A multifactorial assessment of carcinogenic risks of radon for the population residing in a Russian radon hazard zone

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SUMMARY

Background: *Results of numerous epidemiologic studies of carcinogenic effects of indoor radon conducted in different countries in the past 40 years remain controversial. To assess the contribution of the residential radon exposure in the development of lung cancer in the population of the Russian region with a high radon hazard we conducted a cancer epidemiology study based on a multifactorial analysis.*

Methods: *The study was conducted in the town of Lermontov situated in the area with high background radon concentrations and lung cancer rates of the Caucasian Mineral Water Region of Russia. High indoor radon levels were found in the houses of urban residents, mostly employed by the mining and chemical enterprise. The cohort consisted of 122 lung cancer cases and 208 controls. Each of 330 study participants was characterized by a set of 23 indices reflecting known lung cancer risk factors. We also collected data on occupational and residential radon exposure of all subjects.*

Results: *The analysis of a combined effect of 23 different lung cancer risk factors based on pattern recognition methods showed that the contribution of the non-occupational radon exposure was only about 2% whereas that of the occupational radon exposure equaled 15%.*

Conclusion: *Our findings showed that the effect of the residential radon exposure on the lung cancer rate was 15-20 times weaker than the effects of the main risk factors such as smoking, occupational hazards, chronic lung diseases, social and household factors, etc., although for the population of Lermontov this factor was 2-3 times stronger than that found in the Ural towns of Russia.*

Key words: Lung Neoplasms; Risk Factors; Russia; Air Pollution, Indoor; Occupational Exposure

INTRODUCTION

Carcinogenic risks of the radioactive radon and its decay products are extremely important but, at the same time, poorly studied. Epidemiologic studies of uranium and other miners showed that the occupational exposure to high radon concentrations posed the risk of lung cancer. Based on epidemiologic and experimental data, the experts of the International Agency for Research on Cancer stated that radon and its decay products were carcinogenic to humans (1).

Special attention is paid to this problem due to high concentrations of this radioactive gas in residential and public buildings that pose the carcinogenic risk for a significant part of population rather than occupational hazards for small groups of miners (2-4). Yet, results of numerous risk assessment studies are inconsistent. Stidley and Samet analyzed 15 radiation epidemiology studies, and noted that only seven of them demonstrated the correlation between radon and cancer; six studies showed no relationship at all and two studies even revealed a negative correlation between indoor radon concentrations and lung cancer (5). Ten years later Krewski et al. reported similar findings when they summarized the results of 20 epidemiologic studies conducted in different countries (6).

Many specialists believe that contradictory results of these studies are the result of method errors made by the researchers, and this is one of the main reasons for the remaining uncertainty in the issue of carcinogenic risks of the residential radon exposure (7-10). Our own experience in applying multiple factor techniques of the epidemiologic analysis gives

grounds to consider this point of view well-founded. Results of our earlier radiation epidemiology studies based on the multiple factor approach gave evidence that the effect of indoor radon concentrations < 100 Bq/m^3, observed in two towns of the Sverdlovsk Region, Russian Federation, was extremely low on the incidence of lung cancer. Yet, when the same data were fed in the radiation risk model BEIR VI, which is now considered to be most precise in the carcinogenic risk assessment of radon exposure, the results appeared to be several times higher (2). Additional arguments were necessary to confirm this conclusion and the question about the extent of carcinogenic risks of environmental radon exposures that were higher than those found in the study areas of the Sverdlovsk Region remained open.

In order to eliminate existing uncertainties we conducted additional radiation epidemiology studies in one of the Russian regions with a high background radon hazard; we used the multiple factor analysis.

MATERIALS AND METHODS

The study was conducted in the town of Lermontov situated in the North Caucasus of the Russian Federation (the Caucasian Mineral Water Region). At the time of the study the size of population in the town was 24,898 people. Lermontov is characterized by high cancer incidence rates and a high intensity of radon emissions from soils in residential areas. The main sources of the high background radiation are elements of natural radionuclides such as uranium-238 and thorium-232 and decay products of radon and thorium found in building materials and soil under residential

and public buildings. A mining and chemical enterprise *Almaz* in the vicinity of the town also contributes to the background radiation since tailings and dumps of radioactive rocks have been left after closing of the enterprise. As a result, a unique for Russia radiation epidemiology situation has formed in the town of Lermontov in the past 50 years causing medical and social tension among the residents and requiring a scientifically founded conclusion about its carcinogenic risks. At the same time, while developing the latter it was necessary to take into account the fact that from 1950 to1990s a significant part of the town population worked at the *Almaz*, the first Russian uranium mine and mill, and was occupationally exposed to high levels of radiation related to radon and its daughters. The radiation hygiene expert examination of the study area and of the type of its residential development enabled us to select four urban sectors with account for the following features. The **first sector** represented the oldest low-storey (1, 2 and 3-storey) part of the town constructed before 1970. The distinctive feature of the "old" residential development was the use of local building materials and wastes of uranium mines with a higher level of natural radionuclides compared to other parts of the town. Besides, many residential buildings had no basements and stood immediately on the ground.

The **second sector** included the part of the town developed after 1970 with modern multi-storey (5- and 9-storey) buildings constructed of environmentally friendly materials with low concentrations of natural radionuclides brought from other regions of Russia. The radiation control was performed during the development. All buildings of this sector have uninhabited basements preventing the penetration of radon to living quarters. The **third sector** included private, mainly 1-storey houses built at different time periods and the quality of building materials was poorly controlled. Most houses were constructed of local building materials. Some houses of this sector have basements opening to the inhabited rooms. The significant part of the sector has a high level of standing groundwater and this can be a determinant of the process of bringing the radioactive radon gas to living quarters.

The fourth sector consisted of private houses of Ostrogorka village joined to Lermontov in 1988. This sector had been mainly built of environmentally friendly materials with low concentrations of natural radionuclides brought from other regions of Russia under proper radiation control. Basements were well isolated, thus preventing the penetration of radon to inhabited spaces. The distinctive feature of Ostrogorka was that not all houses were connected to the central water supply system and 15% to 20% of the population used water from wells and artesian wells for drinking and cooking.

So the exposure of the population of Lermontov to ionizing radiation varied depending on the sector and the type of building materials of their residences. Taking into account the fact that gamma radiation can also contribute to the total background radiation in the town, we established quantitative indices of this type of the radiation exposure. Table 1 shows dose rates established by SanEpid specialists in Lermontov in the course of the pedestrian g-survey. According to them, in a half of the town the rate of the ambient equivalent of the dose of g-radiation exceeded 0.30 μSv/hour and in 2% (about 4.4 hectares) it was over 0.60 μSv/hour.

Table 1. The rate of ambient dose equivalent in the town of Lermontov

Dose rates, μSv/hour	The percentage of the town area
< 0.20	7
0.20-0.30	46
0.31-0.40	30
0.41-0.60	15
0.61-0.80	2
Average: 0.25-0.30	100

The analysis of medical statistics showed a high cancer prevalence rate in Lermontov compared to that in the Stavropol Region as a whole. In 2003 the rate of mortality from cancer of all sites was 255 per 100,000, and that from lung cancer – 58 per 100,000. The comparison of the standardized rates of mortality from lung cancer in Lermontov and in the Stavropol Region showed that the former is 1.5 times higher (for the general population), and 1.9 times higher when recounted for the male population. The occupational pathology of *Almaz* workers was analyzed for the period from 1980 to 1990, the years of the sustainable and stable operation of the uranium mine and mill. Lung cancer ranked first in the structure of the occupational pathology (58%), and the percentage of other occupational diseases, such as silicosis, dust bronchitis, and occupational hearing impairment, varied from 4% to 8%.

The study was based on the following principles:

1. According to available published data the main medico-biological effect of the exposure to radon and its daughters, is the development of lung cancer. At the same time, lung cancer, just like the majority of other tumors, belongs to the diseases induced by a combination of different factors including medico-biological, occupational, social, household, environmental, and others. To our opinion, such a multiple factor conditionality of lung cancer makes traditional single factor epidemiologic techniques ineffective. The reason for limitations is that case-control studies enable one to eliminate the effect of 2-3 confounders whereas it may be assumed *a priori* that effects of a much greater number of confounders must be adjusted for. To our mind, this very circumstance leads to such polar risk estimates of environmental radon exposure obtained in the result of single factor epidemiologic studies. The most adequate to the task in question is the epidemiologic study based on the techniques of a multivariate analysis. In this case adjustment for confounders is unnecessary because the whole aggregate of data is analyzed at a time.

2. The study must be conducted at the individual level because such an approach to collecting epidemiologic data yields most correct results. Thus, specialists think (10) that the main drawback of well-known studies of Cohen et al. (11) is the substitution of individual values and characteristics by values averaged for U.S. administrative districts.

3. Direct measurements of indoor radon concentrations shall be used to establish the level of the radiation exposure of a person.

The case group included 122 people with lung cancer diagnosed in the period 1995-2004. All diagnoses were thoroughly verified by instrumental methods of examination and confirmed morphologically in over 70% of

cases. The control group included 208 people randomly chosen from the population of the town with account for the following criteria: (a) sex and age structure corresponded to that of the adult population of the town as a whole; (b) it included people residing in all parts of the town in proportion close to the existing territorial distribution; (c) the occupational structure of the control group was consistent with that of the town.

As a result, when forming the control group for our study we did our best to bring it in conformity with the age, sex, and occupational structure of the population of Lermontov.

Each of 330 study subjects was characterized by a set of 23 indices reflecting well-known risk factors of lung cancer. In the course of the study we collected personal data on such factors as sex, age, nationality, occupation, the duration of occupational exposure to carcinogens, a family history, chronic lung diseases, bad habits (smoking and alcohol abuse), social and household conditions (the floor of living, a gas stove in the kitchen, the type of building materials of the house, linoleum flooring, the source of drinking water supply), and the data on occupational and environmental radon exposure of all subjects.

One of the most important parts of our study was measuring indoor concentrations of radon and thoron. To estimate radon concentrations we used archive data of radon surveys conducted by specialists of the sanitary and epidemiologic surveillance center of Lermontov in the period 1995-2003 using coal accumulation chambers and results of special measurements taken by integral track radiometers of radon in the period 2004-2005. The period of exposure of coal accumulation chambers and integral track radiometers of radon was one week and 1 to 3 months, respectively. Measurements were performed in bedrooms and living-rooms, i.e. in the rooms where people spent most of their time. The results were brought to annual average values of the radon concentration by using a temperature normalization, which had been verified based on a significant number of test results of SanEpid specialists in Lermontov. In order to estimate the equivalent equilibrium concentration of radon we used the equilibrium factor 0.4 usually applied for regions with a warm climate. At the initial stage of the study we took random one-time measurements of thoron concentrations using a Markov-Terentyev aspiration method. Based on those results indoor levels of accumulation of thoron daughters in Lermontov were found insignificant ($<2\,Bq/m^3$) and so we did not measure them in the rest of homes. Table 2 provides data on indoor radon concentrations measured in residences of cases and controls.

Table 2. Distribution of average indoor radon concentrations in Lermontov

Cohorts	Arithmetic mean, Bq/m³	Geometric mean, Bq/m³	The percentage of residences with radon concentrations >100 Bq™3	The percentage of residences with radon concentrations >200 Bq/m³
Cases	122	64	39%	17%
Controls	107	73	39%	12%

Based on archived and our own results of measuring indoor radon concentrations, we assessed the exposure of cases and controls. We used a common unit *working level month* (WLM) that is numerically equal to the exposure to 3,700 Bq/m³ of radon in equilibrium with daughters for 170

hours (the working time per month). We estimated the exposure D (WLM) according to the number of years Ti of living at each address:

$$D = \sum_i \frac{EEC_i \cdot 7000}{170 \cdot 3700} \cdot T_i \qquad (1)$$

The assessment of occupational exposure was performed based on work histories of *Almaz* employees. Those histories contained personal data on occupational hazards and adverse labor conditions including radon concentrations at workplaces.

For the multiple factor analysis we applied a mathematical tool of pattern recognition. The following tasks were solved during the data processing:

(1) Evaluation of sufficiency of the selected set of factors for a reliable description of differences between observations for cases and controls.

(2) A quantitative evaluation of informational content of each factor interpreted as a power of its effect.

(3) Determination of the character (direction) of the effect of each factor, which within the framework of this study can be interpreted as an increase or a decrease in the probability of the factor-related disease.

The first task was solved using methods of the discriminant analysis. Its essence is as follows. A part of observations for both cases and controls (here, 15%) is allotted for an "examination." Then the computer is "taught" based on the rest of observations that form a so-called "teaching sample" and the discriminant functions (decision rules) dividing analyzed classes are built. The criterion of quality of dividing classes is the percent of correctly recognized observations of the "examination" sample. It is natural to suppose that the higher is the percent, the more substantiated is the conclusion that the selected set of signs (factors), within the scope of which the decision rule was developed, does characterize the observations belonging to different classes.

Solving the task of "teaching the computer" is usually preceded by the procedure of "evaluating informational content of signs" that allows one to rank them by their "usefulness" for dividing the given classes and to determine the number and list of signs according to which the division of the classes under study will be performed.

To evaluate the informational content of signs we used a method based on calculating the difference in the frequencies of occurrence of signs in samples of the classes under consideration. In accordance with this algorithm the range of values of each sign is divided to z intervals and then the relative frequency of occurrence of the values of the signs under study from vectors of different classes in each of these intervals. The informational content of sign i is estimated using the formula (2):

$$J_i = \frac{2}{k(k-1)} \sum_{t=1}^{z} \sum_{l=1}^{k-1} \sum_{m=l+1}^{k} \left| p_{l,t}^{(i)} - p_{m,t}^{(i)} \right|, \qquad (2)$$

Where, $p_{l,t}^{(i)}, p_{m,t}^{(i)}$ are the frequencies of occurrence of values of *i*-sign from vectors of classes *l* and *m* in the *t*-interval. The number of intervals z depends on the size of class samples and is calculated in the KVAZAR package using a well-known formula *1+1.39lnm*, where *m* is the size of the smallest sample.

The obtained values are normalized as follows:

$$\forall i \in \overline{1, \, n} : J_i^H = \frac{J_i - \min\limits_{j \in \overline{1,n}} J_j}{\max\limits_{j \in \overline{1,n}} J_j - \min\limits_{j \in \overline{1,n}} J_j} \qquad (3)$$

And they form relative values of the informational content. At this the most informative sign is given the value 1 and the least informative – 0. As a result, all signs become normalized by the extent of informational content in the decreasing order in the range of 1 to 0. The first n' signs are used as the desired subsystem. Since the optimal value n' is unknown in advance, teaching is usually performed in several different subspaces with different n'. The best solution is chosen out of all obtained.

The directivity of effects of factors was assessed based on the analysis of their average values in the samples of classes under study. All tasks were solved in the package of applied programs KVAZAR (12).

It was interesting to compare results of direct epidemiologic studies of the radon exposure and lung cancer with the results of risk assessment obtained using special mathematical models. To do this, we made calculations using a multiplicative model BEIR VI, which is considered by many specialists to be most appropriate for assessment of the risk of radiation-induced lung cancer (2).

RESULTS AND DISCUSSION

During the mathematical data processing we first decided on the sufficiency of information about 23 examined factors for a reliable description of differences between classes. The best result of recognizing the examination sample 92.3% was obtained when using 13 most informative signs. On the whole, decision rules correctly recognizing 87% to 92% of vectors of the examination sample were obtained using different subsets of 11 to 22 signs. The fact that high results were obtained during recognition of the "examination" material gives grounds to state that the selected complex of indices includes the most important risk factors of lung cancer for the contingent under study. Besides, it should be noted that these results were obtained by using three different algorithms of recognition, which certainly makes them more trustworthy. Using a special algorithm (13) we estimated the confidence interval of the results of recognition that equaled 81-96%. On its basis we can state that the size of our samples was quite sufficient for obtaining reliable results.

At the second stage of the mathematical processing of epidemiologic data we analyzed the power of effect of each factor on the development of lung cancer. Table 3 presents aggregated data on effects of the factors considered in the epidemiologic study on the development of this pathology. In this table the factors are ranked in the decreasing order by their informational content values calculated based on difference in frequencies of occurrence. Besides, the table contains values of Student t criteria for each factor and ranks corresponding to the criteria. The last column shows the direction of the effect of each factor: the plus indicates a positive link between the factor and cancer, and the minus – a negative one.

The well-known risk factors of lung cancer such as duration and intensity and smoking, sex, age, and chronic lung diseases ranked highest. Working at *Almaz,* the sign indicating the occupational exposure to radon,

ranked among the highest. At the same time the indicator that directly characterized the occupational radon exposure ranked 15, and according to Student t criterion – even 18. We are of the opinion that the reasons for such inconsistency might be due to insufficient reliability of the information taken from archived data and applied to the assessment of the occupational radon exposure.

The parameter characterizing the radon exposure in the household ranked 19 and 20 by Student t criterion. The parameter of the district of Lermontov where the subject lived also ranked low.

On the whole, if we consider the total effect of all factors under study on the development of lung cancer in the residents of Lermontov as 100%, then the contribution of the environmental radon exposure was 2%, whereas that of the occupational radon exposure exceeded 15% (Figure 1).
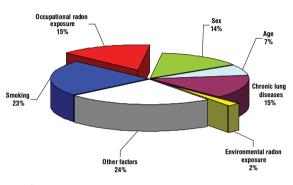

Figure 1. Relative contribution of the main groups of factors in the risk of lung cancer for the population of Lermontov

When assessing the character of effect of each factor we generally obtained quite predictable results: men were at higher risk of lung cancer; as expected, this risk depended on the duration and intensity of smoking and on age; it was higher in people with chronic lung diseases and ex-workers of *Almaz*. The only exception in this case was the factor of "having relatives with the verified diagnosis of cancer" that showed an inverse relationship with diseases of the observed cases. The reason for such a contradiction might be an insufficient reliability of information about this factor.

Figures 2 and 3 show that there exists a direct correlation between the risk of lung cancer and the level of both occupational and non-occupational radon exposure.
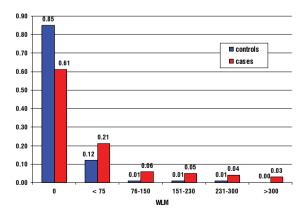

Figure 2. Distribution of lung cancer cases and controls depending on the level of occupational radon exposure

Table 3. Informational content and directivity of factors contributing to the lung cancer risk for the population of Lermontov, Russia

Factors	Coding and units	Informational content by the difference in frequencies	The rank by the difference in the frequency of occurrence	Student's t criterion	The rank by Student's t criterion	Vectors of effects of the factors
Smoking history	Years	1.000	1	13.19	1	+
Age	Years	0.816	2	9.813	3	+
Male gender	0 – no, 1 – yes	0.789	3	9.533	4	+
Employment at *Almaz*	0 – no, 1 – yes	0,777	4	10.059	2	+
Smoking intensity	0 - none, 1 – <10 cigarettes a day, 2 – 10 to 20, 3 - > 20	0.686	5	7.221	5	+
Exposure to occupational hazards	Years	0.526	6	6.656	6	+
Smoking at home	0 – never, 1 – occasionally, 2 – constantly	0.476	7	4.055	8	+
Chronic lung diseases	0 – no, 1 – yes	0.466	8	5.707	7	+
The area of the dwelling space per person	In m^2	0.357	9	2.947	9	+
Alcohol consumption	0 – none, 1 – rare, 2 – once a week, 3 – more than once a week, 4 – almost daily	0.269	10	2.046	14	+
The floor of living	Floor No.	0.255	11	1.971	16	–
Family history	The number of relatives with cancer	0.206	12	2.407	11	–
Type of heating	1 – central, 2 – gas, 3 – oven	0.188	13	2.268	12	+
Duration of living in Lermontov	Number of years	0.177	14	2.493	10	+
Occupational radon exposure	In WLM units	0.153	15	1.386	18	+
Local building materials in the residence	0 – not used, 1 – sand, clay, etc., 2 – uranium wastes	0.128	16	2.199	13	+
Dwelling in the Lower town	0 – no, 1 – yes	0.105	17	1.188	19	–
Dwelling in the private sector	0 – no, 1 – yes	0.096	18	1.806	17	+
Residential radon exposure	In WLM units	0.045	19	1.159	20	+
Type of water supply	1 – centralized, 2 – a well	0.038	20	2.005	15	+
Kitchen equipment	1 – an electric stove, 2 – a gas stove, 3 – an oven	0.026	21	1.040	21	+
Dwelling in Ostrogorka	0 – no, 1 – yes	0.009	22	0.377	22	+
Dwelling in the Upper town	0 – no, 1 – yes	0	23	0.102	23	–

Notes:

1. Values of the informational content of factors are given in relative units.

2. The "+" indicates the positive link between the factor and lung cancer and "-" – a negative one.
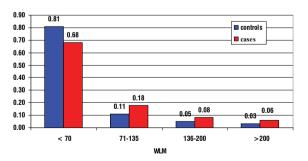

Figure 3. Distribution of lung cancer cases and controls depending on the level of environmental radon exposure

Apart from direct epidemiologic studies the data were analyzed using the methodology of risk assessment with the multiplicative model of radiation risk BEIR VI applied. According to the results produced by this model the contribution of environmental exposure to the risk of lung cancer among the population of Lermontov was 30%, and thus it could be referred to one of the main factors inducing lung cancer in the residents of Lermontov. At the same time the results of the multiple factor analysis gave evidence of its low contribution to the development of lung cancer.

The following conclusions can be made based on the study results. One of the main risk factors of lung cancer in Lermontov is the occupational radon exposure (the major part of the population used to work for the uranium mine and mill). The contribution of the environmental radon exposure, in its turn, was significantly lower. Taking into account the fact that the town of Lermontov is characterized by one of the highest levels of natural background radiation in Russia, it may be assumed that on

the whole the value of indoor radon as a carcinogenic risk factor in the country is small.

The study results show that the effect of the indoor radon exposure on the incidence of lung cancer in the town of Lermontov is 15 to 20 times lower than that of the main risk factors (Table 3), even though it is 2 to 3 times stronger than that found in the Ural towns (8, 14).

Based on these facts we think it expedient to preserve the existing system of radiation hygiene control in Lermontov and to continue implementing the program of decreasing indoor radon concentrations. At the same time for the individuals making a short visit to the town (i.e. for holidays) the existing background radiation poses no carcinogenic risk at all.

The following arguments for the reliability of our results can be offered:

- A significant degree of their consistency with the findings of similar studies conducted in the Ural towns of Pervouralsk and Karpinsk (14);
- The achievement of high results of recognizing the case and control groups when using algorithms of pattern recognition based on different principles;
- The confidence interval of obtained values enabling one to consider the size of the case and control groups sufficient to obtain statistically significant results;
- The fact of establishing the expected character of the relationship between lung cancer and many well-known carcinogenic risk factors unrelated to radiation such as smoking, occupational exposure to carcinogens, age, chronic lung diseases, etc. during the systems analysis.

In conclusion it should be noted that the results of the multi-factor epidemiologic study are consistent with the opinion of those specialists who insist on a weak effect of the radiation related to low indoor concentrations of radon and its daughters on the development of lung cancer (7, 9). At the same time the comparative analysis of the contribution of the radon exposure to the development of lung cancer among the residents of Lermontov and two towns of the Sverdlovsk Region gives evidence of the increase in the risk of lung cancer with the increase in the indoor radon concentration even though its value is generally small.

Conflict of interest

We declare no conflicts of interest.

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