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RADON IN HUMAN ENVIRONMENT AND CARCINOMA – PART 2

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Abstract: The article describes basic theories of small doses of ionizing radiation's impact on an organism and the current views on mechanisms of cancer emergence influenced by radiation. The risk estimation of lung carcinoma caused by inhalation of radon present in human environment was provided.

Key words: radon, ionizing radiation, lung carcinoma.

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Oncogenesis and ionizing radiation

Mechanisms leading to the development of cancer caused by exposure to radon are not yet sufficiently known, however, it can be stated with a high dose of probability that genetic and epigenetic[1] changes are engaged in this process [1]. Unscear's article contains a review of latest information gathered in recent years pertaining to biological mechanisms of low doses impact [2].

Organism's exposure to ionizing radiation causes impacts and reactions in atoms and particles, which result in changes emerging in DNA, cells, tissues and organs. The most significant damage relates to DNA and may influence only the particle or histone proteins connected with it. In a DNA molecule, the DNA strands may break or nucleotides may be modified, which consequently may distort gene expression due to the mutation. Radon may also cause changes in genes responsible for proliferation of cancer cells and their diversification [3]. The research on miners employed in a radon mine revealed that 31% of lung carcinomas have the same mutation in 249 codon of the p53 gene [4]. Other genetic damages are chromosome aberrations and the induction of micronuclei, which in certain conditions may cause cancer [5].

There are constantly more evidence that the results of DNA damages caused by ionizing radiation vary from spontaneous DNA damages [6]. The difference lies in a distinct microdistribution of damages along the DNA strands [7]. It is assumed that ionization produced by secondary electrons causes the emergence of grons or clusters of OH radicals, which mostly destroy DNA sections existing near the areas with high local concentration of radicals [8]. Due to the fact that OH radicals have very limited range (3nm), resulting from their high radioactivity, the produced damages are included along the DNA strands in the area of a few pairs of bases. In order for the produced DNA damage not to cause mutation, it should be precisely repaired. There are observations that contrary to spontaneous damages, the DNA damages caused by ionizing radiation are repaired with difficulties or are repaired incorrectly or are impossible to repair [9]. This observation proves the thesis that there is no threshold of ionizing radiation dose below which this radiation does not evoke considerable biological effects in a cell [10]. The majority of damages is repaired but it is not always complete and it may cause the cell's death or its further functioning with a faulty repair. Death of a small number of somatic cells due to ionizing radiation does not cause perceptible health effects. If, however, a greater dose of radiation (from 0.5 Sv to several Sv) evokes elimination of a large number of stem cells and progenitur cells, it causes various symptoms of disease, such as: reduced number of white blood cells, erythema, skin ulcers, tissue necrosis, vomiting, diarrhea, the rise in body temperature. The enumerated symptoms are called deterministic effects. They emerge in a short intervening period after the exposure (hours, days), usually after a short organism's irradiation with high doses. Intensification of disease symptoms is proportional to the absorbed dose. If damages impair elementary living functions, it may lead to death of an organism. For example, 4 Sv dose covering the whole body leads to death of half of the people in the irradiated group during the period of two months. The literature includes extensive documentation of deterministic damages based mostly on observations of people after radiological accidents [11, 12].

[1]Epigenetic modification, the modification of DNA or associated chromatin proteins that leads to altered expression of genes. DNA methylation, histone acetylation and methylation are among the epigenetic marks currently known.

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If, however, cell damage is not fatal but only some of its functions are disorganized, the produced mutation can be transmitted to progeny cells. Mutations in somatic cells' genes may lead to initiation, promotion and cancer cells progression, which ends in cancer. Mutations and their clinical consequences appear randomly (stochastically).

After the date of irradiation, cancer can develop in a few or even a few dozen years. Leukemia appears the quickest after the exposure – about two years and for solid tumors the period without symptoms lasts from 8 to 10 years [13]. If the mutations develop in reproductive cells (sperm, egg cells), it is possible that children will develop hereditary diseases or congenital malfunctions. Such observations are well documented on animal testing [14].

The risk coefficient of cancer in the exposed population depends on dose amount, but the size of health detriment and the clinical course of disease do not depend on the amount of the absorbed dose [15]. In the range of moderate and high doses, the frequency of stochastic effects emergence (cancers) increases together with the dose's quantity. However, after exceeding certain limit, its further increase causes the decrease in the number of people suffering from cancer in relation to the number of irradiated ones. It is the result of a larger number of cells damaged by radiation in relation to the number of mutated cells [11, 16].

Linear and threshold theory

ICRP believes that only linear theory is applicable, which connects the dose with the result. However, several hypotheses are considered that try to link the amount of absorbed dose of ionizing radiation with the caused radiobiological effects. The most intense discussion and experimental works focus on detecting the dose threshold and its potential value below which there are no harmful radiobiological effects. Up to now, this issue has not been settled, although there are constantly more evidence on the possibility of such a threshold's existence.

Linear theory

This theory assumes the possibility of linear extrapolation of consequences caused by harmful impact of radiation in the range of average and higher doses up to the range of small[2] and very small ones. The basic assumption of this theory is the statement that even one cell modified by radiation, in further stages of its development, may lead to the emergence of cancer. There are experimental evidence that the general number of DNA damages depends linearly on radiation dose [10,18]. This theory silently assumes that mechanisms of repairing post-radiation damages existing in an organism and immunological protection are not always reliable. Theoretical considerations of α radiation's impact on DNA seem to prove the validity of linear dependence between the effective dose of ionizing radiation absorbed by a tissue and the initiation of cancer process [19]. Relative risk of lung carcinoma increases together with radon concentration in houses [20].

Threshold theory

If we assume that in order for cancer to initiate, it needs post-radiation modifications in more than one cell, then the existence of threshold dose becomes understandable. The published observations carried out in recent years, call into question the linear theory. The examinations of non-targed effects and genes expression suggest that cell reaction to small doses may vary from processes caused by the exposure with average and higher doses [21, 22].

Non-linear dependence of biological reactions to small doses was revealed, which differs in nature from the reaction to high doses [23]. Moreover, the so-called 'bystander effects'[3], dependent on the dose, visibly vary from linearity.

Portess et al. observed that stimulation of pre-cancer cells apoptosis increases after exposure to gamma radiations with small doses starting with 2 mGy. The magnitude of apoptosis raises together with increasing the dose to about 100 mGy, however, further increase in the dose does not cause apoptosis growth [24].

On the other hand, there are experimental evidence that the general number of damages in the cell DNA depends linearly on the radiation dose [10,18]. It leads to assume that there is no ionizing radiation dose threshold below which ionizing radiation does not cause significant biological effects in the cell [10]. It should be noticed that the linear theory is the assumption dictated by cautiousness and held for radiological protection reasons and it is not the proved scientific fact [25]. Up to the present, in radiological protection, the so-called 'linear dependence dose-response' is in force. This dependence implies that even the dose of ionizing radiation slightly higher than zero absorbed by cells causes the possibility (although minimal) of cancer processes initiation [19, 26].

Epidemiological studies

The dependence between radon concentration in the air and lung carcinoma was noticed in the second half of the 20^{th} century. The systematized observations of miners began in the 60s of the 20^{th} century [27–29]. A majority of epidemiological evidence for the cancerogenic activity of radon derives from the analysis of registries of lung carcinoma

[2] Up to the present, there is no clear limit below which the doses should be called small [17].

[3] Bystander effects – effects observed in non-radiated cells surrounding cells that were directly irradiated.

among the miners working in uranium mines [30, 31]. The results of the studies indicated that the number of registries of lung carcinoma increased together with the amount of accumulated dose absorbed by tissues and constituted linear dependence between exposure and the risk of cancer.

In order to increase the statistical power of conclusions, several meta analyses were carried out (collective analyses) by combining and summarizing the statistical risk coefficients, such as relative risks from an individual cohort. The first such meta analysis including miners from the three mines: The Colorado Plateau, USA, The Eldorado mine in Ontario, Canada, and Swedish iron miners in Malmberget, was published in 1988 by BEIR IV Committee [32]. The next work was published in 2003 by Lubin et al. and covered 11 mining cohorts [33]. The collective analysis of people at risk of relatively small exposure (4 WL)[4] with the data including 10100 miners and 574 cases of lung carcinoma, was presented by Tomasek et al. in 2008 [34]. The most robust overview was published by Grosche et al. in 2006 [35]. It included meta analysis of data pertaining to 59000 miners of uranium mines, where 2388 cases of lung carcinoma were detected. These data were collected in the period of 52 years (1946-1988). The meta analyses presented above provided convincing evidence on the increase in lung carcinoma risk as a result of long lasting exposure to higher radon concentration.

Radon in houses (indoor) and the risk of lung carcinoma

The case that is still left open is the possibility of using the data obtained from mining cohorts observations to assess harmfulness of radon exposure in apartments [36]. According to the authors, this remark pertains to the doses received throughout lifetime that are higher than 50 WLM[5]. However, exposure in houses[6] is usually considerably lower, as it amounts to 15-20 WLM[7] [41]. The U.S. Environmental Protection Agency estimated that due to radon occurrence in houses, in the USA during a year, 7000 – 30000 citizens die of lung carcinoma [42].

[4]WL – working level, one WL equals any combination of radon progeny in 1 litre of air that gives the ultimate emission of 1.3×10^5 MeV of energy of α particles

[5]WLM – Working Level Months is defined as exposure resulting from inhalation of air with a 1 WL concentration for 170 hours (a typical working month).

[6]The precise conversion of exposure in WLM units obtained by miners in mines to the exposure received by people in houses is not possible without knowing the F balance coefficient, which depends on local exposure conditions. By assuming that F balance coefficient = 0.4 we obtain 1 WLM that equals the annual exposition absorption by bronchi, with radon concentration of 225 Bq/m^3 in the indoor air [37].

[7]In the state of radioactive balance with its progeny (1WL=3700 Bq of radon in m^3) [38]. In apartments, where generally F=0.5, 1WL=7400 Bq/m^3 [39]. In epidemiological studies, the conversion coefficient of 4 mSv/WLM is often used [40].

Lubin et al. similarly assessed the number of people dying of lung carcinoma in the USA caused by radon in houses. According to them, this number is contained within the range from 6000 to 36000 people annually [42, 43]. Several studies have also detected an inverse exposure rate effect, i.e. low exposure rates for protracted duration of exposure are more hazardous than equivalent cumulative exposures received at higher rates for shorter period of time [44, 45]. Hill et al. agree with this conclusion [45]. Lubin et al. also claim that lowering the dose with the same total exposure increases the risk of cancer [41].

However, the evidence on lung carcinoma caused by radon present in houses were not explicit until the end of the 20^{th} century. Meta analysis of eight works conducted by Lubin and Boice in 1997 indicated the visible causal relationship between radon presence in houses and lung carcinoma [39]. However, there are also epidemiological reports analyzing the connection between lung carcinoma and the presence of radon in houses that did not reveal any visible dependence [46–48].

As can be concluded from the above description, the issue of the influence of radon in houses on lung carcinoma had not been resolved for many years. Dary and 26 coauthors conducted pooled analysis of the raw data from separate residential case-control of 13 studies carried out in Europe. The whole analyzed pool covered 21.356 people including 7148 with lung carcinoma and 14.208 people constituted a control group. The collected detailed data from all the people were transmitted to the questionnaires prepared according to one scheme. In the questionnaires, apart from radon concentration in houses, there were data on: smoking, age, sex and many different information that could be connected with lung carcinoma. Much effort was made to collect information on radon concentration in houses inhabited for 30 years. In the group of the ill, the indoor radon concentration amounted on average to 104 Bq m^{-3}, and 97 Bq m^{-3} in the control group. In group of the ill, there was a significant statistical excess relative risk (ERR) amounting to 0.08/100 Bq m^{-3} (95% CI: 0.03 – 0.16). The dependence dose-response seemed to be linear (the threshold with p = 0.04 was not detected). In the assessment of the authors, radon causes a significant risk in apartments especially to the smokers and ex-smokers. The authors of this work concluded that radon inhalation in houses is the reason for 9% of deaths caused by lung carcinoma or 2% of deaths in relation to all deaths caused by cancers in Europe [49].

Radon and other cancers

The doses from radon and its progeny received by other organs were estimated by Miles and Cliff in 1992. The inhaled radon, after dissolution in blood, is transported to all organs. Radon concentration in tissues and the doses

of radon depend on the amount of fat in the organs. Radon dissolution in fats is 16 times higher than in blood. With radon concentration of 20 Bq m^{-3} in the surrounding, it is assumed that the tissues with 1% of fat undergo the exposure of 16 μSv [50]. According to Richardson et al. estimations, with the same concentration, the doses on marrow from radon may amount to 96 μSv as marrow contains about 40% of fat [51]. With the action level of 200-600 Bq m^{-3}, the dose on marrow lies within the range 100-300 μSv, and according to ICRP estimations, it can be two rates higher in the lung area [52].

Some authors claim that the occurrence of other cancers than lung carcinoma caused by radon seems doubtful. The research conducted by Butland et al. [53] and Muirhead et al. [54] do not indicate any connections between an indoor exposure to radon and leukemia [55]. However, there are reports from other researchers that radon also causes other cancers. Henshaw et al. claim that an indoor exposure to radon is connected with an increased risk of leukemia and other cancers such as melanomas, kidney and prostate cancers [56].

Darby et al. presented data indicating the increased occurrence frequency of other cancers than lung carcinoma among iron mines' workers exposed to radon. Those miners, in relation to the control group, had increased mortality caused by other cancers than lung carcinoma and this mortality was 21% higher with the confidence level of 95%. Stomach cancer developed 45% more often and anal cancer – 94% more often, with the same confidence level [57]. In another study, Darby et al. analyzed 11 mining cohorts composed of 64000 miners, who on average were employed for 6.4 years. The average exposure of those miners amounted to 155 WLM. Those authors did not notice the increase in the general number of cancers. However, they observed certain increase in stomach and liver cancers and decrease in the number of tongue and pharynx cancers [58]. In the neighborhood of the uranium reserves next to New Mexico (USA), Wilkinson reported increased mortality caused by stomach cancer [59]. Forastiere et al. observed, in the selected Italian area (Viterbo) with the increased exposure to radon, 2-3 times increase in risk of kidney cancer, melanomas and marrow leukemia [60]. Edling et al. noticed extender number of pancreaic cancer [61]. Bean et al. described increased number of bladder and breast cancers [62]. Tomasek et al. published observation on enhanced number of stomach, liver, gallbladder and bile ducts cancers among miners of uranium mines in the Chech Republic [63].

Smoking as a factor distorting the observation of cancerogenic effect of exposure to radon

The risk of lung carcinoma caused by exposure to radon and its progeny should be assessed by taking into consideration the widely described and well documented cancerogenic effects of smoking [64]. The development of lung carcinoma among the non-smokers is much lower in relation to the group of smokers. Only 5-10% of all lung carcinoma cases occur in the non-smoking group [64]. The risk of lung carcinoma increases together with the length of smoking and number of cigarettes smoked daily. The risk of lung carcinoma in smokers is 10 times higher and in people smoking large number of cigarettes – even 20 times higher [65]. Smoking is a decisive factor inducing lung carcinoma in relation to the effects of radon exposure [66]. Due to this, the cancerogenic effects of exposure to radon should be separately estimated for the group of smokers and non-smokers. In case when one cancerogenic factor changes the effects of another cancerogenic factor, we speak about interaction. In the discussed case, smoking changes the effects of exposure to radon and more precisely the effects of mucosa of bronchi tree exposure on radon decay products [67]. The simultaneous activity of smoking and exposing oneself to radon provides synergic effects. This synergy can be a multiplier and in such a case, the risk of cancer is the product of risk caused by smoking and the risk caused by exposure to radon [67]. The possible synergy is also the one in which the risk volume derived from every cancerogenic factor is added up and then we may speak about the summary effect [68]. Risk volume caused by simultaneous activity of ionizing radiation and smoking is not clearly established and there are differences in its estimation in particular works [67, 69, 70].

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