NUKLEONIKA 2020;65(2):83–88
doi: 10.2478/nuka-2020-0012

ORIGINAL PAPER

Combined analysis of onco-epidemiological studies of the relationship between lung cancer and indoor radon exposure

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Abstract. *Objectives*: Recent results of epidemiological and medical statistics studies of lung cancer and indoor radon in different regions of the world make a relevant new combined analysis of residential exposure health effects. In particular, new data were obtained by means of a meta-analysis of case-control studies as well as taking into account a confounding effect of human papillomavirus infection in studies of geographically aggregated data. *Materials and methods*: Two sources of epidemiological data are considered: (1) studies of ecological design and (2) case-control studies. Ecological studies included the analysis performed for the USA counties and Russian oblasts with adjusting for the main confounders. Data on the case-control studies were gained from the meta-analysis of 31 individual studies with a weighting of obtained odds ratios according to the quality of radon exposure reconstruction and size of the reference group. Estimations of lung cancer excess relative risk (ERR) associated with indoor radon exposure are combined. *Results*: Two types of epidemiological study design provided generally consistent EER estimations. The combined value of ERR due to radon exposure is 0.14 (90% CI: 0.10–0.18) per 100 Bq/m^3. *Conclusion*: Available geographically aggregated data in regions of Russia and the United States and the meta-analysis of case-control studies conducted in a large number of countries confirm the association of lung cancer with indoor radon exposure.

Keywords: Lung cancer • Radon • Relative risk

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Received: 21 November 2019
Accepted: 29 January 2020

Introduction

Radon is a global natural radiation risk factor. While radon concentration in the atmosphere is relatively low, radon accumulation in buildings may be significant. Over the past 50 years, direct measurements of radon concentration in dwellings have been carried out in many buildings, in particular, within the frames of thoroughly organized national and regional radon surveys. According to the UNSCEAR report, the worldwide average indoor radon concentration is about 50 Bq/m^3 [1], and it exceeds 150 Bq/m^3 in about 5% of the buildings [2].

The relationship between the radiation dose received due to the inhalation of radon and its daughter products and the consequences for human health have been analysed in a number of epidemiological studies. With regard to the applied epidemiological methods and considered populations, these studies mostly belong to one of three types: cohort studies of miners, case-control studies of lung cancer and radon exposure in dwellings, and ecological studies of the association between average levels of radon concentration and lung cancer mortality in the same regions. The main result of miners cohort studies is that the increase of lung cancer is a statistically significant health effect of the high radon exposure

[3, 4]. The pooled analysis of 13 European case--control studies [5] provided the excess relative risk (ERR) 16% per 100 Bq/m^3 (95% CI: 5–31%) taking into account the correction for measurement uncertainty. The linear no-threshold model was justified for the radon exposure in dwellings with radon concentration above 150 Bq/m^3 during up to 30 years. After the joint analysis of the main results of the epidemiological studies of occupational exposures of miners and domestic exposures of the public, ICRP concluded that the strong and complementary evidence of the risks of lung cancer following inhalation of radon and its progeny is provided. Such a conclusion was further used for developing the system of radiation protection against radon exposure [6].

Ecological studies (geographical correlation) performed during the last decades provided contradictory results due to inherent methodologic limitations. Stidley and Samet [7] suggested that further ecologic studies of indoor radon and lung cancer are to be discouraged, and the ethiological (case control and cohort) studies design should be used for testing hypotheses on the association between lung cancer and radon exposure. However, the ecologic studies could be used for hypotheses generation.

The ecological studies are highly sensitive to the quality and completeness of the information on influencing factors. The most important factor causing lung cancer in the present-day population is tobacco smoking. However, other factors influence as well. Recently, speculations on the possible association of lung cancer with human papillomavirus (HPV), especially for nonsmokers, were published. For example, Klein *et al*. [8], in the review of 53 publications on HPV in lung carcinomas, suggested that HPV is the second most important cause of lung cancer after cigarette smoking. More recent meta--analyses [9] show that HPV infection, especially HPV 16 and 18 infections, significantly increases lung cancer risk. At the same time, the overview [10] concluded, that the published data do not provide evidence of the involvement of HPV in the pathogenesis of lung cancer. A recent ecological study in Russia and the USA with the inclusion of possible HPV association with lung cancer have provided results coherent with linear no-threshold dependency between lung cancer mortality and radon concentration in dwellings [11].

The meta-analysis of the most complete set of the individual case-control studies [12] that investigated the relationship between lung cancer incidence and mortality and indoor radon also confirms the significant linear no-threshold exposure effect relationship for radon concentrations above 100 Bq/m^3. A slope factor of this dependence was obtained to be 0.14 (95% confidence interval 0.08–0.21) per 100 Bq/m^3. The case and control groups included in this meta-analysis have exceeded the total size of groups involved in the European and North American pooled analyses.

New data on the lung cancer risk factors, as well as a significant amount of the results of new epidemiological and medical statistics analyses in different regions of the world, performed recently, make relevant a combined analysis of the information on the relationship between lung cancer and radon exposure in dwellings. The purpose of this study is to analyse the available results of studies on the effects of radon exposure on human health, based on an approach using aggregated territorial-based medical statistical data and case-control studies.

Materials and methods

The present study is based on a joint analysis the results of the meta-analysis of 31 case-control studies presented in [12] and ecological studies in the United States and Russia [11, 13, 14].

In [13], smoking has been shown to be an important factor in modifying the dose-effect relationship in an ecological type of study. In [14], on the example of the Russian population, the role of HPV as a confounder in studies of the relationship between radon and lung cancer was demonstrated. In the study [11], the analysis was performed for the US and Russian populations using the most relevant and reliable data on smoking prevalence. The risk of lung cancer associated with radon exposure in homes was analysed using geographically aggregated data on lung cancer mortality and radon concentration, taking into account new data on the possible association of lung cancer with HPV. As a surrogate of the HPV infection prevalence, medical statistics on cervical cancer incidences were used. For the USA and Russian Federation, the cancer statistics were collected from cancer statistics review of the National Cancer Institute and reports of Herzen Moscow Oncology Research Institute, respectively. Significant estimates of cervical cancer incidence rates were found for 611 US counties. The average radon concentration for the investigated regions was 59 Bq/m^3. In the Russian Federation, 64 oblasts with available medical statistics were included in the analysis. Average radon concentration – 55 Bq/m^3. According to the results of the research, it was obtained that the use of actual data on the prevalence of smoking and infection with HPV increases consistency of radon risk assessments related to indoor radon. The estimates of lung cancer ERR due to radon exposure obtained for US and Russian males are 0.08 ± 0.04 and 0.01 ± 0.03 and for females 0.11 ± 0.07 and 0.36 ± 0.15 per 100 Bq/m^3 (with 90% confidence interval), respectively [11].

A recent meta-analysis of case-control studies of the relationship between lung cancer and radon exposure included 31 studies conducted in different countries [12]. For each study, the following information was entered into the database: author, year of publication, location of the study, the total number of cases, the total number of controls, method, and duration of the radon measurement, period of exposure reconstruction, type of control group, sex and smoking status of participants, and the presence of histological diagnosis verification. For each radon concentration interval for which the odds ratio (OR) was determined in the original study, a new record was created in the meta-analysis database indicating the lower and upper bound of the interval, the number of cases and controls in this interval, the OR calculated for this interval, adjusted OR, and its confidence interval and other information. In total, the database included 140 records. In each study, the mean radon concentration was determined by assigned exposure intervals. In a number of cases, these values were given in the original publication. In other cases, the distribution of radon concentration in the sample of participants in the study was reconstructed assuming log-normality and using published information on the arithmetic mean, geometric mean, geometric standard deviation, and the distribution of the number of controls by intervals. In the meta-analysis, the OR was combined according to the number of the radon concentration interval for which they were estimated. The OR values referred to the last concentration intervals were combined into a separate group.

In each group, the weighted mean value of the OR was calculated. Three parameters were used as weights: the reciprocal of the standard deviation of the OR logarithm; coefficient taking into account the duration of measurement of radon concentration; and coefficient taking into account the reliability of using the first interval as a reference category. The greatest weights have been assigned to the largest studies (more than 1000 persons totally), with a duration of measurements 6–12 months and the size of reference category more than 30% of the total group. The results of risk factors assessment were not sensitive to the exclusion of any study from the analysis separately.

Scattering of OR values obtained for the meta-analysis depending on the estimated weights is presented in Fig. 1. The confidence intervals and the standard errors of OR in the interval were calculated by the Monte Carlo simulation. For each group, the weighted median value of radon concentration was calculated, using the same weights. ERR was estimated as a slope factor of the linear dependence between weighted median radon concentration and OR. The value obtained was 0.14 (95% confidence interval 0.08–0.21) per 100 Bq/m^3 [12].

The analysis of the consistency of the case-control and ecological studies was performed by several stages. At the first stage, the results of the ecological study were combined by gender. The ERR for women and men was calculated on the basis of risk assessments for the US and Russia female and male populations, respectively. At the second stage, the final average value of the ERR was calculated based on the results of the ecological study. At the third stage, the result of the ecological study was compared with the result of the meta-analysis. The combination was conducted supposing the equivalency of the results of two study types. At each stage, the combination of the two values of ERR was made according to the following scheme. Two sets of 10 000 random numbers distributed according to the normal law around the average ERR with known standard errors were generated. Then, the average of two numbers was calculated 10 000 times and the average, as well as standard deviations, were calculated in the obtained array.

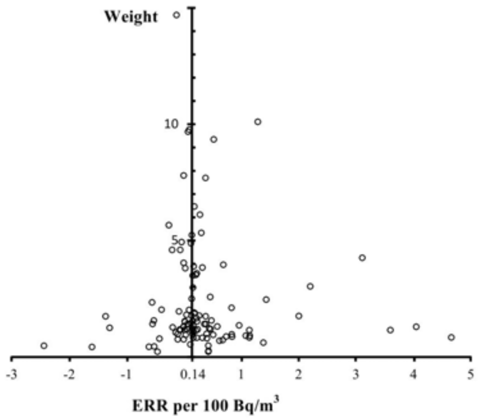

Fig. 1. Scattering of OR values obtained for the meta-analysis [12] depending on the estimated weights.

Results

Figure 2 presents the results of the ecological study [11] and ERR estimates obtained after their combining. As can be seen in the figure, the ERR estimates obtained in the ecological study are homogeneous. While there is some inconsistency between the ERR for the US and Russian females, ERR for male populations is consistent and combined estimates for women and for men are consistent as well. The final value of ERR calculated using the results of the ecological study is 0.14 ± 0.04 (with a standard error), which is consistent with the result of a meta-analysis of the case-control studies (0.14 per 100 Bq/m^3, 95% confidence interval 0.08–0.21 [12]). The values of lung cancer ERR due to radon exposure in dwellings, given in meta-analysis [12],

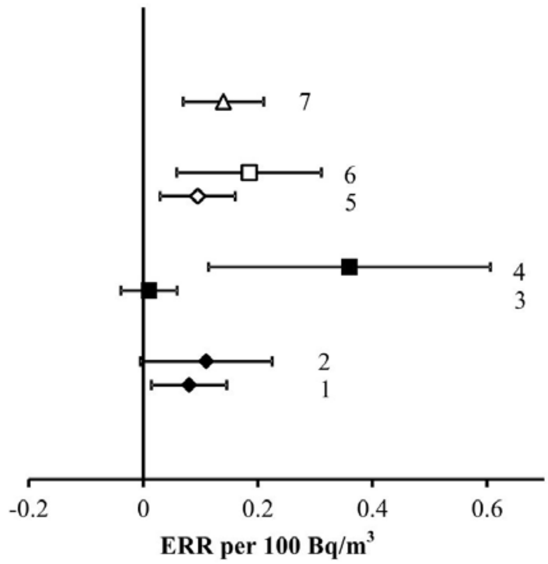

Fig. 2. Results of the ecological study [11] and ERR estimates obtained after its combining. 1 – US males, 2 – Russian males, 3 – US females, 4 – Russian females, 5 – combined estimation for males, 6 – combined estimation for females, and 7 – the combined result of ecological study. Whiskers – 90% confidence interval.

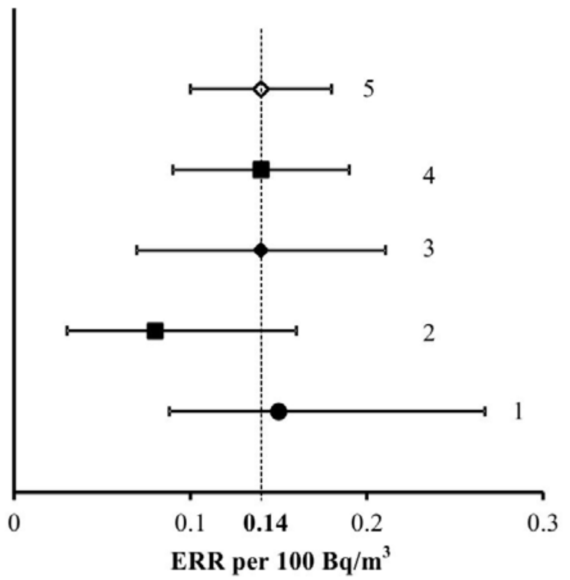

Fig. 3. Comparison of estimations of radon-induced lung cancer ERR by the results of a combined analysis of different types of studies. 1 – miners cohort study [3], 2 – European pooling analysis [5], 3 – the combined result of ecological study, 4 – meta-analysis [12], 5 – final combined estimation of radon-induced lung cancer (a combination of risk values 3 and 4). Whiskers – 90% confidence interval.

obtained from the results of the ecological study [11], and the combined result are shown in Fig. 3. The value obtained after combining the results of the ecological study and meta-analysis is 0.14 (90% CI: 0.10–0.18) per 100 Bq/m^3.

Discussion

To date, the most valid scientific evidence of the risk of lung cancer due to radon exposure can be obtained from two main sources [15]. Persuasive and unambiguous results were given by epidemiological studies of workers of uranium mines subjected to high levels of exposure at workplaces [3]. A combined analysis of case-control studies that assessed the levels of exposure in the dwellings was carried out separately in Western Europe [5], North America [16], and China [17]. These studies confirmed the risk of lung cancer with radon concentration in the dwellings below 200 Bq/m^3 [15].

Within the frame of the present work, new data of regression analysis of territory aggregated data and meta-analysis of case-control studies performed in different regions of the world are analysed. For comparison, regional lung cancer mortality and average radon concentration in dwellings, the most reliable estimates of smoking prevalence in the regions were used. In addition, new data on the possible association of lung cancer with HPV infection were taken into account. The combined ecological studies included data for the two largest countries for which reliable data on cancer mortality and radon survey by administrative regions are available (Russia and the United States).

Previously, Cohen presented the results of a large ecological study revealing a negative correlation between lung cancer mortality and mean indoor radon concentration in the US counties [18]. Later, Puskin [19] concluded that the negative association observed for lung cancer and radon can be explained in terms of confounding by smoking. Malinovsky *et al.* suggested that the consideration of relevant smoking data together with adjusting for HPV infection could minimize the unknown effect of confounders in radon ecological studies [11].

Within the framework of the meta-analysis, data on 31 case-control studies of the dependence of lung cancer on radon exposure in dwellings were collected. These studies were conducted in 13 countries located in Europe (19 studies, including two in Russia), North America (9 studies), and Asia (3 studies). The collected data set included a significant amount of total case and control groups of 20 703 and 34 518 people, respectively [12]. The size of studied groups is 2–3 times higher than in European pooled analysis and 6–7 times higher than in the North American pooled analysis.

The results of the assessment of lung cancer risk due to radon exposure in dwellings by two different applied approaches turned out to be generally consistent. Some differences were shown by risk assessments for the female populations of the US and Russia, which may appear due to significant differences in the prevalence of smoking in two countries. It was confirmed that the dose-effect dependence in the case of radon exposure at levels typical for dwellings can be described by a linear no-threshold model. The final combined estimation of lung cancer ERR due to radon, was 0.14 per 100 Bq/m^3 in both types of studies. It should be noted that an impact of radon exposure uncertainty on the estimated risks both in meta-analysis and ecological studies was not considered. As shown earlier, the uncertainties in radon exposure assessment in case-control studies result in an underestimation of the ERR [20, 21].

When extrapolating the obtained value of a life-long additional relative risk 0.14 per 100 Bq/m^3 to the conditions of the radon exposure in residential areas of Russia (mean radon concentration 48 Bq/m^3 [22]), the average ERR value will be 0.067. With this value of ERR, the contribution of radon to lung cancer morbidity and mortality from all causes is approximately 6.3%. Taking into account the incidence of lung cancer observed in 2018 [23], the total number of cases of lung cancer due to radon exposure in Russia is approximately 3900 per year. The findings can be used to develop and verify more complex risk models, which consider the duration of exposure, the age reached, and other parameters.

Conclusion

1. Recent data on the relationship between the incidence of lung cancer and average radon concentration in regions of Russia and the United States, as well as the meta-analysis of case-control studies conducted in a large number of countries, confirm the association of lung cancer with radon.

2. The generalized analysis made it possible to reduce the uncertainty of the assessment of lung cancer ERR due to radon exposure. For the risk assessment, a value of 0.14 (90% CI: 0.10–0.18) per 100 Bq/m^3 can be recommended.
3. Radon is estimated to cause 6% of cases of lung cancer in Russia, which corresponds to approximately 3900 cases per year.

Acknowledgments. The study was supported by the Russian Science Foundation (Grant no. 19-19-00191).

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References

1. United Nations Environment Programme. (2016). *Radiation: effects and sources*. UNEP.
2. Yarmoshenko, I., Vasilyev, A., Malinovsky, G., Bossew, P., Žunić, Z. S., Onischenko, A. & Zhukovsky, M. (2016). Variance of indoor radon concentration: Major influencing factors. *Sci. Total Environ.*, *15*(541), 155–160. DOI: 10.1016/j.scitotenv.2015.09.077.
3. Lubin, J. H., Boice, J. D., Edling, C., Hornung, R. W., Howe, G., Kunz, E., Kusiak, R. A., Morrison, H. I., Radford, E. P., Samet, J. M., Tirmarche, M., Woodward, A., Xiang, Y. S., & Pierce, D. A. (1994). *Radon and lung cancer risk: A joint analysis of 11 underground miner studies*. Bethesda, MD: U.S. Department of Health and Human Services, Public Health Service, National Institutes of Health. (NIH Publication no. 94-3644).
4. Committee on Health Risks of Exposure to Radon (BEIR VI). (1999). *Health effects of exposure to radon*. Washington, D.C.: National Academy Press.
5. Darby, S., Hill, D., Auvinen, A., Barros-Dios, J. M., Baysson, H., Bochicchio, F., Deo, H., Falk, R., Forastiere, F., Hakama, M., Heid, I., Kreienbrock, L., Kreuzer, M., Lagarde, F., Mäkeläinen, I., Muirhead, C., Oberaigner, W., Pershagen, G., Ruano-Ravina, A., Ruosteenoja, E., Schaffrath Rosario, A., Tirmarche, M., Tomáscaronek, L., Whitley, E., Wichmann, H. -E., & Doll, R. (2005). Radon in homes and risk of lung cancer: collaborative analysis of individual data from 13 European case-control studies. *Br. Med. J.*, *330*(7485), 223–227. DOI: 10.1136/bmj.38308.477650.63.
6. International Commission on Radiological Protection. (2014). *Radiological protection against radon exposure*. (ICRP Publication 126). *Ann. ICRP*, *43*(3).
7. Stidley, C. A., & Samet, J. M. (1993). A review of ecologic studies of lung cancer and indoor radon. *Health Phys.*, *65*(3), 234–251. DOI: 10.1097/00004032-199309000-00001.
8. Klein, F., Amin Kotb, W. F., & Petersen, I. (2009). Incidence of human papilloma virus in lung cancer. *Lung Cancer*, *65*(1), 13–18. DOI: 10.1016/j.lungcan.2008.10.003.
9. Xiong, W. M., Xu, Q. P., Li, X., Xiao, R. D., Cai, L., & He, F. (2017). The association between human papillomavirus infection and lung cancer: a system review and meta-analysis. *Oncotarget*, *8*(56), 96419–96432. DOI: 10.18632/oncotarget.21682.
10. Tsyganov, M. M., Pevzner, A. M., Ibragimova, M. K., Deryusheva, I. V., & Litviakov, N. V. (2019). Human papillomavirus and lung cancer: an overview and a meta-analysis. *J. Cancer Res. Clin. Oncol.*, *145*(8), 1919–1937. DOI: 10.1007/s00432-019-02960-w.
11. Malinovsky, G., Yarmoshenko, I., & Zhukovsky, M. (2018). Radon, smoking and HPV as lung cancer risk factors in ecological studies. *Int. J. Radiat. Biol.*, *94*(1), 62–69. DOI: 10.1080/09553002.2018.1399225.
12. Malinovsky, G., Yarmoshenko, I., & Vasilyev, A. (2019). Meta-analysis of case-control studies on the relationship between lung cancer and indoor radon exposure. *Radiat. Environ. Biophys.*, *58*(1), 39–47. DOI: 10.1007/s00411-018-0770-5.
13. Yarmoshenko, I. V., & Malinovsky, G. P. (2016). Lung cancer mortality and radon exposure in Russia. *Nukleonika*, *61*(3), 263–268. DOI: 10.1515/nuka-2016-0044.
14. Malinovsky, G. P., Yarmoshenko, I. V., & Zhukovsky, M. V. (2017). Radon, smoking and human papilloma virus as risk factors for lung cancer in an environmental epidemiological study. *Radiatsionnaya Gygiena*, *10*(2), 106–114. DOI: 10.21514/1998-426X-2017-10-2-106-114. (in Russian).
15. International Commission on Radiological Protection. (2010). *Lung cancer risk from radon and progeny and statement on radon*. (ICRP Publication 115). *Ann. ICRP*, *40*(1).
16. Krewski, D., Lubin, J. H., Zielinski, J. M., Alavanja, M., Catalan, V. S., Field, R. W., Klotz, J. B., Létourneau, E. G., Lynch, C. F., Lyon, J. I., Sandler, D. P., Schoenberg, J. B., Steck, J. A., Stolwijk, J. A., Weinberg, C., & Wilcox, H. B. (2005). Residential radon and risk of lung cancer. A combined analysis of 7 North American case-control studies. *Epidemiology*, *16*(2), 137–145. DOI: 10.1097/01.ede.0000152522.80261.e3.
17. Lubin, J. H., Wang, Z. Y., Boice, J. D. Jr, Xu, Z. Y., Blot, W. J., De Wang, L., & Kleinerman, R. A. (2004). Risk of lung cancer and residential radon in China: pooled results of two studies. *Int. J. Cancer*, *109*(1), 132–137. DOI: 10.1002/ijc.11683.
18. Cohen, B. L. (1995). Test of the linear-no threshold theory of radiation carcinogenesis for inhaled radon decay products. *Health Phys.*, *68*(2), 157–174. DOI: 10.1097/00004032-199502000-00002.
19. Puskin, J. S. (2003). Smoking as a confounder in ecologic correlations of cancer mortality rates with average county radon levels. *Health Phys.*, *84*(4), 526–532. DOI: 10.1097/00004032-200304000-00012.
20. Onishchenko, A., & Zhukovsky, M. (2019). The influence of uncertainties of radon exposure on the results of case-control epidemiological study. *Int. J. Radiat. Biol.*, *95*(3), 354–359. DOI: 10.1080/09553002.2019.1547846.
21. Fearn, T., Hill, D. C., & Darby, S. C. (2008). Measurement error in the explanatory variable of a binary regression: regression calibration and integrated conditional likelihood in studies of residential radon and lung cancer. *Statist. Med.*, *27*, 2159–2176. DOI: 10.1002/sim.3163.

22. Yarmoshenko, I., Malinovsky, G., Vasilyev, A., & Zhukovsky, M. (2015). Reconstruction of national distribution of indoor radon concentration in Russia using results of regional indoor radon measurement programs. *J. Environ. Radioact.*, *150*, 99–103. DOI: 10.1016/j.jenvrad.2015.08.007.

23. Kaprin, A. D., Starinsky, V. V., & Petrova, G. V. (2019). *Malignant neoplasm in Russia in 2018 (morbidity and mortality)*. Moscow: P. Herzen Moscow Oncology Research Institute. (in Russian).