have showed evidence that indoor radon exposure is strongly related to small cell carcinoma and squamous cell carcinoma of the lung.

It is considered worldwide that 3–20% of all lung cancer deaths are caused by indoor radon exposure [42]. The highest estimate of percent risk of lung cancer deaths, which consist 20% from whole mortality of lung cancer, was reported in the study for an average radon concentration of 110 Bq/m^3 [43]. The lowest indoor radon concentration (21 Bq/m^3) was measured in the UK, which also showed the lowest percent risk (3.3%) of lung cancer deaths [44].

The recent studies in Spain have shown a statistical association between indoor radon and lung, stomach, and brain cancer in women [45]. Thus, the effect of radon is not limited to an increased risk of lung cancer, but it can also lead to the development of pathological changes in other organs. The results of mortality studies in North Carolina showed that groundwater

radon is associated with increased risk not only for lung but also for stomach cancer [46]. Barbosa-Lorenzo et al. also observed a strong and significant association between residential radon and the incidence of stomach cancer, but their findings were limited by a low number of cases [47]. There are very few studies on other cancers different than lung and stomach cancer.

Bräuner et al. [48] found significant associations between long-term exposure of radon to Danish population and risk of primary brain tumors. Exposure of ionizing radiations has been shown to increase the risk of central nervous system tumors in children and adolescents exposed to computed tomography scans [49]. Some epidemiological studies have suggested a positive correlation between environmental radon exposure and prostate cancer [50]. A study in Galicia (Spain) showed a correlation between brain cancer mortality and indoor radon exposure [51].

Li and colleagues' study demonstrated the evidence of malignant transformation of human benign prostatic epithelial cells exposed to a single dose of alpha radiation [52]. The results of study for breast cancer in Spain shown a certain association between breast cancer risk and radon exposure might be present [45]. However, Turner et al. did not find any association for radon exposure and breast cancer mortality [53].

Recent study observed a significant positive association between mean county-level residential radon concentrations and chronic obstructive pulmonary disease mortality [54].

The risk for bronchopulmonary system following inhalation of radon is significantly higher than for other organs. A detailed study of lung cancer showed that due to the peculiarities of the movement of the mucus and the depth of the location of the basal cells, there are some "risk cells" that receive the highest dose of alpha radiation on exposure to radon.

From the molecular viewpoint, the mechanism of lung cancer induction by radon is not known in detail, but involves both genetic and epigenetic pathways [55, 56].

Because radon is inert, nearly all of the gas that is inhaled is subsequently exhaled. However, ^{222}Rn decays into a series of solid short-lived radioisotopes depositing within the respiratory tract. Because of its relatively short half-lives, the radon-progeny mainly decay in the lung before clearance can take place. Two of these short-lived progeny, Polonium-218 and Polonium-214, emit radioactive alpha particles that, impacting pulmonary epithelium, may genetic-molecular alterations that are mutagenic and result in an increased risk of carcinogenesis [57].

8. Health effect of radon on the population of Kazakhstan

Epidemiological studies show that age-standardized cancer rate in former NIS countries (New Independent States), including Kazakhstan, doubled during the last 20 years. Release of radioactive and toxic debris into the environment could contribute to such an increase.

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During the last decades, contamination by industrial or military wastes in Kazakhstan may have contributed to the observed health problems. One of the most heavily polluted areas in Kazakhstan, where environmental pollution exceeds permissible standards, is the East Kazakhstan province. In this area mining and smelting industries and metallurgic complexes are extensive. About half of solid toxic waste (49.2%) accumulated in Kazakhstan are located around enterprises. Surveys of environment exposure to genotoxic agents, including uranium and its short-lived radioactive alpha- and beta-emitting particles, show that environmental health problems in this region are critical, due to the industrial activity of different metallurgic complexes and accumulation of high concentrations of hazardous toxicants.

For the first time in Kazachstan, complex studies on the effect of radon on the incidence disease were conducted in the Zhezkazgan region [58]. In 1985, the high level of radon in the village of Akshatau was detected. The morbidity of 2166 inhabitants of all social and age groups of this settlement was studied. From 1986 to 1990 average morbidity was 19,927 cases per 10,000 of the population, which was 2.9 times higher than in Zhezkazgan region.

The highest percentage of all diseases was accruing to respiratory diseases (62.2%). The second place was occupied by diseases of the nervous system and sense organs (9.3%), the third place—diseases of the circulatory system (7.1%). Analysis of the morbidity structure showed that people living in houses with a high indoor radon level often sought medical advice, especially with symptoms of bronchopulmonary diseases. These cases of seeking medical advice accounted for 63.1% of all diseases and 66.2% of bronchopulmonary diseases. The highest morbidity was observed among children who lived in houses and visited kindergartens functioning in buildings with high indoor radon level (48,625 cases per 10,000 of the population of this age), which 4.6 times higher comparing with children who living in homes with low radon levels. A significant difference in the incidence of respiratory organs was observed in newborns living in houses built using waste from uranium production. The morbidity reached 40,866 cases per 10,000 populations, accounting for 81.1% of the total respiratory morbidity in children of this age. About 65.6% of seeking medical advice among children of school age due to respiratory diseases occurred in those living in houses with a high level of radon and attending school, in which the level of natural gamma background exceeded the permissible level 7.7 times. The most common forms of respiratory diseases in the children, described above, were acute bronchitis, pneumonia and acute infections of the upper respiratory tract. In the adult population of the Akshatau village the highest morbidity level was among people working with the extraction and processing of uranium-bearing ore. Among morbidity of adults were most common chronic and acute bronchitis, chronic diseases of tonsils and adenoids, chronic pharyngitis and nasopharyngitis, acute laryngitis and tracheitis, pneumonia and emphysema [58].

Scientific-research Institute for Radiation Medicine and Ecology of Semey in 2013–2014 conducted a study of radon symptoms in the Kalachi village of Akmola region because of the increase of cases of so-called "Kalachi syndrome" among residents of the village. Of the 59 investigated buildings (residential and social significance) 20% of the buildings' mean values of radon volume activity do not meet the requirements of existing regulations. There is a relationship of "Kalachi syndrome" with points of high radon concentrations. In addition to the

risk of developing lung cancer should be noted the property of radon as inert gas to exhibit an anesthetic effect [59].

In accordance with the Decree of the Government of the Republic of Kazakhstan No. 34 of 13-01-2004, "On the approval of the list of diseases associated with exposure to ionizing radiation and the Rules for Determining the Causation of Diseases from Exposure to Ionizing Radiation" the following list of diseases associated with exposure to ionizing radiation was approved:

1. Acute leukemia (leukemia)
2. Malignant lymphomas
3. Solid malignant neoplasm
4. Lung cancer
5. Thyroid cancer
6. Breast cancer
7. Urologic cancer
8. Gastric cancer (including oral, pharynx, esophagus, stomach and colon cancer).

The analysis showed that the population of Kazakhstan lives primarily in potentially dangerous areas from the radioactivity exposure point of view. According to studies, level of radon in premises where people stay for long times may exceed allowable levels by several times. Accordingly, the study of the risks of radon-induced diseases, and primarily lung cancer, is necessary.

9. Lung cancer in Kazakhstan

The incidence rates of malignant diseases in various areas vary quite widely (**Table 1**). It can be noted that the average number of diseases per 100,000 population in regions with an increased level of radon hazard (North Kazakhstan, Pavlodar, East Kazakhstan, Kostanay, Karaganda, Akmola, and Almaty) is 276, while the average number of diseases per 100,000 population by regions with a normal level of radon hazard (Aktobe, Atyrau, Zhambyl, West Kazakhstan, Kyzylorda, Mangystau, and South Kazakhstan)—145.5.

The data on cancer incidence by regions are given in **Table 1** and in **Figure 2**. A comparative analysis of this map and a map of radon-affected areas (**Figure 1**) indicates a correlation between the incidence of cancer and the level of radon hazard.

Of course, for this analysis, more detailed studies are needed. For example, the areas of South Kazakhstan, Almaty, and parts of Kyzylorda regions are classified as potentially radon-affected

areas because they are located in the territories of uranium provinces. However, these areas are characterized by low cancer rate. This is explained by the fact that unlike typical uranium provinces (e.g. the North Kazakhstan province), uranium deposits in these areas are located at great depths and do not surface.

However, when comparing the levels of radon and the cancer rate, there is a sufficient correlation, indicating an undoubted dependence of oncological morbidity and radon hazard. This dependence is complex and requires a more detailed study, on the one hand, of various factors affecting the health of the population: chemical pollution, smoking, etc., and on the other hand— natural geological features of the territory.

It is possible to distinguish two groups of sources of radon intake from the subsoil. Firstly, the sources are the rocks themselves with a high geochemical background, which can have a radon concentration in the ground up to 50–100 Bq/l, which can form radon-affected areas. Secondly, the source is radon-bearing tectonic zones with well-defined linear parameters. The level of radon in the air of houses located in such zones can reach very high values, reaching 10 thousands of Bq/m^3.

The frequency of lung cancer by region almost completely coincides with the incidence of cancer.

Region	2012	2013	Rate of increase (%)
Republic Kazakhstan	190.6	193.9	1.7
Akmola	233.6	248.5	6.4
Aktobe	173.9	179.1	3.0
Atyrau	124.4	140.5	13.0
East Kazakhstan	276.2	285.5	3.4
Zhambyl	129.5	139.9	8.1
West Kazakhstan	207.5	207.3	–
Karaganda	257.1	258	0.4
Kyzylorda	139.6	138	–
Kostanay	291.9	278	–
Mangystau	113.9	123.6	8.6
Pavlodar	301.5	301.9	0.1
North Kazakhstan	309.2	312.5	1.1
South Kazakhstan	93.3	98.6	5.7
Astana	169.2	172.3	l.8
Almaty	245.2	247.9	1.1

Table 1. Cancer morbidity in Kazakhstan (per 100,000 people).

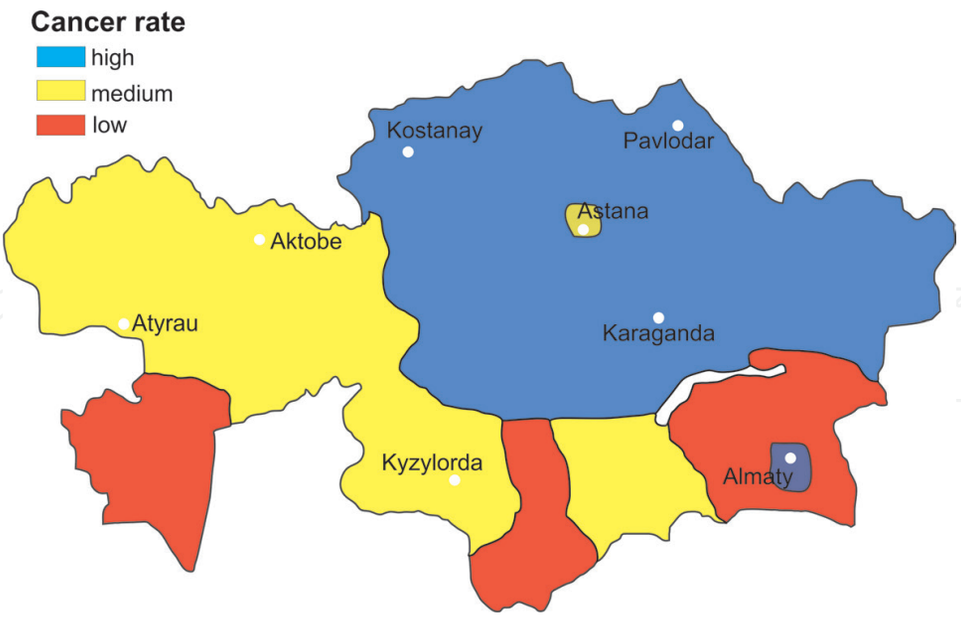

Figure 2. Cancer rate in the Republic of Kazakhstan.

In the structure of the incidence of cancer lung ranks first place in Akmola, Aktyubinsk, Atyrau, Kostanay, Pavlodar, and North Kazakhstan regions, the second place in East Kazakhstan, Zhambyl, West Kazakhstan, Mangystau regions, and Astana city, the third place in Karaganda, South Kazakhstan, and Almaty.

Lung cancer in the structure of oncology occupies the second rank position, and its share at the moment was 11.4%. This is the most widely distributed form of cancer which leading since 1985 in Republic. The highest morbidity of lung cancer is observed in the North Kazakhstan, Pavlodar, and Akmola regions.

When analyzing the morbidity of lung cancer in the East Kazakhstan region, the areas with a higher lung cancer rate (more than 40/100,000 of population) are clearly associated with a radon-affected territory in the northern part of the region. In 15 settlements of 18 examined in this area, the excess of the norm (sometimes significant—up to 40 times) of radon concentration was established.

The area with increased oncological morbidity in the northeast of the East Kazakhstan region borders on the territory with an increased incidence in the Altai territory (Russia) [58].

However, the genotoxic effects of radon on population of Kazakhstan are poorly understood, in spite of the fact that many regions of the country contain the high levels of radon. Studies elucidating potential health risk among population exposed to radon and genotoxic effect of radon in Kazakhstan are very limited or these studies have never conducted in some areas.

10. Genetics and epigenetic effects of radon

Alpha particles interact with DNA either directly or indirectly through the generation of free radicals, leading to double-strand breaks, large chromosomal aberrations, and point

mutations. In a previous cytogenetic study conducted on a population residing near uranium tailings and mining activities in North Kazakhstan, we have demonstrated an increased frequency of chromosomal aberrations in uranium miners compared to matched control subjects, who were not exposed to uranium compounds or to any other known chemical or physical mutagens. The data on aberration type frequency showed a predominance of aberrations of chromosome type in the exposed group, mainly including paired acentric fragments, dicentric chromosomes, and centric rings [60].

Several investigations on chromosome aberrations of blood lymphocytes due to radon exposure were previously carried out. In a study by Hellman et al. with human blood samples to detect DNA damage, an increased concentration of radon in indoor air was found to be associated with enhanced DNA damage in peripheral lymphocytes [61]. The findings of Li's study demonstrated that DNA damage in peripheral blood mononuclear cells was significantly increased in a dose-dependent manner [62]. Abo-Elmagd et al. [63] showed the formation of different types of structural chromosomal aberrations, where chromosomal and chromatid breaks had the dominant incidence. Moreover, damaging effect of radon in the blood and bone marrow was expressed as a reduction in the mitotic index and an increase in chromosome damage. The average frequencies of single and double fragments, chromosomal exchanges, total number of aberrations, chromatid type, chromosome type, and all types of aberrations were significantly increased in the radon-exposed group [64]. As reported by several authors, there is a synergistic effect of smoking and radon on increasing the frequency of chromosomal aberrations. Meenakshi and Mohankumar showed that the frequency of dicentrics in radon-exposed smoker cells was found to be higher than non-smokers by factor of 3.8 [65]. Moreover the comparison of three groups: miners, workers of uranium enterprises, and a control group revealed that chromosomal aberrations were a consequence of the effect of radon, but not of uranium [66]. Disruptions to normal chromosomal arrangement represent a major contribution to carcinogenesis. Cytogenetic analysis, including the detection of chromosomal aberrations, has been used for many decades as a tool to determine mutagenic and carcinogenic risks. Chromosomal aberrations (insertions, deletions, translocations, ring formation, duplication, and inversions) as a result of radon exposure significantly increase the risk of developing neoplastic processes and enhance carcinogenic ability and this can be one of the mechanisms of development of radon-induced lung cancer.

In addition to chromosomal aberrations, gene mutations play an important role in the pathogenesis of lung cancer. Specific "hotspot" mutations in cancer-relevant genes have been described in radon-induced lung cancer. Sequencing of the TP53 tumor-suppressor gene has provided links between specific mutations and radon exposure. TP53, also known as the "guardian of the genome" owing to its involvement in regulation of the cell cycle and apoptosis upon DNA damage, plays a critical role in the cellular response to genetic damage caused by radiation. Most papers on TP53 mutations in radon-associated lung cancer consist of occupational studies in uranium miners [67, 68]. These studies showed a TP53 mutational spectrum different from those seen in lung cancers caused by tobacco smoke. Vähäkangas et al. showed that most frequent base substitutions associated with tobacco smoking (G:C to T:A transversions) were not identified in uranium miners [67]. The study of Popp et al. indicated an overrepresentation of codon 213/3 polymorphism in p53 in radiation-caused cancers [69]. Some studies reported a radon-related TP53 hotspot

in codon 249, exon 7. These mutations, mostly transversions and small deletions very uncommon in smoke-induced lung cancers, were mainly identified in squamous cell carcinomas (SCC) and in large cell carcinomas. In the same cohort of miners, the presence of codon 249 transversion was not demonstrated in lung adenocarcinomas, thus implicating tumor histology as determinant for this specific mutation [70]. Only few studies analyzed TP53 punctual mutations in lung tumors from residential radon-exposed individuals and their results are not univocally supportive of the mentioned hotspot in codon 249 [71, 72]. However, Hollstein et al. proposed that loss of tumor-suppressor function of TP53 due to α-particle radiation may occur preferentially by mechanisms such as intrachromosomal deletions, rather than by base substitution mutations [73].

Accordingly, single nucleotide polymorphisms (SNPs) in TP53 sequence may affect lung cancer susceptibility by influencing hundreds of target genes. Nevertheless, the mechanistic details underlying the molecular pathways by which TP53 gene polymorphisms are associated with radon-induced lung cancer remain unclear.

Further investigations are required in order to understand if it is possible to identify hotspot regions for radon-induced lung cancers, providing a unique biomarker that contributes to understand the etiology of the disease and to elucidate the risk as occurring at low exposure levels.

There is growing evidence that the tumor suppressive activity of TP53 is related with miRNA expression. miRNAs are small, non-coding RNAs regulating gene expression at the post-transcriptional level. microRNAs bind to complementary sequences on target messenger RNA transcripts, usually resulting in translational repression or target mRNA degradation and gene silencing.

miRNA profiling after TP53 induction, pointed miR-34a/b/c as the most up-regulated miRNAs identifying miR-34 as a main TP53 gene effector [74]. The expression of miR-34 family members is induced after genotoxic stress in a p53-dependent manner in cultured cells as well as in irradiated mice [74–76]. Notably, overexpression of miR-34a increases apoptosis, whereas miR-34a inactivation strongly attenuates p53-mediated apoptosis in cells exposed to genotoxic stress. Further miRNAs, including miR-125a, have recently been linked to p53-regulated apoptosis in lung cancer cells [77]. Several TP53 mutants, linked to oncogenic progression, suppress post-transcriptional maturation of miRNAs bearing growth-suppressive functions [78].

As shown in a number of studies, the profile of microRNA can vary both under the action of chemical agents [79, 80] and radiation [81–86].

Recently, it has been shown that ionizing radiation can induce changes in miRNA expression profiles in normal human fibroblasts [87] and immortalized cell lines [88, 89]. In vivo studies found that miRNA signatures induced by ionizing radiations in mouse blood are dose and radiation type-specific [90] indicating that miRNAs can be exploited as biomarkers of exposure to radiation [91].

Studies in humans also highlighted the importance of miRNAs to evaluate the biological outcomes of radiation exposure. Evidence from a study conducted in patients undergoing

radiotherapy, indicated that miRNA expression can be used as biomarker of radiation exposure in humans [92]. Another study examined the utility of miRNA signatures in lung cancer screening using blood samples from computerized tomography trials. The authors performed extensive miRNA profiling of primary lung tumors, paired normal lung tissues, and multiple plasma samples collected before and at the time of the disease. This approach was able to define a plasma miRNA signature associated with increased risk of lung cancer [93]. Also other groups have integrated miRNA profiles into computerized tomography-screening programs [94, 95].

A number of studies have shown the radioprotective role of some types of microRNA. In vitro studies using the human diploid fibroblast cell line WI-38 demonstrated that the mature form of the miR-155 inhibits premature "cell aging" induced by radiation [96].

In this regard some scientists make a supposition that some microRNAs can determine the resistance of tumor cells to radiotherapy and be a prognostic biomarker for monitoring of cancer treatment strategy.

Ma et al. demonstrated that overexpression of miR-622 in colon cancer cells inhibits Rb by directly binding to RB1-3'UTR, thus inactivating the Rb-E2F1-P/CAF complex, which is responsible for the activation of pro-apoptotic genes in response to the effect of radiation [97].

On the other hand, many studies have shown that overexpression is one of the most common types of cancer. A study of 48 patients diagnosed with cervical cancer revealed the effect of miR-18a function in the regulation of cellular radiosensitivity. Liu et al. showed that miR-18a suppresses the activity of ATM, reduces the repair of double-strand breaks and stimulates apoptosis of irradiated cancer cells [98].

Similar results were obtained by Lan and colleagues in their study of non-small cell lung cancer. According to their results, miR-15 and miR-16 increase the radiosensitivity of H358 and A549 cell lines and the level of apoptosis in vitro [99].

Thus, the level of expression of different types of microRNA can react differently to the effect of ionizing radiation [100]. Most likely the effect of radiation depends on target genes inhibited by a specific microRNA. However, according to numerous literature data, it is impossible to identify a clear separation of microRNAs with respect to radioactive effects. Expression of most of the currently known microRNAs can be amplified or suppressed by ionizing radiation depending on the type of cells of their producing [100].

Other researchers believe that a change in the level of microRNA expression under the influence of radiation has a dose-dependent effect [101]. Lee et al. showed that the greatest effect on the profile of microRNAs in the mononuclear phagocytes of human blood exposed to different doses of radiation had 1 Gy irradiation, while 0.5 and 2.5 Gy irradiation showed very slight changes in the level of microRNA expression [101]. In order to explain the results obtained, the authors compared the biological effect in the cells and target genes of miRNAs sensitive to radiation. It turned out that the majority of these microRNAs were involved in the control of homeostasis, neuronal survival, and regulation of the cell cycle and proliferation. Thus, sensitive to radiation microRNA (including the action of small radiation doses) can be

involved in the pathogenesis of cancer caused by the action of radiation. Moreover, Japanese scientists from the University of Hiroshima, after conducting a study of patients diagnosed with stomach cancer exposed to large and small doses of radiation, found that the miR-24 expression profile was largely changed in the first group. Based on the results obtained, Naito et al. suggest that miR-24 can be use as a biomarker risk of developing gastric cancer induced by radiation [102].

Despite the large number of works devoted to the study of the relationship between microRNA, radiation, and carcinogenesis, there are few studies about the role of microRNA in radon-induced lung cancer. Chen et al. reported that the level of expression of let-7 microRNA in human bronchial epithelial (HBE) cells due to radon exposure is decreasing, which results in activation of the K-ras oncogene. Furthermore, a significant down-regulation of K-ras was then confirmed in both let-7b-3p and let-7a-2-3p transfected HBE cells [103]. The results of this study proposed that let-7 microRNA and K-ras are involved in radon-induced lung damage both in vivo and in vitro. In vitro study of malignant transformation due to radon exposure showed the change in the expression level of a number of microRNAs, including hsa-miR-483-3p, hsa-miR-494, hsa-miR-2115*, hsa-miR-33b, hsa-miR-1246, hsa-miR-3202, hsa-miR-18a, hsa-miR-125b, hsa-miR-17*, and hsa-miR-886-3p. These miRNAs target genes play key role in the regulation of cell proliferation, differentiation, adhesion during the process of malignant transformation, which are associated with different signal pathways such as mitogen-activated protein kinase (MAPK), Int and Wg (Wnt), reactive oxygen species (ROS), and nuclear factor κB (NF-κB) [104]. Recent study showed an increase in the expression of some circular RNA (class of endogenous non-protein coding RNAs that contain a circular loop) in mouse lung tissues due to radon exposure and 5 microRNAs binding sites detected for each circRNA. The authors suggest that these circRNAs and miRNAs could play important and synergistic roles in radon-induced lung damage, even in lung cancer [105].

Thus, the role of microRNA in the pathogenesis of radon-induced lung cancer is still unclear. Nevertheless, the search for biomarkers for early diagnosis of lung cancer, which can be useful, especially for Kazakhstan, since most of the Republic's territory has a high natural level of radon.

At the epigenetic level, not only miRNAs expression patterns, but specific alterations including alterations in DNA methylation, histone modifications leading to generation of γ-H2AX species (indicative of double-strand DNA breaks) have been associated with radon exposure [106].

Masoomi et al. showed that people living in regions with a high natural background of radiation had faster DNA repair [107]. Earlier, Fernandez-Capetillo et al. was proposed that H2AX phosphorylation may play an important role in the low-dose radiation adaptive response [108]. H2AX phosphorylation-induced chromatin restructuring for DNA repair/signaling factors and/or tether DNA ends. If this process is induced by low-dose radiation and if there is a memory for mounting this process in the event of a later enhanced genomic stress (e.g. high dose of carcinogen), more rapid and more efficient DNA repair might be expected to occur [109].

DNA methylation is well-described in lung cancer and is considered to be potentially reversible [110]. There is much less information about the effect of radon on the status of DNA methylation. In study of Chinese uranium workers has shown the methylation of O-6-methylguanine-DNA methyltransferase (MGMT) and p16 gene in the sputum cells is related to the accumulate exposure dosage of the radon [111]. p16 is a tumor suppression gene, which plays key role in cell cycle regulation and methylation p16 gene is significantly associated with non-small cell lung cancer (NSCLC) [112]. O-6-methylguanine-DNA methyltransferase is a DNA repair enzyme which protected cells from the carcinogenic effect of alkylating agents. The hypermethylation of the MGMT gene's promoter may play a significant role in lung carcinogenesis [113]. Belinsky et al. has shown that exposure to plutonium, which similar to radon exerts its effects through alpha particles, can induce p16 gene inactivation by promoter methylation [114].

It is known, that radon is the first reason of lung cancer in never smoking population. But some studies showed that higher methylation rate in p16 is dependent on the amount of exposure to tobacco smoke and this epigenetic change is specific to smokers with lung cancer [115]. By comparison in non-smokers patients with lung cancer, the methylation rate in p16 is low [116]. Bastide et al. concluded that, in radon-induced rat lung tumors, promoter methylation did not affect the p16 gene inactivation although the lack of p16 protein expression in lung tumors remains to be established [117].

The study in United States showed exposure to radon through uranium mining did not affect the prevalence for MGMT methylation [118].

Perhaps, in this case we are talking about the dose-dependent effect of radon on epigenetic reprogramming. High-dose radiation can promote epigenetically silencing of adaptive-response genes, while low doses of natural radiation can, on the contrary, have a protective effect and activate the same genes through changes at the epigenetic level. More importantly, according to the Environmental Protection Agency low-level radon exposure (4 pCi L − 1) may actually be protective against lung cancer [119]. Some study demonstrated cancer prevention after low-level radiation exposure [120, 121]. For this reason it will require more research to reconcile these contradictory data.

There is not much information about the effect of radon exposure on histone modification. The study by Pogribny has shown the effect of low-dose radiation exposure on histone H4-Lys 20 trimethylation in the thymus tissue using an in vivo murine model. In such a case, the loss of histone H4-Lys20 trimethylation was accompanied by a significant increase in global DNA hypomethylation and reduced expression of DNMT1 and DNMT3b. Moreover, the levels of methyl-binding proteins MeCP2 and MBD2 were significantly reduced in thymus of exposed females and males mice compared with respective controls. In such a case, the loss of histone H4-Lys20 trimethylation was accompanied by a significant increase in global DNA hypomethylation and reduced expression of DNMT1 and DNMT3b. Moreover, the levels of methyl-binding proteins MeCP2 and MBD2 were significant decreased in thymus of exposed females and males mice compared with respective controls [122].

The studies of specific molecular mechanisms that can lead to genetic and epigenetic aberrations in lung tumor genomes as a result of exposure to radon can give a unique opportunity for further developing diagnostic and identification of candidates for therapeutic targets. However future studies are needed to explore both the genetic and epigenetic mechanisms in pathogenesis of cancer and fully elucidate the effects of radon on health and disease.

11. Lung cancer studies in Kazakhstan

According to the latest WHO data published in May 2014, lung cancers deaths in Kazakhstan reached 3836 or 2.58% of total deaths. The age adjusted death rate is 26.24 per 100,000 of population ranks Kazakhstan #36 in the world [123]. Currently, Kazakhstan is in need of advanced actions to reduce lung cancer rate. However, unfortunately, in Kazakhstan there are very few studies of the genetic and epigenetic mechanisms of the lung cancer pathogenesis, especially the radon-induced action.

Sagyndykova studied the cellular and molecular carcinogenic effects on lung tissue due to radiation exposure on the population, lived on the territories of Semipalatinsk region. These territories were used for testing nuclear weapons for the Soviet army during the period 1949–1989. The results of the study showed a higher level of expression of IGFBP1, IGFBP2, p53, c-mus, bax and reduced expression of IGFBP3, IGFBP4, IGFBP5, bcl-2 in tumor cells compared to the control group (patients with lung cancer not due to radiation). Probably there are some differences in the mechanisms of proliferation, differentiation, and apoptosis in radiation-induced lung tumors [124]. We have long been studying the effect of radiation in the population of Kazakhstan [125]. In our previously study, we showed the association between the Gln/Gln genotype of gene XRCC1 and the frequency of chromosomal aberrations in the uranium workers. The frequency of chromosomal aberrations in heterozygous carriers of the XRCC3gene Thr/Met was lower than in the homozygous carriers of the wild type Thr/Thr [126]. It is known that DNA repair genes are involved in the formation of individual sensitivity to radiation exposure. Larionov et al. showed that three SNP of DNA repair genes may be considered as radon-sensitive markers [127]. Considering the fact, that the association between the DNA repair genes polymorphisms and radon exposure was found, similar studies indicate a prospect of searching for markers of individual sensitivity to radon among allelic variants of key DNA repair genes.

As discussed previously in the review, in addition to genetic factors, the epigenetic changes play an important role in the pathogenesis of lung cancer, including radon-induced lung cancer. One of the goals of contemporary cancer research is the development of new markers that facilitate earlier and non-invasive diagnosis. Studies have shown that miRNAs expression levels are altered in cancer. Recently, extra-cellular miRNAs have been detected in biological fluids and studied as possible cancer markers that can be detected by non-invasive procedures. The serum concentrations of several microRNAs have been associated with lung cancer [128]. Moreover, miRNAs have been reported to play an important role in inducing resistance to anti-cancer drugs [129]. miRNAs can be exploited not only as biomarkers of radiation exposure but also as biomarkers of lung cancer. The problem of the health risk

exposed to radon is not sufficiently studied on the populations of Kazakhstan, although the country (mainly its East and North areas) has the regions containing the high levels of radon [10]. Currently, we aim at addressing the role of genetic and epigenetic factors affecting susceptibility to radon exposure. At epigenetic level, we investigate the effects of radon on the expression of miRNAs in the blood plasma of exposed subjects. This will allow us to validate circulating miRNAs as a reliable biomarker of early biological effect to be used prior to the development of lung cancer in a high-risk population. Particularly, it is very promising to develop highly specific and efficient test systems of lung cancer based on molecular markers, which levels the change due to radon exposure.

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